ORGANOCATALYTIC STRATEGIES TOWARDS CHIRAL FLUORINATED MOLECULES AS PRECURSORS OF BIOACTIVE COMPOUNDS

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I hereby declare that this thesis is my original work and it has been written by me in its entirety. I have duly acknowledged all the sources of information which have been used in the thesis. This thesis has not been submitted for any degree in any university previously.

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1. Xiao Han, Jacek Kwiatkowski, Feng Xue, Kuo-Wei Huang, Yixin Lu "Asymmetric Mannich Reaction of Fluorinated Ketoesters with a Tryptophan-Derived Bifunctional Thiourea Catalyst", *Angew. Chem. Int. Ed.*, 2009, **48**, 7604.

2. Jacek Kwiatkowski, Yixin Lu "Highly Enantioselective Preparation of Fluorinated Phosphonates by Michael Addition of α-Fluoro-β-ketophosphonates to Nitroalkenes", *Asian J.O.C.*, 2013, *Early View*, DOI 10.1002/ajoc.201300211.

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3. Jacek Kwiatkowski, Yixin Lu "Organocatalytic Michael Addition of α-Fluoro-α-nitro Benzyls to Nitroalkenes: Facile Preparation of Fluorinated Amines and Pyrimidines".

4. Jacek Kwiatkowski, Yixin Lu "Towards the Enantioselective Synthesis of Divergent and Functionalised α-Fluoro-α-amino acids: Organocatalytic Michael Addition/hydrogenation of Ethyl Fluoronitroacetate".

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II. Research results

IV - Experimental

Summary

This thesis describes development of organocatalytic methods for the synthesis of chiral organofluorine molecules with focus on nitrogen-containing species as potentially bioactive compounds or synthons towards bioactive scaffolds. The methodology relied on seeking suitable fluorinated substrates to achieve molecules containing novel α-fluoro-α-amino core as well as α-fluoro-β-amino core via organocatalytic enantioselective C–C bond forming reactions.

Chapter one describes the use of fluoronitroacetic acid esters as donors in organocatalytic Michael addition to nitroalkenes to achieve enantioenriched products, which were derived into novel α-fluoro-α-amino ester, α-fluoro-α,γ-diamine precursors as well as α-fluoroesters.

Chapter two details the development of 1-fluoro-1-nitro-1-arylmethanes as prochiral donors which in enantioselective Michael addition led to direct precursors of α-fluorinated diamines. The method was applied to synthesize fluorinated mono- and diamines and heterocycle - tetrahydropyrimidine.

In the third chapter, route towards fluorinated phosphonates as phosphates mimics is presented. Application of racemic α-fluoro-β-ketophosphonates in organocatalytic Michael addition resulted in highly enantioselective preparation of branched and functionalized α-fluoro-γ-nitrophosphonates. Further manipulation of the product structure led to the preparation of pyrrolidine containing α-fluorophosphonate, structure being analogue of recently developed endothelin-A receptor antagonist.

Chapter four describes the further study on application of 2-fluoro-1,3-dicarbonyl compounds as Michael addition donors, which results in enantioselective preparation of compounds being direct precursors of fluoro-isosteres of glycerine. The facile reduction of the representative product led to trisubstituted 2-fluoro-1,3-diol with three tertiary stereogenic centers surrounding the fluorinated quaternary asymmetric carbon.

The last chapter in the results section - chapter five - shows how simple manipulations of enantiomerically enriched Mannich addition product led to valuable and potentially bioactive molecules such as α-fluoro-β-amino ester, α-fluoro-β-lactam and lactone. The following, studies on tandem mono-decarboxylation / asymmetric protonation of the fluoromoalonate Mannich adducts resulted in preliminary development of interesting methodology for enantioselective preparation of linear α-fluoro-β-amino acids and β-lactams.

Section three provides a brief summary and conclusion, as well as preliminary results and future perspective. As an implication of studies towards decarboxylation/asymmetric protonation, decarboxylative addition of fluoromalonate halfesters was designed and in-principle proven as an effective synthetic pathway towards linear α-fluoro-β-amino acids, which substantiate further investigation on its asymmetric version.

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List of Schemes

List of Abbreviations

Ac	Acetyl
Å	Ångström
Aq	Aqueous
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bz	Benzoyl
Cat.	Catalysts
Conc.	Concentrated
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	Diethylaminosulfur trifluoride
DCE	1,2-Dichloroethylene
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DIPA	Diisopropylamine
d	Doublet
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
Equiv.	Equivalent
EWG	Electron-withdrawing group
h	Hour
HPLC	High performance liquid chromatography
IPA	*iso*-Propanol
i-Pr	*iso*-Propyl
m	Multiplet
m/z	Mass-to-charge ratio
mmol	millimole

MBH	Morita-Bayliss-Hillman
Me	Methyl
Ms	Methyl sulfonyl
mL	Microlitre
Morpho-DAST	Morpholinosulfur trifluoride
NFSI	N-fluorobenzenesulfonimide
NR	No reaction
Nu	Nucleophile
Ph	Phenyl
Pr	Propyl
ppm	parts per million
q	Quartet
RT	Room temperature
s	Singlet
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
TEA	Triethylamine
TFA	Trifluoromethylacetic acid
THF	Tetrahydrofuran
TLC	thin-layer chromatography
Ts (Tos)	*p*-Toluenesulfonyl

List of publications

Journal articles:

Pending submissions:

1. Jacek Kwiatkowski, Yixin Lu "Organocatalytic Michael addition of α-fluoro-α-nitro benzyls to nitroalkenes: facile preparation of fluorinated amines and pyrimidines".

2. Jacek Kwiatkowski, Yixin Lu "Towards the enantioselective synthesis of divergent and functionalised α-fluoro-α-amino acids: organocatalytic Michael addition/ hydrogenation of ethyl fluoronitroacetate".

3. Xiaoyu. Han, Yong Ran Tan, Ziyu Yan, Jacek Kwiatkowski, Yixin Lu "Asymmetric synthesis of spiropyrazolones *via* phosphine-promoted [4+1] annulations", *Angew. Chem. Int. Ed.*, 2013, **53**, *submitted.*

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4. Jacek Kwiatkowski, Yixin Lu "Highly enantioselective preparation of fluorinated phosphonates by Michael addition of α-fluoro-β-ketophosphonates to nitroalkenes", *Asian J.O.C.*, 2013, *Early View*, DOI 10.1002/ajoc.201300211.

5. Xiao Han, Jacek Kwiatkowski, Feng Xue, Kuo-Wei Huang, Yixin Lu "Asymmetric Mannich reaction of fluorinated ketoesters with a tryptophan-derived bifunctional thiourea catalyst", *Angew. Chem. Int. Ed.*, 2009, **48**, 7604.

6. Jie Luo, Haifei Wang, Fangrui Zhong, Jacek Kwiatkowski, Li-Wen Xu, Yixin Lu "Highly diastereoselective and enantioselective direct Michael addition of phthalide derivatives to nitroolefins", *Chem. Commun.*, 2013, **49**, 5775

7. Jie Luo, Haifei Wang, Fangrui Zhong, Jacek Kwiatkowski, Li-Wen Xu, Yixin Lu "Direct asymmetric Mannich-type reaction of Phthalides: facile access to chiral substituted Isoquinolines and Isoquinolinones", *Chem. Commun.*, 2012, **48**, 4707.

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Conference presentations:

1. Jacek Kwiatkowski, Han Xiao, Yixin Lu "*The Enantioselective Mannich Reaction of Fluorinated β-Keto-esters with N-Boc Imines Catalyzed by Novel Bifunctional Tryptophane Derived Catalyst*", **poster presentations**:
   - *16th European Symposium on Organic Chemistry*, Prague, Czech Republic, July, 2009;
   - *6th Singapore International Chemical Conference* (*SICC-6*), Singapore, December, 2009.
   - *The 6th Asian European Symposium*, Singapore, May, 2010.
2. Jacek Kwiatkowski, Yixin Lu "*Organocatalytic Michael addition of Novel α-Fluoro-β-ketophosphonates to Nitroolefins*", **poster presentation**, *19th International Conference on Organic Synthesis & The 24th Royal Australian Chemical Institute Organic Conference (ICOS 19),* Melbourne, Australia, July, 2012.

For my father

I. Introduction: chiral organofluorine compounds

I.1.Importance of organofluorine in medicinal chemistry

I.2. Synthesis of chiral fluorinated molecules

I.3. Summary

I. Introduction: chiral organofluorine compounds

The introduction is divided into two sections. In the first part, physicochemical properties of fluorine atom are briefly described, followed by a few selected examples of incorporating fluorine atoms into specific bioactive compounds to alter targeted properties. The second part summarizes synthetic methods for making fluorinated molecules: direct and indirect fluorination. The section on direct fluorination is further divided into organocatalytic and metal-catalytic methodologies.

I-1. Importance of organofluorine in medicinal chemistry

Fluorine is a unique atom in the periodic table and has a very special place in modern science.[1] Even though human body contains an average of only 3 mg of this element,[2] there has been much interest in selective introduction of fluorine into organic compounds in the last few decades. This section aims to describe the basic characteristics of fluorine atom and carbon–fluorine (C–F) bond, and briefly discuss the various effects of fluorination on the properties of bioactive compounds using specific examples; and in such a way explain and substantiate the interest in fluorine of life and chemical sciences.

I-1.1. Properties of fluorine and the C–F bond.

Fluorine has an extreme electronegativity of κ = 4 on Pauling's scale, with that of oxygen (κ = 3.5) being the closest. In comparison, the next most electronegative halogen, chlorine, has the electronegativity of κ = 3. Having the largest electronegativity of all elements, fluorine has a small size - its van der Waals radius is estimated as 1.47 Å, which is 0.27 Å more than hydrogen and 0.28 Å less than chlorine, while being very close to that of oxygen (1.52 Å).

[1] a) V. Gouverneur, K. Müller "*Fluorine in Pharmaceutical and Medicinal Chemistry: From*
[2] http://www.rsc.org/periodic-table/element/9/fluorine

The C-F bond length is estimated to be 1.35 Å and is only longer than C-H bond (1.09 Å) and shorter than all other C-X bonds, with C-O (1.43 Å) and C-N bonds (1.47 Å) being of the most similar length.[3] The high electronegativity paired with small size results in a very low polarizability of fluorine atom. At the same time, the C-F bond has a very large dipole moment of 1.85 D for fluoromethane and 1.97 for difluoromethane, decreasing with further fluorination. It is the strongest of all covalent bonds in organic chemistry with dissociation energy calculated as 105.4 kcal/mol (in comparison, the second strongest bond C-H has dissociation energy of 98.8 kcal/mol). Interestingly, the C-F bond is hydrophobic despite its high dipole moment (polar hydrophobicity), and the effect translates to the whole molecule - the electron withdrawing character of fluorine decreases polarizability, and consequently increases hydrophobicity of the whole compound. Despite the high dipole moment, which would favor H-bonding interactions, the low polarizability of the fluorine prevails, and as a result fluorine is a very weak hydrogen bond acceptor, yet during recent computational study of the protein database bank,[4] hydrogen bonding interactions involving fluorine were found in 18% of screened protein-ligand complexes, while coordination of metals to hydrocarbons through organofluorine is a fact.[5]

These characteristics of fluorine result in its increasing applications in the fields of medicinal chemistry and biochemistry. Having the basic characteristics so close to those of oxygen, fluorine can mimic oxygen or hydroxy group in bioactive compounds (fluoro-isostere). Replacement of C-H with a stronger C-F bond results in minimal steric but dramatic electronic alteration, which understandingly became a useful tool in drug design and biochemistry. The high electronegativity of fluorine with its minimal steric effects are utilized to tune acidity and basicity of neighboring functional groups, thus influencing lipophilicity, tuning potency and modifying pharmacokinetic properties of a compound. For example, the pK_a values of acetic acid and its fluorine-incorporating analogues are as follows: 4.76

[3] D. O'Hagan, *Chem. Soc. Rev*., 2008, **37**, 308.
4 E. Carosati, S. Sciabola, G. Cruciani, *J. Med. Chem*. 2004, **47**, 5114.
[5] H. Plenio, *ChemBioChem*, 2004, **5**, 650.

(CH_3CO_2H), 2.59 (CH_2FCO_2H), 1.24 (CF_2HCO_2H) and 0.23 (CF_3CO_2H); pK_b values for ethylamines increase with fluorination: 3.3 ($CH_3CH_2NH_2$), 4.03 ($CH_2FCH_2NH_2$), 6.48 ($CF_2HCH_2NH_2$) and 8.3 ($CF_3CH_2NH_2$).[6] Moreover, due to the rarity of occurrence of fluorine in natural peptides and proteins, as well as its very low background signal, high sensitivity and large chemical shift, ^{19}F NMR is a powerful tool in peptide analysis and could also be used to elucidate reaction mechanisms. Fluorine's unnatural isotope ^{18}F is the most widely used isotope in positron emission tomography (PET) – a now common method in medical diagnostics, because of its low positron energy (safe for patient) and relatively long half-life (110 mins) to allow sophisticated measurements (yet short enough to conduct kinetic studies). The characteristics of fluorine listed above are the reason why this element found application in "rational" drug design. In the following section, some specific examples will be reviewed, where certain effects were observed after selective incorporation of fluorine into the molecular structure.

I-1.2. Altering characteristics of molecules by selective incorporation of fluorine.

Campothecin (CPT, Figure 2) is a pentacyclic alkaloid isolated from *Camptotheca Acuminate* and was found to possess high antitumor activity by inhibiting topoisomerase I (Top1). However the potential applications of this compound was hampered by its instability, attributed to the vulnerability of the lactone moiety. Moreover, this compound was also hepatoxic. In fact, lactone is a common motif in bioactive compounds, therefore, improving the stability of CPT could help resolve similar issues with other leads. It was proposed that substitution of carbonyl oxygen with fluorine would increase hydrolytic stability of the compound, without generating excessive steric hindrance.[7]

[6] MedChem Database, Biobyte Corporation and Pomona College, 2002.
[7] Z. Miao, C. Sheng, et al., *J. Med. Chem.*,2013, **56**, 7902.

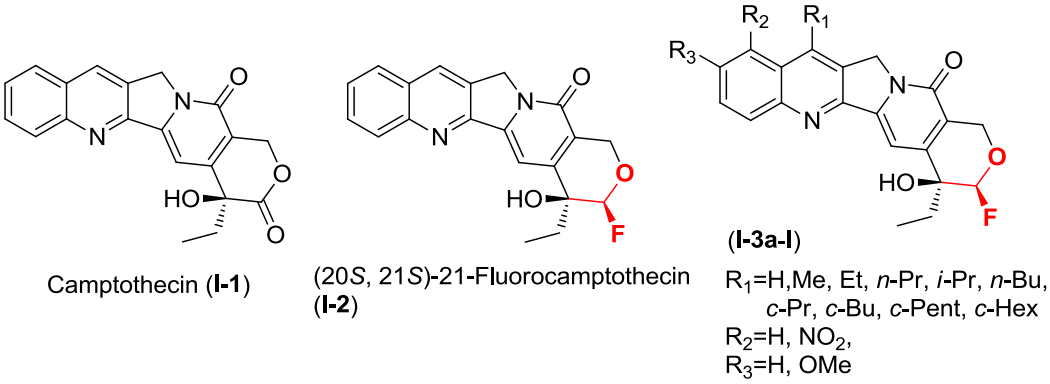


Figure 2. The structure of Campothecin and the proposed alteration by fluorination.

Indeed, upon fluorination, the stability was dramatically improved; after 6 hours the CPT analogues (**I-2**) and (**I-3l**, R_1 = *c*-hex, R_2 = R_3 = H) were both hardly affected (96% in original form), while only 42.7% of CPT remained intact (Figure 3, **C**). Understandably, fluorination affected other features of the compound as well, and not all in a positive way. It was found that fluorocampothecin was less active against common cancers. This problem was resolved by structural optimization and eventually highly potent compound **I-3l** was identified as a potential lead, exhibiting the same potency as the clinically relevant reference - Topotecan (TPT, Figure 3, **A** - inhibition of tumor growth), while at the same time causing almost no loss in mice body weight - which can be approximated to low toxicity - as compared to significant weight loss caused by TPT (**B**, Figure 3).

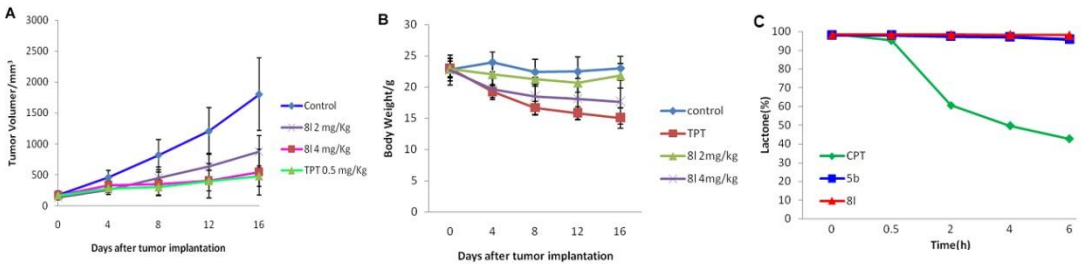


Figure 3. A) Potency of compound **I-3l** (**1-3l:** purple-2 mg/kg, pink-4 mg/kg; green-TPT-0.5 mg/kg; blue-control; **B**) Weight loss of mice (**8l:** green-2 mg/kg, violet-4 mg/kg; red-TPT; blue-control); **C**) Hydrolytic stability of CPT (green) and its two fluorinated analogues at pH = 7.4: **1-2** (blue), **1-3l** (red).

Lipophilic compounds are thought to be metabolized by liver enzymes (especially cytochrome P450). Two strategies are: increasing polarity of the compound (however,

decreasing membrane permeation) or blocking metabolically vulnerable points with fluorine (however, some other effects may also emerge). The latter strategy was successfully employed to reinforce the stability of SCH48461 (**I-4**, Figure 4) - a cholesterol absorption inhibitor. Incorporation of fluorine into the phenyl ring of SCH48461 prevented its oxidation to phenol, while substitution of labile methoxy with fluorine prevented its dealkylation. As a result, Ezetimib (**I-5**), which is a stable compound and is 55 times more potent than **I-4**, has been approved by FDA .[1e]

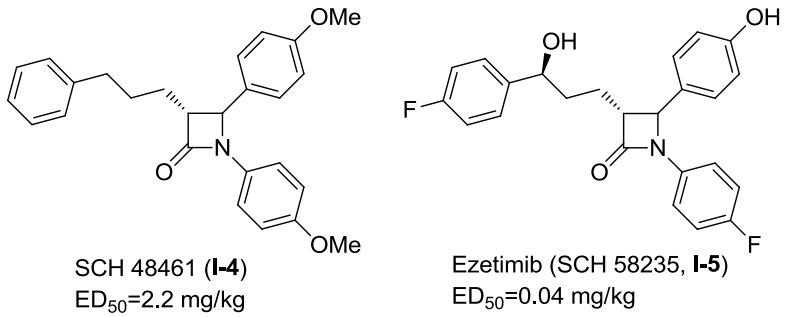


Figure 4. Development of Ezetimib **I-5** - a more stable and potent version of lead SCH48461.

Sugar nucleosides play multiple roles in biological systems such as neurotransmission, regulation of cardiovascular activity and signaling, in addition to being key compounds in cellular biosynthesis. As such, they constitute an important pool for development of antiviral and antitumor agents in medicinal chemistry. Since fluorine is an excellent hydroxyl surrogate, incorporation of fluorine atom into nucleoside structures has become an important approach in drug development. The most profound effects of fluorine incorporation include: strengthening of glycosyl bond and consequently increasing stability against phosphorylases, increasing lipophilicity and decreasing polarizability of nucleoside (polar hydrophobicity) and inducing strong stereoelectronic effects due to fluorine's preference for *gauche* and antiperiplanar orientation. Following the discovery of novel carbocyclic-, thio-, phospha- and azanucleosides, and their potent antiviral activities, a series of nucleosides either directly fluorinated at 2', 3', 5', 6' positions, or substituted with various fluoroalkyl substituents have been prepared and evaluated for their antiviral properties. For instance, FdC (**I-6**, Figure 5)

was developed as an inhibitor for hepatitis C RNA replication and found highly potent;[8a] FMAU (**I-7**) [8b] and FIAC (**I-8**)[8c] were found very active against *herpex simplex, varicella zoster* (VZV), *cytomegalovirus* (CMV), and *Epstein–Barr* (EBV) viruses; Gemcitabine (**I-9**) is an FDA approved drug against pancreatic cancer and solid tumors.[8d,e]

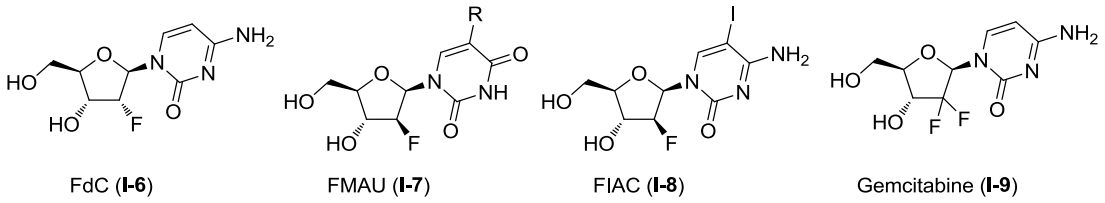


Figure 5. Fluorinated nucleosides with biomedical applications.

The development of fluoroquinolone antibiotics began with the discovery of nalidixic acid (**I-10**, Figure 6) as an impurity in quinine, and its following application in treating urinary tract infection.[9] After 25 years, during which period occasional research eventually shed light on the effects of fluorination on properties of quinolones, several antibiotic agents have been developed, such as: perfloxacin (**I-11**), ciprofloxacin (**I-12**), levofloxacin (**I-13**), moxifloxacin (**I-14**) and the newest - sitafloxacin (**I-15**). Notably, all the compounds bear a fluorine atom at C6 of the aromatic ring. This substitution was found to dramatically increase potency of the leads (2 – 17-fold increase in DNA *gyrase*-inhibitory and 2 – 100-fold increase in cellular potency). These observations are rationalized and attributed to the effects of fluorine on binding, cell penetration and pKa modulation.[1a] Interestingly, the unusual fluorocyclopropyl substituent on sitafloxacin was found to decrease the overall lipophilicity and improve selectivity against mammalian topoisomerase II.[10]

[8] a) L. J. Stuyver, T. R. McBrayer, T. Whitaker, *et al*., *Antimicrob. Agents Chemother*., 2004, **48**, 651; b) C. K. Chu, T. Ma, K. Shanmuganathan, et al., *Antimicrob Agents Chemother.* 1995, **39**, 979; c) K. A. Watanabe, U. Reichman, K. Hirota, *et al*., *J Med Chem*., 1979, **22**, 21; d) S. Noble, K. L. Goa, *Drugs*, 1997, **54**, 447; e) L. W. Hertel, G. B. Boder, J. S. Kroin, *et. al*., *Cancer Res*., 1990, **50**, 4417.
[9] M. I. Andersson, A. P. Macgowan, *J. Antimicrob. Chemoth*., 2003, **51**, S1.
[10] Y. Kimura, S. Atarashi, K. Kawakami, *et al*., *J. Med. Chem*., 1994, **37**, 3344.

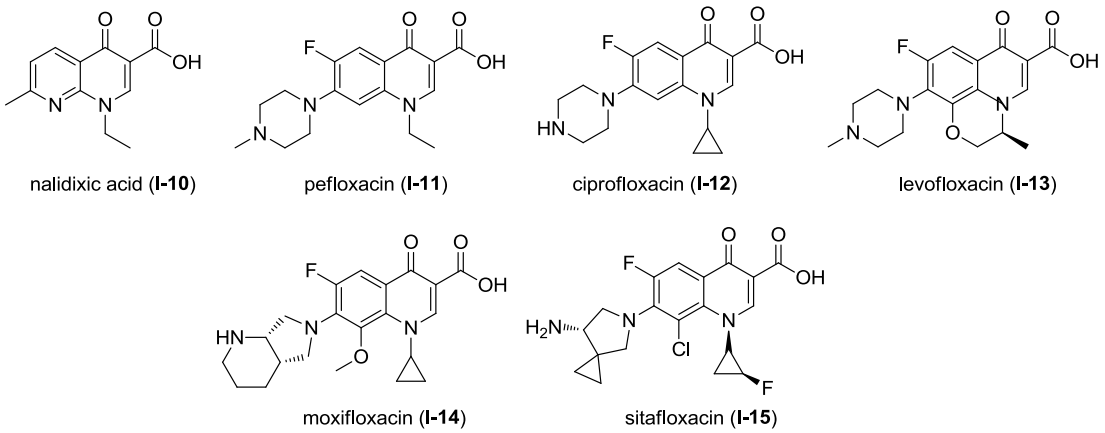


Figure 6. Fluoroquinolone antibiotics.

Strategic incorporation of fluorine to modify pK_b was used as a tool in the development of MK-0731 (**I-17**, Figure 7), a taxane-refractory antitumor agent, currently in clinical trials.[11] The lead compounds (**I-16a-c**) were found to exhibit promising kinesin spindle protein (KSP)[12] inhibiting properties. It was found that the basicity of the piperidine ring was crucial in further optimization. In order to bring the pK_b to the envisioned optimum range (6.5-8.0), installation of substituents on piperidine nitrogen was attempted. *N*-Cyclopropyl substituent in **I-16a** resulted in unintentional time-dependent cytochrome P450 inhibition; fluoroalkyl group on the piperidine nitrogen in **I-16b** was found to transform into **I-16c** and produce fluoroacetic acid as highly toxic metabolite. On the other hand, introduction of fluorine into the piperidine ring resulted in achieving the desired pK_b range, while not causing any major additional side effects. Interestingly, the effect of fluorination on pK_b was found to depend on configuration; the diastereomer with equatorial (or *trans*) fluorine (**I-18**) had pK_b = 6.6 (brought down from 8.8 in parent compound), while (**1-17**) with axially installed fluorine (*cis*) exhibited pK_b of 7.6 and was eventually advanced into clinical trials.

[11] C. C. Cox, *et al*., *J. Med. Chem*., 2008, **51**, 4239.
[12] KSP belongs to the family of motor proteins, which were recently identified as mechanistic targets in the treatment of taxane-refractory solid tumors.

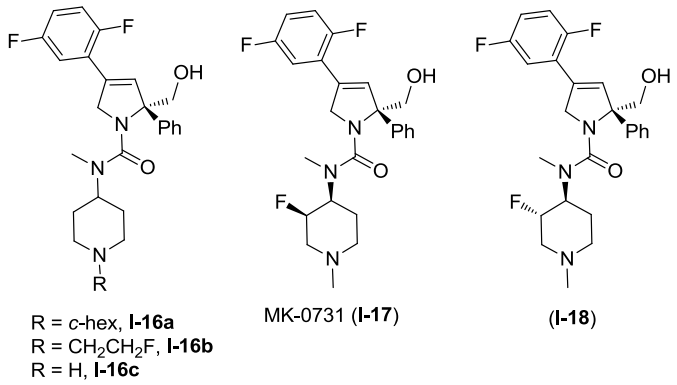


Figure 7. Modulating pK_b by fluorination in the development of MK-0731 **(I-17)**.

The structural motif of fluorinated cyclic amine is established as a valuable component in drug design.[13] Variations of such fluorinated cyclic-amines were targeted during the course of our research and resulted in the development of general route towards α-fluoro-tetrahydropyrimidines (see Chapter II-2) and phosphonate-containing pyrrolidines (Chapter II-3).

Amino acids are the basic building blocks of peptides, which in turn are larger building units for a variety of biomolecules, e.g. proteins. The development of functional peptides is a daunting challenge, suffering from limited structural variation within the pool of proteinogenic amino acids, as well as poor metabolic stability, bioavailability and lacking potency of peptides consisting of natural amino acids units. On the other hand, fluorinated amino acids are interesting analogues of natural and synthetic amino acids, with some unique properties attributed to fluorination. However, due to the complexity of biological systems, specific applications of fluorinated amino acids are rare and underdeveloped. Given the unique properties of fluorine, this will certainly emerge with further advancements in life sciences and synthetic chemistry - broadening the pool of tunable, fluorinated molecules. Electronic properties of fluorine could be used to alter pKa and pK_b values and lipophilicity of individual amino acids or the whole peptide, increasing membrane permeation, affecting metabolism, or binding to molecular plasma. Fluorine also affects the stability, flexibility and

[13] See for example: S. J. Shaw, D. A. Goff, L. A. Boralsky, M. Irving, R. Singh, *J. Org. Chem.*, 2013, **78**, 8892.

conformation of peptides, their higher order structures and interactions with proteins.[14] Furthermore, interesting reactivity may also emerge. For example, elimination of hydrogen fluoride from fluorinated amino acids and formation of active α-carbanion Michael acceptors could inactivate decarboxylases or transferases (suicide inhibitors).[15]

The effect of fluorination on interactions between peptide and receptor was studied on a model example of chemotactic peptide For-Met-Leu-PheNH_2 (fMLF) from *Escherichia coli*. The role of the chemoattractant is to bind to the hydrophobic receptor of neutrophil, which initiates chemotaxis, as a response to infection. Therefore, it is a good system to study the effects of fluorination on hydrophobicity versus polarity and sterics.[16] The analogues of fMLF were prepared in which leucine was replaced with (*R*) or (*S*) difluoro- or trifluoro- glycines or alanines. In general, it was found that all new peptides were active, however their activities were lower than that of the native peptide. Moreover, the *R/S* configuration was crucial and brought 100% increases or decreases in binding affinity. The steric demands of trifluoromethyl group were confirmed and found favorable in this case, while the polarity of difluoromethyl group was detrimental. This example illustrated complexity that may arise from fluorinated analogues of peptides. Similarly complex, favorable effects were observed for a similar complex. Enkephalins - one of native peptide ligands of opioid receptors, play an important part in regulation of central nervous system pathways.[17] The targeted δ-opioid peptide - [D-Pen^2, D-Pen^5]enkephalin (DPDPE) was modified by introducing either (D) or (L) 4,4-difluoro-2-aminobutyric acid ((D) or (L)-DFAB, **I-19**, Figure 8). The analogues showed unexpected selectivity patterns compared to the non-fluorinated modifications, and improved selectivities were observed for (*D*)-fluorinated amino acids (as compared to preference for (*L*)-natural amino acids).

[14] C. Jäckel, B. Koksch, *Eur. J. Org. Chem*.,2005, 4483.
[15] For a review see: C. Walsh, *Tetrahedron*, 1982, **38**, 871.
[16] B. Koksch, C. Dahl, G. Radics, A. Vocks, K. Arnold, J. Arnhold, J. Sieler, K. Burger, *J. Pept. Sci*., 2004, **10**, 67.
[17] D. Winkler, N. Sewald, K. Burger, N. Chung, P. W. Schiller, *J. Peptide Sci*., 1998, **4**, 496.

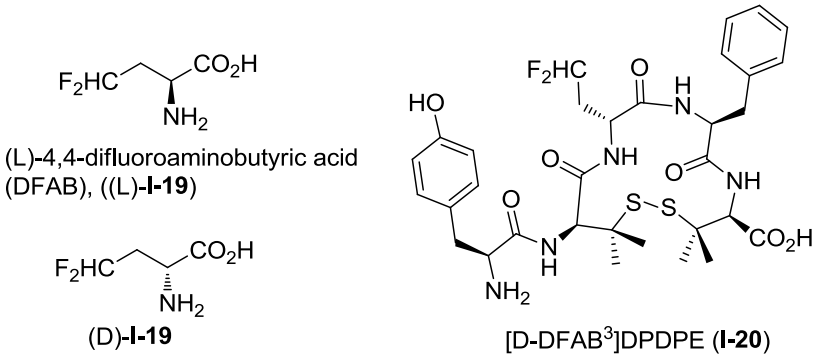


Figure 8. Modification of encephalin δ-opioid peptide DPDPE (**I-20**).

At the same time, a pronounced fluorine effect was observed and the newly developed peptide (**I-20**) displayed 100-fold higher δ agonist potency than its non-fluorinated counterpart. The increase in potency and reversed configuration/selectivity pattern was rationalized as increase in hydrophobic contact, hydrogen bridges with fluorine, modified electrostatics *via* polarized C-F bonds as well as displacement of water molecules from the binding site.

The complexity and the scale of the observed effects caused by incorporation of fluorinated amino acids into bioactive molecules, motivate the search and development of general synthetic routes towards those molecules. Such studies were undertaken during the course of our research and reported in chapters II-1, II-2 and II-5 and the future perspectives section.

I-2. Synthesis of chiral fluorinated molecules

This section summarizes the synthesis of organofluorine compounds with focus on the classes of chiral, functionalized molecules, relevant to the overlapping fields of synthetic, medicinal- and bio-chemistry. Due to constrain as to the volume of this chapter, racemic perfluorinated molecules and asymmetric trifluoromethylation, will not be discussed. The section is divided into two parts: direct fluorination (organocatalytic and metal-promoted methodologies) and indirect fluorination (the use of fluorinated prochiral donors).

I-2.1. Direct asymmetric fluorination

The most straightforward method to access chiral fluorinated molecules is enantioselective fluorination. It is a difficult synthetic task that requires addressing several challenges such as: chemo- and enantioselectivity, activation of unreactive substrates while avoiding bis- or perfluorination. Due to the characteristics of fluorine atom, the fluorinating reagents in general are reactive and can breakdown functionalized molecules. Therefore, preparation of fluorine-containing substrates or target molecules *via* direct fluorination has been and will remain a challenge for many years to come. The practical enantioselective methods for enantioselective installation of fluorine employ electrophilic N-F reagents, such as: Selectfluor®, NFSI (*N*-Fluorobenzenesulfonimide) as well as N-S-F reagents such as: DAST (Diethylaminosulfur trifluoride), morpho-DAST (Morpholinosulfur trifluoride) or metal or ammonium fluorides - MF and $R4N^{+}F^{-}$ (Figure 9). This introduction will explore and present the most practical enantioselective fluorination methodologies based on the application of common mild electrophilic fluorinating reagents and activation by metal or metal-free catalysts, with focus on the scope and diversity of synthetic molecules[18]

[18] For a more complete account see: a) C. Hollingworth, V. Gouverneur, *Chem. Commun*. 2012, **48**, 2929; b) J.-A. Ma, D. Cahard, *Chem. Rev*.2008, **108**, PR1–PR43; c) S. Lectard, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal*.2010, **352**, 2708.

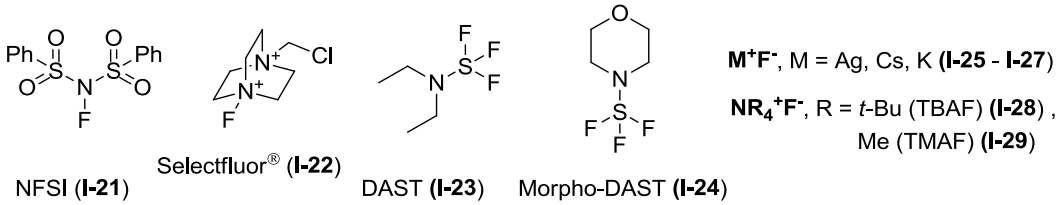


Figure 9. Common fluorinating reagents.

I-2.1.1. Organocatalytic enantioselective fluorination

In the late 1980s, attention was given to the development of chiral, stoichiometric fluorinating agents, such as N-fluorocamphorsultams[19] and N-F sulphonamides.[20] These fluorinating agents will not be covered in this introduction, as their synthesis require multistep procedure and the usage of elemental fluorine or perchloryl fluoride, while the ee values of products were usually low to moderate and substrate scope was limited. In the early 2000s, improved chiral fluorinating agents (**I-30** – **I-32**, Figure 10) were prepared from *Cinchona* alkaloids or its simple derivatives, with the aid of mild N-F fluorinating agents such as NFSI, Selectfluor® and others.

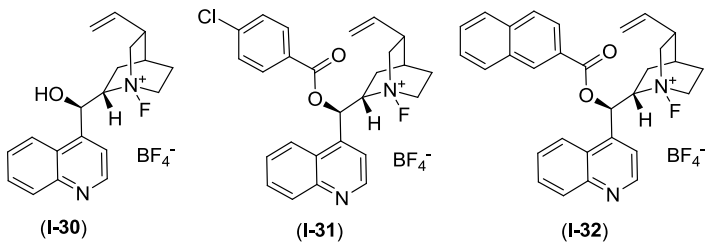


Figure 10. *Cinchona* alkaloid-derived enantioselective fluorinating agents.

These chiral N-fluoroammonium salts were used as pure compounds, or generated *in situ*, in enantioselective fluorinations of enolates of selected ketones (**I-35a - I-35e**, Figure 11), a few β-ketoesters (**I-33 - I-34**) and β-cyanoesters (**I-43 - I-47**) as well as oxindoles with moderate

[19] a) E. Differding, R. W. Lang, *Tetrahedron Lett.*, 1988, **29**, 6087; b) F. A. Davis, P. Zhou, C. K. Murphy, *Tetrahedron Lett.*, 1993, **34**, 3971.
[20] Z. Liu, N. Shibata, Y. Takeuchi, *J. Org. Chem.*, 2000, **65**, 7583.

to high ee values of 37% ee – 91% ee and good to excellent yields of 55 (12)% - 99% (**I-37** - **I-42**) and later on - nitroesters with poor enantioselectivities of up to 40% ee and substrate-dependent yields of 8% - 85% (**I-48** - **I-51**).[21] Notably, the special oxindole derivative prepared in 5 steps from 3-trifluoromethylaniline was efficiently fluorinated with these reagents by two groups independently, leading to (S)-BMS-204352 in 88% ee or 84% ee with enantiopure form attainable after recrystallization (**I-52**); (S)-BMS-204352 is an anti-ischemic stroke phase III clinical trial drug candidate - MaxiPost™).[22]

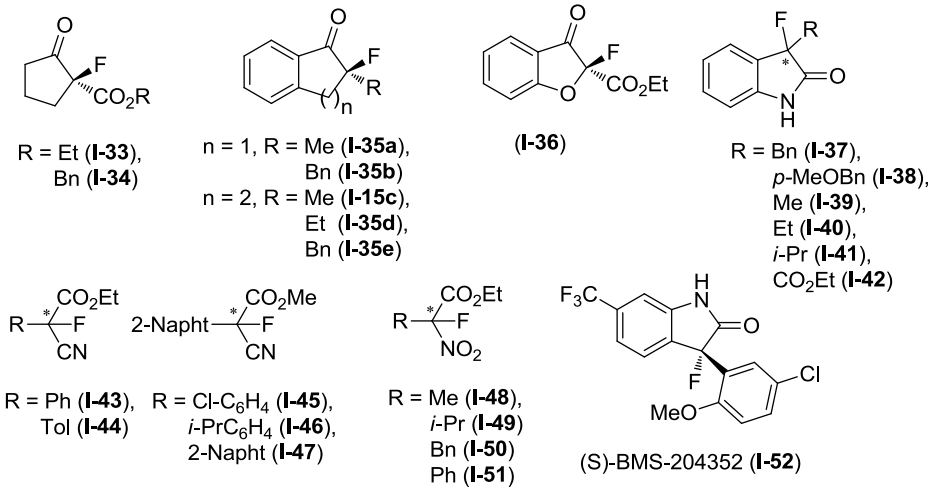
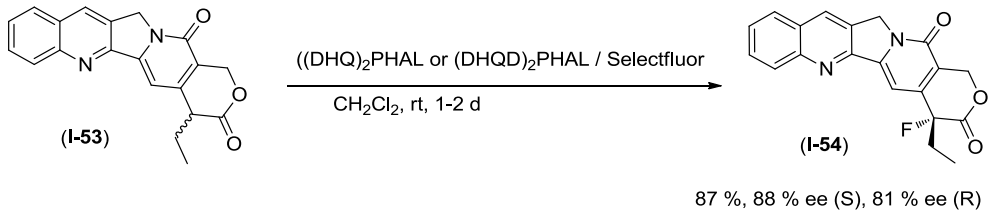


Figure 11. Products attainable *via* fluorination with *Cinchona* alkaloid-derived enantioselective fluorinating agents

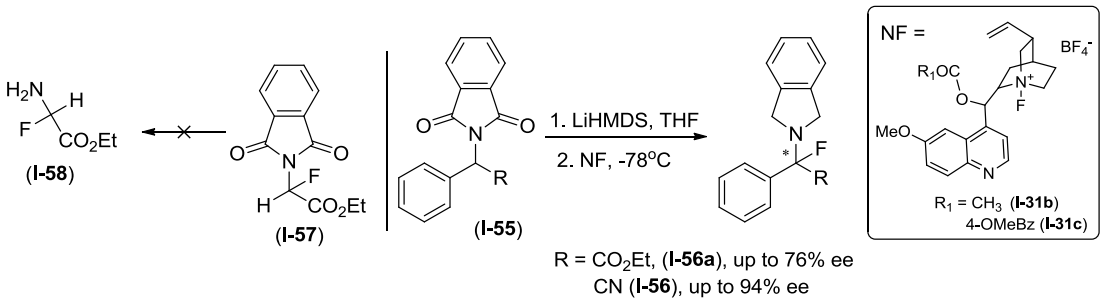
In a similar fashion, fluorination with *in situ* generated N-fluoroammonium salts of pseudo-enantiomeric bis-*Cinchona* alkaloid ($(DHQ)_2PHAL$), both enantiomers of 20-deoxy-20-fluorocamptothecin were obtained with 88% ee (*R* enantiomer) and 81% ee (*S* enantiomer) by Shibata and coworkers (**I-54**, Scheme 1; an isosteric analogue of camptothecin).[23]

[21] a) D. Cahard, C. Audouard, J.-C. Plaquevent, N. Roques, *Org. Lett.*, 2000, **2**, 3699; b) N. Shibata, E. Suzuki, T. Asahi, M. Shiro, *J. Am. Chem. Soc*., 2001, **123**, 7001; c) J. Ramirez, D. P. Huber, A. Togni, *Synlett*, 2007, 1143.
[22] a) L. Zoute, C. Audouard, J. -C. Plaquevent, D. Cahard, *Org. Biomol.Chem.*, 2003, **1**, 1833; b) N. Shibata, T. Ishimaru, E. Suzuki, K. L. Kirk, *J. Org. Chem.*, 2003, **68**, 2494; c) F. Laumonnier, D. Cahard, *et. al*., *Am. J. Psychiatry*, 2006, **163**, 1622.
[23] N. Shibata, T. Ishimaru, M. Nakamura, T. Toru, *Synlett*, 2004, 2509.



Scheme 1. Enantioselective fluorination of 20-deoxycamptothecin.

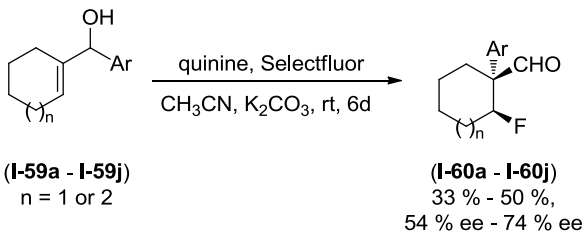
Attempts to enantioselectively fluorinate amino acids analogues are rare, due to the basicity of the amino function and the difficulty in controlling the stereoselectivities. To date, there is only one report by the group of Cahard on fluorination of N-phthaloylphenylglycine (**I-56a**, Scheme 2) and its nitrile analogue (**I-56a**) achieving 76% ee (94% ee for nitrile).[24] However, hydrolysis to free the amino group (and/or hydrolyze nitrile to acid) was not attempted and doubtful (harsh and/or acidic conditions usually lead to de-fluorination; unsuccessful cleavage of N-phthaloyl protecting group to free fluorinated glycine derivative was reported ten years before by the same group[25]).



Scheme 2. Fluorination of N-phthaloylphenylglycine.

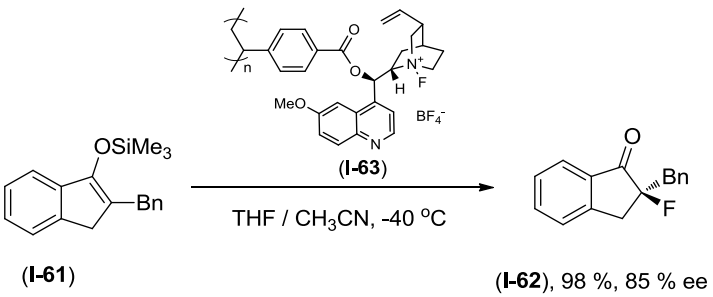
Semi-pinacol rearrangement, a different type of transformation, yet still based on the same *in situ*-generated N-F *Cinchona* alkaloid-derived salts, was reported by the group of Tu (Scheme 3).[26] The results, however were far from practical, with yields ranging from 33 % - 50 % and enantioselectivities from 54 % to 74 %.

[24] B. Mohar, J. Baudoux, J. -C. Plaquevent, D. Cahard, *Angew. Chem.,Int. Ed.*, 2001, **40**, 4214.
[25] Y. Takeuchi, M. Nabetani, K. Takagi, T. Hagi, T. Koizumi, *J. Chem. Soc. Perkin Trans. 1*, 1991, **0,** 41.
[26] W. Wang, B. M. Wang, L. Shi, Y. Q. Tu, C. A. Fan, S. H. Wang, X. D. Hu, S. Y. Zhang, *Chem. Commun.*, 2005, **44**, 5580.



Scheme 3. Semi-pinacol rearrangement with chiral N-F salt.

The major drawback of the methodology is the requirement for stoichiometric amount of chiral promoter. The use of catalytic amount of chiral inductor in fluorination of silyl enol ethers of selected ketones (**I-35a**–**I-35e**) led to expected products in racemic form. Racemization was due to the background fluorination by Selectfluor® and not chiral *Cinchona*-derived N-F salt; which was later overcome by employing acyl enol ethers, which were unreactive towards Selectfluor® alone, leading to improved enantioselectivities of up to 54 %.[27] Efforts were put into developing polymeric or polymer-supported *Cinchona* alkaloid-based N-fluoroammonium salts as a practical and industry-friendly approach. The application of one of the polymeric fluorinating agents was demonstrated on the enantioselective fluorination of silyl enol ether of aromatic bicyclic ketone (Scheme 4), where good enantioselectivity of 84 % was obtained, and the promoter was recycled three times without any loss of activity or selectivity.[28]

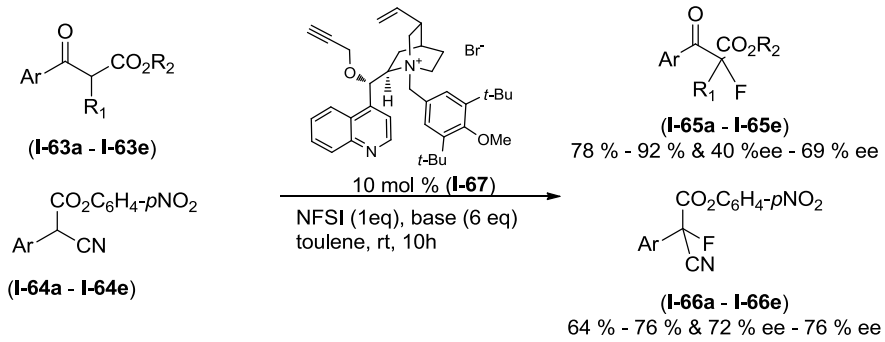


Scheme 4. Fluorination with polymer-supported N-F salt.

Apart from the application of stoichiometric chiral N-F reagents, other methods were recently developed, based on the application of organocatalysts in combination with NFSI and

[27] T. Fukuzumi, N. Shibata, M. Sugiura, S. Nakamura, T. Toru, *J.Fluorine Chem*., 2006, **127**, 548.
[28] a) B. Thierry, J. -C. Plaquevent, D. Cahard, *Mol. Diversity*, 2005, **9**, 277; b) B. Thierry, C. Audouard, J. -C. Plaquevent, D. Cahard, *Synlett*, 2004, 856.

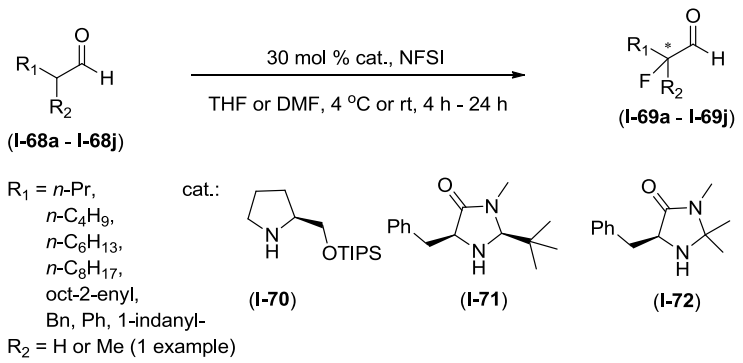
Selectfluor®. One of the first reported organocatalytic methodologies relied on phase-trasfer catalysis (PTC), as demonstrated by several contributors following the first report by Kim and Park.[29] Enantioselective fluorination on simple substrate - cyclic β-ketoesters (**I-63a**–**e**, Scheme 5) was performed by using *Cinchona* alkaloid-derived PTC catalyst (**I-67**), and very good yields (78 % - 92 %) and modest enantioselectivities of up to 69% were achieved. Later, the scope of substrates was expanded to α-cyanoesters (**I-64a**–**e**), from which the corresponding products were obtained with good enantioselectivities in the range of 72% - 76%.[30]



Scheme 5. PTC fluorination of keto- and cyanoesters by Kim and Park.

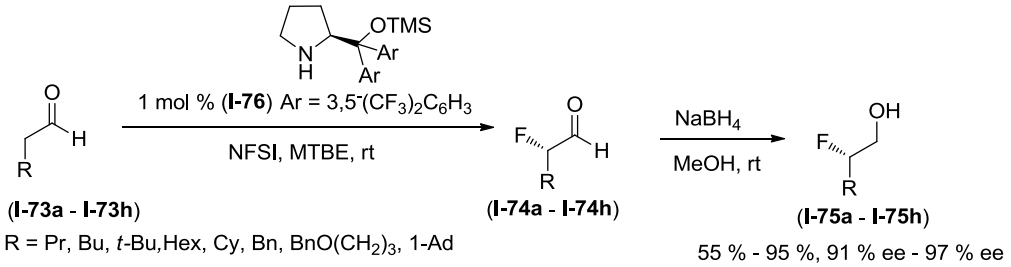
Shortly after, reports appeared on the development of simple organocatalysts for the enantioselective fluorination of aldehydes by three groups independently and almost simultaneously, all applying enamine catalysis. Barbas and co-workers demonstrated the application of prolinol derivatives as catalysts for arrange of aldehydes (**I-68a** – **j**, Scheme 6) achieving up 96 % ee.[31]

[29] D. Y. Kim, E. J. Park, *Org. Lett.*, 2002, **4**, 545.
[30] E. J. Park, H. R. Kim, C. U. Joung, D. Y. Kim, *Bull. Korean Chem. Soc.*, 2004, **25**, 1451.
[31] D. D. Steiner, N. Mase, C. F. Barbas, *Angew. Chem., Int. Ed.*, 2005, **44**, 3706.



Scheme 6. Fluorination of aldehydes by Barbas and coworkers.

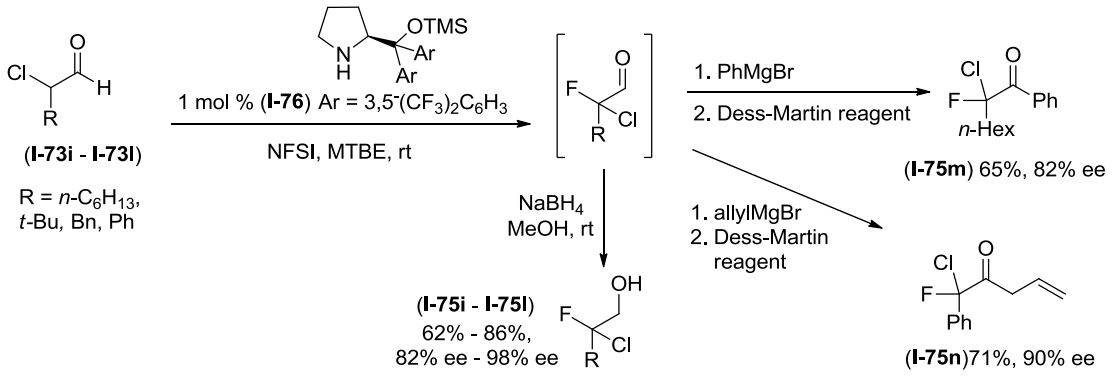
Jorgensen and coworkers reported similar fluorination of simple aldehydes mediated also by prolinol derivative (**I-76**, Scheme 7), with subsequent reduction yielding sterically stable alcohols (**I-75a - h**) with excellent ee values (91 % - 97 %).[32]



Scheme 7. Jorgensen's fluorination of simple aldehydes.

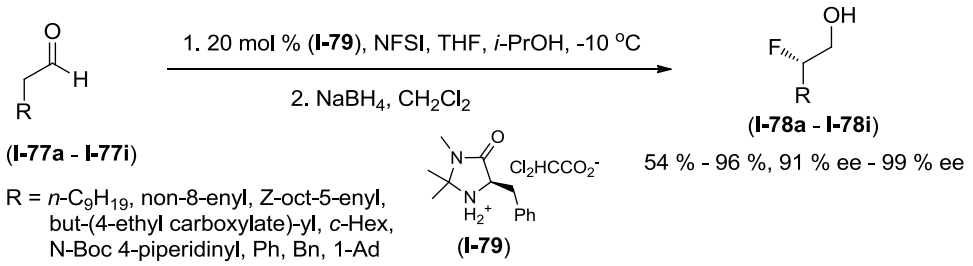
The same methodology was later applied by the Yamamoto group in the synthesis of highly enantioenriched chlorofluorohydrins (**I-73i**–**I-75l**, Scheme 8) and two ketones *via* 3-step procedure (**I-75m-n**).[33]

[32] a) M. Marigo, D. Fielenbach, A. Braunton, A. Kjœrsgaard, K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 3703; b) S. Brandes, B. Niess, M. Bella, A. Prieto, J. Overgaard, K. A. Jørgensen, *Chem. Eur. J.*, 2006, 6039.
[33] K. Shibatomi, H. Yamamoto, *Angew. Chem. Int. Ed.*, 2008, **47**, 5796.



Scheme 8. Synthesis of chlorofluorohydrins and functionalized ketones.

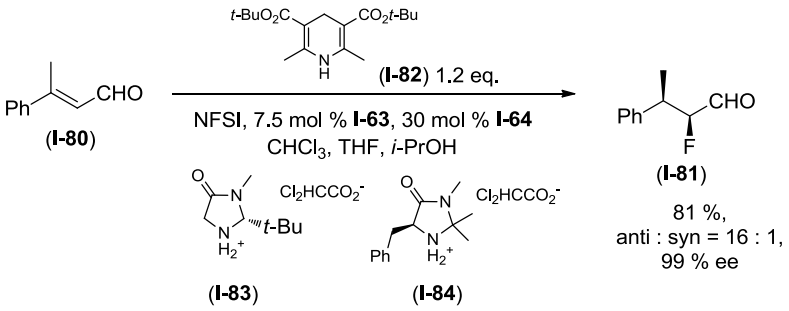
Equally effective results were obtained by the MacMillan group (however with higher catalyst loading to that of Jorgensen's) – aldehydes were fluorinated and reduced to corresponding 2-fluoro alcohols in good to excellent yields and with excellent enantiomeric control (91 % ee – 99 % ee, Scheme 9).[34]



Scheme 9. MacMillan's organocatalytic fluorination of aldehydes

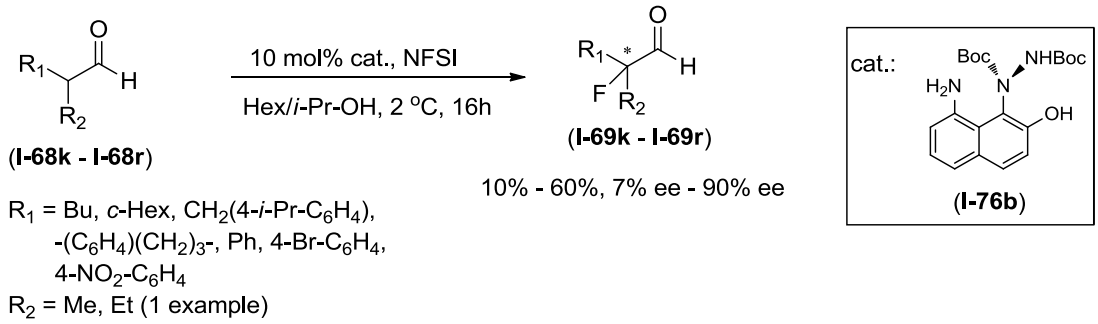
The same group also demonstrated formal addition of HF in the tandem transfer hydrogenation / fluorination of an α,β-unsaturated aldehyde (**I-80**, Scheme 10), in good yields and with excellent enantio- and diastereocontrols; however the usage of a pair of organocatalysts was required.[35]

[34] T. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc*., 2005, **127**, 8826.
[35] Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc*., 2005, **127**, 15051.



Scheme 10. Formal addition of HF by tandem transfer hydrogenation / fluorination.

Fluorination of α-branched aldehydes is much less common. One example was demonstrated by Barbas (Scheme 6). More extensive study was undertaken by the Jorgensen group, and resulted in the development of atropoisomeric catalyst (**I-76b**, Scheme 11).[36] The methodology was found applicable mostly to aldehydes with one aromatic substituent (36%–60%, 78% ee - 90% ee), while aldehydes with all aliphatic substituents were found unreactive (10% - 29%, 7% ee - 31% ee).

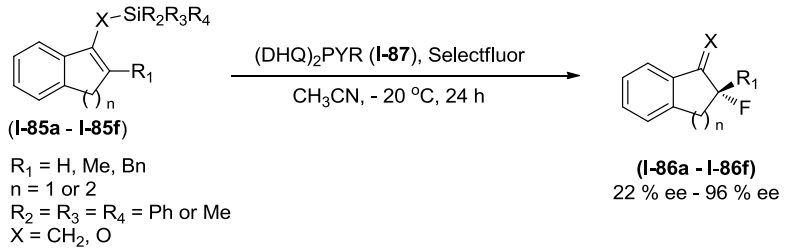


Scheme 11. Fluorination of branched aldehydes by Jorgensen.

Fluorodesilylation reactions are of practical interest as these methods leading to allylic fluorides. One such organocatalytic transformation was reported by the group of Gouverneur; allyl fluorides were obtained, with substrate dependent enantioselectivities ranging from 22 % to 96 % (Scheme 12, X = CH_2 only).[37] The original method requiring an equivalent amount of

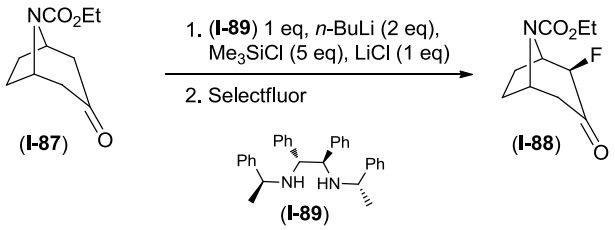
[36] S. Brandes, B. Niess, M. Bella, A. Prieto, J. Overgaard, K. A. Jørgensen, *Chem. Eur. J.* 2006, **12**, 6039.
[37] B. Greedy, J. M. Paris, T. Vidal, V. Gouverneur, *Angew. Chem. Int. Ed.*, 2003, **42**, 3291.

alkaloid was later improved by Shibata and coworkers, who achieved similar transformation with catalytic amount of organocatalysts, extended also to oxindoles (X = O, Scheme 12).[38]



Scheme 12. Fluorodesilylation by Gouverneur and coworkers.

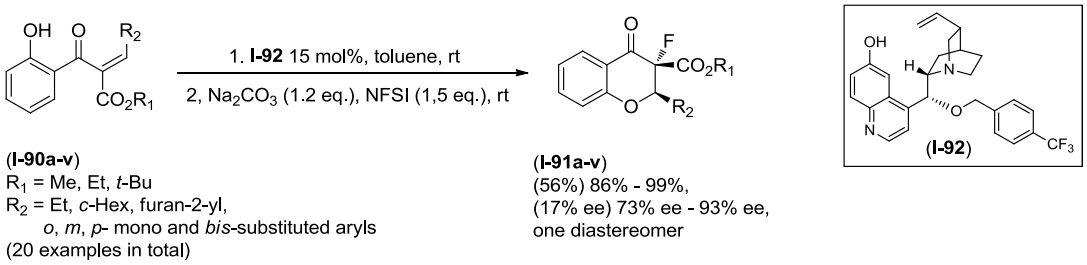
Fluorination of silyl enol ether was also realized in a desymmetrization process with chirality induced by C2-symmetrical base (**I-89**, Scheme 13).[39] The interesting bicyclic fluorinated ketone (**I-88**) was obtained in 55% yield and with 60 % ee. Unfortunately the transformation required an equivalent amount of chiral base.



Scheme 13. Fluorination of bicyclic ketone mediated by chiral base.

Biologically-relevant fluorinated flavones were synthesized in a tandem process developed by Zhao and co-workers (Scheme 14).[40] Extensive investigation of scope revealed the reaction was general and highly effective for substrates with aromatic substituents (R_2, **I-90a-v**) - 86% ee – 93% ee and high yield, but less stereoselective for substrate with heterocyclic substituent (73% ee) and hardly enantioselective for substrate with two aliphatic substituents (R_1 and R_2 – only 17% ee).

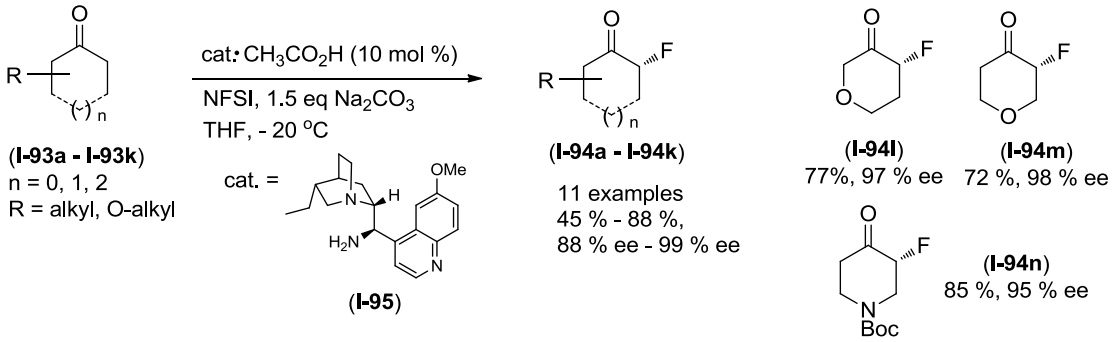
[38] T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem. Int. Ed*., 2008, **47**, 4157.
[39] A. Armstrong, G. Ahmed, B. Dominguez-Fernandez, B. R. Hayter, J. S. Wailes, *J. Org. Chem*., 2002, **67**, 8610.
[40] H.-F. Wang, H.-F. Cui, Z. Chai, P. Li, C.-W. Zheng, Y.-Q. Yang, G. Zhao, *Chem. Eur. J*., 2009, **15**, 13299.



Scheme 14. Tandem Michael addition/fluorination leading to fluorinated flavones.

The transformation is believed to be a stepwise process – oxa-Michael intramolecular cyclization with diastereoselective fluorination of the intermediate enolate.

Until recently, effective enantioselective fluorination of ketones has not been realized by means of organocatalysis, due to low reactivity (slow enamine formation) and existence of rotational isomers of enamine active species. The breakthrough report came recently from MacMillan's group communicating the first organocatalytic fluorination of simple cyclic ketones, catalyzed by dihydroquinidine (**I-92**, Scheme 15), with extension to three heterocycles (**I-91m – n**).[41]

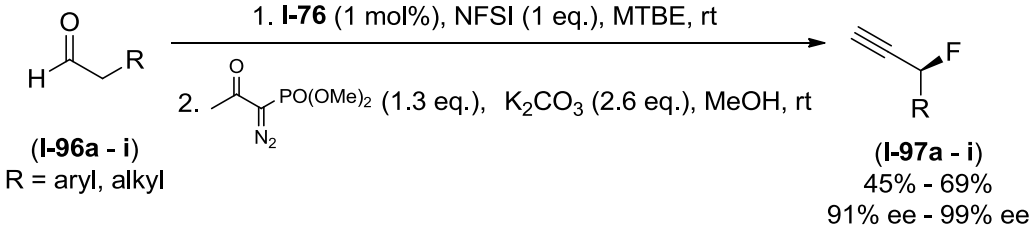


Scheme 15. Organocatalytic fluorination of cyclic ketones.

This method was only applicable to cyclic ketones, mostly cyclohexananone derivatives, with no advancement or further development to date. Practical extension of Jorgensen's enantioselective fluorination of aldehydes was developed by the same group - one pot

[41] P. Kwiatkowski, T. D. Beeson, J. C. Conrad, W. C. MacMillan, *J. Am. Chem. Soc.*, 2011, **133**, 1738.

synthesis of propargylic fluorides.[42] The first step in the process was asymmetric fluorination of aldehydes as reported by Jorgensen earlier (see Scheme 7), followed by Seyferth–Gilbert reaction (with Ohira–Bestmann modification – to avoid racemization), leading to the desired propargylic fluorides in fair yields and with excellent enantioselectivities (up to 99%, Scheme 15).



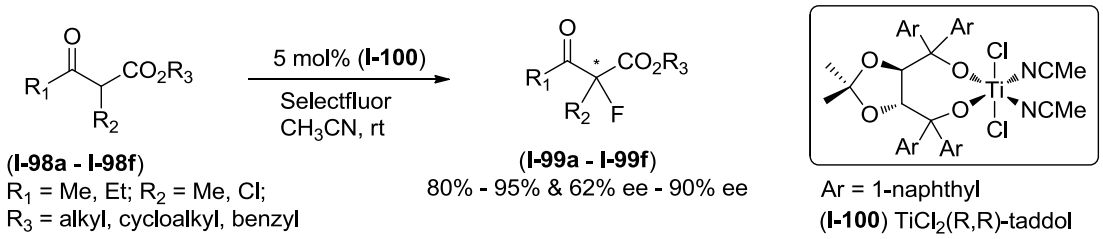
Scheme 16. One-pot synthesis of propargylic fluorides.

In the young field of organocatalytic enantioselective fluorination, the single most general methodology is to carry out fluorination of aldehydes *via* iminium/enamine-catalysis, followed by reduction. The obtained fluorinated alcohols could then be used in target synthesis. Of practical importance is synthesis of fluorinated propargylic fluorides - class of compound directly applicable to further coupling. Further advancement of ketone fluorination, would be of great importance, as such stable synthons could later be transformed into fluorinated nitrogen-containing species.

[42] a) For a review on propargylic fluorides and their importance see: M. C. Pacheco, S. Purser, V. Gouverneur, Chem. Rev., 2008, **108**, 1943; b) H. Jiang, A. Falcicchio, K. L. Jensen, M. W. Paixao, S.Bertelsen, K. A. Jørgensen, *J. Am. Chem. Soc*., 2009,**131**, 7153.

I-2.1.2. Transition metal-catalyzed enantioselective fluorination

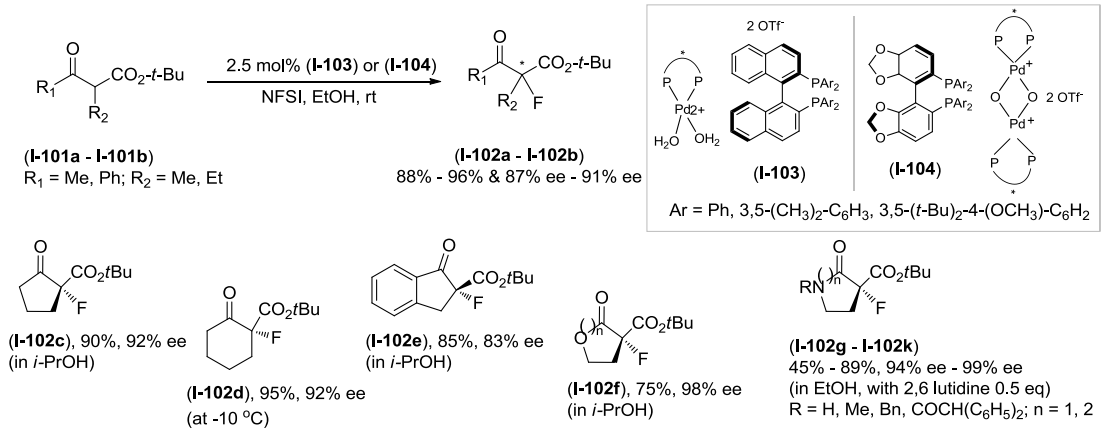
The very first enantioselective fluorination was achieved with titanium-taddol complex (**I-100**, Scheme 17) and reported by Togni and Hintermann on linear β-ketoesters, with Selectfluor® as a fluorine source.[43] Since then, similar methodologies employing various transition metals and ligands appeared, with β-ketoesters as model substrates - owing to their acidic α-proton and two carbonyl groups capable of coordination with the transition metal to form stable 6-membered ring intermediate.



Scheme 17. The first enantiocatalytic fluorination by Togni and Hintermann.

In 2002 Sodeoka *et al*. disclosed the use of Pd-BINAP catalytic systems for highly enantioselective fluorination with NFSI (Scheme 18).[44] Cyclic and linear fluorinated β-ketoesters (**I-101a-e**) were obtained in very good yields and with high enantioselectivities (83% to 92% ee). Later on, the scope of the reaction was expanded to include lactone and lactams (**I-102f-k**).[45] In the case of lactone, more sterically demanding solvent (isopropanol) was found advantageous for high level of stereo-control (98% ee eventually), while less reactive lactams (less acidic α-proton) required the addition of 0.5 equiv. of organic base (2,6 lutidine) to facilitate formation of palladium enolate and bolster the yields of desired products to 45% - 89%, while retaining excellent enantioselectivities of 94% to 99%.

[43] L. Hintermann, A. Togni, *Angew. Chem. Int. Ed*., 2000, **39**, 4359.
[44] Y. Hamashima, K. Yagi, H. Takano, L. Tamas, M. Sodeoka, *J. Am. Chem. Soc*., 2002, **124**, 14530.
[45] T. Suzuki, T. Goto, Y. Hamashima, M. Sodeoka, *J. Org.Chem*., 2007, **72**, 246.



Scheme 18. Sodeoka's fluorination of β-ketoesters.

Similar results were later obtained for enantioselective fluorination of similar β-ketoesters using chiral oxazolidine-featuring complexes (**I-105**, Figure 12) with copper as metal promoter (up to 96% yield and 85% ee),[46] and copper and nickel in the study by Shibata and Toru (**I-105** and **I-106**, up to 93% yield and 99% ee).[47] Improved results for the same reactions were achieved subsequently by employing tridentate oxazoline-incorporating ligands (**I-107** and **I-108**) with nickel, as reported by Shibatomi and Iwasa (up to 99% yield and 99% ee).[48]

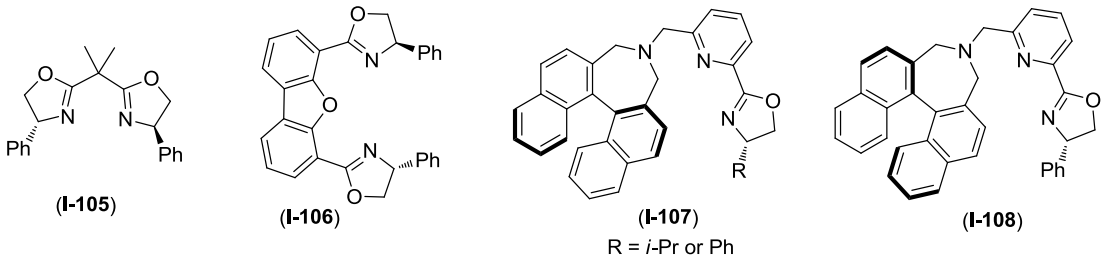
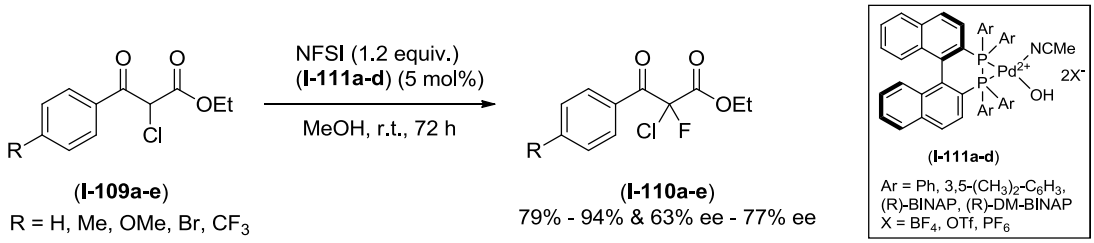


Figure 12. Oxazoline-featuring ligands in enantioselective fluorination of β-ketoesters.

β-Ketoesters, so thoroughly explored by numerous groups, were shown to be suitable substrates for one-pot sequential chlorination-fluorination or fluorination-chlorination reactions. This was first reported by the Togni group in 2003, utilizing their previously employed Ti-taddol complex (**I-100**, Scheme 17); however only moderate enantioselectivities

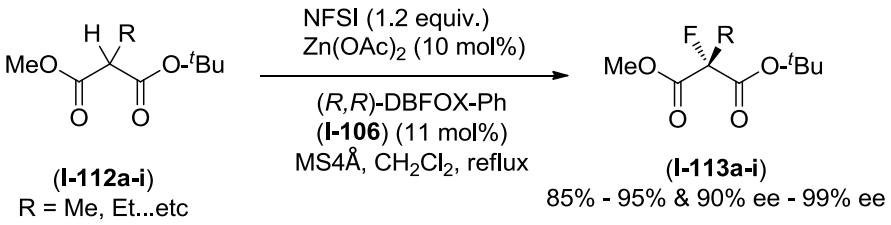
[46] J.-A. Ma, D. Cahard, *Tetrahedron: Asymmetry*, 2004, **15**,1007.
[47] a) N. Shibata, T. Ishimaru, T. Nagai, J. Kohno, T. Toru, *Synlett*, 2004, 1703; b) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem. Int. Ed.*, 2005, **44**, 4204.
[48] K. Shibatomi, Y. Tsuzuki, S.-I. Nakata, Y. Sumikawa, S. Iwasa, *Synlett*, 2007, 551.

were obtained (up to 65%).[49] Later the same reaction was reported by Kim and co-workers, achieving similar results with palladium aqueous complexes (**I-111a-d**, Scheme 19),[50] while slightly better results (up to 77% ee) were obtained when pre-formed α-chloro-β-ketoester was fluorinated using the same palladium complexes (Scheme 19).



Scheme 19. Fluorination of α-chloro-β-ketoesters.

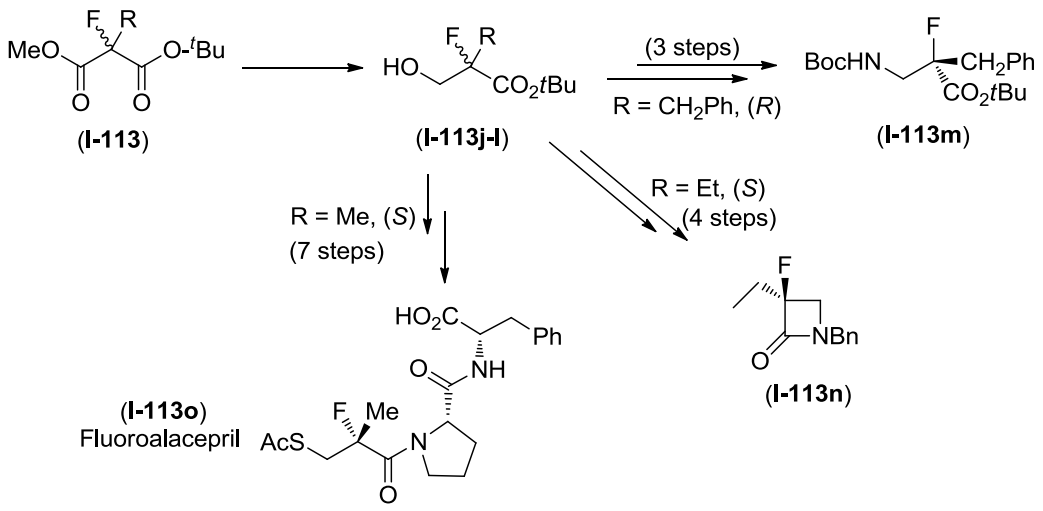
Other 1,3-dicarbonyl compounds were also found suitable for enantioselective fluorination – such as malonates and β-ketophosphonates. Asymmetrical *tert*-butyl-methyl malonate was enantioselectively fluorinated using NFSI and zinc complex analogical to one used previously by Kanemasa and Shibata and Toru (**I-106**, Figure 12).[51] Notably, the protocol is tolerant of several functional groups such as thio-, ether and *tert*-amine (**I-112a-I**, Scheme 20); however unsubstituted (R = H) malonates have not been reported, presumably due to bis-fluorination.



Scheme 20. Enantioselective fluorination of malonates.

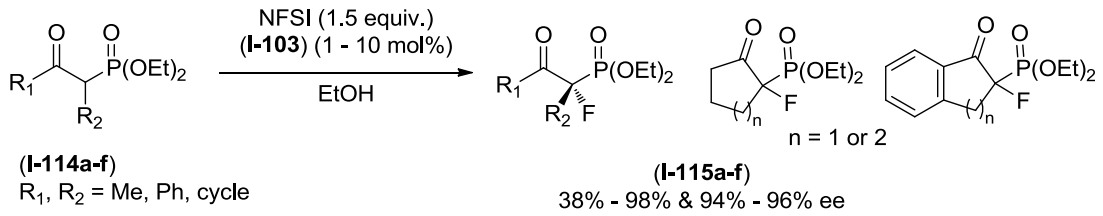
Synthetic utility of the fluorinated malonates was explored thoroughly, and simple yet lengthy routes towards valuable molecules were demonstrated: α-fluoro-β-amino acid (**I-113m**, Scheme 21), fluorinated β-lactam and fluorinated drug analogue - fluoroalacepril (**I-113o**).

[49] R. Frantz, L. Hintermann, M. Perseghini, D. Broggini,A. Togni, *Org. Lett*., 2003, **5**, 1709.
[50] M. J. Cho, Y. K. Kang, N. R. Lee, D. Y. Kim, *Bull.Korean Chem. Soc.*, 2007, **28**, 2191.
[51] D. S. Reddy, N. Shibata, J. Nagai, S. Nakamura, T.Toru, S. Kanemasa, *Angew. Chem. Int. Ed*., 2008, **47**, 164.



Scheme 21. Transformations of fluorinated malonate into amine, lactam and drug analogue.

An interesting example of 1,3-dicarbonyl compounds which have been efficiently fluorinated with the use of transition metal complexes are β-ketophosphonates. Previously reported complexes were successfully employed with this class of compounds as well. The Sodeka group reported BINAP complex (**I-103**, Scheme 18) to catalyze enantioselective fluorination of cyclic and acyclic β-ketophosphonates with excellent enantiocontrol (up to 96% ee), and highly substrate dependent yields (Scheme 22).[52]

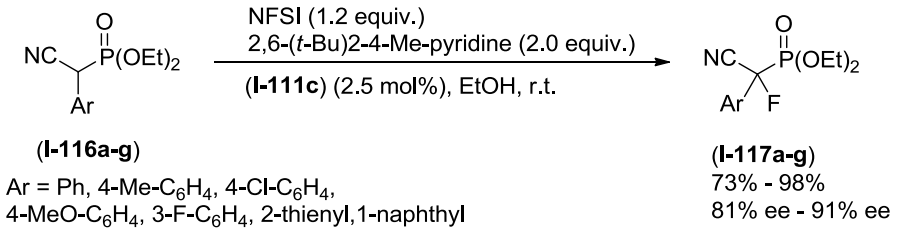


Scheme 22. Enantioselective fluorination of β-ketophosphonates by Sodeoka and coworkers.

Similar results were obtained by Kim utilizing cationic palladium complexes,[53] and also in ionic liquids with recycled catalyst (after seven cycles, only insignificant effect on yields and enantioselectivities was observed).[54] In addition to abovementioned β-ketophosphonates, α-cyanophosphonates were shown to undergo enantioselective fluorination as well. However,

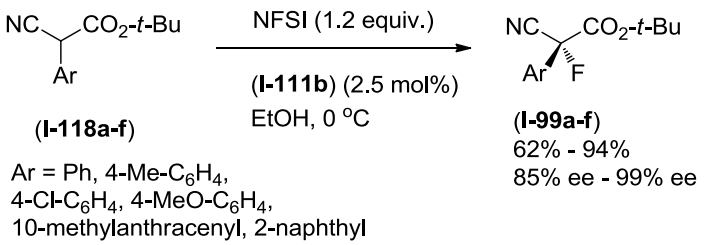
[52] Y. Hamashima, T. Suzuki, Y. Shimura, T. Shimizu, N.Umebayashi, T. Tamura, N. Sasamoto, M. Sodeoka, *Tetrahedron Lett*., 2005, **46**, 1447.
[53] S. M. Kim, H. R. Kim, D. Y. Kim, *Org. Lett*., 2005, **7**, 2309.
[54] S. M. Kim, Y. K. Kang, K. S. Lee, J. Y. Mang, D. Y. Kim, *Bull. Korean Chem. Soc*., 2006, **27**, 423.

significantly lower acidity of α-proton, as compared to β-ketophosphonates, required the use of additional base to facilitate deprotonation. This could have resulted in lower enantioselectivities observed by the groups of Kim (81% ee – 91% ee, Scheme 23)[55] and Sodeoka (24% ee – 78% ee)[56] in reactions catalyzed by previously reported palladium complexes (**I-111c** and **I-104**).



Scheme 23. Kim's fluorination of α-cyanophosphonates.

Kim and co-workers have further extended their methodology to α-cyanoacetates (**I-118a-f**, Scheme 24),[55b,57] obtaining excellent results (62% – 94% and 85% ee – 99% ee). In this case, the use of external base was unnecessary.

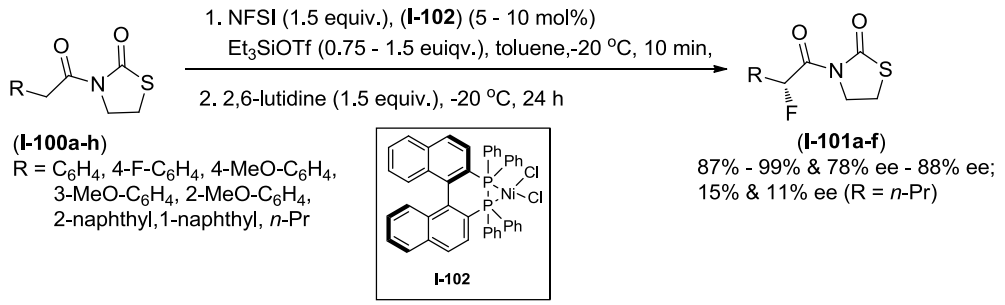


Scheme 24. Enantioselective fluorination of α-cyanoesters.

Apart from acidic 1,3-dicarbonyl compounds, efforts were devoted to fluorination of more challenging (less acidic α-proton) α-arylacetic acid derivatives. Sodeoka devised a catalytic system consisting of Ni-BINAP complex (**I-102**, Scheme 25) with addition of 2,6-lutidine and triethylsilyl triflate, for effective fluorination of α-arylacetic acid derivatives (**I-100a-h**).[58]

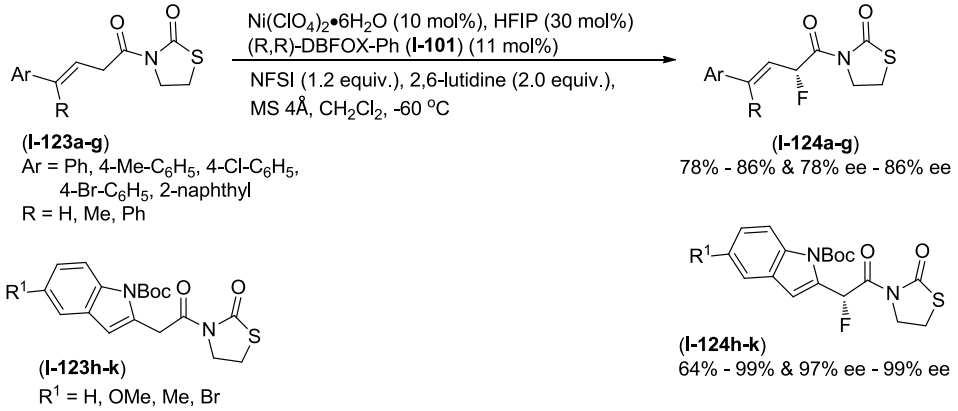
[55] a) Y. K. Kang, M. J. Cho, S. M. Kim, D. Y. Kim, *Synlett*, 2007, 1135; b) S. M. Kim, Y. K. Kang, M. J. Cho, J. Y. Mang, D. Y. Kim, *Bull. Korean Chem. Soc*., 2007, **28**, 2435.
[56] K.-I. Moriya, Y. Hamashima, M. Sodeoka, *Synlett*, 2007,1139.
[57] H. R. Kim, D. Y. Kim, *Tetrahedron Lett*., 2005, **46**, 3115.
[58] Y. Hamashima, T, Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc*., 2005, **127**, 10164.

Very good yields and enantioselectivities were attainable with aromatic substrates, while only very low yield (15%) and hardly any enantiocontrol (11% ee) were attainable for aliphatic *n*-butanoic acid thiazolidin.



Scheme 25. Sodeoka's fluorination of arylacetic acid derivatives.

Later, these results were improved by Shibata and Toru – their system consisting of oxazoline-containing ligand (**I-86**, Figure 12), nickel perchlorate, 2,6-lutidine and importantly - 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as additive, lead to products (with slightly extended scope as compared to **I-100a-h**) with excellent enantioselectivities of 92% - 98% and yields (87% - 96%), albeit missing any aliphatic example.[59] In the same paper, the authors presented an extension to disubstituted arylvinyl-containg thiazolidin derivatives (**I-103a-g**, Scheme 26) and indole-containing substrates (**I-103h-k**), the former obtained with up to 86% ee, the latter with excellent, up to 99% ee.

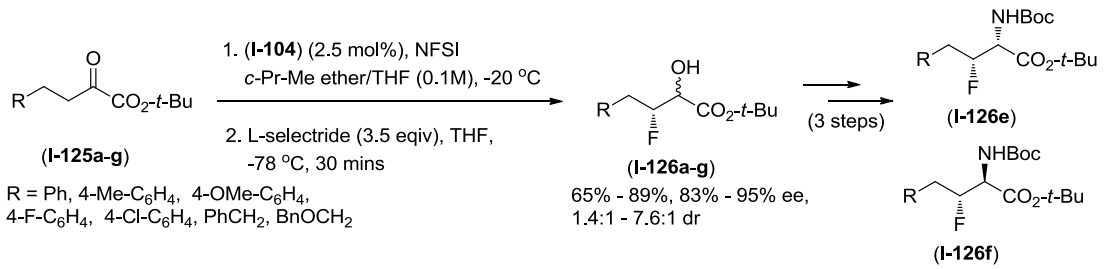


Scheme 26. Enantioselective fluorination of other arylacetic acid derivatives and indoles.

[59] a) T. Ishimaru, N. Shibata, D. S. Reddy, T. Horikawa, S. Nakamura, T. Toru, *Beilstein J. Org. Chem.*, 2008, 4; b) D. S. Reddy, N. Shibata, T. Horikawa, S. Suzuki, S. Nakamura, T. Toru, M. Shiro, *Chem. Asian J.*, 2009, **4**, 1411.

The lower acidity of α-proton in substrates other than 1,3-dicarbonyls required the addition of external base. The other limiting requirement remained - the use of substrate with carbonyl group for facile coordination to metal promoter. The bidentate manner of binding of the two carbonyl groups in β-ketoesters was translated here to analogous binding of one carbonyl of the substrate and the other from the auxiliary – thiazolidin, and found indispensable for enantiocontrol.

Later on, α-ketoesters (as another example of substrates with bidentate binding capabilities to the metal) were reported as suitable substrates for enantioselective fluorination with the use of previously developed DBFOX nickel complex, as reported by Sodeoka and coworkers (Scheme 27).[60] The products were obtained in high chemical yields, and with high to excellent ee values, with low to decent diastereoselectivities (1.4:1 – 7.6:1). Despite the narrow substrate scope, this first example of direct fluorination of α-ketoesters stood as a useful method for the synthesis of linear β-fluoro-α-amino acids (**I-126e-f**).

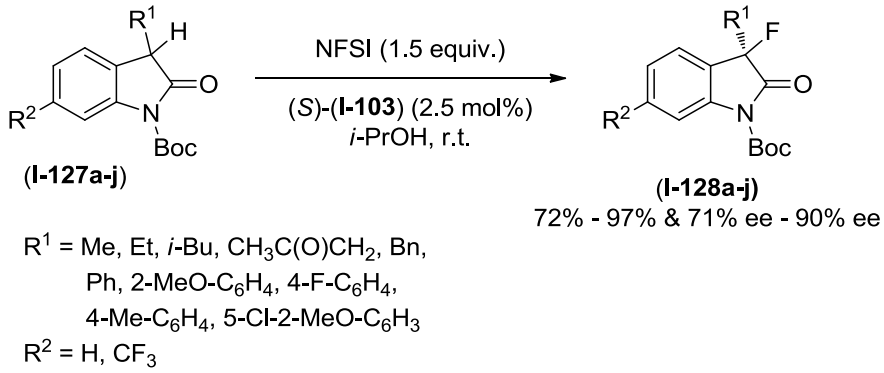


Scheme 27. Sodeoka's fluorination of α-ketoesters.

Attention to fluorinated oxindoles was probably drawn by development of anti-stroke drug - MaxiPost™ (**I-56**, Figure 11). Initial reports involved N-Boc protected oxindole substrates being fluorinated with the aid of aqueous palladium BINAP complex (**I-103**, Scheme 18). Good to excellent yields (up to 97%) and decent to very good enantioselectivities (up to 90%) were achieved, as reported by Sodeoka's group (Scheme 28).[61] This protocol was employed

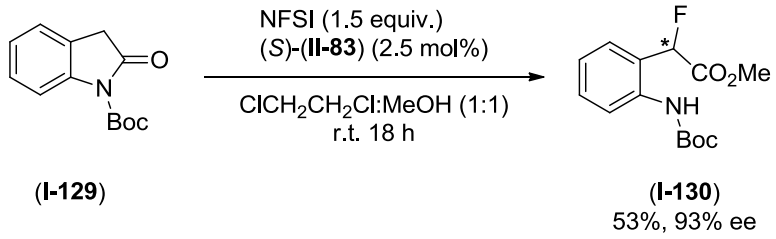
[60] S. Suzuki, Y. Kitamura, Y. Hamashima, M. Sodeoka, *Angew. Chem. Int. Ed*., 2012, **124**, 4659.
[61] Y. Hamashima, T, Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc*., 2005, **127**, 10164.

for the synthesis of MaxiPost, leading to 57% yield of the enantio-pure compound (after recrystallization).



Scheme 28. Sodeoka's fluorination of N-Boc protected oxindoles.

Interestingly, the authors also disclosed a strategy for monofluorination of unsubstituted oxindole (**I-129**) avoiding bisfluorination by *in situ* solvolysis of oxindole moiety, resulting in generation of monofluorinated α-arylacetic acid ester (**I-130**) with 93% ee and 53% yield.



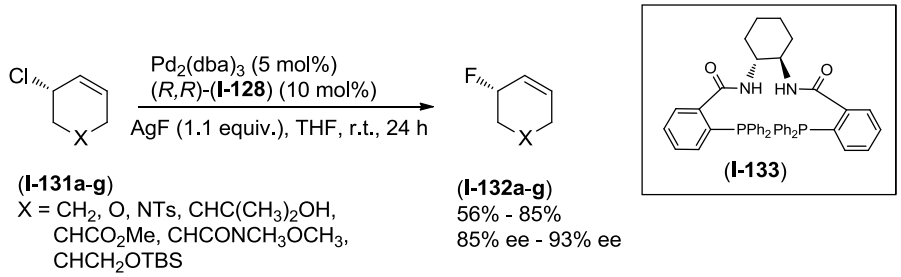
Scheme 29. Fluorination of unsubstituted oxindole leading to arylacetic ester.

Similar results for substituted N-Boc-oxindoles were independently reported by Shibata and Toru (and also MaxiPost synthesis), who described enantioselective fluorination employing their oxazoline-containing nickel DBFOX complex (**I-106**, Figure 12), achieving up to 73% yield and up to 93% ee.[62]

Investigations on fluorination of compounds not capable of H-bonding to catalyst or ligand are less common. One method would be to utilize the ability of palladium (0) to form complexes with alkyl/aryl halides in an oxidative process; a truly complementary approach to

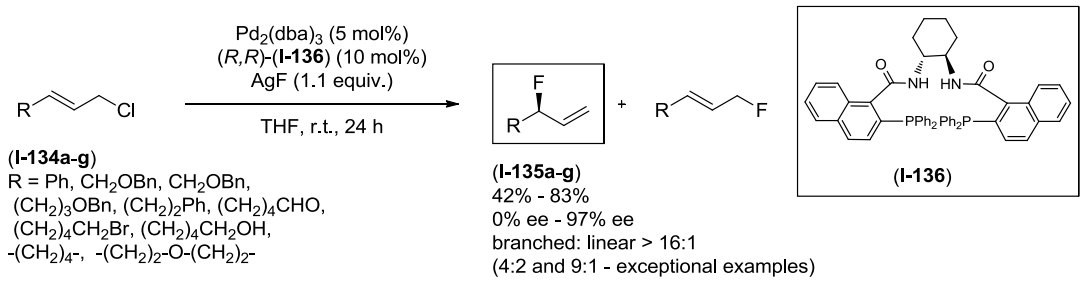
[62] N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem. Int. Ed.*, 2005, **44**, 4204.

organocatalysis. One such methodology was developed by the Doyle group, where cyclic allyl chlorides (**I-131a - g**, Scheme 30) were transformed into corresponding fluorides in a palladium catalyzed reaction in the presence of the Trost ligand (**I-133**).[63] Decent yields (56% - 85%) and high enantioselectivities (85% ee – 93% ee) were achieved for various substrates containing carbocyle, as well as oxygen- or nitrogen-containing heterocycles, and several functional groups such as: alcohol, ester, amide.



Scheme 30. Pd-catalyzed enantioselective formation of cyclic allyl fluorides.

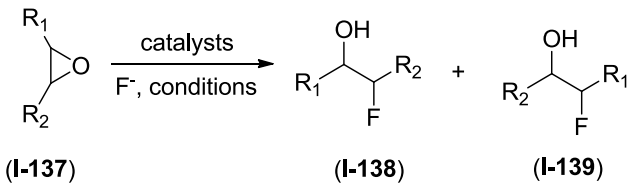
This methodology was later extended to allylic fluorination of linear allyl chlorides (**I-134a**–**g**, Scheme 31), leading to formation of branched products, rather than linear isomers.[64] Reasons for such preference (branched:linear > 20:1 for most examples) were unclear, however it was suggested that the fluoride anion is involved in H-bonding interactions with the ligand and results in its subsequent stereo-directed delivery to the reactant. Enantioselectivity of the reaction is highly substrate dependent and can range from 0% to 97%.



Scheme 31. Asymmetric allylic fluorination by Doyle and coworkers.

[63] M. H. Katcher, A. G. Doyle, *J. Am.Chem. Soc.*, 2010, **132**, 17402.
[64] M. H. Katcher, A. Sha, A. G. Doyle, *J. Am. Chem. Soc.*, 2011, **133**, 15902.

Simple, general method to access diverse fluorinated alcohols from easily available sources would be of interest to both academia and industry. Such alcohols can be obtained *via* two-step one-pot procedures based on aldehyde fluorination/reduction process utilizing organocatalysts or transition metal-based catalysts (see above). Another subarea of research capable of such output would be enantioselective epoxide opening with fluoride anion (Scheme 32). Significant efforts were put towards this goal, however up to date results inferior to those offered by aldehyde fluorination/reduction were obtained.



Scheme 32. Epoxide opening with nucleophilic fluoride.

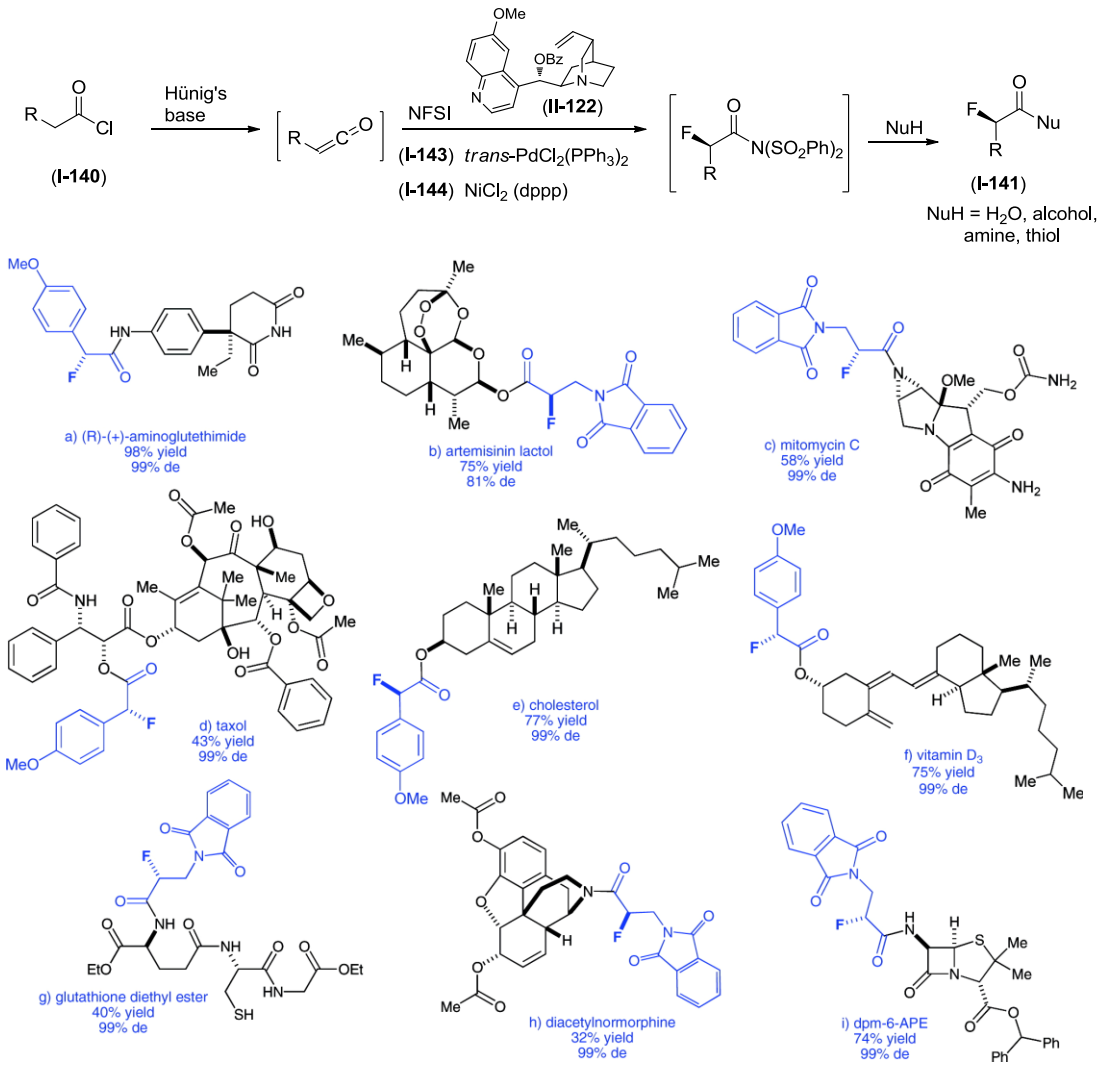
Salen complexes were used as catalyst or promoter to desymmetrize meso epoxide in a pioneering report by Bruns and Haufe in 2000, achieving 55% ee (1 eq. of catalysts) or 11% ee in the catalytic version,[65] while salen-promoted opening/fluorination of styrene oxide afforded the desired product in up to 90% ee. This methodology was than reinvestigated by Mazzetti and coworkers,[66] without significant improvement. Eventually, breakthrough came when Doyle and Karlow used a similar approach to achieve the desired epoxide opening/fluorination products in good yields (55% - 88%) and enantioselectivities (58% ee - 95% ee) under catalytic protocol, with kinetic resolution involved in some cases (90% ee - 99% ee).[67]

Interestingly, excellent results were obtained in reactions performed *via* cooperative catalysis involving organocatalyst (chiral organic base) and metal complex (Lewis acid). This was demonstrated in α-fluorination of acyl chlorides (**I-140**, Scheme 33) *via* a process involving dually activated enolate (by chiral *tert*-amine **I-142** and achiral metal complex **I-143** or **I-**

[65] S. Bruns, G. Haufe, *J. Fluorine Chem*., 2000, **104**, 247.
[66] M. Althaus, A. Togni and A. Mezzetti, *J. Fluorine Chem*., 2009, **130**, 702.
[67] a) J. A. Kalow, A. G. Doyle, *J. Am. Chem. Soc*., 2010, **132**, 3268; b) J. A. Kalow, A. G. Doyle, *J. Am. Chem. Soc*., 2011, **133**, 16001.

144). Release of the final product is done by subsequent reaction of fluorinated intermediate with nucleophile of choice - water, thiol, amine or alcohol, giving rise to a range of diverse products with excellent optical purity (up to 99% ee) in very good yields (up to 91%).[68] This methodology was later applied to a two-step fluorofunctionalization of nuclephilic, large and complex molecules such as: artemisinin lactol, mitomycin C, taxol, cholesterol, vitamin D_3 and aminoglutethimide, providing the selectively monofluorinated products with excellent sterocontrol (all 99% de, one example 81% de) with acceptable to excellent yield (43% - 98%).[69] The novelty lies in using nucleophilic macromolecules to quench sulphonamide - an intermediate arose form addition of one molecule of NFSI to ketene.

[68] a) D. H. Paull, M. T. Scerba, E. Alden-Danforth, L. R. Widger, T. Lectka, *J. Am. Chem. Soc*. 2008, **130**, 17260; b) J. Erb, D. H. Paul, T. Dudding, L. Belding,T. Lectka, *J. Am. Chem. Soc*., 2011, **133**, 7536.
[69] J. Erb, E. Alden-Danforth, N. Kopf, M. T. Scerba, T. Lectka, *J. Org. Chem*., 2010, **75**, 969.



Scheme 33. α-Fluorination *via* cooperative catalysis.[69]

Similarly to organocatalytic methodologies, transition-metal involving procedures also give rise to variety of fluorinated quaternary carbon-containing molecules. Such adducts can be manipulated to yield general synthons in certain cases, e.g. malonates (Scheme 20 and Scheme 21). Further manipulation of fluorinated malonates - namely decarboxylation/ asymmetric protonation would be desired, as it would yield linear α-fluoro-β-amino acids. Such transformation was investigated during the course of our research and results are reported in chapters II-5 and the future perspectives section. Notably, there has been several reports where more challenging substrates were successfully fluorinated, yielding linear molecules such as allylic fluorination (Scheme 30), fluorination of chloroketoesters (Scheme 18), cyanoesters or cyanoposphonates (Scheme 22 and Scheme 23). Further development of

fluorination of α-ketoesters (Scheme 27) and arylacetic acid derivatives (Scheme 25 and Scheme 26) would greatly broaden the pool of useful synthons. Lastly, advancement of Lectka's cooperative catalytic system for fluorination/addition of small fluorinated synthons to complex molecules (Scheme 33) would be very beneficial to the development of practical approaches in fluoro-modifcation of large bioactive molecules, perhaps harnessed from natural sources.

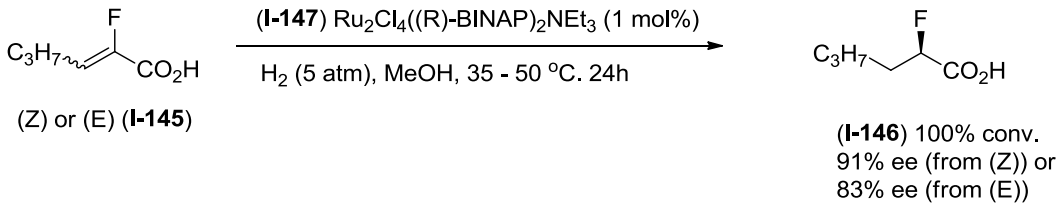
I-2.2. Indirect fluorination

While direct fluorination remains as an important method for synthesis of fluorinated molecules, alternative approaches for construction of chiral fluorinated species can also be employed - namely C–C or C–X bond formation using pro-chiral fluorinated synthons (i.e. indirect fluorination). This methodology presents truly complementary approach to the above mentioned direct fluorination, as some functional groups are rather sensitive or could quench fluorinating reagents. In such cases, fluorinated synthon may be prepared and subsequently reacted with the more sensitive substrate, yielding the desired functionalized and fluorinated molecule. Furthermore, in some cases, cheaper non-selective fluorinating agents for the preparation of substrates may be used, while some fluorine-containing starting materials may be commercially available. At first glance, it may seem that general methods for enantioselective C–C or C–X bond forming reactions could be employed straightforwardly to analogous reactions with fluorinated substrates. However, the presence of fluorine in one of the substrates usually influences the reactivity and selectivity greatly, thus requiring elaboration of reaction conditions. The most appealing cause of such altered reactivity may be the electron withdrawing properties of fluorine, together with its small size, which on one hand presents new possibilities and enhanced reactivity in sluggish reactions between non-fluorinated reaction partners; on the other hand, it may cause over-stabilization of anions or anionic transition states - slowing down, inhibiting or directing reactions to new, unexpected routes. Therefore organofluorine chemistry is of importance not only with regards to preparation of important or alternative compounds but also for broadening the general knowledge and understanding of organic chemistry, including elucidation of reaction mechanisms and biotransformation pathways.

This section aims to present the currently available methods for enantioselective C–C, C–N and C–H bond forming reactions involving pro-chiral, fluorinated substrates, as well as cascade or domino processes consisting of fluorination and C–C or C–N bond forming

reactions. Similar to the above introduction on direct fluorination, the focus will be on the scope of attainable chiral fluorinated molecules. General class of substrates, regardless of activation mode, be it organocatalytic or *via* metal-containing catalysts will be discussed below.

The simplest pro-chiral fluorinated substrates used so far are fluorinated alkenes in enantioselective hydrogenation. Such transformations lead to simple and usually linear, chiral fluorinated products which are quite unique in reactions employing fluorinated synthons (in most cases branched molecules are the reaction outcome). Employing simple ruthenium-(R)-BINAP complex, Uchida and co-workers achieved enantioselective hydrogenation of 2-fluoro-2-hexenoic acid (**I-145**, Scheme 34), and the reaction proceeded efficiently and with good enantiomeric control.[70]

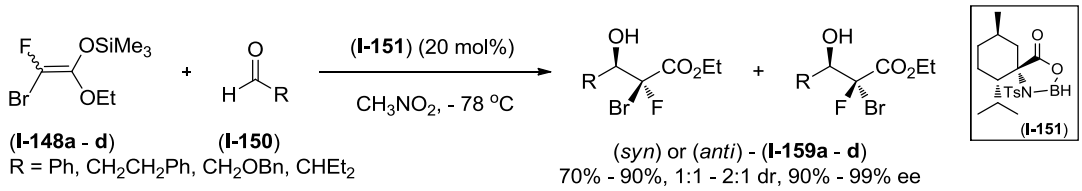


Scheme 34. Enantioselective hydrogenation of (Z) or (E) alkenes.

Besides the one isolated report on hydrogenation of monofluorinated compounds, there were several reports on enantioselective hydrogenation of trifluoromethyl-containing alkenes and ketones, which will not be covered herein. Much more common are methodologies for carbon-carbon bond formation between two reaction partners, one of which contains fluorine, such as aldol, Mannich, Michael additions or, in broader sense, alkylations.

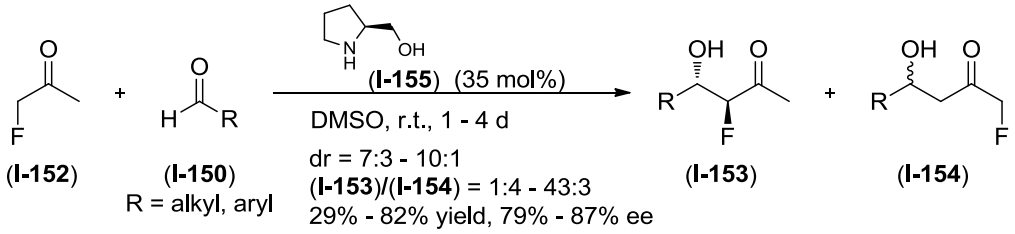
Mukayama aldol reaction of pre-formed ketene silyl acetals with simple aldehydes was developed by Kobayashi and co-workers (Scheme 35).[71] When the reaction was performed at -78 °C in the presence of 20 mol% Masamune's catalyst (**I-150**), a range of aldol products was obtained in high yields and with excellent enantioselectivities, albeit with very poor diastereoselectivities.

[70] M. Saburi, L. Shao, T. Sakurai, Y. Uchida, *Tetrahedron Lett*., 1992, **33**, 7877.
[71] K. Iseki, Y. Kuroki, Y. Kobayashi, *Tetrahedron Lett*., 1997, **38**,7209.



Scheme 35. Mukayama-aldol addition of fluorinated ketene silyl acetals to aldehydes.

General and simple monofluorinated substrate for aldol reaction - fluoroacetone - has been studied by several research groups. Fluoroacetone, represents one type of substrate where fluorination causes additional selectivity issues - the reaction can occur on either one of the α-carbons - the fluorinated or the non-fluorinated. Barbas and co-workers reported a simple addition of fluoroacetone to aliphatic and aromatic aldehydes catalyzed by prolinol (**I-155**, Scheme 36).[72] High catalyst loading of 35 mol% was necessary to maintain moderate yield of the reaction, which ranges from 29% to 82%, with good enantiomeric control (79% to 87%), and regioselectivity ranging from 4:1 to 11:1. Similar method was later reported by Guillena and co-workers, achieving up to 80% ee in analogous aldol addition to fluoroacetone catalyzed by proline-amide BINAM catalyst.[73]

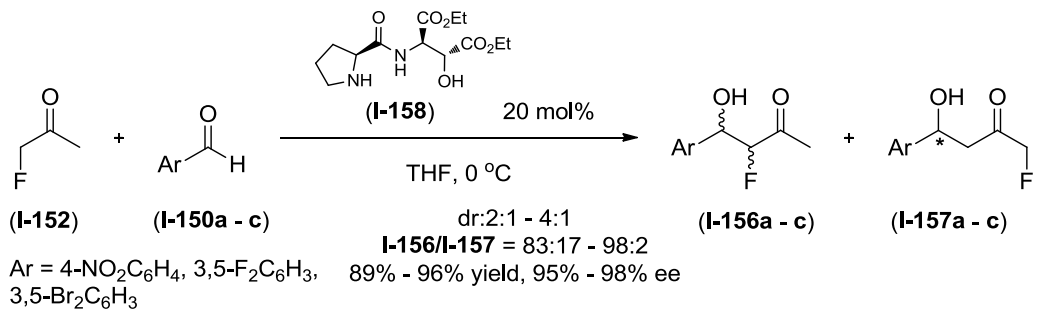


Scheme 36. Aldol reaction of fluoroacetone catalyzed by prolinol.

Gong and co-workers reported the utilization of fluoroacetone in similar aldol addition to aromatic aldehydes (**I-150a** – **c**, Scheme 37) catalyzed by proline-amide catalyst (**I-158**).[74] Although high enantioselectivity (95% – 98% ee) and excellent chemical yields (89% - 96%) were attainable, the diastereoselectivity remained poor (2:1 - 4:1), and the regioselectivity

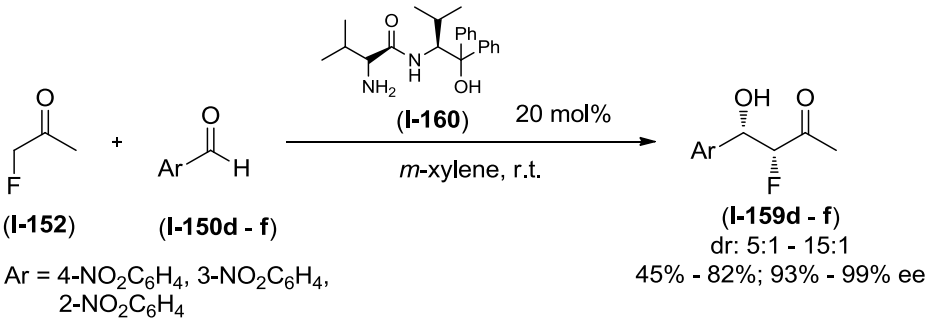
[72] G. Zhong, J. Fan and C. F. Barbas III, *Tetrahedron Lett*., 2004, **45**, 5681.
[73] G. Guillena, M. d. C. Hita, C. Najera, S. F. Viozquez, *J. Org. Chem*., 2008, **73**, 5933.
[74] X.-Y. Xu, Y.-Z. Wang, L.-F. Cui, L.-Z. Gong, *Tetrahedron: Asymmetry*, 2007, **18**, 237.

ranged from 5:1 to 49:1. This reaction was narrow in substrate scope - only aromatic aldehydes with electron-withdrawing substituents were found to be suitable.



Scheme 37. Aldol addition of fluoroacetone to aromatic aldehydes catalyzed by proline-amide.

Notably, the major diastereomer in such aldol addition had *anti* configuration. However, similar type of dipeptide catalyst developed later by the Gong group (**I-160**, Scheme 38) was shown to direct the aldol addition to fluoroacetone towards the challenging *syn* products (**I-159d-f**).[75] The three products were obtained in moderate to good yields (45% – 82%), with excellent enantiomeric control (93% ee - 99% ee), and high to excellent diastereoselectivity (5:1 to 15:1). However, once again the reaction suffered from very narrow scope of suitable aldol acceptors.

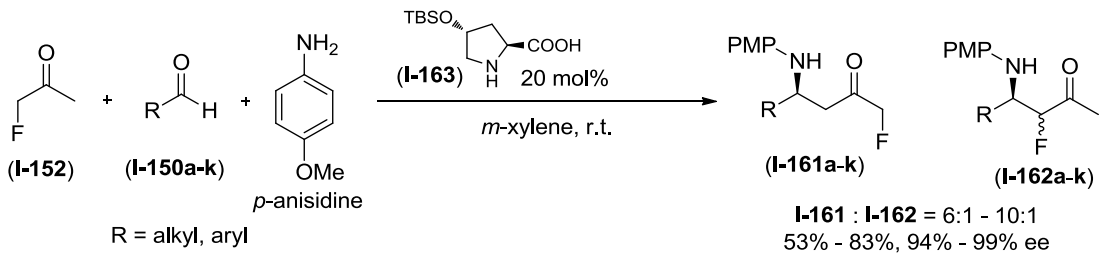


Scheme 38. *Syn*-selective aldol addition of aromatic aldehydes to fluoroacetone.

Fluoroacetone was also found suitable for three-component Mannich reaction catalyzed by simple proline-derived catalyst (**I-163**, Scheme 39).[76] Regioselectivity of the reaction was studied and it was unexpectedly found that polar solvents directed the reaction towards the

[75] X.-Y. Xu, Y.-Z. Wangand L.-Z. Gong, *Org. Lett.*, 2007, **9**, 4247.
[76] G. Zhong, M. Lu, Y. Lu, P. Tan, Q. Lau, *Synlett*, 2011, 477.

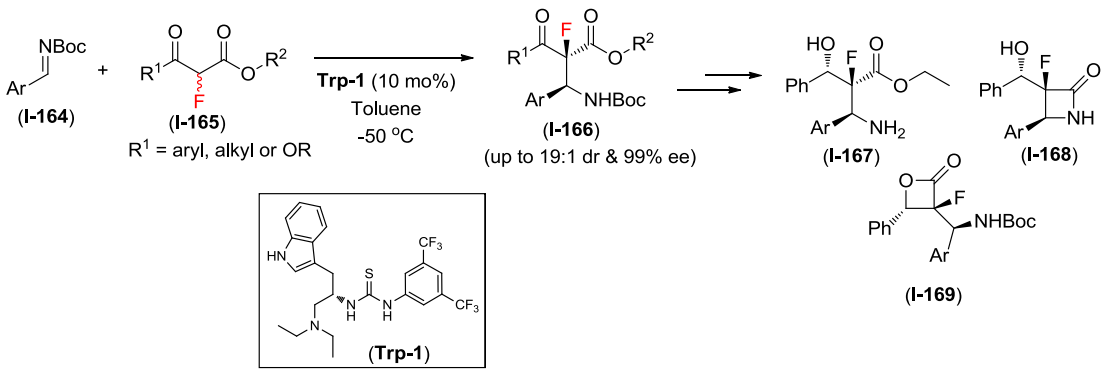
formation of products of addition of non-fluorinated side of fluoroacetone (**I-161**), while in non-polar solvents - no selectivity was observed.



Scheme 39. Three-component Mannich reaction with fluoroacetone.

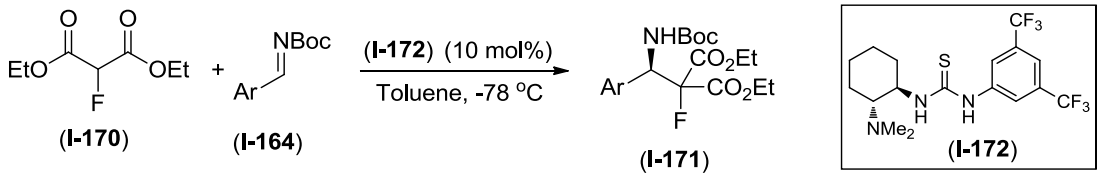
Much more common was to use fluorinate ketoesters and malonates in Mannich-type additions. Generally, α-fluorinated 1,3-dicarbonyl compounds are good and convenient substrates for enantioselective reactions as deprotonation of the acidic α-proton require the use of only mild bases, while carbonyl groups possess strong H-bond acceptor properties, rendering possible interactions with suitable H-bond donors in the catalysts. Direct fluorination of 1,3-dicarbonyl compounds yields linear fluorinated molecules, whereas the use of these substrates in C-C or C-N bond forming reactions leads to branched compounds. On the other hand, further manipulations of the products were troublesome, due to high degree of functionalization of the relatively small carbon core. As such, decompositions or defluorinations during even fundamental functional group transformations, such as reductive amination, are common. Nevertheless, some successful methods for effective handling of such compounds have been demonstrated. A highly enantioselective Mannich addition of fluorinated ketoesters to N-Boc imines leading to synthetically useful adducts has been developed (Scheme 40)[77] and the reaction and manipulation of the products will be discussed in chapter II-5.

[77] X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.*, 2009, **48**, 7604; *Angew. Chem. Int. Ed.*, 2011, **50**, 2653.



Scheme 40. Mannich addition of fluorinated ketoesters to N-Boc imines.

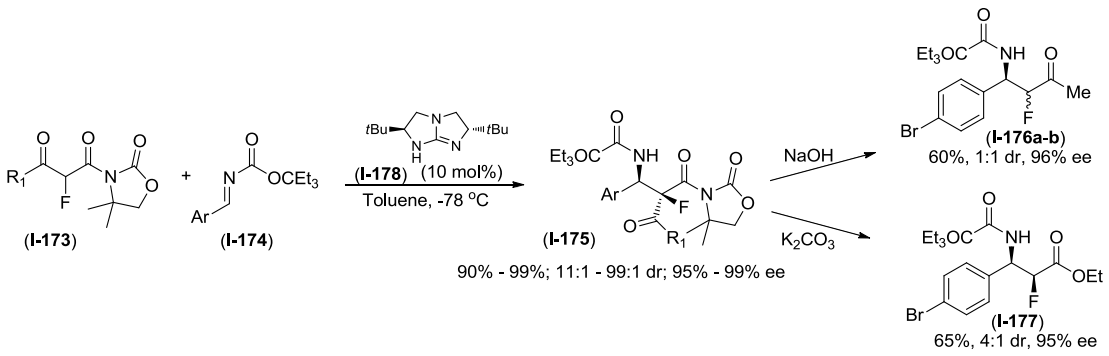
Identical reaction was later reported by a Korean group,[78] with following extension to fluorinated malonate as a donor (Scheme 41); however no manipulation of the generated adducts was demonstrated.[79] In parallel, the same transformation together with studies on mono-decarboxylation/asymmetric protonation, leading to linear α-fluoro-β-amino esters, were the subject of our research; preliminary results will be described in chapter II-5 and in the future perspectives section of this thesis.



Scheme 41. Mannich addition of fluoromalonate to N-Boc aldimines.

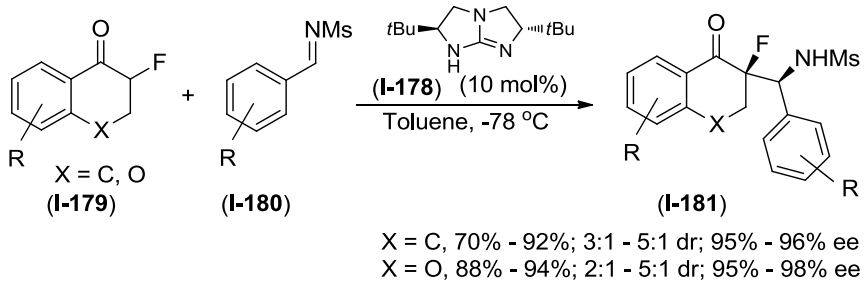
Structurally similar dicarbonyl compounds, β-keto-acetyloxazolidinones (**I-173**, Scheme 42) were found suitable in Mannich reaction with N-Eoc imines (**I-174**), yielding the desired products with excellent levels of stereo-chemical control (>95% ee & >11: 1 dr) and yields (>90%).[80] More importantly, useful structural manipulations of the obtained products were demonstrated; decarboxylation leading to two diastereomeric fluorinated ketoamines (**I-176a**,**b**) and deacylation, being one possible route to linear α-fluoro-β-amino esters (**I-177**).

[78] S. J. Yoon, Y. K. Kang, D. Y. Kim, *Synlett*, 2011, **3**, 420.
[79] J. H. Lee, D. Y. Kim, Synthesis, 2010, **11**, 1860.
[80] Y. Pan, Y. Zhao, T. Ma, Y. Yang, H. Liu, Z. Jiang, C.-H. Tan, *Chem. Eur. J.*, 2010, **16**, 779.



Scheme 42. Mannich addition of β-keto-acetyloxazolidinones.

Bicyclic α-fluorotetralones (**I-179**, X=C, Scheme 43) and α-fluorochromanones (**I-179**, X=O) were all found to be suitable substrates for bicyclic guanidine (**I-178**) catalyzed Mannich-type addition to aromatic N-mesyl imines (**I-180**), affording the corresponding products with excellent enantioselectivities (>95%), good yields (70% - 94%) but low diastereoselectivities (2:1 – 5:1).[81]

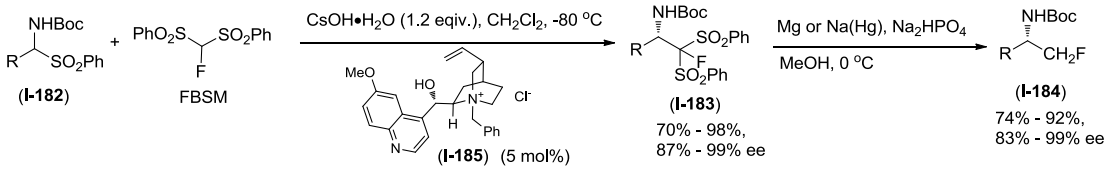


Scheme 43. Mannich addition of tetralones.

The other good fluorinated donors for Mannich-type additions are fluorinated phenylsulfonylmethanes: 1-fluorobis (phenylsulfonyl)methane (FBSM), fluoro-(phenylsulfonyl)methane (FSM) and its derivatives: 1-fluoro-1-nitro(phenylsulfonyl)methane (FNSM) and ester-incorporating (**I-186**, Scheme 45), also described as monofluoromethyl-(monofluoronitromethyl-) equivalents. Addition of FBSM to air- and moisture-stable N-Boc imine precursors (II-150, Scheme 44) *via* PTC methodology was demonstrated as a

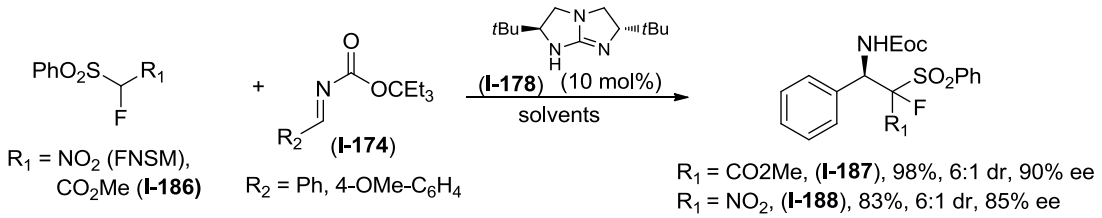
[81] Y. Zhao, Y. Pan, H. Liu, Y. Yang, Z. Jiang, C.-H. Tan, *Chem. Eur. J.*, 2011, **17**, 3571.

stereoselective 2-step route towards monofluoromethylated amines (**I-184**), involving magnesium or sodium amalgam induced cleavage of phenylsulfonyl groups.[82]



Scheme 44. Mannich-type addition of FBSM leading to monofluoromethylated amines.

Similar work, this time with FSM derivatives (FNSM and **I-186**, Scheme 45) and pre-formed N-Eoc imines was later demonstrated by Tan and co-workers.[80] Unfortunately, cleavage of phenylsulfonyl- moiety was not shown, presumably due to de-fluorination or decomposition of products. Therefore practical applications of such adducts remain unexplored and somewhat dubious.



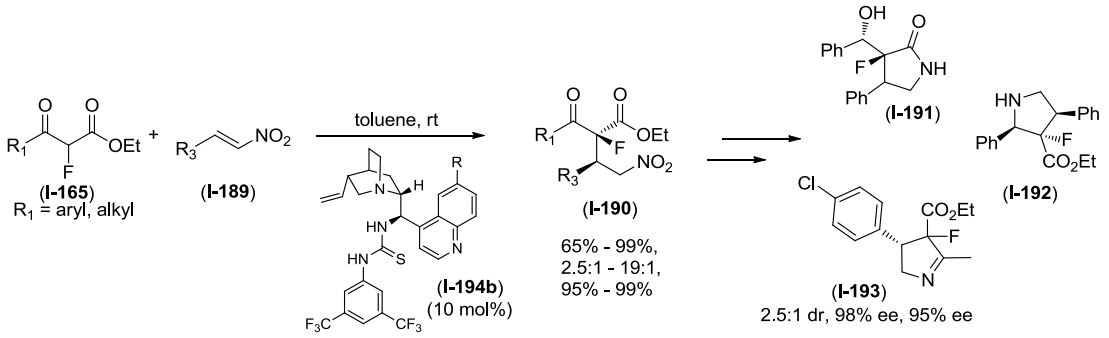
Scheme 45. Mannich-type addition of FSM derivatives.

The same fluorinated donors found application in numerous Michael additions. We and two other groups have reported organocatalytic coupling of the same fluorinated ketoesters (**I-165**, Scheme 46) with nitroalkenes (**I-169**).[83] The best results in terms of stereocontrol were obtained by using bifunctional *Quinidine*-derived organocatalysts (**I-194b**): 95% - 99% ee, and 5:2 - 19:1 dr. The adducts were then transformed into chiral amide (**I-191**), pyrrolidine (**I-192**) and cyclic iminoester (**I-193**).[83a] The same ketoesters were also employed in analogous

[82] S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura, T.Toru, *J. Am. Chem. Soc*., 2007, **129**, 6394.

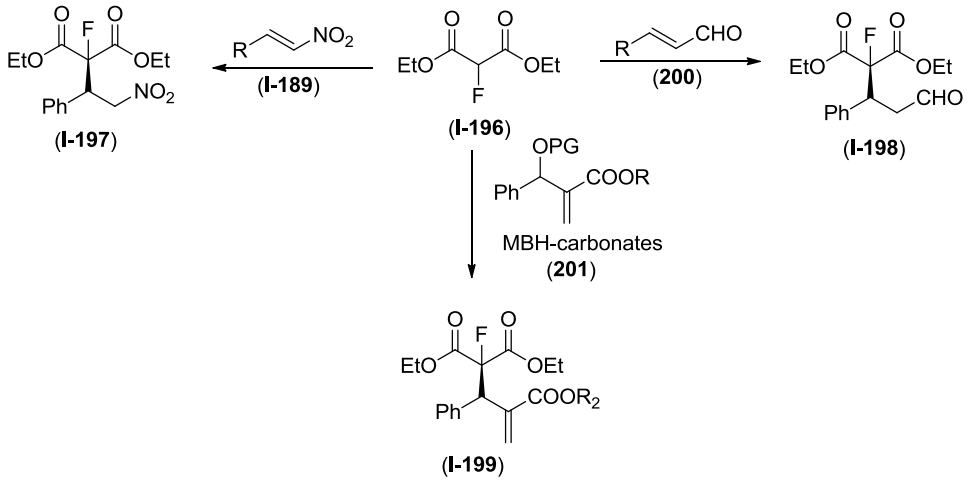
[83] a) X.Han, J.Luo, C.Liu, Y.Lu, *Chem. Commun*., 2009, 2044; b) H. Li, S. Zhang, C. Yu, X. Song, W. Wang, *Chem. Commun*., 2009, 2136; c) Y. Oh, S. M. Kim, D. Y. Kim, *Tetrahedron Lett*., 2009, **50**, 4674; (d) B. K. Kwon, S. M. Kim, D. Y. Kim, *J. Fluorine Chem*., 2009, **130**, 759.

reaction with N-alkyl maleimides, catalyzed by guanidine (**I-178**) yielding complex structures under excellent stereocontrol but with no apparent application.[84]



Scheme 46. Michael addition of fluorinated ketoester to nitroalkenes.

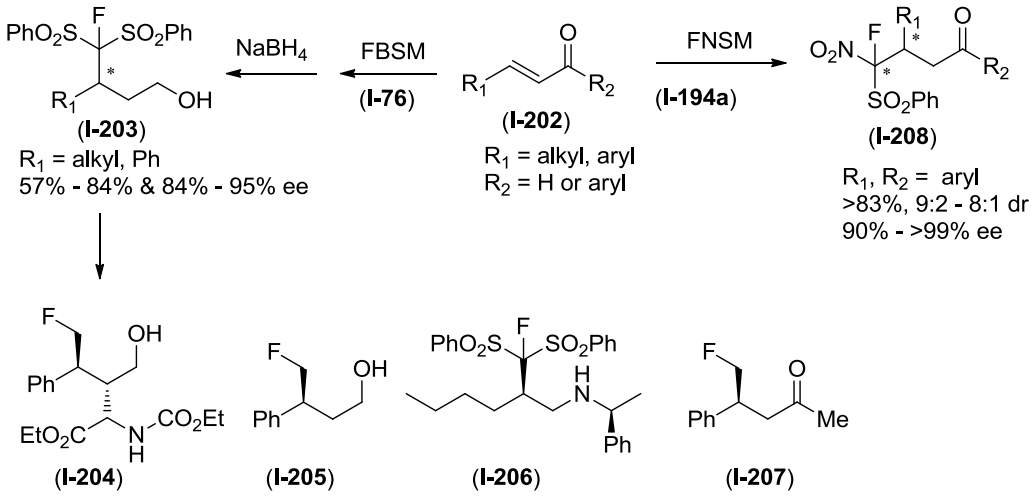
α-Fluoromalonate (Scheme 47) was also shown to be an excellent Michael donor in reactions with nitroalkenes,[85] α,β-unsaturated aldehydes[86] and MBH carbonates,[87] leading to seemingly useful products. However no manipulations of those structures obtained were described and therefore it was difficult to assess the practical utility of such adducts.



Scheme 47. Michael additions of fluoromalonate.

[84] Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K. -W. Huang, M. W. Wong, C.-H. Tan, *Angew. Chem., Int. Ed.*, 2009, **48**, 3627.
[85] H. Li, L. Zu, H. Xie, W. Wang, *Synthesis*, 2009, **9**, 1525.
[86] X. Companyo, M. Hejnova, M. Kamlar, J. Vesely, A. Moyano, R. Rios, *Tetrahedron Lett.*, 2009, **50**, 5021.
[87] B. Wang, X. Companyó, J. Li, A. Moyano, R. Rios, *Tetrahedron Letters*, 2012, **53**, 4124.

FBSM[88] and FNSM[89] were also employed in Michael addition, leading to a range of enantioenriched adducts (**I-203** and **I-208**, Scheme 48). However, only FBSM addition products were demonstrated as useful intermediates, yielding monofluoromethylated aminoalcohols (**I-204**), alcohols (**I-205**), ketones (**I-207**) and amines (however, still bearing the uncleaved sulfonyl moieties, **I-206**).



Scheme 48. Michael addition of phenylsulfonylmethanes.

Alkylations of fluorine-containing prochiral nucleophiles have also been achieved by means of organo- and metal catalysis,[90] one representative example being organocatalytic alkylation of α-fluorotetralone (**I-179**, Scheme 49).[91] Chemical yields of 33% – 83%, fair to very good enantioselectivities (70% – 91%) were achieved under PTC catalysis with **I-211**. Similar alkylation was also reported by Maruoka and coworkers,[92] however, the substrates were more challenging with regards to stereocontrol - linear α-fluoro-β-ketoester (**I-165**). Under similar

[88] (a) F. Ullah, G.-L. Zhao, L. Deiana, M. Zhu, P. Dziedzic, I. Ibrahem,P. Hammar, J. Sun and A. Cordova, *Chem. Eur. J.*, 2009, **15**, 10013; (b) S. Zhang, Y. Zhang, Y. Ji, H. Li, W. Wang, *Chem.Commun.*, 2009, 4886; (c) A.-N. Alba, X. Companyo, A. Moyano, R. Rios, *Chem. Eur. J.*, 2009, **15**, 7035; (d) M. Kamlar, N. Bravo, A.-N. R. Alba, S. Hybelbauerova, I. Cisarova, J. Vesely, A. Moyano, R. Rios, *Eur. J. Org. Chem.*, 2010, 5464; d) H. W. Moon, M. J. Cho, D. Y. Kim, *Tetrahedron Lett.*, 2009, **50**,4896.

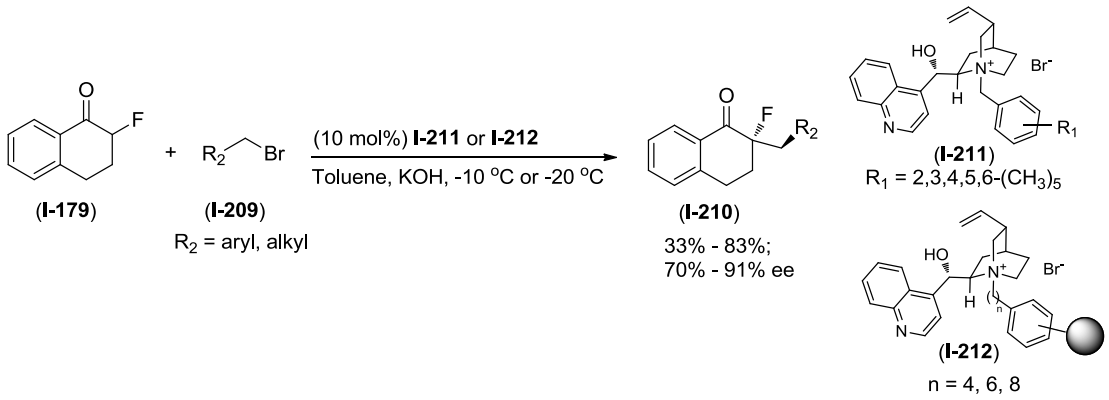
[89] G. K. S. Prakash, F. Wang, T. Stewart, T. Mathew, G. A. Olah, *Proc. Natl. Acad. Sci*. U. S. A., 2009, **106**, 4090.

[90] Silyl enol ethers of cyclic ketones in transition-metal alkylations, see: E. Belanger, K. Cantin, O. Messe, M. Tremblay, J.-F. Paquin, *J. Am. Chem. Soc.*, 2007, **129**, 1034.

[91] S. Arai, M. Oku, T. Ishida, T. Shioiri, *Tetrahedron Lett.*, 1999, **40**, 6785; b) for the example with polymer-supported organocatalysts, see: B. Thierry, T. Perrard, C. Audouard, J.-C. Plaquevent, D. Cahard, *Synthesis*, 2001, 1742.

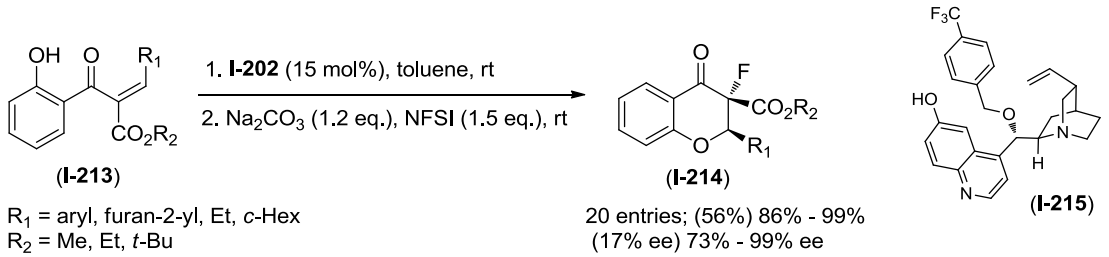
[92] C. Ding, K. Maruoka, *Synlett*, 2009, 611.

phase-transfer organocatalysis, the corresponding products were obtained with modest enantioselectivities (up to 88% ee).



Scheme 49. Alkylation of fluorinated tetralones.

Fluorinated flavanones (**I-214**, Scheme 50) were prepared in tandem oxa-Michael addition/diastereoselective fluorination, catalyzed by simple de-methylated *Cinchona* alkaloid-derived catalyst (**I-215**). Excellent results were reported for this transformation; very high ee values (88% ee - 99% ee), yields over 86% were attainable with single examples where lower level of stereocontrol was observed (heterocyclic and aliphatic substituents).[93]

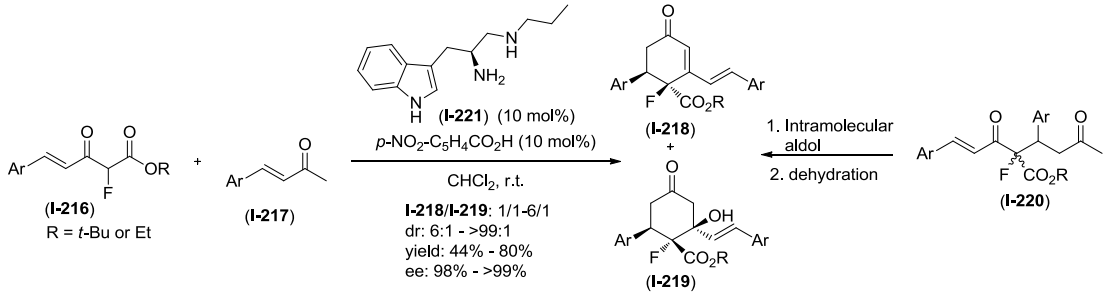


Scheme 50. Tandem intramolecular oxa-Michael/fluorination.

Much simpler substrates were used in the synthesis of functionalized cyclohexanones, featuring α-fluoroester moiety; diastereomers of α-fluoro-β,γ-diketoester (**I-220**, Scheme 51) in intramolecular aldol reaction, or prochiral, unsaturated α-fluoro-β-ketoester (**I-216**) and

[93] H.-F. Wang, H.-F. Cui, Z. Chai, P. Li, C.-W. Zheng,Y.-Q. Yang, G. Zhao, *Chem. Eur. J.*, 2009, **15**, 13299.

α,β-unsaturated methyl ketone (**I-217**) in Robinson annulation.[94] The tryptophan-derived diamine (**I-221**) could control the stereoselectivity well, leading to products with excellent enantioselectivities (98% – 99%), good to excellent diastereomeric ratios (6:1 – 99:1) and fair to good yields (44% – 80%).

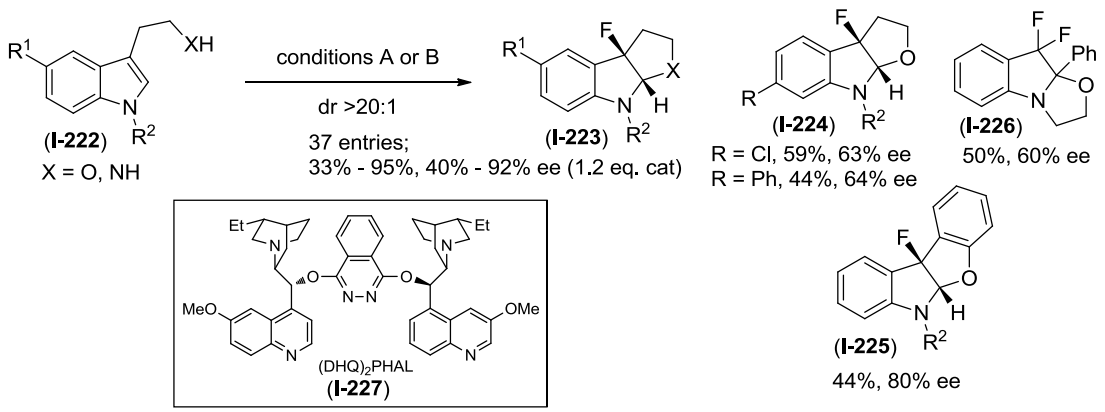


Scheme 51. Synthesis of fluorinated cyclohexanes with α-fluoroester core.

Stereoselective methods, towards bi- or tricyclic fluorinated structures are rare. Besides the two rather limited methods (oxa-Michael and alkylation of tetralones), there is one emerging methodology of great potential - fluorocyclization. To date there is only two reports on its enantioselective version, both by Gouverneur and co-workers.[95] In the presence of 1.2 equivalent of commercially available *Cinchona* alkaloid-derived chiral promoter ($(DHQ)_2$PHAL, the fluorinated hetero-tricycles (**I-223**–**I-226**, Scheme 52) were obtained in moderate to high ee values, and fair to very good yields. The reaction could also be performed using 20 mol% catalyst, the chemical yields of the reaction were maintained, but the enantioselectivities dropped by 10% on the average. Further development of this method is desirable, as it would significantly bolster access to fluorinated heterocycles from simple starting materials.

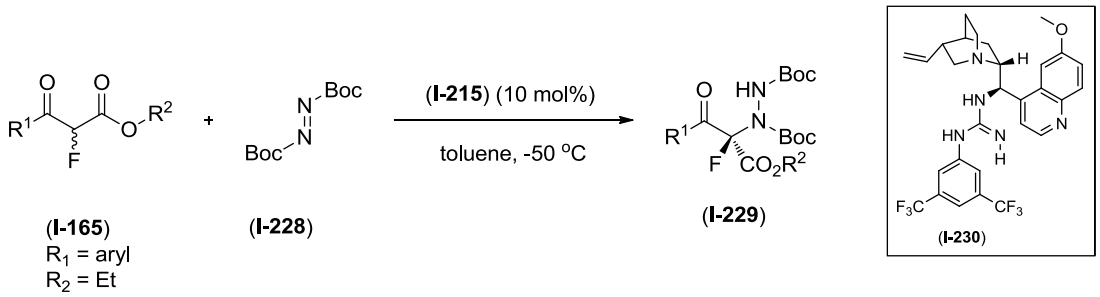
[94] (a) H.-F. Cui, Y.-Q. Yang, Z. Chai, P. Li, C.-W. Zheng, S.-Z. Zhu, G. Zhao, *J. Org. Chem.*, 2010, **75**, 117; (b) H.-F. Cui, P. Li, X.-W. Wang, Z. Chai, Y.-Q. Yang, Y.-P. Cai, S.-Z. Zhu, G. Zhao, *Tetrahedron*, 2011, **67**, 312.

[95] a) for a review see: S. C. Wilkinson, R. Salmon, V. Gouverneur, *Future Med. Chem.*, 2009, **1**, 847; b) O. Lozano, G. Blessley, T. M. del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem. Int. Ed.*, 2011, **50**, 8105; c) S. C. Wilkinson, O. Lozano, M. Schuler, M. C. Pacheco, R. Salmon, V. Gouverneur, *Angew. Chem. Int. Ed.*, 2009, **48**, 7083.



Scheme 52. Asymmetric fluorocyclization.

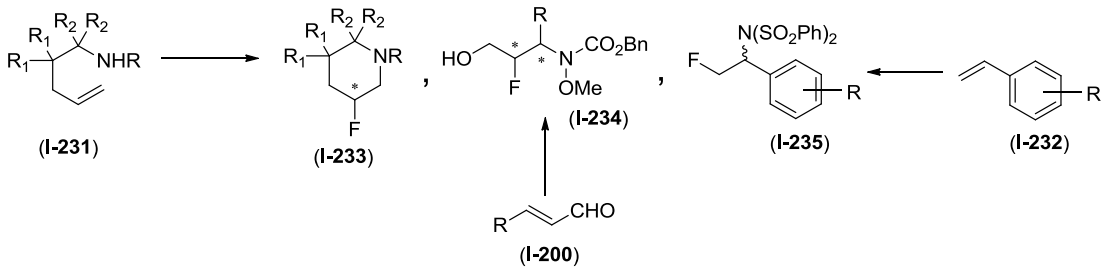
In addition to C–C bond forming reactions, some C–N bond formations *via* amination were also reported. However, practical applications of such molecules are limited due to lack of methods for cleaving the N–N bond to free the amino functionality. Enantioselective aminations were achieved by means of metal catalysis,[96] phase-transfer organocatalysis (one example)[97] and organocatalysis (Scheme 53).[98] *Quinidine*-derived guanidine (**I-230**) was found effective in amination of fluorinated ketoesters (**I-165**) achieving up to 92% ee with aromatic ketoesters and 47% - 87% ee for aliphatic substrates,[98a] while simple bicyclic guanidine (**I-178**) led to amination of α-fluorotetralones and α-fluorochromanones (**I-179**, X = C and X=O respectively) with 86% - 96% ee.[98b]



Scheme 53. Amination of α-fluoro-β-ketoester.

[96] D. P. Huber, K. Stanek, A. Togni, *Tetrahedron:Asymmetry*, 2006, **17**, 658.
[97] R. He, X. Wang, T. Hashimoto, K. Maruoka, *Angew. Chem. Int. Ed.*, 2008, **47**, 9466.
[98] a) X. Han, F. Zhong, Y. Lu, *Adv. Synth. Catal.*, 2010, **352**, 2778; b) Y. Zhao, Y. Pan, H. Liu, Y. Yang, Z. Jiang, C.-H. Tan, *Chem. Eur. J.*, 2011, **17**, 3571.

An interesting variation of the above methods is tandem formation of C–F and C–N bonds through fluoroamination of alkenes. Cyclic β-fluoroamines (**I-233**, Scheme 54) were obtained as racemate *via* palladium catalysis [99a] or as enantio-enriched mixture in reaction promoted by an interesting C-2 symmetric hypervalent iodine catalyst (up to 81% ee).[99b] Linear fluorinated hydroxyamines (**I-234**) were attainable from simple α,β-unsaturated aldehydes, using prolinol-derived organocatalysts (with excellent 98% - 99% ee (80% ee - one example) and 6:1 - 49:1 dr)[99c], while aromatic β-fluoroamines (**I-235**) were obtained from simple, unactivated styrenes, by Pd-catalysis.[99d] Further development of enantioselective fluoroamination would certainly offer new opportunities for generation of valuable fluorinated precursors of bioactive compounds from simple starting materials.



Scheme 54. Fluoroamination of olefins.

[99] a) T. Wu, G. Yin, G. Liu, *J. Am. Chem. Soc.*, 2009, **131**, 16354; b) W. Kong, P. Feige, T. de Haro, C. Nevado, *Angew. Chem. Int. Ed.*, 2013, **52**, 2469; c) C. Appayee, S. E. Brenner-Moyer, *Org. Lett.*, 2010, **12**, 3356; d) S. Qiu, T. Xu, J. Zhou, Y. Guo, G. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 2856.

I.3. Summary

Given all the unique properties of fluorine, its small size alongside the extreme electronegativity, and resulting significant (frequently beneficial) influence of selective fluorination on activities and characteristics of bioactive compounds, it is easily understandable that the utility of fluorine in pharmaceutical research, biological sciences and medicinal chemistry is expanding. Approximately 20% of today's pharmaceuticals are fluorine-containing compounds, whereas in 1957 there was none. However, two major challenges have to be met to further advance the applications of fluorinated compounds, namely: insufficient understanding of complex biological systems, pathways and molecular interactions, as well as lacking methodology to access selectively fluorinated, chiral compounds in a practical way. The shortcomings include: substrate scope, resolution of diastereomers, laborious catalyst preparation and necessity for multistep transformations to access precursors of practical synthetic value. As much as general methods are highly desirable, one must think realistically, that generalization may be possible only to a certain extent. Therefore, one must consider the limits, benefits and mutual complementarity of all methods, be it organo- or metal-catalytic, with direct or indirect incorporation of fluorine, when designing routes towards target molecules. Undoubtedly, invention of mild N-F fluorination agents such as NFSI and Selectfluor® had a great impact on advancing the field of preparation of chiral organofluorine compounds. The two fluorinating agents are nowadays almost sole agents used in enantioselective fluorine incorporation. Direct, enantioselective fluorination offers straightforward approach towards fluorine-containing compounds usually at very low catalyst loadings. However the common disadvantage is restriction to generation of quaternary fluorine-containing centers, to avoid bis-fluorination, e.g. fluorination of β-ketoesters (Scheme 17). Of course in certain cases, this is favorable - whenever fluorinated quaternary carbon is the synthetic aim itself (see for example fluorination of oxindoles leading to MaxiPost® analogues, Scheme 28). However, it may also be seen as a significant restriction. Additionally, influence of fluorination on neighboring groups (which is a desired

property) is tuned down by the presence of substituents with electron-donating capabilities at the fluorinated, quaternary carbon (common are alkyl or aryl groups). Therefore, some strategies emerged to nullify or at least temper this limitation; for example: a tunable substituent was installed on the fluorinated quaternary carbon prior to reaction, or in tandem process, to block bis-fluorination and later exchanged to other functional group with retention of optical purity (e.g. the fluorination of α-chloro-β-ketoester, Scheme 19; the chlorine could later be substituted by azide - however reduction to amine was unsuccessful). Some practical methodologies leading to linear fluorinated molecules (without quaternary fluorinated carbon center) have emerged in more or less optimized forms, such as: fluorination of arylacetic acids (Scheme 25), fluorination of α-ketoester with successful conversion to linear β-fluoro-α-aminoesters (Scheme 27), allylic fluorination (Scheme 31) or brilliant fluorination of acyl chlorides *via* cooperative catalysis through *in-situ* generated ketenes, leading to a range of products - acids, esters, thioesters, amides - depending on the quenching reagent (Scheme 33), with following extension to the state of the art chemo selective fluorination of macromolecules,[69] a strategy certainly worth further development. Alternatively, activation *via* imine-enamine organocatalytic systems was broadly successful in monofluorination of aldehydes (Scheme 6 - Scheme 9), with emerging fluorination of ketones (Scheme 15).

Apart from direct fluorination - another practical approach towards chiral, fluorinated molecules is based on application of prochiral fluorine-containing substrates or tandem processes. Multitude of interesting and valuable synthons can be accessed *via* this methodology, however, the generation of branched molecules with quaternary fluorinated centers is favored, lacking routes towards linear synthons. Unarguably, generation of such branched molecules is desired - see for example route towards fluorinated tri-heterocycles in a tandem process (Scheme 52) or bio-relevant fluorinated flavanones (Scheme 50). Nevertheless, the development in the direction of practical preparation of chiral, linear, fluorinated molecules is certainly also of great importance. Isolated examples of such methods include: monofluoromethylation (Scheme 44 and Scheme 48, with troublesome

removal of phenylsulfonyl moieties), Mannich and aldol additions of fluoroacetone (Scheme 36 – Scheme 39; low stereocontrol) and fluoroaminations of olefins and simple styrenes (Scheme 54; low stereocontrol). On the other hand, skillful manipulation of branched adducts can also lead to optically enriched, linear product (e.g. deacylation or decarboxylation of Mannich adduct (Scheme 42)). A good alternative would also be, selective mono-decarboxylation of fluoromalonate adducts, which is unknown to date and has been tackled during the course of our research (results are presented in chapter II-5 and the future perspective section). The remaining, long-standing challenge - cleavage of N–N bond in amination products, retaining the C–F bond intact (e.g. Scheme 53), to yield α-fluoro-α-amino acid core is of great interest and one alternative approach towards it is described in chapters II-1 and II-2.

II. Research results

II-1. Towards the enantioselective synthesis of functionalized α-fluoro-α-amino acids: organocatalytic Michael addition/hydrogenation of ethyl fluoronitroacetate

II-2. Organocatalytic Michael addition of α-fluoro-α-nitro benzyls to nitroalkenes: facile preparation of fluorinated amines and pyrimidines

II-3. Enantioselective synthesis of functionalized fluorinated phosphonates *via* Michael addition of α-fluoro-β-ketophosphonates to nitroalkenes

II-4. Organocatalytic Michael addition of 2-fluoro-1,3-diketones to nitroalkenes: towards fluoro-isosteres of glycerine

II-5 Asymmetric Mannich reaction - towards fluorinated amino acids, lactones and β-lactams

II-1. Towards the enantioselective synthesis of functionalized α-fluoro-α-amino acids: organocatalytic Michael addition/hydrogenation of ethyl fluoronitroacetate

In search for practical methodologies for preparation of fluorinated bioactive molecules, attention was given to the very basic bio-compounds - amino acids. There are several examples in the literature of methodologies leading to α-fluoro-β-amino acids *via* multiple-step synthesis, but no method for the preparation of α-fluoro-α-amino acids. Being interested in developing a general methodology towards fluorinated amino acids, we envisioned designing a donor containing the α-fluoro-α-amino acid core for Michael and Mannich additions. In this chapter, the work on the use of fluoronitroacetate as a synthon for the preparation of α-fluoro-α-amino acids is disclosed.

II-1.1. Introduction

Alteration of amino acids, the very basic bioactive molecules and building units of peptides and enzymes, by fluorination is especially sought-after, due to the little steric disruption caused, while greatly affecting compound's properties in a predictable manner.[100] Despite the great efforts to date, stereoselective synthesis of fluorinated amino acids remains a formidable task requiring multistep procedures, while allowing only for generation of specific compounds with no structural variation.[101] The common approach towards fluorine-containing amino acids derivatives is through enantioselective Mannich reactions with

[100] a) I. Ojima, *New Developments in the Synthesis and Medical applications of Fluoroamino Acids and Peptides*, ed. R. Filler, Y. Kobayashi, L. M. Yagupolskii, Elsevier, Amsterdam, The Netherlands, 1993; b) C. Jäckel, B. Koksch, *Eur. J. Org. Chem.*, 2005, 4483; c) D. F. Hook, F. Gessier, C. Noti, P. Kast, D. Seebach, *ChemBioChem*, 2004, **5**, 691; d) C. Jackel, W. Seufert, S. Thust, B. Koksch, *ChemBioChem*, 2004, **5**, 717

[101] a) A. Sutherland, C. L. Willis, *Nat. Prod. Rep.*, 2000, **17**, 621-631; b) X.-L. Qiu, W.-D. Meng, F.-L. Qing, *Tetrahedron*, 2004, **60**, 6711-6745; c) V. P. Kukhar, A. E. Sorochinsky, V. A. Soloshonok, *Futur. Med. Chem.*, 2009, **1**, 793; d) A. Tarui, K. Sato, M. Omote, I. Kumadaki, A. Ando, *Adv. Synth. Catal.*, 2010, **352**, 2733.

fluorinated ketoesters (**I**, Figure 13) or malonates.[102] This methodology leads to molecules with amino- and fluoro- functionalities installed on the neighboring carbon atoms (**II**), while the strongest effects of fluorination on the amine and carboxylic acid functionalities would be observed if fluorine is attached to the α-carbon in α–amino acid (**III**).

One straightforward method to access such motif would be the amination of α-fluorinated ketoesters,[103] however all attempts to cleave the N-N bond and free the amino- functionality failed. Thus α-fluro-α-amino acids were never achieved before in enantioselective fashion, except *via* the resolution with chiral amines,[104] and for a single example of fluorination of N-phthaloylphenylglycine derivative with stoichiometric amounts of chiral *Cinchona* alkaloid-derived N-fluoroammonium salts, sadly with no follow up or any extension of scope.[105] Notably, it was reported that removal of the phthaloyl amino protecting group while retaining C-F bond intact is not possible, due to de-fluorination.[106a] We envisioned that a general method for asymmetric construction of the α-fluoro-α-amino acid scaffold would be of great interest in the overlapping areas of synthetic, bio- and medicinal chemistry.

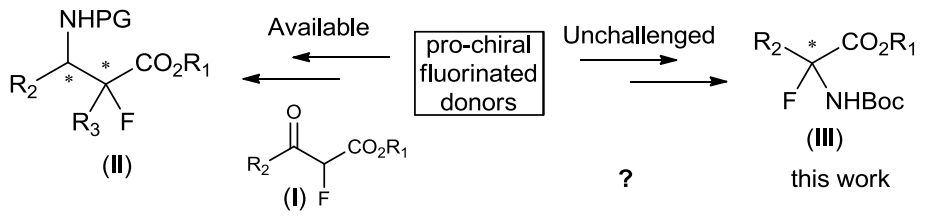


Figure 13. Construction of fluorinated amino esters.

[102] a) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.*, 2009, **48**, 7604; b) S. J. Yoon, Y. K. Kang, D. Y. Kim, *Synlett*, 2011, **3**, 420; c) for the use of malonate, see: J. H. Lee, D. Y. Kim, *Synthesis*, 2010, **11**, 1860; There is no example of reductive amination of carbonyl function of Mannich or Michael products leading to α-fluoro-β-amino acid derivatives, presumably due to cleavage of C-F bond; for example see: d) H. Li, S. Zhang, C. Yu, X. Song and W. Wang, *Chem. Commun.*, 2009, 2136; e) X. Han, J. Luo, C. Liu, Y. Lu, *Chem. Commun.*, 2009, 2044.

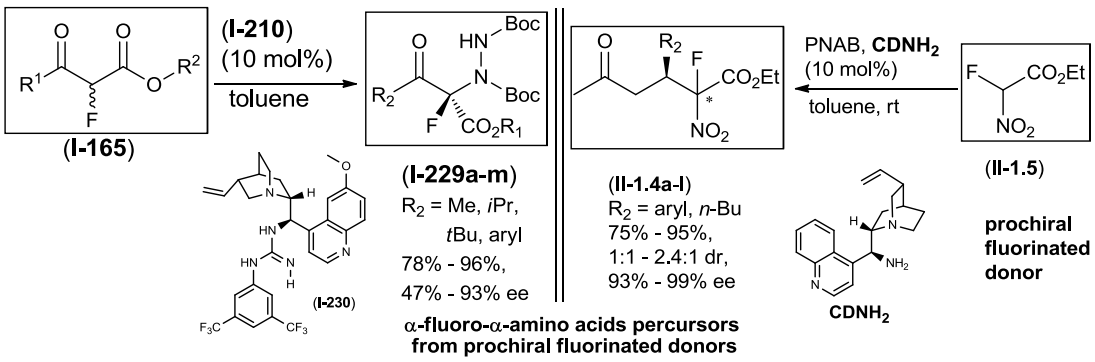
[103] a) D. P. Huber, K. Stanek, A. Togni, *Tetrahedron:Asymmetry*, 2006, **17**, 658; b) R. He, X. Wang, T. Hashimoto, K. Maruoka, *Angew. Chem. Int. Ed.*, 2008, **47**, 9466; c) X. Han, F. Zhong, Y. Lu, *Adv. Synth. Catal.*, 2010, **352**, 2778.

[104] a) E. Hayashi, H. Furukaya, T. Abe, *J. Fluor. Chem.*, 1991, **52**, 133; b) resolution *via* esters, see: Y. Takeuchi, M. Asahina, K. Nagata, T. Koizumi, *J. Chem. Soc. Perkin Trans. 1*, 1987, 2203; c) Y. Takeuchi, M. Kamezaki, K. Kirihara, G. Haufe, K. W. Laue, N. Shibata, *Chem. Pharm. Bull.* 1998, **46**, 1062

[105] B. Mohar, J. Baudoux, J.-C. Plaquevent, D. Cahard, *Angew. Chem. Int. Ed.*, 2001, **40**, 4214

[106] a) Y. Takeuchi, M. Nabetani, K. Takagi, T. Hagi, T. Koizumi, *J. Chem. Soc. Perkin Trans. 1*, 1991, **0**, 41; b) S. C. Annedi, W. Li, S. Samson, L. P. Kotra, *J. Org. Chem.*, 2003, **68**, 1043.

Nitroacetic acid esters have been recognized as valuable intermediates leading towards α-amino acids and heterocycles,[107] with little attention paid to fluoronitroacetic acid esters,[108] the latter being the simplest and easy accessible synthon towards α-fluoro-α-amino acids.[106] To date, there are four reports on the use of prochiral fluorinated donors for the construction of α-fluoro-α-nitrogen-containing compounds. Two methodologies utilize pro-chiral fluorinated donors (Scheme 55), while the two other describe direct fluorination (Scheme 56). Fluorinated ketoesters were used in amination, leading to adducts **I-229a-m** (Scheme 55) effectively and with enantioselectivities ranging from 47% to 93%.[109] The other example utilizes ethyl fluoronitroacetate in Michael addition to α,β-unsaturated ketones, leading to products **II-1.4a–l** in good to excellent yields (75% – 95%) and excellent enantioselectivities (93% – 99% ee).



Scheme 55. Preparation of α-fluoro-α-nitrogen-containing core *via* the use of fluorinated donors.

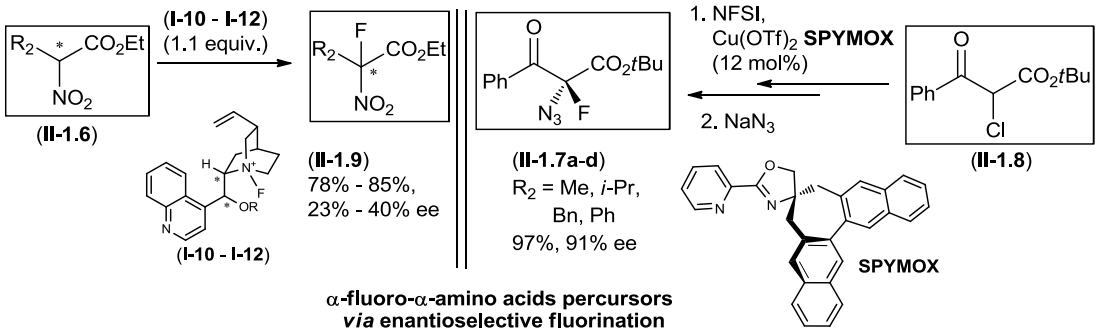
Enantioselective fluorination of nitroacetic ester was reported with the use of *Cinchona* alkaloid-derived chiral stoichiometric fluorinating agents (**I-10**–**I-12**, Scheme 56) affording

[107] a) For a review see: M. T. Shipchandler, *Synthesis*, 1979, 666; b) H. Jiang, P. Elsner, K. L. Jensen, A. Falcicchio, V. Marcos, K. J. Jørgensen, *Angew. Chem. Int. Ed.*, 2009, **48**, 6844; c) B. Moreau, A. B. Charette, *J. Am. Chem. Soc.*, 2005, **127**, 18014; d) A. Singh, R. A. Yoder, B. Shen, J. N. Johnston, *J. Am. Chem. Soc.*, 2007, **129**, 3466; e) R. S. Fornicola, E. Oblinger, J. Montgomery, *J. Org. Chem.*, 1988, **63**, 3528; f) C. Liu, Y. Lu, *Org. Lett.*, 2010, **12**, 2278; g) R.-J. Lu, W.-T. Wei, J.-J. Wang, S.-Z. Nie, X.-J. Zhang, M. Yan, *Tetrahedron*, 2012, **68**, 9397; h) Y. Zhou, Q. Li, Y. Gong, *Tetrahedron Lett.*, 2013, **54**, 3011.

[108] a) H.-F. Cui, P. Li, X.-W. Wang, Z. Chai, Y.-Q. Yang, Y.-P. Cai, S.-Z. Zhu, G. Zhao, *Tetrahedron*, 2011, **67**, 312; b) X.-W. Wang, H.-F. Cui, H.-F. Wang, Y.-Q. Yang, G. Zhao, S.-Z. Zhu, *Tetrahedron*, 2011, **67**, 2468.

[109] X. Han, F. Zhong, Y. Lu, *Adv. Synth. Catal.*, 2010, **352**, 2778.

the products (**II-1.9a**–**d**) in good yields (78% – 85%) but low enantioselectivities (23% – 40% ee). The other methodology is based on copper-catalyzed *gem*-chlorofluorination, followed by substitution of chlorine with azide. The α-fluoro-α-azidoester (**II-1.7**) was obtained in excellent yield (97%) and high ee (91%).



Scheme 56. Preparation of α-fluoro-α-nitrogen-containing core *via* enantioselective fluorination.

Despite the attempts shown above, the α-nitrogen-containing group was never successfully transformed to the amino functionality; de-nitration was observed for α-fluoro-α-nitro compounds, while de-fluorination under palladium catalyzed azide reduction was anticipated. Hence the potential applications of α-fluoro-α-amino acid scaffold in medicinal chemistry together with the unchallenged attempts of their synthesis prompted us to investigate a general and tunable method to access such compounds. Furthermore, the the use of fluoronitroacetate as Michael donor instead of non-fluorinated ethyl nitroacetate has several advantages. Firstly, Michael addition product of ethyl nitroacetate would contain highly acidic α-proton, which would lead to racemization (Figure 14). Secondly, fluorination of Michael addition product of ethyl nitroacetate would be difficult due to selectivity issues (possible side products marked in red). Lastly, asymmetric fluorination is in general considered as more challenging to control than Michael addition.

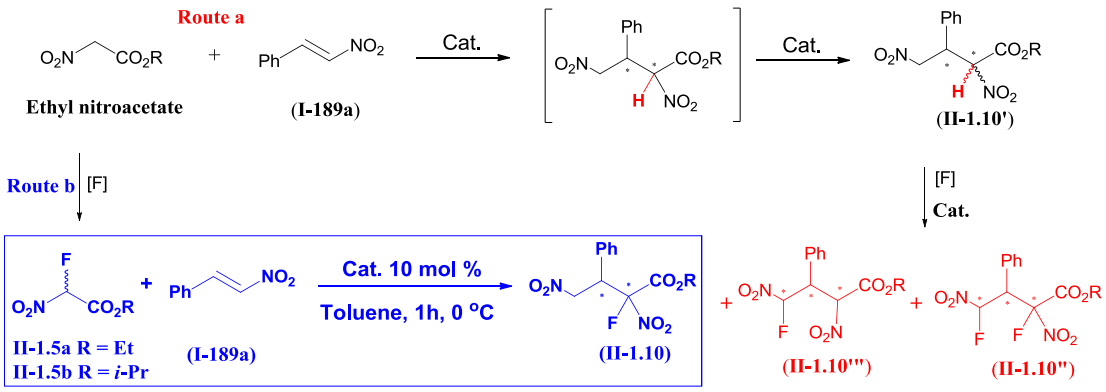
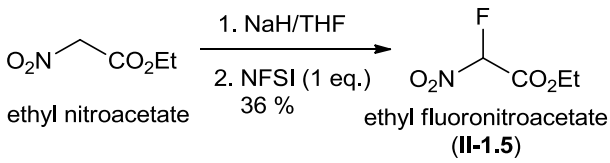


Figure 14. Two alternative Michael addition-fluorination sequences.

II-1.2. Organocatalytic Michael addition of ethyl fluoronitroacetate to nitroalkenes - reaction optimization

We were intrigued, whether the easily accessible ethyl fluoronitroacetate would be a viable precursor for α-fluoro-α-amino acids, through Michael or Mannich additions. Nitroalkenes, which are stable and excellent acceptors, were chosen as model reaction partners for Michael additions, allowing for diverse structural manipulations of the products *via* the chemistry of the nitromethyl group – potentially leading to di-amino acids or amino di-acids through the Nef oxidation.[110]

To validate our hypothesis, the substrate was prepared by fluorination of commercially available ethyl nitroacetate, using sodium hydride as base and THF as solvent (Scheme 57).



Scheme 57. Preparation of ethyl fluoronitroacetate.

The isolated yield of the product was only 36%, even though the reaction was clean and the crude ^{1}H NMR indicated up to 60% conversion of ethyl nitroacetate to the desired monofluorinated product. Notably, ethyl fluoronitroacetate was found to be stable at room temperature a few hours, therefore it was freshly prepared before each batch of reactions.

[110] For a recent review see R. Ballini, M. Petri, *Tetrahedron*, 2004, **60**, 1017.

Optimization of the fluorination was attempted; however no better method was found, with the microwave-assisted fluorination under neutral conditions leading to conversions not exceeding 40%. The nitroalkenes - were prepared from the respective aldehyde and nitromethane, according to the known procedures.

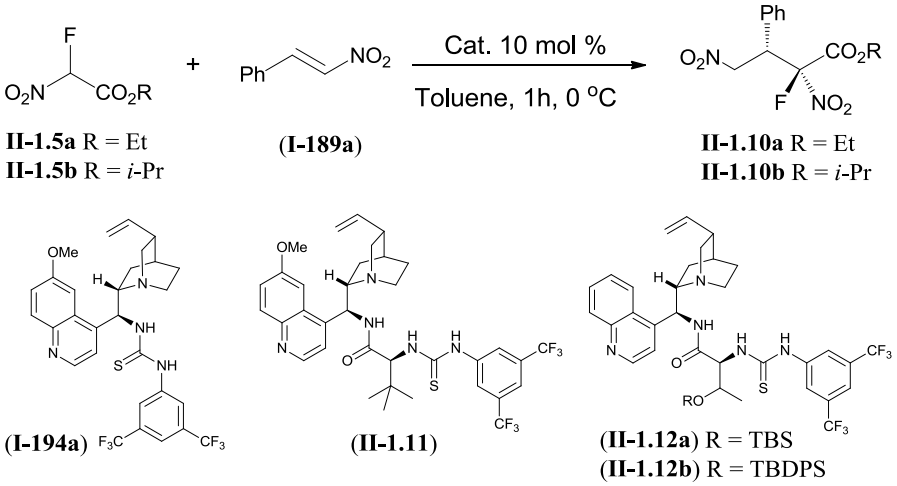
Reaction optimization

With the substrates in hand, we began our studies on the model reaction of ethyl fluoronitroacetate with (*E*)-β-nitrostyrene. Firstly, the common *Quinine*-derived thiourea catalyst was screened (**I-194a**, Table 1), leading to poor enantio- and diastereoselectivities (19% ee & 5:2 dr), with excellent yield (97%, entry 1). To our satisfaction, the catalyst previously developed in our laboratory, incorporating L-*tert*-leucine unit in-between the alkaloid core and the thiourea moiety (**II-1.11**),[111] led to the desired product with dramatically increased enantioselectivity (89% ee, entry 2), while retaining the very high yield (95%). Further fine-tuning of the catalyst structure by modifying the silyl protecting group (TBS in **II-1.12a** and TBDPS in **II-1.12b**) on the *L*-Threonine unit, led to the identification of **II-1.12b** as the optimum catalyst, affording the product with 97% ee and excellent yield (entry 4). Next, we attempted to further optimize the reaction by lowering or increasing the reaction temperature (entries 5–6) but observed only 10% decrease in ee values in both cases. The addition of 4 Å molecular sieves resulted in significant decrease of ee value to 72% (entry 6), while 10 equiv. of water as additive, caused a slight decrease in enantioselectivity by 5% (entry 7). The subsequent, screening of solvents (entries 8–10) reassured us that toluene is the preferred solvent with xylene being the second best in terms of enantioselectivity (94% ee), while yields and dr values were unaffected in all cases. In a final attempt to increase the diastereoselectivity of the reaction, the ethyl ester of the fluoronitroacetate was changed to *iso*-propyl. Unfortunately a slight decrease in ee value and the lack of dr improvement was

[111] Q. Zhu, Y. Lu, *Angew. Chem. Int. Ed.*, 2010, **49**, 7753.

observed (entry 11), and we decided that the troublesome transesterification of the commercially available ethyl ester would unlikely yield any benefits to the reaction.[112]

Table 1. Michael addition of ethyl fluoronitroacetate **II-1.5** to (*E*)-nitrostyrene **I-189a** catalyzed by organocatalysts.[a]



Entry	R	Catalyst	Solvent	Yield (%)[b]	Ee (%)[c]	Dr[d]
1	Et	**I-194a**	Toluene	97	19	5:2
2	Et	**II-1.11**	Toluene	95	89	3:1
3	Et	**II-1.12a**	Toluene	96	88	3:1
4	Et	**II-1.12b**	Toluene	96	97	3:1
5[e]	Et	**II-1.12b**	Toluene	94	88	3:1
6[f]	Et	**II-1.12b**	Toluene	96	87	3:1
6[g]	Et	**II-1.12b**	Toluene	95	72	5:2
7[h]	Et	**II-1.12b**	Toluene	95	92	5:2
8	Et	**II-1.12b**	$CHCl_3$	92	87	5:2
9	Et	**II-1.12b**	Et_2O	94	87	3:1
10	Et	**II-1.12b**	Xylene	95	94	3:1
11	*i*-Pr	**II-1.12b**	Toluene	95	86	3:1

[a] Reaction conditions: **II-1.5a** or **II-1.5b** (0.1 mmol), the catalyst (0.01 mmol) in the solvent (1ml) with nitrostyrene (0.11 mmol) at 0 °C unless noted otherwise. [b] Isolated yield.[c] Determined by HPLC analysis on a chiral stationary phase. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Reaction in -30 °C. [f] Reaction in rt. [g] Reaction in the presence of 4Å molecular sieves (10 mg). [h] 10 equiv. of H_2O added.

In fact, the easy separability of diastereomers of the products provided routes towards both geometrical isomers of the molecules of interest (the dr value corresponds to configuration on

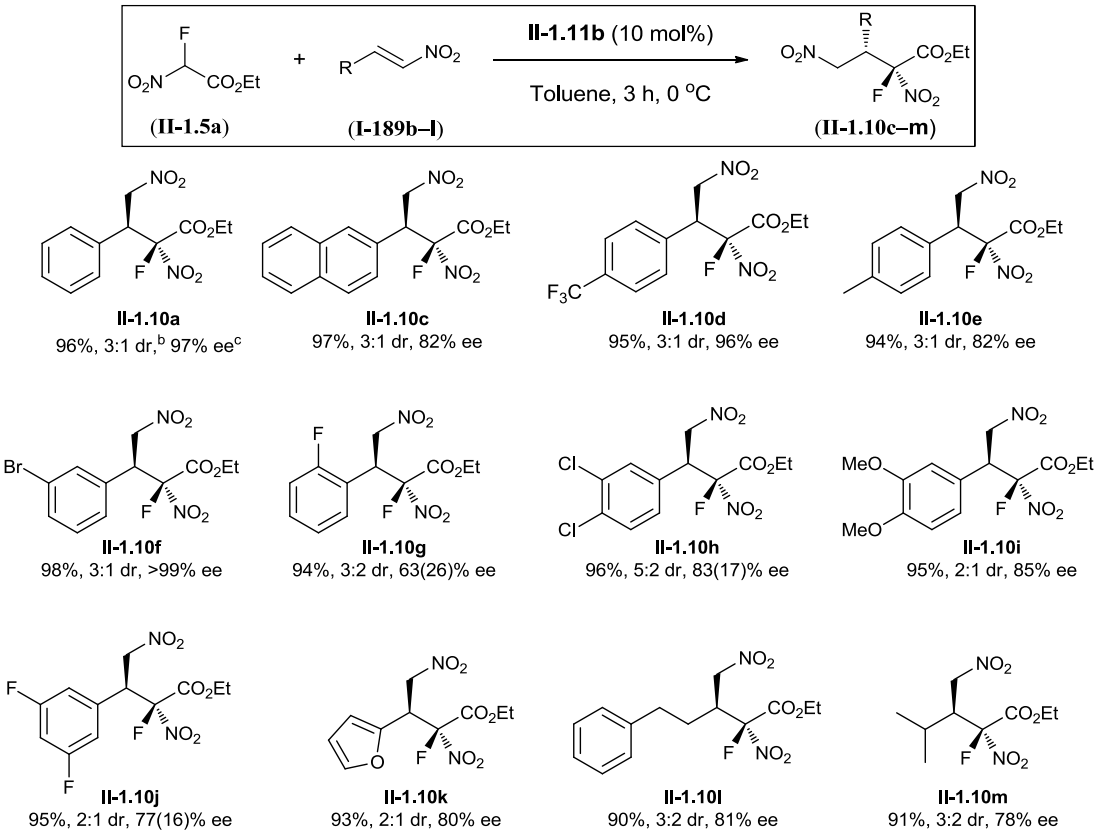
[112] The nitroacetic acid is unstable and undergoes decarboxylation, see: ref. 107a; our attempted transesterifications of commercially available ethyl ester with *t*-BuOH, BnOH, 2-naphtol and 9-phenanthrol led to partial convertions regardless of reactions conditions, with both esters very difficult to separate *via* chromatography on silica gel column. Transesterification with *i*-PrOH was successful and separation was easy.

the fluorinated carbon, while ee value corresponds to the centre of asymmetry originating from nitroalkene - see the next section). Furthermore, we have found that the reaction proceeded in the absence of catalyst as well, which implied that the optimum stereocontrol of the process depends on the ratio of catalyzed versus the unanalyzed reaction's rates, which could explain our findings on the preferred moderate temperature for high ee.

II-1.3. Scope of the reaction and determination of the absolute configuration

With optimum conditions in hand, reaction scope with regards to the nitroalkenes was investigated (Table 2). When 2-napthalene replaced phenyl ring in our model nitrostyrene, the enantioselectivity dropped to 82% but the excellent yield and dr of 3:1 was maintained (**II-1.10c**). Electron withdrawing substituent at *para*- orientation on aryl ring was found to be advantageous as the corresponding product **II-1.10d** was obtained in very high yield with 96% ee and 3:1 dr. On the other hand, installing a methyl group in *para* position resulted in a drop in enantioselectivity to 82% (**II-1.10e**). 3-bromonitrostyrene was found to be the best substrate, leading to the corresponding product **II-1.10f** in enantiopure form in excellent yield and dr maintained at 3:1. Substitution of the aryl ring in nitrostyrene with fluorine in *ortho* orientation resulted in a large drop in enantioselectivity to 63% for the major diastereomer **II-1.10g**, obtained in 2:1 dr ratio, with overall high yield of 94%. Bis-substitution of the aryl ring with either halogen (**II-1.10h**) or methoxy- group in 3,4- orientation (**II-1.10i**) was well tolerated and the corresponding products were obtained with very high yields and good enantioselectivities of 83% and 85% respectively. However, when two fluorine atoms were installed in both *meta* positions on the nitrostyrene aryl ring, the enantioselectivity was found to drop to 77% and dr to 2:1, while very high yield was maintained (**II-1.10j**). We next examined heterocyclic (**II-1.10k**) as well as two aliphatic nitroalkenes (one linear (**II-1.10l**) and one branched (**II-1.10m**)) and found the high yield maintained with enantioselectivity remaining at decent 80% – 81% level, albeit lower diastereoselectivity (2:1 – 3:2).

Table 2. Scope of the Michael addition of ethyl fluoronitroacetate to nitroalkenes **I-189b-l**.[a]



[a] Reaction conditions: **II-1.5a** (0.1 mmol), **II-1.11b** (0.01 mmol) in toluene (1ml) with nitroalkene **I-189b–l** (0.11 mmol) at 0 °C. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase.

The configuration of the major products was assessed as (*S*, *S*) by X-ray analysis of single crystal of **II-1.10a** (Figure 15).

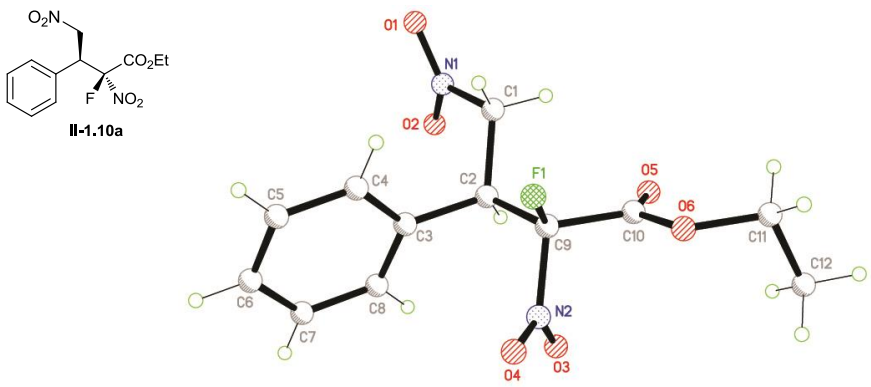
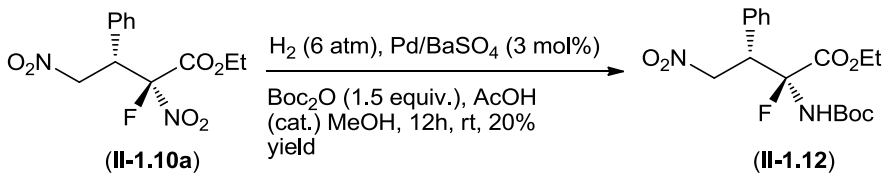


Figure 15. Single crystal X-ray structure of **II-1.10a**.

II-1.4. Synthesis of α-fluoro-α-amino acid

Aware of the reaction potential and limitations, we then investigated the synthetic utility of the products obtained. Our main goal was to reduce the nitro group on the α-carbon, with regards to ester moiety, to access the unprecedented α-fluoro-α-amino acid ester (**II-1.12**, Scheme 58). As expected, the reduction of the nitro group turned out to be difficult. Common methods, such as Fe/AcOH, Zn/AcOH/Ac_2O, nickel boride ($NiCl_2/NaBH_4$) and H_2/Pd(C) resulted in defluorination in addition to reducing both of the nitro groups. Zirconium boride ($ZrCl_4/NaBH_4$), which has been reported as effective in reducing aliphatic nitro compounds, [113] did not induce any reaction of our substrate **II-1.10a**.



Scheme 58. Reduction of nitro group leading to α-fluoro-α-amino acid ester.

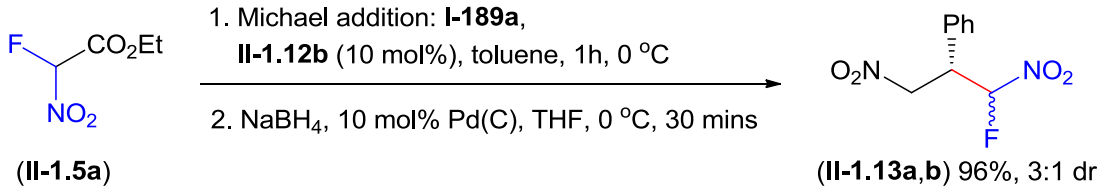
In our search for suitable conditions, we turned our attention to poisoned palladium catalysts for catalytic hydrogenation, varying the hydrogen pressure as well (autoclave was used). Lindlar's catalyst (Pd/$CaCO_3$, lead poisoned) was ineffective at 1 atm of hydrogen, while at 12 atm of hydrogen led to defluorination and reduction of the α-nitro moiety. Finally, it was found that employing 3 mol% of palladium on barium sulphate, the nitro group can be reduced, while retaining fluorine on the α-carbon and the desired α-fluoro-α-amino acid (**II-1.12**) was isolated in 20% yield together with 65% yield of defluorinated amino acid (identical yield of **II-1.12** was achieved in a reaction with 1 atm of hydrogen over 3 days). While we believe that the yield of the catalytic hydrogenation could be further improved by optimization of the conditions, our synthesis of compound **II-1.12** marks the first asymmetric synthesis of α-fluoro-α-amino acid ester in a simple two step procedure from accessible fluoronitroacetate. Importantly, the methodology is general as the alkyl/aryl substituent at β

[113] K. P. Chary, S. R. Ram, D. S. Iyengar, *Synlett*, 2000, **5**, 683.

position is easily tunable by employing different nitroalkenes in the Michael reaction, while additional function at γ position could be further derived into other functionalities leading to sought-after fluorinated diaminoacids and amino diacids.[101c] Such a general methodology was not reported before.

II-1.5. Denitration and decarboethoxylation of the Michael adduct

Next, we further explored synthetic applications of our products. Firstly, noticing the facile decarboethoxylation under reductive conditions, we investigated the issue finding out that sodium borohydride in THF at 0 °C can afford the transformation with ease, leading to 2:1 ratio of diastereomeric α-fluoro-α,γ-dinitro compounds **II-1.13a** and **II-1.13b** (Scheme 59), regardless whether pure diastereomers of **II-1.10a** or crude Michael reaction mixture was used.

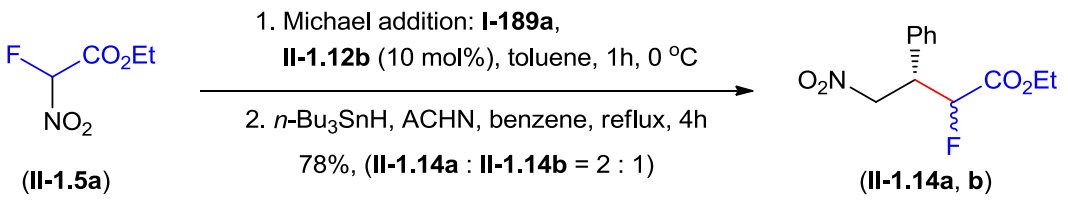


Scheme 59. Monofluoronitromethylation *via* Michael addition/decarboethoxylation.

DIBALH as well as *L*-selectride (both reactions at -35 °C) were found to lead to the mixture of diastereomeric compounds **II-1.13** in the same ratio. Surprisingly, the addition of 10 mol% of palladium on carbon to the reaction with $NaBH_4$ in THF at 0 °C, resulted in an increase in the diasteromeric ratio of decarboethoxylated products to 3:1. The α-fluorinated dinitro compounds **II-1.13** synthesized represents direct precursors of fluorinated 1,3 diamines.

Secondly, understanding the value of simple α-fluorinated esters, we quickly established a route towards this class of compounds by means of radical denitration (Scheme 60). Under the conditions employed, only the α-nitro group was removed, with the other one intact. Notably, the crude Michael reaction mixture (after filtering off the catalyst) could be used

directly for the generation of the desired fluorinated esters (**II-1.14a** and **II-1.14b**) with 2:1 diastereomeric ratio (diastereomers easily separable on silica gel column). Such esters were used as key-step intermediates in the synthesis of fluorinated analogues of Merck's HIV protease inhibitor Indinavir.[114]



Scheme 60. Denitration of Michael addition adduct leading to α-fluoroesters.

Interestingly, compounds **II-1.13** and **II-1.14** represent the products of respectively - monofluoronitromethylation and monofluorocarboethoxymethylation of Michael acceptors (nitroalkenes) respectively. Such simple two-step procedures to install functionalized C1 or C2 synthons could provide valuable contributions in the field of total synthesis of target molecules. The observed reactivity of the α-fluoro-α-nitroacetate, re-establishes this compound as an interesting alternative monofluoromethylation reagent, complementary to (fluoro-*bis*(phenyl)sulphonylmethane - FBSM), commonly used for the purpose.[115]

II-1.6. Summary and future perspective

In conclusion, fluoronitroacetate was successfully used as a donor in Michael addition to nitroalkenes yielding functionalized adducts with tunable aryl/alkyl substituents in good to excellent enantioselectivities (63% – >99% ee) in very high yields (90% – 98%) but low diastereoselectivities (3:2 – 3:1). Catalytic hydrogenation of the Michael adduct led to the

[114] A. G. Myers, J. K. Barbay, B. Zhong, *J. Am. Chem. Soc.*, 2001, **123**, 7207.

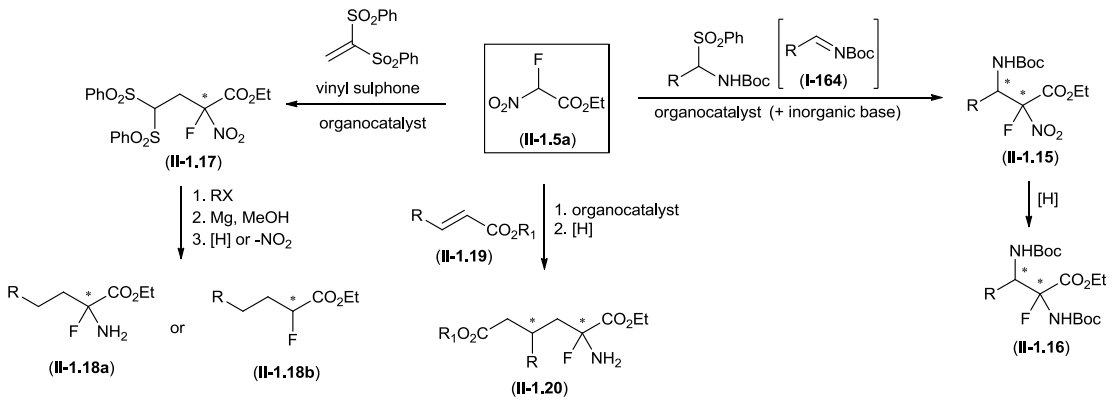
[115] a) For a review see: J. Hu, W. Zhang, F.Wang, *Chem. Commun.*, 2009, **0**, 7465; b) S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura, T. Toru, *J. Am. Chem. Soc.*, 2007, **129**, 6394; c) G. K. S. Prakash, S. Chacko, S. Alconcel, T. Stewart, T. Mathew, G. A. Olah, *Angew. Chem.*, 2007, **119**, 5021*; Angew. Chem. Int. Ed.*, 2007, **46,** 4933; d) H. W. Moon, D. Y. Kim, *Bull. Korean Chem. Soc.*, 2012, **33**, 2845; e) Y. Takeuchi, K. Nagata, T. Koizumi, *J. Org. Chem.*, 1989, **54**, 5453; f) M. Sekine, L. S. Peshakova, T. Hata, S. Yokoyama, T. Miyazawa, *J. Org. Chem.*, 1987, **52**, 5061.

first asymmetric synthesis of tunable α-fluoro-α-amino acid ester, while denitration afforded functionalized α-fluoroesters. Facile and diastereoselective decarboethoxylation led to fluorinated dinitro compounds being precursors of α-fluoro-α,γ-diamines. Thus ethyl fluoronitroacetate emerged as a convenient synthon for diverse range of fluorinated precursors of bioactive compounds and an alternative monofluoromethylation reagent.

Future perspective

The Michael addition of ethyl fluoronitroacetate and subsequent catalytic hydrogenation led to the first general synthesis of α-fluoro-α-amino acids esters; however the yields for the reduction of the nitro moiety are far from being practical. Therefore, the reaction should be optimized and the yield improved. Perhaps variation of solvents, hydrogen pressure and temperature, which has not been explored, could result in finding more suitable reaction conditions. Additionally, hydrogen sources other than hydrogen gas could also be screened (e.g. ammonium formate), as well as other metal based reductive conditions. The major difficulty to tackle is to reduce the α-nitro moiety without affecting the C-F bond.

Ethyl fluoronitroacetate has emerged as an interesting synthon towards α-fluoro(amino) acids, which could be applied in various stereo-controlled transformations, such as addition to N-Boc imines (ideally generated *in situ* from their stable sulphonates) leading to α-fluoro-β-amino acids (**II-1.15**, Scheme 61) or α-fluoro-α,β-diaminoesters (**II-1.16**) upon successful hydrogenation of the α-nitro group. Additions to vinyl sulphone, followed by diastereoselective alkylation could lead to a broad range of fluorinated amino acids (**II-1.18a**) including leucines after reduction of nitro group, or fluoroesters (**II-1.18b**) upon denitration. Sought-after bifunctional fluorinated amino acids,[101c] other than abovementioned diamino acids, could also be accessed *via* addition of fluoronitroacetate to acrylates yielding alkylated dicarboxylic acids (**II-1.20**). The reactions mentioned above remain unexplored to date.



Scheme 61. Utility of ethyl fluoronitroacetate in the synthesis of precursors of bioactive compounds.

Furthermore, as mentioned in the results section, the facile decarboethoxylation or denitration render further exploration of ethyl fluoronitroacetate as a monofluoromethylating reagent. Addition and the following decarboethoxylation or denitration would be equivalent to stereoselective introduction of either fluoroester or fluoronitromethyl synthon onto the acceptor molecule, in two steps.

II-2. Organocatalytic Michael addition of α-fluoro-α-nitro benzyls to nitroalkenes: facile preparation of fluorinated amines and pyrimidines

In line with our research interests toward the synthesis of general molecules with α-fluoro-α-amino core, attention was given to very simple and accessible substituted nitrobenzyls. These compounds upon fluorination become potential donors for various additions and subsequent reduction of their nitro group if successful, would render them synthons for the generation of the sought-after α-fluoro-α-amino core. In this chapter, development of α-fluoro-α-nitrobenzyls as Michael donors for the preparation of fluorinated nitrogen-containing linear and heterocyclic compounds is examined.

II-2.1. Introduction

One of the important class of synthons for the construction of biologically active molecules are fluorinated amines, which could be used in fluoro-peptidomimetics[116] or preparation of fluorinated nitrogen heterocycles[117] - especially fluorinated pyrimidines and uracils - a common motif in recently developed drugs (Figure 16),[118] as well as piperidines - named "building blocks for medicinal chemistry".[117l]

[116] M. Molteni, C. Pesenti, M. Sani, A. Volonterio, M. Zanda, *J. Fluor. Chem.*, 2004, **125**, 1735.

[117] a) for a review see: K. S. Jain, T. S. Chitre, P. B. Miniyar, M. K. Kathiravan, V. S. Bendre, V. S. Veer, S. R. Shahane, C. J. Shishoo, *Curr. Sci.*, 2006, **6**, 90; b) G. L. Grunewald, M. R. Seim, J. Lu, M. Makboul, K. R. Criscione, *J. Med. Chem.*, 2006, **49**, 2939; c) F. Reck, *et. al., J. Med. Chem.*, 2012, **59**, 6916; d) W. D. Shipe, *et. al., J. Med. Chem.*, 2008, **51**, 3692; e) J. M. Mason, A. S. Murkin, L. Li, V. L. Schramm, G. J. Gainsford, B. W. Skelton, *J. Med. Chem.*, 2008, **51**, 5880; f) Z.-Q. Yang, *et. al., J. Med. Chem.*, 2008, **51**, 6571; g) M. B. van Niel, *et. al., J. Med. Chem.*, 1999, **42**, 2087; h) A. D. Kerekes, *et. al., J. Med. Chem.*, 2011, **54**, 201; i) S. J. Shaw, D. A. Goff, L. A. Boralsky, M.K. Irving, R. Singh, *J. Org. Chem.*, 2013, **78**, 8892; j) E. Vardelle, A. Martin-Mingot, M.-P. Jouannetaud, C. Bachmann, J. Marrot, S. Thibaudeau, *J. Org. Chem.*, 2009, **74**, 6025; k) E. J. Hicken, *et. al., ACS Med. Chem. Lett.*, 2013, DOI: dx.doi.org/10.1021/ml4003953.

[118] J. Wang, M. Sanchez-Roselló, J. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.*, 2013, DOI**:** 10.1021/cr4002879.

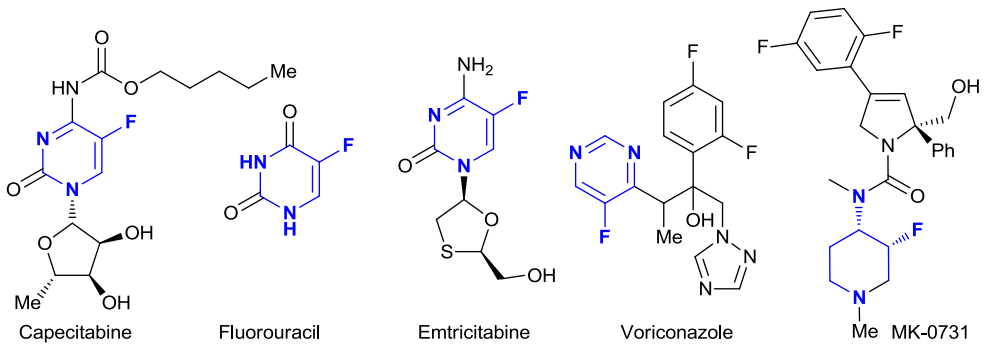


Figure 16. Selected drugs containing fluorinated amine or nitrogen-heterocycle scaffold.

Synthesis of fluorinated amines is accomplished *via* two step procedure involving reductive amination of carbonyl function,[119] olefin aminofluorination,[120] transformations of iminoesters and enamides,[121] N-tert-butylsulfinyl imines,[122] or fluorocyclizations (Figure 17).[123]

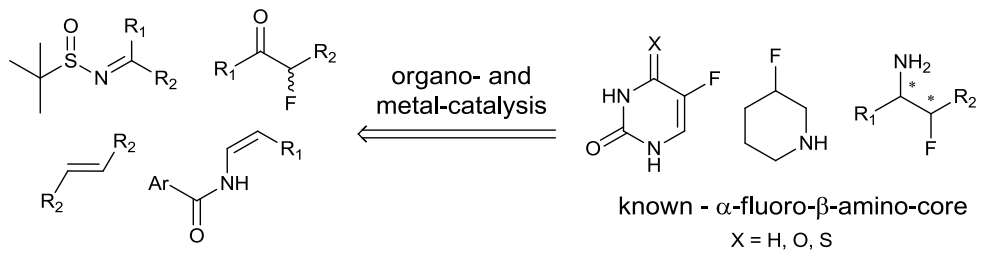


Figure 17. Key intermediates towards fluorinated nitrogen species.

One common feature of these methodologies is that they lead to β-fluoroamines. Fluorination is a known way to modulate pK_b of nitrogen-containing species, and it is somewhat surprising that to the best of our knowledge, the stereoselective construction of molecules containing α-fluoro-α-amino core (fluorine and amine installed on the same carbon) has not been reported even though the effect of fluorine on amino functionality would be the most profound in such

[119] a) M. L. Schulte, C. W. Lindsley, *Org. Lett.*, 2011, **13**, 5684; b) O. O. Fadeyi, C. W. Lindsley, *Org. Lett.*, 2009, **11**, 943.

[120] a) T. Wu, G. Yin, G. Liu, *J. Am. Chem. Soc.*, 2009, **131**, 16354; b) S. Qiu, T. Xu, J. Zhou, Y. Guo, G. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 2856; c) C. Appayee, S. E. Brenner-Moyer, *Org. Lett.*, 2010, **12**, 3356; d) W. Kong, P. Feige, T. de Haro, C. Nevado, *Angew. Chem. Int. Ed.*, 2013, **52**, 2469.

[121] a) for a review see: S. Fustero, J. F. Sanz-Cervera, J. L. Aceña, M. Sánchez-Roselló, *Synlett*, 2009, **4**, 525; b) T. Honjo, R. J. Phipps, V. Rauniyar, F. D. Toste, *Angew. Chem.*, 2012, **124**, 9822*; Angew. Chem. Int. Ed.*, 2012, **51**, 9684; c) R. J. Phipps, K. Hiramatsu, F. D. Toste, *J. Am. Chem. Soc.*, 2012, **134**, 8376.

[122] for a review see: J. Liu, J. Hu, *Future Med. Chem.*, 2009, **1**, 875.

[123] a) For a review see: S. C. Wilkinson, R. Salmon, V. Gouverneur, *Future Med. Chem.*, 2009, **1**, 847; b) O. Lozano, G. Blessley, T. M. del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem. Int. Ed.*, 2011, **50**, 8105.

compounds. The extremely rare examples of such F-C-NH core-containing molecules include racemic 1-fluoro-pentanamine (Figure 18), polycyclic trifluorinated compound (**II-2.6a**),[124] arylpiperidinylsulfonamide CCR3 antagonist (**II-2.6b**),[125] pyridopyrazine[126] and polyfluorinated amines.[127]

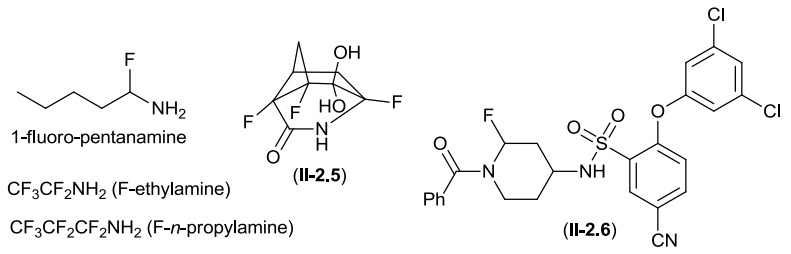


Figure 18. Known compounds with α-fluoro-α-amino core.

Reports on applications of α-fluoro-α-nitro-containing substrates are rare (all reported reactions are shown on Scheme 62).[128] α–Fluoro-α-nitrobenzyls (**II-2.1**) were used in two racemic reactions – addition to aldehydes leading to nitro-Henry product (**II-2.11**) and addition to acrylates leading to adducts **II-2.12**. Ethyl ester of fluoronitroacetic acid was used in Michael addition to enones yielding enantio-enriched products (**II-2.9**) and heterocycles (**II-2.10**) after denitration. Allyl ester of the same fluoronitroacetic acid was demonstrated to undergo palladium catalyzed rearrangement/decarboxylation leading to fluoronitroalkene **II-2.13**. Recently, fluoronitro(phenylsulphone)methane (FNSM) emerged as a reagent for the monofluoromethylation of α,β-unsaturated aldehydes or ketones, leading to products like **II-2.15**; however cleavage of the phenylsulfonyl moieties without breaking down the molecule has not been realized.

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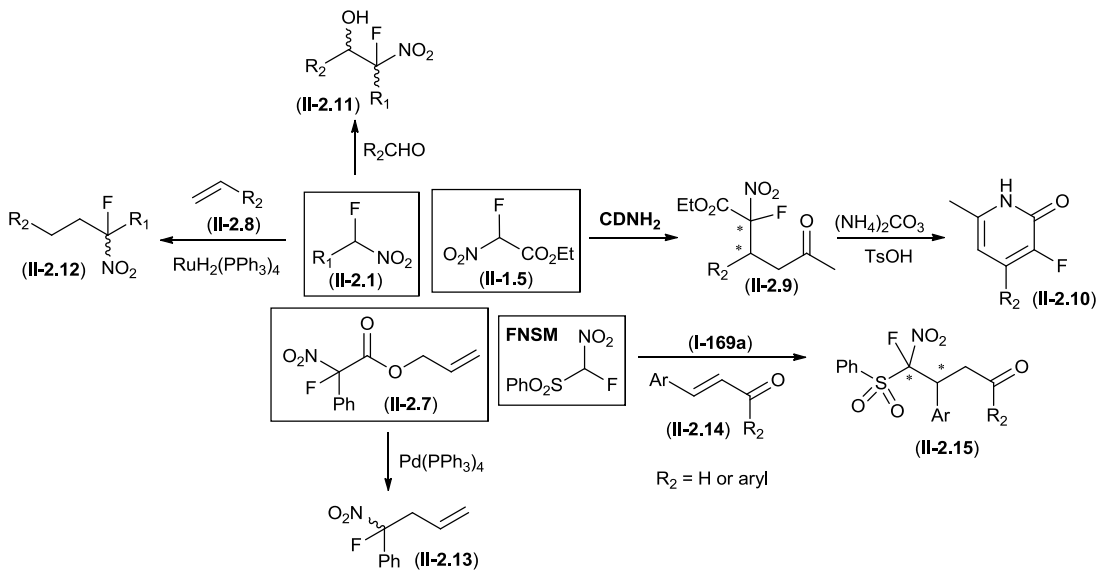
[124] G. M. Brooke, R. S. Matthews, N. S. Robson, *J. Chem. Soc. Perkin Trans I*, 1980, **0**, 102.
[125] *PCT Int. Appl*., 2011116161, 2011.
[126] M. Sako, *Science of Synthesis*, 2004, **16**, 1269.
[127] a) R. C. Kumar, J. M. Shreeve, *J. Am. Chem. Soc.*, 1980, **102**, 4958; b) V. A. Petrov, T. E. Mlsna, D. D. DesMarteau, *J. Fluor. Chem.*, 1994, **68**, 277.
[128] a) H. Hu, Y. Huang, Y. Guo, *J. Fluor. Chem.*, 2012, **133**,108; b) A. J. Grenning, J. A. Tunge, *Org. Lett.*, 2010, **12**, 740; c) Q. Wang, Q.-Y. Chen, X. Yang, Y. Guo, *Synthesis*, 2012, **44**, 3815; d) F. Huan H. Hu, Y. Huang, Q. Chen, Y. C. Guo, *Chin. J. Chem.*, 2012, **30**, 798; e) H.-F. Cui, P. Li, X.-W. Wang, Z. Chai, Y.-Q. Yang, Y.-P. Cai, S.-Z. Zhu, G. Zhao, *Tetrahedron*, 2011, **67**, 312; f) X.-W. Wang, H.-F. Cui, H.-F. Wang, Y.-Q. Yang, G. Zhao, S.-Z. Zhu, *Tetrahedron*, 2011, **67**, 2468. g) G. K. S. Prakash, F. Wang, T. Stewart, T. Mathew, G. A. Olah, *PNAS*, 2009, **106**, 4090; h) G. K. S. Prakash, L. Gurung, P. V. Jog, S. Tanaka, T. E. Thomas, N. Ganesh, R. Haiges, T. Mathew, G. A. Olah, *Chem. Eur. J.*, 2013, **19**, 3579; i) M. Kamlar, N. Bravo, A.-N. R. Alba, S. Hybelbauerová, I. Císarová, J. Veselý, A. Moyano, R. Rios, *Eur. J. Org. Chem.*, 2010, 5464.



Scheme 62. Reported reactions with α-fluoro-α-nitro-containing substrates.

We were intrigued by the elusive α-fluoro-α-amino- motif and envisioned that accessible pro-chiral α-fluoro-α-nitro-containing benzylic compounds (**II-2.1**, Figure 19) could be used in generating the F-C-NH core (**II-2.4**), as well as novel fluorinated six-member heterocyclic structures such as pyrimidines (**II-2.5a**).

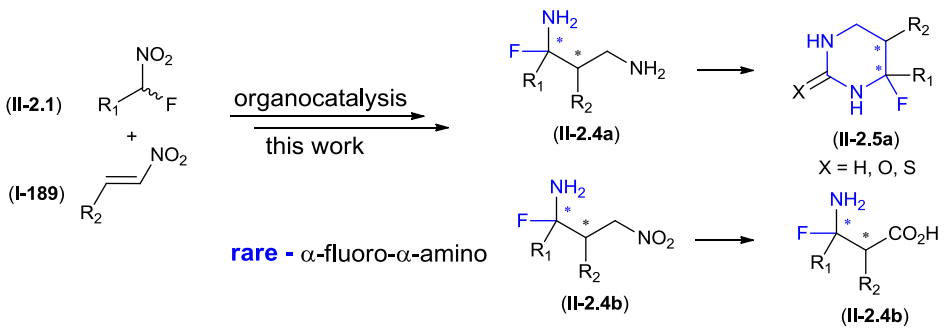


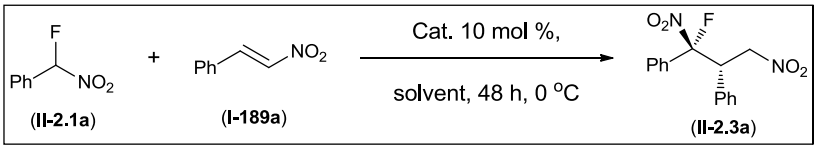
Figure 19. Hypothetical approach towards α-fluoro-α-amino-containing compounds.

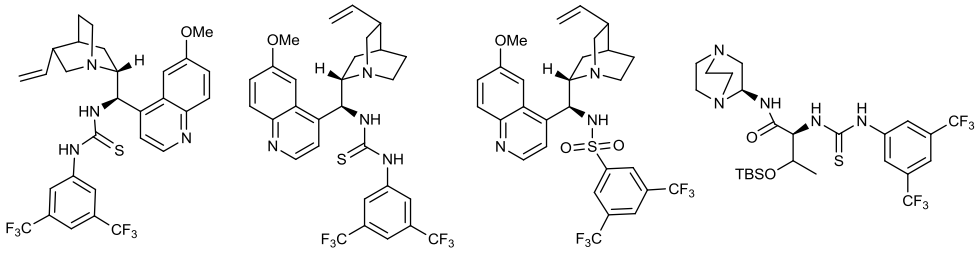
The nitroalkenes were the acceptors of choice as the nitro functionalities in both reactants could be subsequently reduced to amine and cyclized to pyrimidines. Alternatively, the nitromethyl- function originating from nitroolefin could be oxidized to yield β-fluoro-β-amino acids (**II-2.4b**).

II-2.2. Organocatalytic Michael addition of α-fluoro-α-nitro benzyls to nitroalkenes: reaction optimization

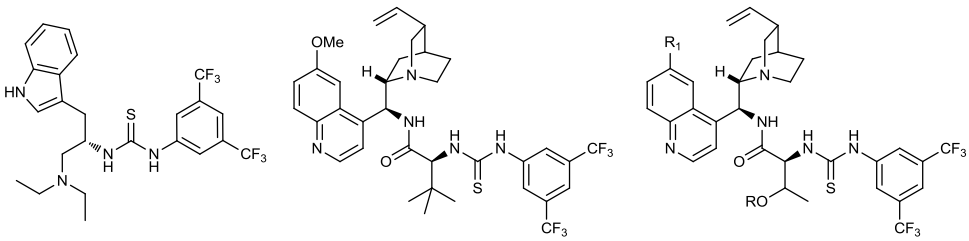
We began our investigation on a model Michael addition of α-fluoro-α-nitro benzyl to (*E*)-β-nitrostyrene catalyzed by *Cinchona* alkaloid-derived organocatalysts (Table 3). We found that both pseudo-enantiomers of simple *Quinidine* or *Quinine*-derived thioureas (**I-194b** and **I-194a** respectively) were effective in terms of yields but poorly stereoselective (entries 1–2). Replacing thiourea with sulphonamide in *Quinine*-derived catalyst (**II-2.16**) resulted in a slow reaction (entry 3), just as replacing *Cinchona* alkaloid core with DABCO did (entry 4). The tryptophan-derived organocatalyst (**Trp1**), highly enantioselective in Mannich addition of fluorinated ketoesters (chapter II-5), was not stereoselective here, although high yield of the desired product could be obtained (entry 5).

Table 3. Optimization of organocatalyzed Michael addition of fluoronitrobenzyl (**II-2.1a**) to (*E*)-β-nitrostyrene (**I-189a**).[a]





(**I-194b**) (**I-194a**) (**II-2.16**) (**II-2.17**)



(**Trp1**) (**II-1.11**)

(**II-2.18**) R_1= OMe, R_2 = TBDPS
(**II-1.12a**) R_1= H, R_2 = TBS
(**II-1.12b**) R_1= H, R_2 = TBDPS

Entry	Catalyst	Solvent	Yield (%)[b]	Ee (%)[c]	Dr[d]
1[e]	**I-194b**	Toluene	90	9	1:1
2[e]	**I-194a**	Toluene	91	19	1:1
3[e]	**II-2.16**	Toluene	<15	n.d.	n.d.
4[e]	**II-2.17**	Toluene	30	n.d.	n.d.
5[e]	**Trp1**	Toluene	88	18	1:1
6[e]	**II-1.11**	Toluene	92	86	3:1
7	**II-1.11**	Toluene	85	90	7:2
8	**II-2.18**	Toluene	66	86	3:1
9	**II-1.12a**	Toluene	87	86	5:1
10	**II-1.12b**	Toluene	85	90	5:1
11	**II-1.11**	CH_2Cl_2	51	88	2:1
12	**II-1.11**	Et_2O	20	87	2:1
13	**II-1.11**	THF	90	78	3:2
14	**II-1.11**	$CHCl_3$	62	86	5:2
15	**II-1.11**	Xylene	72	89	3:1
16[f]	**II-1.11**	Toluene	78	86	5:1
17[g]	**II-1.11**	Toluene	80	91	3:1
18[h]	**II-1.11**	Toluene	86	78	5:2
19	**II-1.12b**	Toluene	85	90	5:1

[a] Reaction conditions: **II-2.1a** (0.1 mmol), the catalyst (0.01 mmol) in the solvent (1ml) with nitrostyrene **I-189a** (0.11 mmol) at 0 ^{o}C unless noted otherwise. [b] Isolated yield.[c] Determined by HPLC analysis on a chiral stationary phase. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Reaction at rt, over 3 days. [f] Reaction in the presence of 3Å molecular sieves (10 mg). [g] Reaction in the presence of 4Å molecular sieves (10 mg); [h] Reaction in the presence of 5Å molecular sieves (10 mg).

We then surveyed our *Cinchona* alkaloid-derived catalysts incorporating amino acid in-between the *tert*-amine and thiourea moieties, and found to our satisfaction that dramatically improved enantioselectivities and high yield could be achieved with *Quinine-tert*-leucine incorporating catalyst **II-1.11** (entry 6). Lowering the reaction temperature to 0°C did not affect the yield but slightly improved the ee and dr values (entry 7), therefore all the

subsequent reactions were conducted at 0°C. Unexpectedly, by replacing *tert*-Leucine with TBDPS-protected *L*-Threonine (**II-2.18**), we noticed a large drop in yield and slight decrease in stereocontrol (entry 8). In the following attempt to improve dr values, two *Cinchonidine*-derived organocatalysts incorporating *L*-Threonine with (TBS, **II-1.12a**) or (TBDPS, **II-1.12b**) protecting groups were screened. To our satisfaction, we found the yields of the reaction improved, while catalyst **II-1.12b** (with TBDPS-protected *L*-Threonine) led to the desired product with the best stereocontrol (90% ee & 5:1 dr, entry 10). We then performed solvent and additive screening using catalyst **II-1.11**, and identified toluene, followed by xylene (entry 15) to be the best solvents. Other common solvents were generally well tolerated, except for diethyl ether (low yield, entry 12) and THF (lower ee, entry 13). We were intrigued by the noticeable (negative) influence of molecular sieves (3Å, 4Å, 5Å) on enantioselectivities (entries 16–18), which is difficult to rationalize. The optimum conditions were found to be: 10 mol% of catalyst **II-1.12b** in toluene, at 0 °C in the absence of any additives, leading to the desired product **II-2.3a** in high yield (85%), very good ee (90%) and decent diastereocontrol (5:1).

II-2.3. Preparation of substrates

The α-fluoro-α-nitro benzyls were prepared from the respective benzyl or alkyl bromides using sodium nitrite and urea in DMF at -20 °C over 2 - 5 hours, an adaptation of the previously reported procedure.[129] The key issue was controlling the reaction temperature and time, as prolonged reaction time or increase in reaction temperature resulted in the generation of side products of similar polarity to the desired nitro compound leading to difficulties in isolation. Over the course of substrate preparation, one incorrect literature report was identified, concerning facile preparation of nitro compounds from respective alcohols, which led to nitrites instead.[130] The fluorination was performed using Selectfluor® in

[129] *N. Kornblum , W. M. Weaver , J. Am. Chem. Soc.* 1958 , **80** , 4333.
[130] a) A. Baruah, B. Kalita, N. C. Barua, *Synlett*, 2000, 1064; b) the critique: M. Makosza, M. Barbasiewicz, K. Wojciechowski, *Synlett*, 2001, 1121.

acetonitrile/water (1/1) at rt over 12h with KOH as base, using the modified reported procedure.[131] A representative range of α-fluoro-α-nitro-containing substrates was prepared, some novel, in the two-step sequence (Figure 20). *Para*-halobenzyl bromides, 3,4-dichlorobenzylbromide, 9-(bromomethyl)-anthracene and phenanthrene all gave complex mixture of products in the nitration reaction and were not isolated. Alkyl nitro compounds were volatile (such as 2-methyl-1-fluoro-1-nitropropane and 3-methyl-1-fluoro-1-nitrobutane) and therefore difficult to isolate.

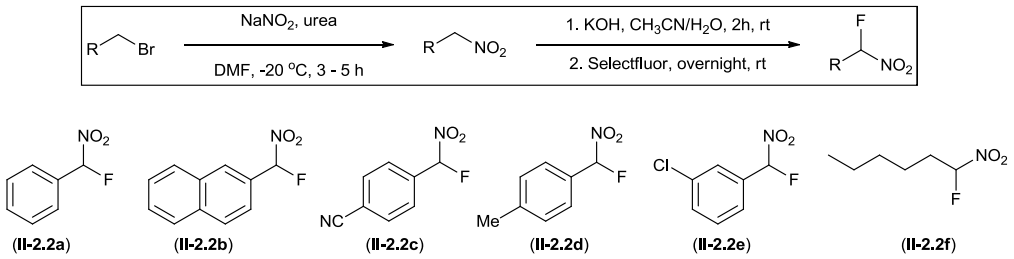


Figure 20. Substrates prepared for the Michael addition.

Nitroalkenes were prepared according to known procedures from the corresponding aldehydes and nitromethane.

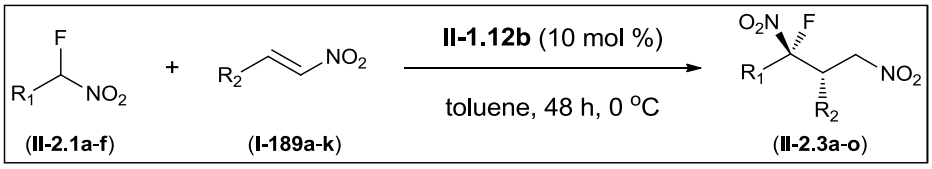
II-2.4 Scope of the reaction and absolute configuration

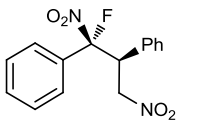
With optimum conditions in hand, we then investigated the reaction scope with regards to both substrates (Table 4). Electron withdrawing group on the phenyl ring in the fluoro-nitroaryl substrate was well tolerated and the corresponding product (**II-2.3b**) was obtained in quantitative yield with 6:1 dr and 88% ee. Furthermore, the reaction was faster and reached completion in 12h. High yields, diastereo- and enantio-selectivities were maintained when methyl substituent was installed in *para*- orientation or halogen in *meta*- position on aryl ring in fluorinated donor (**II-2.3c** and **II-2.3d**, respectively). The same trend was maintained with regards to substitution pattern on nitroalkene - halogen, electron donating or withdrawing substituents in *para*- or *meta*- positions on aryl ring in β-nitrostyrene were all well tolerated,

[131] W. Peng, J. M. Shreeve, *Tetrahedron Letters*, 2005, **46**, 4905.

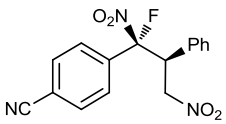
leading to products in very high yields (80% – 90%), good dr values (5:1 – 8:1) and high enantioselectivities (88% – 91%, **II-2.3e**–**h**). It was found that enantioselectivity is significantly lower (70% ee) when nitrostyrene with chlorine substituent in *ortho*- position was employed as an acceptor (**II-2.3i**). On the other hand, that negative effect can be nullified by the application of catalyst **II-1.12a** - with TBS protecting group on *L*-Threonine scaffold instead of TBDPS as in **II-1.12b**. Thus, the desired product of addition to *ortho*-fluoro-nitrostyrene (**II-2.3j**) was obtained with 85% ee, 5:1 dr and high yield. Bis-substitution with two fluorine atoms, both in *meta*- orientation on nitrostyrene, was especially favored, as the corresponding product (**II-2.3k**) was obtained with excellent 96% ee in quantitative yield and good 8:1 dr. Heterocyclic nitroalkene was found well tolerated in the reaction system, affording the desired product (**II-2.3l**) with high yield (91%), enantio- and diastereoselectivities (88% ee and 7:1 dr). Lastly, alkyl substituted nitroolefins, the more difficult substrates, required the use of more reactive *para*-cyano-substituted Michael donor to allow reaction completion. In fact, under these conditions, the corresponding products (**II-2.3m** and **II-2.3n**) were obtained within one day in very high yields (90% - 95%), decent dr (5:1 – 6:1) and 82% ee, while the use of 20 mol% of catalyst was found unnecessary. The aliphatic 1-fluoro-1-nitroalkanes were found unreactive and only trace amount of product (**II-2.3o**) was obtained regardless of increased catalyst loading or extended reaction time. The absolute configuration of the Michael addition products was assigned by X-ray analysis of single crystal of compound **II-2.3e** (Figure 21).

Table 4. Scope of organocatalyzed Michael addition of α-fluoro-α-nitro-benzyls to nitroalkenes.[a]

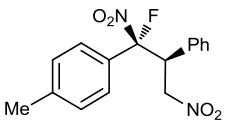




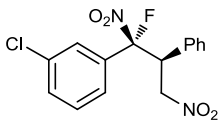
(**II-2.3a**)
85%,[b] 5:1 dr,[c] 90% ee[d]



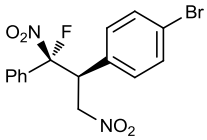
(**II-2.3b**)[e]
99%, 6:1 dr, 88% ee



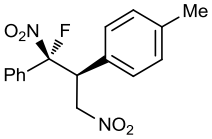
(**II-2.3c**)
90%, 7:1 dr, 91% ee



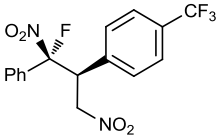
(**II-2.3d**)
96%, 7:1 dr, 87% ee



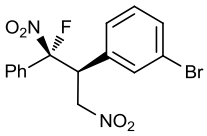
(**II-2.3e**)
85%, 7:1 dr, 90% ee



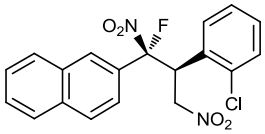
(**II-2.3f**)
80%, 8:1 dr, 88% ee



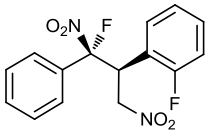
(**II-2.3g**)
90%, 5:1 dr, 91% ee



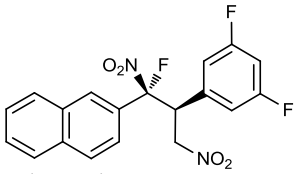
(**II-2.3h**)
80%, 8:1 dr, 90% ee



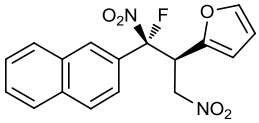
(**II-2.3i**)
90%, 9:1 dr, 70% ee



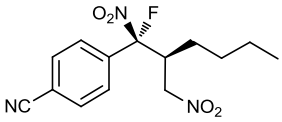
(**II-2.3j**)[f]
76%, 5:1 dr, 85% ee



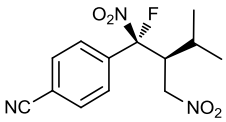
(**II-2.3k**)
98%, 8:1 dr, 96% ee



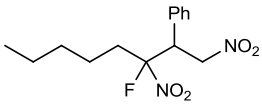
(**II-2.3l**)
91%, 7:1 dr, 88% ee



(**II-2.3m**)[g]
90%, 5:1 dr, 82% ee



(**II-2.3n**)[e]
95%, 6:1 dr, 82% ee



(**II-2.3o**)
Trace

[a] Reaction conditions: **Michael donor** (**II-2.1a-1f**, 0.1 mmol), the catalyst (0.01 mmol) in toluene (1ml) with nitroalkene (**I-189a-k**, 0.11 mmol) at 0 °C unless noted otherwise. [b] Isolated yield.[c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase; [e] reaction time: 12 h; [f] **II-2.12a** (10 mol%) was used as catalyst [g] 20 mol% of catalyst used; reaction time 14 h.

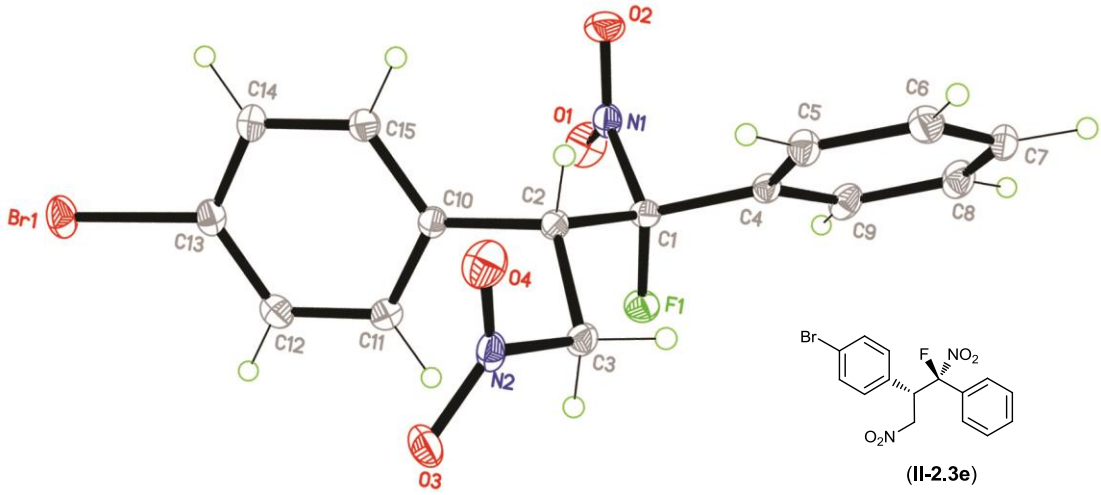
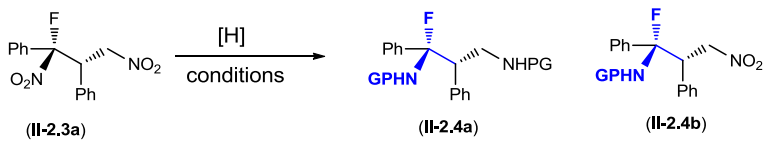


Figure 21. X-ray structure of single crystal of **II-2.3e**.

II-2.5. Reduction of the nitro groups and synthesis of tetrahydropyrimidine

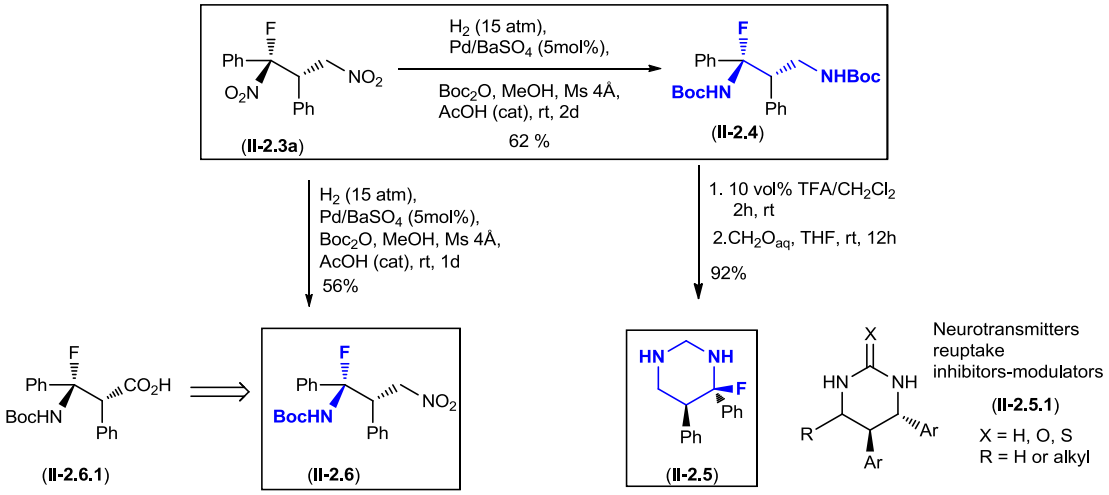
Having assessed the reaction scope, the synthetic utility of thus prepared Michael addition products was then investigated. Our main objective was to find an effective route to molecules with sought-after α-fluoro-α-amino core, by reducing the nitro groups of the Michael adducts (Scheme 63).



Scheme 63. Reduction of nitro group(s) leading to amines (**II-2.4**).

Reductions with the robust nickel boride ($Ni/NaBH_4$), as well as classical Fe/AcOH, led to de-fluorinated products, while zirconium boride ($ZrCl_4/NaBH_4$) was unreactive. Standard palladium on carbon (Pd/C) also led to defluorination of our substrate **II-2.3a** at 1 atm of hydrogen; however the reaction seemed cleaner as compared to reduction with metal borides. Therefore, attention was turned towards less reactive palladium sources and it was found that Lindlar's catalyst ($Pd/CaCO_3$, lead poisoned) could afford the desired reduction, however with low yield due to defluorination. On the contrary, C-F cleavage was mostly suppressed when palladium on barium sulphate was used as a catalyst, yet the yield remained unsatisfactory and only trace amount of desired product was detected under 1 atm of hydrogen. Eventually, by increasing the pressure of hydrogen to 15 atm, the desired fluorinated diamine (**II-2.4**, Scheme 64) could be isolated in 62% yield after 2 days. The novel, fluorinated tetrahydropyrrolidine (**II-2.5**) with fluorine and amino moieties installed on the same carbon, was then easily obtained in a high-yielding condensation with formaldehyde. It is reasonable to assume that, analogical condensation with acid chlorides or anhydrides could also be performed leading to deoxo-uracil-like heterocycles, while the two hydrocarbon substituents could be easily tuned by means of applying different Michael

donors/acceptors. We believe that such general methodology could be of interest with regards to preparation of fluorinated precursors of bioactive compounds. Notably the substitution pattern on the fluorinated pyrimidine (**II-2.5**) resembles closely to that of the non-fluorinated compounds of recent interest for their modulating-inhibiting properties of neurotransmitters reuptake (**II-2.5.1**).[132] Additionally, isolation of the functionalized mono-amine (**II-2.6**) was attempted and successful in a reasonable 56% yield after 12 hours of reduction. The nitromethylene group of the amine could possibly be oxidized under the Nef reaction protocol, leading to β-fluoro-β-amino acid; however this was not attempted due to time limitation (nevertheless, similar oxidation was performed on non-fluorinated substrate).[133]



Scheme 64. Preparation of fluorinated amines and tetrahydropyrimidine.

[132] a) R. W. Lewis, J. Mabry, J. G. Polisar, K. P. Eagen, B. Ganem, G. P. Hess, *Biochemistry*, 2010, **49**, 4841; b) *PCT Int. Appl*., WO 2009/089479 A2, 2009.

[133] a) F. A. Luzzio, D. Y. Duveau, W. D. Figg, *Heterocycles*, 2006, **70**, 321; b) for a recent review on Nef oxidation see R. Ballini, M. Petri, *Tetrahedron*, 2004, **60**, 1017.

II-2.6. Summary

In summary, Michael donors containing the α-fluoro-α-nitro- core, some prepared for the first time, were successfully applied in organocatalytic addition to nitroalkenes, generating a broad scope of enantioenriched fluorinated di-nitro products in high yields (76% - 99%) and under good stereo-control (82% – 91% ee with 5:1 – 8:1 dr). Synthetic application of this methodology was assessed by converting one of the Michael addition products to fluorinated amine, diamine and tetrahydropyrrolidine, all containing vastly unknown - α-fluoro-α-amino core. Such fluorinated heterocycles would potentially be useful in medicinal chemistry.

II-3. Enantioselective preparation of functionalized fluorinated phosphonates *via* Michael addition of α-fluoro-β-ketophosphonates to nitroalkenes.

Undoubtedly, phosphate is one of the most important functional groups in bio-sciences and therefore synthesis of its analogues and isosteres is of great importance. Knowing fluorinated phosphonates for being excellent phosphate mimics we decided to design enantioselective route towards this class of compounds. This chapter describes our research efforts in the development of asymmetric Michael addition of prochiral α-fluoro-β-ketophosphonates to nitroalkenes with subsequent application in preparation of pyrrolidines.

II-3.1. Introduction

Phosphates are fundamental functional groups present in bioactive molecules[134] and as such they seem to be an excellent unit to incorporate into the design of pharmaceutical agents. However, due to numerous roles they have played in biological systems, phosphates are susceptible to hydrolytic cleavage by a large number of enzymes, which hampers their applications in medicinal chemistry. On the other hand, phosphonates were found to be good mimics of phosphates, while being much more stable in biological systems.[135] Consequently, phosphonate substructures are incorporated in numerous important pharmaceuticals and antibodies.[136] Fluorinated phosphonates (**II-IV**, Scheme 1) were found to match even more

[134] a) F. H. Westheimer, *Science*, 1987, **235**, 1173; (b) M. W. Bowler, M. J. Cliff, J. P. Walthob, G. M. Blackburn, *New J. Chem.*, 2010, **34**, 784.

[135] For a review see: a) R. Engel, *Chem. Rev.*, 1977, **77**, 349; b) D. F. Wiemer, *Tetrahedron*, 1997, **53**, 16609; c) C. S. Demmer, N. Krogsgaard-Larsen, L. Bunch, *Chem. Rev.*, 2011, **111**, 7981; d) For example of application of phosphonates as phosphate surrogates see: F. W. Foss Jr, A. H. Snyder, M. D. Davis, M. Rouse, M. D. Okusa, K. R. Lynch, T. L. Macdonald, *Bioorg. Med. Chem.*, 2007, **15**, 663.

[136] a) For a review on antibodies see: R. A. Lerner, S. J. Benkovic, P. G Schultz, *Science*, 1991, **252**, 659; b) D. V. Patel, K. Rielly-Gauvin, D. E. Ryono, *Tetrahedron Lett.*, 1990, **31**, 5587; c) D. V. Patel, K. Rielly-Gauvin, D. E. Ryono, *Tetrahedron Lett.*, 1990, **31**, 5591; d) D. L. Pompliano, E. Rands, M. D. Schaber, S. D. Mosser, N. J. Anthony, J. B. Gibbs, *Biochemistry*, 1992, **31**, 3800; e) B. Stowasser, K. H. Budt, J. Q. Li, A. Peyman, D. Ruppert, *Tetrahedron Lett.*, 1992, **33**, 6625; f) M. N. Greco, B. F. Maryanoff et al, *J. Am. Chem. Soc.*, 2002, **124**, 3810; g) C. T. Behrendt, T. Kurz et al, *J. Med. Chem.*, 2011, **54**, 6796.

closely the electronic and steric characteristics of phosphates.[137] Therefore, such fluorinated structures were recently recognized as excellent replacements for phosphates in bioactive compounds, offering similar selectivities, increased potency and greatly enhanced resistance to hydrolases.[138] Interest in fluorinated phosphonates as analogs of phosphates can be illustrated by the development of fluoro-phosphonate analogs (**VI**–**VII**) of LPA (**V**, Lysophosphatic Acid) – an important mitogenic signaling molecule in ovarian cancer and in normal cell proliferations and migration.[139] Undoubtedly, asymmetric synthesis of fluorinated phosphonates would be highly desirable.

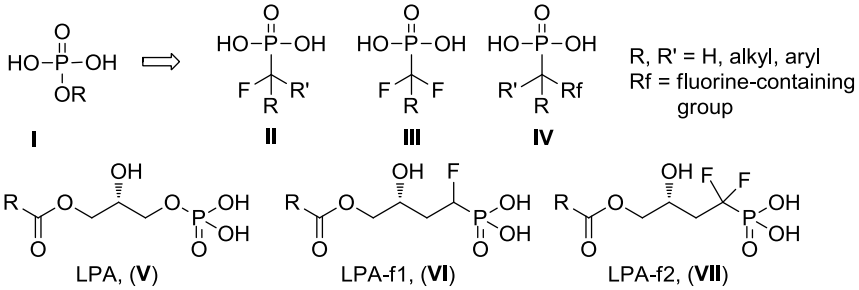


Figure 22. Phosphonate analogs of phosphates

Surprisingly, stereoselective, organocatalytic synthesis of fluorinated phosphonates has not been achieved before. We envisioned that employment of racemic α-fluoro-β-ketophosphonates[140] in the conjugate addition with nitroalkenes could yield structurally

---

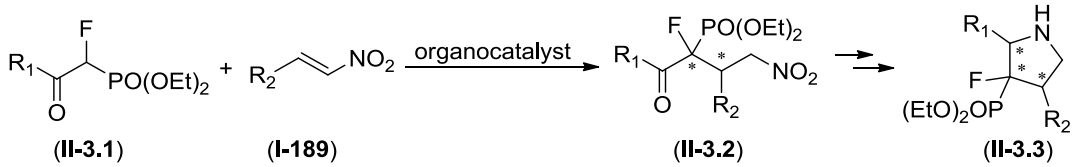
[137] a) D. B. Berkowitz, M. Bose, *J. Fluor. Chem.*, 2001, **112**, 12; b) J. Nieschalk, D. O'Hagan, *J. Chem. Soc. Chem. Commun.*, 1995, 719; c) G. M. Blackburn, D. E. Kent, *J. Chem. Soc., Chem. Commun*., 1981, ***0***, 511; d) G. M. Blackburn, D. E. Kent, *J. Chem. Soc., Perkin Trans. 1*, 1986, ***0***, 913-917; e) G. M. Blackburn, M. J. Parratt, *J. Chem. Soc., Perkin Trans. 1*, 1986, **0**, 1425; f) J. Nieschalk, A. S. Batsanov, D. O'Hagan, J. A. K. Howard, *Tetrahedron*, 1996, **52,** 165.

[138] a) For a review see: V. D. Romanenko, V. P. Kuchar, *Chem. Rev.*, 2006, **106**, 3868; b) S. F. Wnuk, M. J. Robins, *J. Am. Chem. Soc.*, 1996, **118**, 2519; c) For an example where stability was enhanced see: Y. Xu, L. Qian, G. D. Prestwich, *J. Org. Chem.*, 2003, **68**, 5320; for selected applications of fluorinated phosphonates as bio-active compounds, see: d) J. E. Starrett Jr, D. R. Tortolani, M. J. M. Hitchcock, J. C. Martin, M. M. Mansuri, *Antiviral Res.*, 1992, **19**, 267; e) Y. Xu, L. Qian, G. D. Prestwich, *J. Org. Chem.*, 2003, **68**, 5320; f) E. Pfund, T. Lequeux, S. Masson, M. Vazeux, A. Cordi, A. Pierre, V. Serre, G. Herve, *Bioorg. Med. Chem.*, 2005, **13**, 4921; g) R. J. Cox, J. S. Gibson, A. T. Hadfield, *Chem. Bio. Chem.*, 2005, **6,** 2255; h) T. Verbrugghen, P. Cos, L. Maes, S. Van Calenbergh, *J. Med. Chem.*, 2010, **53**, 5342.

[139] a) T. Hla, *et al.*, *Science*, 2001**, 294**, 1875; b) W. H. Moolenaar, *Exp. Cell. Res.*, 1999, **253**, 230; E. J. Goetzl, *et al.*, *Cancer Res.* 1999, **59**, 5370;

[140] For preparation of α-fluoro-β-ketophosphonates, see: a) P. Coutrot, C. Grison, *Tetrahedron Lett.*, 1988, **29**, 2655-2658; b) D. Y. Kim, Y. J. Choi, *Synth. Commun.*, 1998, **28**, 1491-1498; c) R. D. Chambers, J. Hutchinson, *J. Fluorine Chem.*, 1998, **92**, 45-52; d) recently improved preparation of a

challenging α-fluoro-phosphonates containing adjacent quaternary and tertiary stereogenic centers (Scheme 2). Moreover, the rich functionality contained in the targets offers great latitudes for further structural elaborations.



Scheme 65. Michael addition of α-fluoro-β-ketophosphonates to nitroolefins.

II-3.2. Michael addition of α-fluoro-β-ketophosphonates to nitroalkenes: reaction optimization

Our study was initiated by assessing the catalytic activities of *Cinchona* alkaloid-derived bifunctional thioureas in the Michael addition of α-fluoro-β-ketophosphonates to nitroolefins (Table 5). *Cinchona* alkaloid-derived thiourea catalysts (**I-194a-d**) were found to be effective, and the Michael adducts were obtained with high ee values. However, the diastereoselectivities were low (entries 1-4), and such low diastereoselectivity has been common in the literature reports.[141] We then decided to apply amino acid-incorporating multifunctional thiourea catalysts developed in our laboratory.[142] By combining Q*uinidine* with either valine (**II-3.4-5**), *iso*- or *tert*-leucine (**II-3.6-7**), the diastereoselectivity could be improved to 6:1 (entries 5-8). Further fine-tuning was done by employing pseudo-enantiomeric Q*uinine* or *Cinchonidine* with chiral amino acids. Tertiary amine-thiourea catalyst **II-1.11** with incorporated *L-tert*-leucine moiety was found to be the best, affording the desired Michael product with a 16:1 diastereomeric ratio and a 99% ee value (entry 10). Notably, this catalytic system is highly tunable; the different configurations of the *Cinchona*

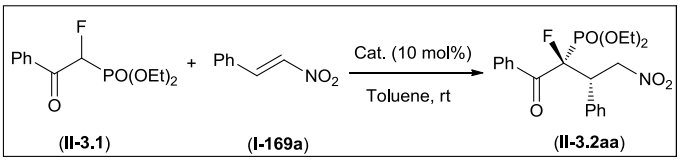
narrow scope of racemic compounds was reported: K. Radwan-Olszewska, F. Palacios, P. Kafarski, *J. Org. Chem*., 2011, **76**, 1170-1173.

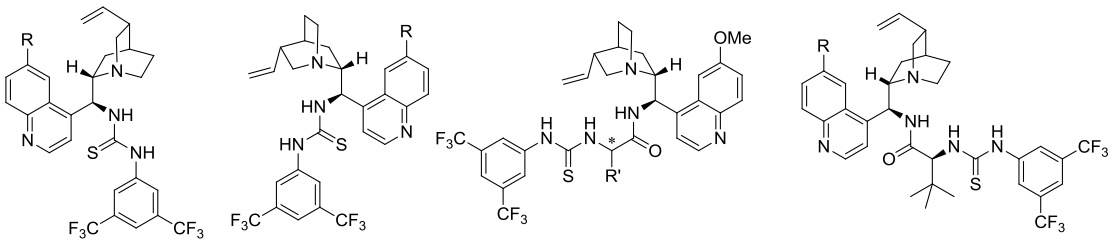
[141] See for example: K. Hu, T. Liu, A. D. Lu, Y. Liu, Y. Wang, G. Wu, Z. Zhou, C. Tang, *Eur. J. Org. Chem.*, 2011, 3507.

[142] Q. Zhu, Y. Lu, *Angew. Chem. Int. Ed.*, 2010, **49**, 7753.

alkaloid structures and the chiral amino acid building blocks make the catalysts versatile with little synthetic efforts.

Table 5. Michael addition of Fluorinated Phosphonate to Nitrostyrene: Catalyst Screening[a]





I-194c: R = H
I-194b: R = OMe

I-194d: R = H
I-194a: R = OMe

II-3.4: R' = i-Pr (S); **II-3.5**: R' = i-Pr (R);
II-3.6: R' = i-Bu (S); **II-3.7**: R' = t-Bu (S)

II-3.8: R = H; **II-1.11**: R = OMe

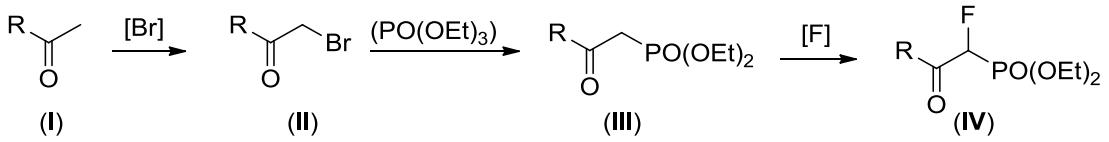
Entry	Cat.	Time (days)	Yield (%)[b]	Dr[c]	Ee (%)[d]
1	**I-194c**	3	90	1.4:1	86
2	**I-194b**	3	80	1.5:1	97
3	**I-194d**	3	81	1.5:1	-84
4	**I-194a**	2	65	1.5:1	-89
5	**II-3.4**	4	45	3:1	53
6	**II-3.5**	4	80	3.3:1	-94
7	**II-3.6**	4	38	3:1	43
8	**II-3.7**	4	45	6:1	99
9	**II-3.8**	4	92	17:1	98
10	**II-1.11**	4	93	16:1	>99

[a] Reaction conditions: **II-3.1** (0.05 mmol), **I-189a** (0.06 mmol), and the catalyst (0.005 mmol) in toluene (0.5 mL) at room temperature; [b] Isolated yield; [c] Determined by ^{1}H NMR analysis of the crude mixture; [d] Determined by HPLC analysis on chiral stationary phase.

Having achieved satisfying level of stereo-control, solvent screening was not performed; in our experience, toluene is usually the optimum solvent for Michael additions catalyzed by the above organocatalysts.

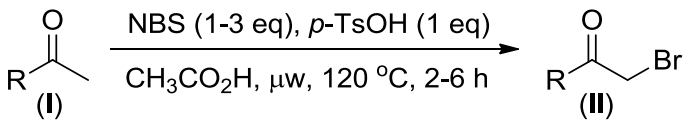
II-3.3. Preparation of substrates

The α-fluoro-β-ketophosphonates can be prepared from easily available methyl ketones and triethylphosphite in a 3-step sequence: bromination, Arbuzov C-P formation and fluorination (Scheme 66).



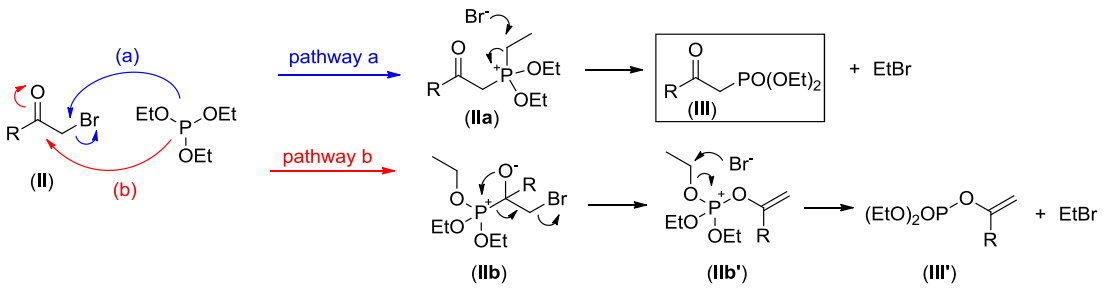
Scheme 66. Preparation of fluorinated phosphonates.

The first step - bromination - was performed using relatively safe, easy to handle and readily available N-bromosuccinimide as the bromine source, *p*-toluenesulphonic acid as promoter and acetic acid as solvent. The ketones, being generally unreactive required the use of microwave irradiation to undergo the bromination.



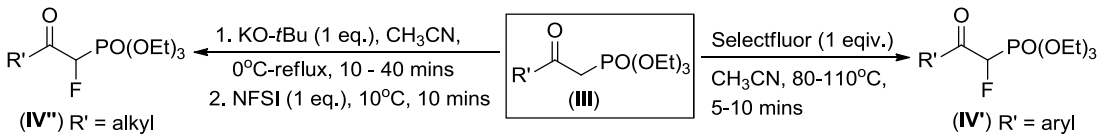
Scheme 67. Bromination of ketones.

Under these conditions, the mono-brominated products could be obtained in high yields within 2 - 6 h. Bis-bromination hardly occurred and could be suppressed by lowering the reaction temperature or shortening the reaction time. The crude intermediates were used without further purification in the next step. Carbon-phosphorus bond formation was achieved *via* Arbuzov reaction (pathway a, Scheme 68). The first step of this transformation is a nucleophilic attack of phosphorus on the halogenated carbon to form cationic intermediate (**IIa**). Following dealkylation induced by the bromide, the formation of the desired phosphonate (**III**) and volatile ethyl bromide resulted.



Scheme 68. Mechanisms of the Arbuzov and Perkov reactions.

However, the presence of the keto group in the substrate would cause a side reaction to occur - Perkov reaction. In the first step, the phosphorus would not attack the halogenated carbon, but the similarly electrophilic carbonyl moiety leading to intermediate **IIb** (pathway b). Subsequent attack of oxygen anion on the electrophilic phosphorus would result in C-P bond cleavage and formation of intermediate **IIb'**. Lastly, bromide-induced dealkylation would yield the undesired vinyl phosphate (**III'**). Indeed, during the preparation of the β-ketophosphonates, the Perkov reaction occurred in all cases, lowering the yields of the desired phosphonate severely (20% - 72%) in some cases. The only strategy to counter the formation of side product was to increase the reaction temperature, as the Arbuzov reaction becomes more favorable in higher temperatures. Fortunately, the two products were easily separable by flash chromatography. The last step of the substrate synthesis was fluorination (Scheme 69).



Scheme 69. Fluorination of β-ketophosphonates.

In many cases, the fluorination was challenging, due to partial conversion of substrate to product and separation difficulties, as well as a facile bis-fluorination. The aromatic β-ketophosphonates could be fluorinated in mild, neutral conditions, using Selectfluor® as the fluorine source and acetonitrile as solvent. The time and temperature were optimized, and 5 – 10 min. of microwave irradiation at 80 – 110 °C was found optimal. Longer reaction times or higher temperatures led to bis-fluorination and product decomposition. The desired aromatic

mono-fluorinated phosphonates (**II-3.1a-I**, Figure 23) could be obtained in moderate yields (34% – 68%). The less reactive alkyl β-ketophosphonates required the use of a strong base, and potassium *tert*-butoxide was found to be optimal (others, such as metal hydrides or strong organic bases, led to bisfluorination or product decomposition). The desired α-fluoro-β-ketophosphonates with alkyl chain could be prepared in moderate yields (32% - 58%, **II-3.1j-k**).

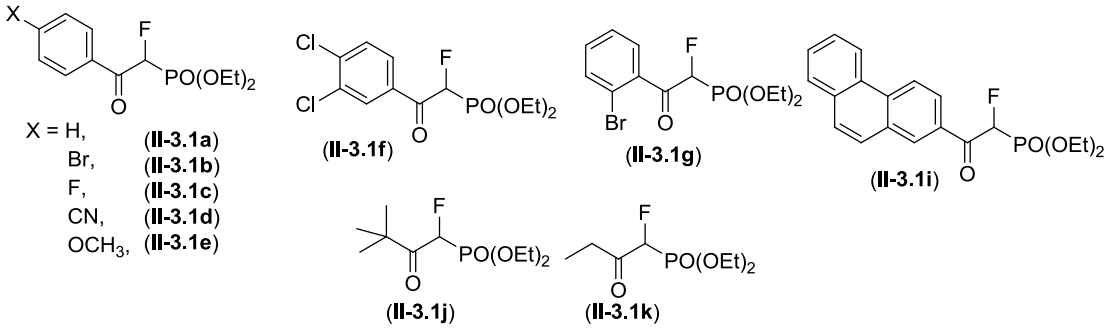


Figure 23. α-Fluoro-β-ketophosphonate donors for Michael addition.

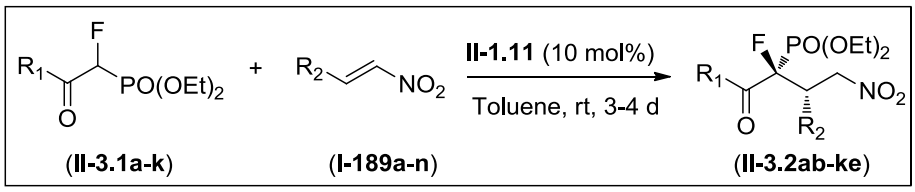
Upon completion of the project, an alternative method for fluorination of some of the phosphonates was published, based on the use of Selectfluor® in aqueous media, which could aid considerably the preparation of the substrates.[143]

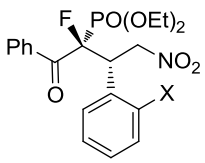
[143] K. Radwan-Olszewska, F. Palacios, P. Kafarski, *J. Org. Chem*., 2011, **76**, 1170.

II-3.4. Reaction scope and determination of the absolute configuration

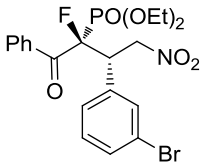
With the optimized reaction conditions in hand, the reaction scope was then investigated (Figure 24). The reaction was found to be broadly applicable to a range of nitroolefins and various fluorinated phosphonate pronucleophiles. Different nitrolefins were suitable substrates, high diastereoselectivities and nearly perfect enantioselectivities were attainable, regardless of the substitution patterns and electronic nature of the aryl moieties (**II-3.2ab** – **II-3.2ag**). Aryl nitroolefins containing a naphthyl, furyl or thionyl moieties were also well tolerated (**II-3.2ah**, **II-3.2ai** and **II-3.2aj** respectively). The reaction scope with regard to the structures of fluorinated ketophosphonates was also examined. Different β-aryl-β-ketophosphonates with different electronic nature and substitution patterns on the aromatic ring could be employed, and the products were obtained in excellent yields (84% – 96%), with high dr (6:1 – >20:1) and very high ee values (98% - 99% ee, **II-3.2ba - II-3.2ge**). Moreover, bis-substituted aryls in fluorinated phosphonates or nitroolefins were all well-tolerated in the reaction (**II-3.2hl** and **II-3.2im**, respectively). Aliphatic nitroolefins could also be used, however, 20 mol% of catalyst was required, and the adducts were obtained in moderate yield (40% – 88%) and dr (3:1 – 5:1), and excellent enantioselectivities (96% – 98% ee, **II-3.2ak** and **II-3.2in**). Similarly, the aliphatic α-fluoro-β-ketophosphonates were found to be less reactive than their aromatic counterparts, yet with the catalyst loading increased to 20 mol%, the reaction proceeded with acceptable yields (55% – 68%) and diastereoselectivities (7:2 – 3:1) and excellent enantiomeric excesses (96% – 99%, **II-3.2je** and **II-3.2ke**).

Figure 24. The substrate scope of Michael addition of α-fluoro-β-ketophosphonates to nitroalkenes[a]

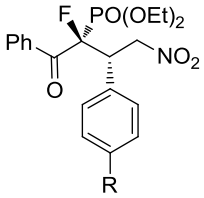




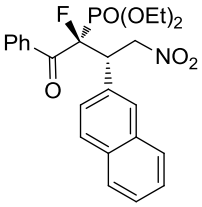
(**II-3.2ab**) X = Br, (4 d)
62%,[b] 17:1 dr,[c] 97% ee[d]
(**II-3.2ac**) X = F, (4 d)
84%, 13:1 dr, 98% ee
(**II-3.2ad**) X = CF_3, (4 d)
63%, >20:1 dr, 96% ee



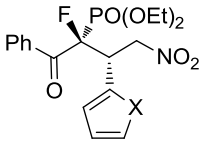
(**II-3.2ae**) (2 d)
88%, 11:1 dr, 99% ee



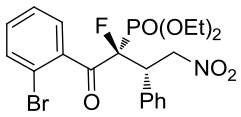
(**II-3.2af**) R = Br, (3 d)
99%, 10:1 dr, 99% ee
(**II-3.2ag**) R = CH_3, (4 d)
78%, >20:1 dr, 99% ee



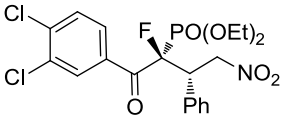
(**II-3.2ah**) (4d)
86%, >20:1, 98% ee



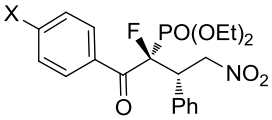
(**II-3.2ai**) X = O, (3 d)
81%, 9:1 dr, 99% ee
(**II-3.2aj**) X = S, (3 d)
92%, 10:1 dr, 99% ee



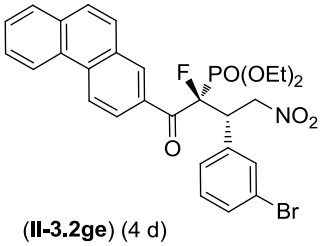
(**II-3.2ba**) (4 d)
84%, 12:1 dr, 99% ee



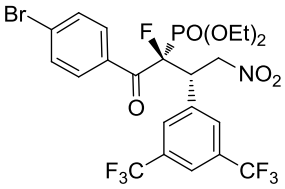
(**II-3.2ca**) (8 h)
88%, 12:1 dr, 99% ee



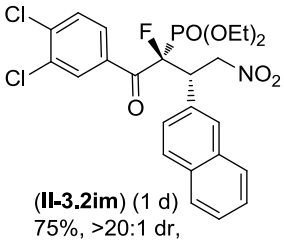
(**II-3.2da**) X = F, (4 d)[f]
92%, 13:1 dr, 99% ee
(**II-3.2ea**) X = CN, (4 d)
90%, 6:1 dr, 99% ee
(**II-3.2fa**) X = OCH_3, (4 d)
90%, 10:1 dr, 98% ee



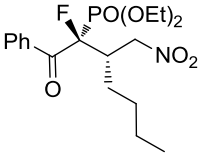
(**II-3.2ge**) (4 d)
96%, >20:1 dr, 99% ee



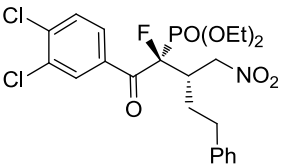
(**II-3.2hl**) (4 d)
80%, >20:1 dr, 99% ee



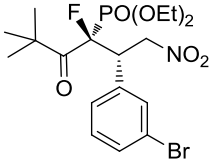
(**II-3.2im**) (1 d)
75%, >20:1 dr,
99% ee



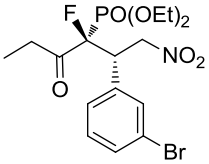
(**II-3.2ak**) (4 d)[e]
40%, 3:1 dr, 96(79)% ee



(**II-3.2in**) (4 d)[e]
88%, 5:1 dr, 98% ee



(**II-3.2je**) (4 d)[e]
55%, 7:2 dr, 99% ee

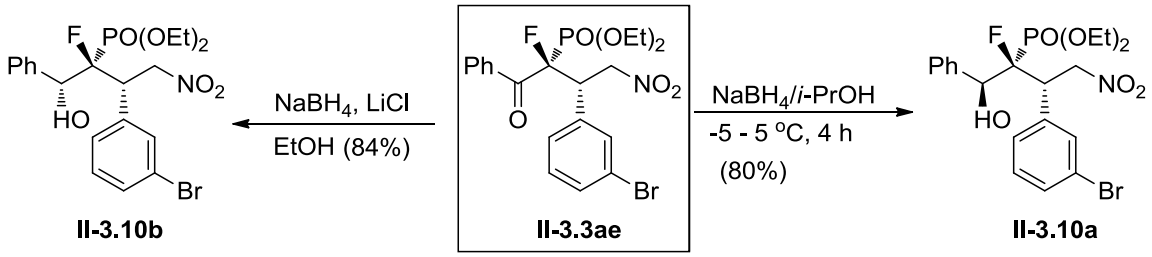


(**II-3.2ke**) (4 d)[e]
68%, 3:1 dr, 96(84)% ee

[a] Reaction conditions: phosphonate **II-3.1a-k** (0.05 mmol), nitroalkene **I-189a-n** (0.06 mmol), **II-1.11** (0.005 mmol) in toluene (0.5 mL) at room temperature; [b] Isolated yield; [c] Determined by ^{1}H NMR analysis of crude product; [d] Determined by HPLC analysis on chiral stationary phase, value in bracket corresponds to the minor diastereomer; [e] 20 mol% of **6b** was used; [f] 10 mol% of **II-3.8** used. When **II-1.11** was used corresponding product was obtained in 95% yield over 3 days with dr of 7:1 and 97% ee.

Although some of the products were solids, attempts to obtain single crystal suitable for X-ray analysis failed. Therefore, the carbonyl group in the Michael adduct **II-3.2ae** was reduced to yield products in solid form (Scheme 70). High diastereoselectivity of the reduction was observed, presumably due to the presence of two asymmetric centers, and the products were

obtained as single diastereomers. Moreover, under different conditions, two different diastereomers of α-fluoro-β-hydroxy-γ-nitro phosphonates were obtained (**II-3.10a** & **II-3.10b**). Presumably, the lithium ion chelates to the keto carbonyl group as well as phosphonate, forming a cyclic complex, which results in the hydroxyl and phosphonate groups positioned on the same side of the carbon chain in the product **II-3.10b**, as opposed to reduction in absence of lithium (**II-3.10a**).



Scheme 70. Reduction of carbonyl leading to diastereomeric β-hydroxy-derivatives.

The single crystal of **II-3.10a** was obtained successfully and its X-ray structure (Figure 25) allowed for the assignment of the absolute configurations of the Michael addition products.

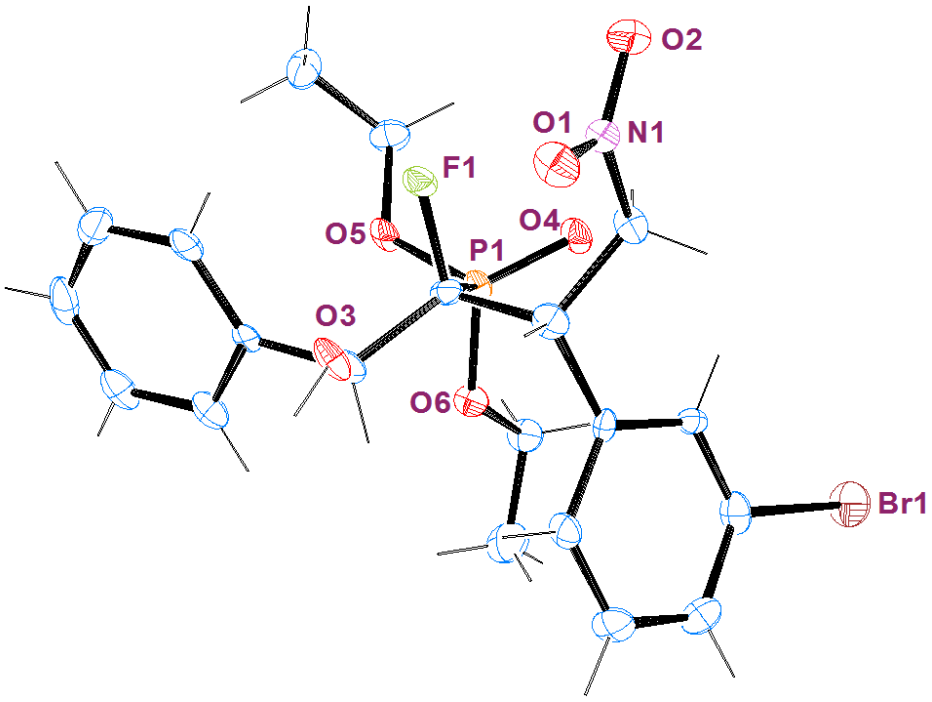


Figure 25. X-ray structure of the single crystal of **II-3.10a**.

II-3.5. Preparation of β-fluoro-pyrrolidine

The Michael adducts contain also several other functionalities than the most valuable fluorinated phosphonate. The keto moiety of β-ketophosphonate, in addition to increasing the reactivity of the Michael donor could also be subsequently subjected to functional group transformations leading to molecules of interest. The nitro group, contributed by nitroalkene, is a masked amino functionality. Having both keto and amino groups in one molecule, cyclization is likely to occur, yielding a heterocyclic structure. Five-member, nitrogen-containing heterocyclic ring - pyrrolidine - is featured in many bioactive and natural compounds (Scheme 71),[144] such as **II-3.13a**&**b** - alkaloids from Japanese "himekouzo" tree, which are highly potent poisons, like Bgugaine (**II-3.15**) and Irniines (**II-3.16a**&**b**). Lapiotin A and B (**II-3.17a**&**b**) were isolated from poisonous mushrooms *Chlorophyllum molybidilis* and *Macrolepiotia neomastoidea*, while **II-3.14** from ant's venom. Such compounds are of interest as they may be derived into pharmaceuticals. The most appealing example of pyrrolidine-containing pharmaceutical was carboxylic acid-featuring Atrasentan, with 2,3,4-substitution pattern on pyrrolidine ring. It is an interesting pharmaceutical of multiple actions - a drug candidate against cancer,[145] as well as endothelin-A receptor antagonist, found to reduce cholesterol and albuminaria, now in phase 3 clinical trials in patients with diabetic Nephropathy.[146]

[144] (*a*) J. R. Lewis, *Nat. Prod. Rep*., 2001, **18**, 95; (*b*) D. O'Hagan, *Nat. Prod. Rep*., 2000, **17**, 435.
[145] A. A. Chiappori at al, *Clin. Cancer. Res*., 2008, **14**, 1464.
[146] http://www.news-medical.net/news/20130521/AbbVie-starts-Phase-3-clinical-study-of-atrasentan-in-patients-with-diabetic-nephropathy.aspx

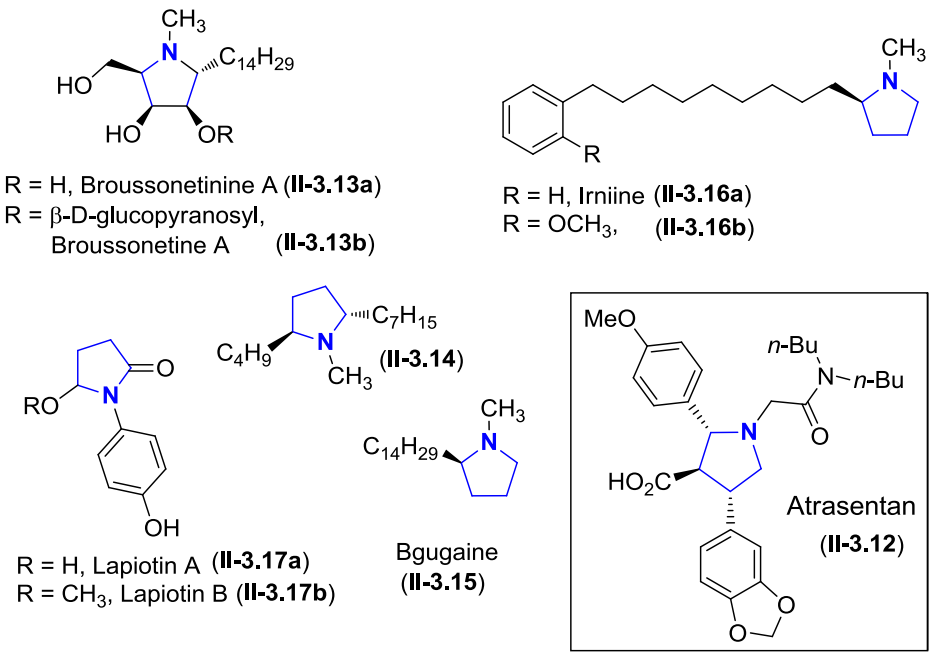
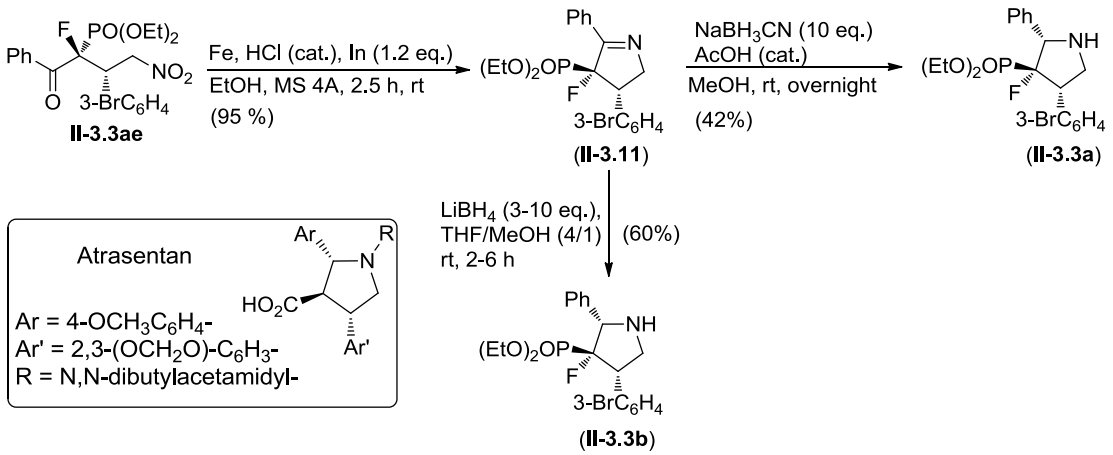


Figure 26. Pyrrolidine- or phosphonate-containing natural products and pharmaceuticals.

We have envisioned that our methodology may lead to molecules containing pyrrolidine ring with the same substitution patterns as seen in Atrasentan, and with carboxylic acid moiety replaced with fluorinated phosphonic acid. Therefore, synthesis of pyrrolidine was attempted (Scheme 71). When the nitro group in **II-3.3ae** was reduced, the cyclization took place spontaneously to afford cyclic imine **II-3.11** in excellent yield. The reduction proceeded smoothly under mild conditions, and it was found that addition of indium[147] led to improved yield of the imine. Surprisingly, the imine **II-3.11** was very stable and could not be easily reduced, presumably due to its intrinsic steric hindrance. By applying two different sets of reaction conditions, two pyrrolidines were obtained, which were revealed by extensive NMR studies[148] to be the stable rotational isomers of the desired pyrrolidine **II-3.3**. The pyrrolidines obtained here represent interesting fluorinated phosphonates as analogues of Atrasentan.

[147] S. Cicchi, M. Bonanni, F. Cardona, J. Revuelta, A. Goti, *Org. Lett.*, 2003, **5**, 1773.
[148] See the experimental for details. See also: M. Michalik, M. Hein, M. Frank, *Carbohydrate Res.*, 2000, **327**, 185.



Scheme 71. Synthesis of pyrrolidine (**II-3.3**).

II-3.6. Summary

In conclusion, α-fluoro-phosphonate pronucleophiles were prepared, some for the first time, and successfully applied in highly stereoselective Michael addition to nitroalkenes, catalyzed by accessible, amino acid-incorporating trifunctional thiourea catalysts. This is the first report for highly diastereoselective and enantioselective organocatalyzed synthesis of α-fluoro-phosphonates. The broad range of products with tunable alkyl/aryl substituents contain several functional groups for further manipulations. Synthesis of pyrrolidine-containing fluorinated-phosphonate analogue of experimental pharmaceutical Atrasentan, was successfully carried out to demonstrate synthetic utility of the Michael adducts.

II-4. Organocatalytic Michael addition of 2-fluoro-1,3-diketones to nitroalkenes: towards fluoro-isosteres of glycerine

Following the successful preparation and application of several fluorinated donors - phosphonates, nitroacetic acid ester and nitrobenzylic compounds, the search for other fluorine-containing prochiral synthons continues. In this chapter, organocatalytic addition of fluorinated diketones to nitroalkenes in its preliminary stage is described. Such reaction would lead to synthesis of fluoro-isosteres of tri-substituted glycerines with additional primary amine functionality.

II-4.1. Introduction

Diols, triols and *tert*-alcohol are common motifs in the structures of marine toxins,[149] macrolide antibiotics (Aspicilin, **II-4.1**, Erythromycin, **II-4.2**)[150] and polyether antibiotics[151], as well as many other sugar- or glycerine-derived bioactive compounds (e.g. 1-Hydroxybrevicomin (**II-4.3**) – a fatty acid metabolism product and insect pheromone),[152] some of which were found active against leukaemia and other cancers (e.g. Fostriecin, **II-4.4**),[153] inhibiting phospholipase A_2 (PLA_2, e.g. Cinatrin B (**II-4.5a**) and C (**II-4.5b**))[154] or T-cell activation genes (e.g. immunosuppressant **FK5061**).[155] Tertiary alcohol moiety was also found crucial in recently investigated HIV protease inhibitors (e.g. **II-4.6**).[156] Such motifs are

[149] T, Yasumoto, M. Murata, *Chem. Rev*., 1993, **93**, 1897.
[150] a) H. Kirst, in: "Recent progress in the chemical synthesis of antibiotics", G. Lukacs, M. Ohno, Eds., Springer-Verlag: Berlin, 1990, 39; b) S. C. Sinha, E. Keinan, *J. Org. Chem*., 1997, **62**, 377.
[151] O. Yonemitsu, K. Horita, in: "Recent progress in the chemical synthesis of antibiotics", G. Lukacs, M. Ohno, Eds., Springer-Verlag: Berlin, 1990, 447.
[152] a) P. Mukerjee, M. Abid, F. C. Schroeder, *Org. Lett.*, 2012, **12**, 3986; b) F. Francke, F. Schroeder, P. Philipp, H. Meyer, V. Sinnwell, G. Gries, *Bioorg. Med. Chem*., 1996, **4**, 363.
[153] Y. Hayashi, H. Yamaguchi, M. Toyoshima, K. Okado, T. Toyo, M. Shoji, *Chem. Eur. J*., 2010, **16**, 10150.
[154] A. N. Cuzzupe, R. Di Florio, J. M. White, M. A. Rizzacasa, *Org. Biomol. Chem*., 2003, **1**, 3572.
[155] a) M. Nakatsuka, J. A. Ragan, T. Sammakia, D. B. Smith, D. E. Uehling, S. L. Schreiber, *J. Am. Chem. Soc.*, 1990, **112**, 5583; b) R. E. Ireland, J. L. Gleason, L. D. Gegnas, T. K. Highsmith, *J. Org. Chem*., 1996, **61**, 6856.
[156] X. Wu, M. Larhed, *et al*, *J. Med. Chem*., 2008, **51**, 1053.

most commonly prepared *via* methodologies based on the asymmetric Sharpless dihydroxylation,[157] Jacobsen's epoxidation[158] or the use of sugar-derived synthons.

The size, electronic configuration and properties of fluorine render it feasible for being an isostere of hydroxyl and oxo groups; such modifications have been applied in lead optimization (e.g. see the case of Camptothecin and nucleoside-derived antiviral agents in the Introduction chapter).

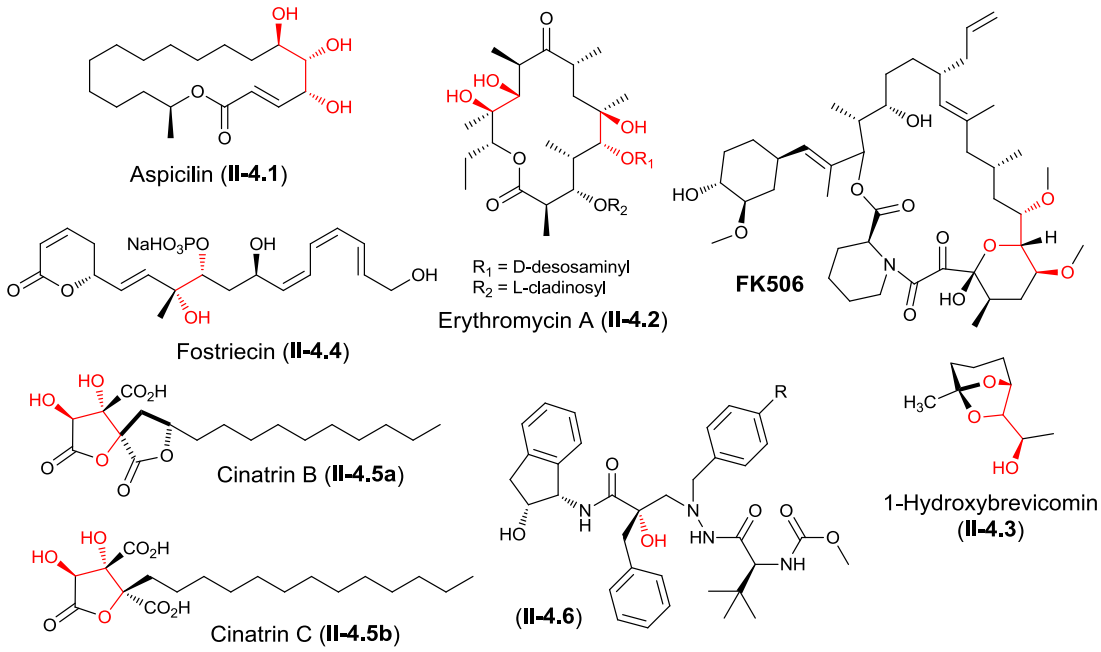


Figure 27. Bioactive compounds with triol, diol and/or *tert*-alcohol.

Considering the potential biological application of such alcohols as seen above, we believe it worthwhile to develop a general route towards partially fluorinated analogues of di- or tri-hydroxy compounds. Such motif (**I**, Figure 28) could be accessed *via* Michael addition of 2-fluoro-1,3-diketone (**II**) to a general acceptor (**III**) and subsequent reduction of the carbonyl moieties. Such reaction has other merits as it would lead to the generation of fluorinated quaternary stereocenter adjacent to three tertiary stereocenters, and as such, constitutes significant synthetic challenge. Furthermore, even though 1,3-dicarbonyl compounds were

[157] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B., *Chem. Rev.*, 1994, 94, 2483.

[158] a) Jacobsen, E. N. In Catalytic Asymmetric Synthesis; Ojima, I., Ed.; VCH Publishers Inc.: New York, 1993; pp 159; b) E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, *J. Am. Chem. Soc.*, 1991, **113,** 7063.

benchmark substrates in the development of stereoselective direct fluorination (see Introduction chapter), enantioselective fluorination of 1,3-diketones has not been realized to date.

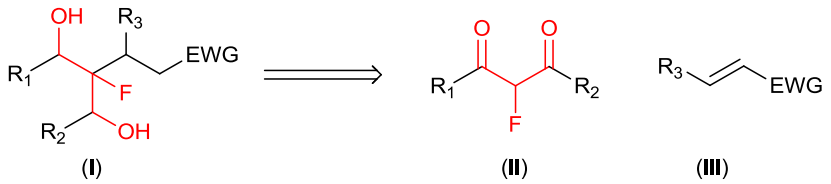


Figure 28. Route towards 2-fluoro-1,3-diols *via* Michael addition.

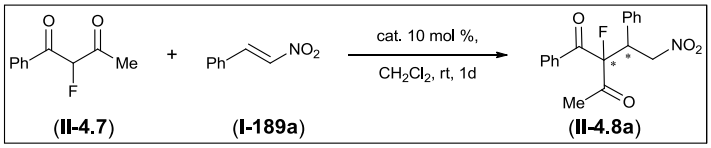
Michael additions of acetylacetone to β-nitrostyrene has become a benchmark model reaction in testing new catalysts, as the symmetrical scaffold provides excellent H-bonding acceptor/donor system without devoid of distereogenic carbon centre. Therefore, it has been reported several times in testing thiourea-, squaramide, primary amine-containing, sugar-, imidazole- or Rosin-derived organocatalysts;[159] however, reports on the use of diketones other than acetylacetone or 1,3-diphenylpropanedione are rare,[159a,g] with fluorinated diketones have never been employed in Michael addition to date. This may also be due to lower reactivity of diketones as compared to aldehydes or ketoesters, in addition to difficulties in controlling the diastereoselectivity of the reaction with unsymmetrical diketones, as differentiation of the two carbonyl groups is a challenging task.

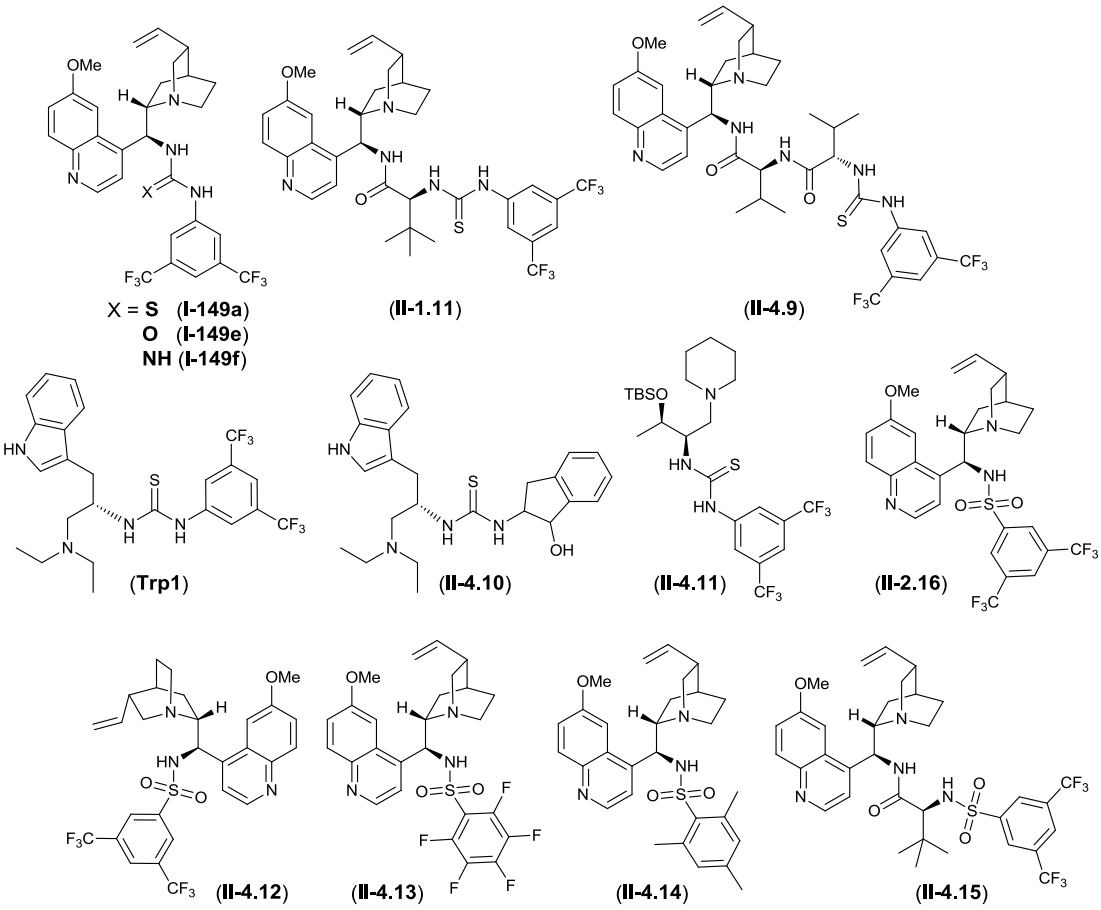
[159]For thiourea organocatalysts, see: a) W. Li, W. Wu, F. Yu, H. Huang, X. Liang, J. Ye, *Org. Biomol. Chem*., 2011, **9**, 2505; b) W. He, B. Zhang, *et al.*, *Adv. Synth. Catal*., 2012, **354**, 2264; c) F.-Z. Peng, Z.-H. Shao, B.-M. Fan, H. Song, G.-P. Li, H.-B. Zhang, *J. Org. Chem*., 2008, **73**, 5202; for sqareamide-incorporating catalysts, see: d) C. Min, C. Dong, *et al*, *Adv. Synth. Catal*., 2011, **353**, 2715; e) for primary amine-containing organocatayst, see: B. Tan, X. Zhang, P. J. Chua, G. Zhong, *Chem. Commun*., 2009, 779; f) for sugar-derived organocatalysts, see: A. Puglisi, M. Benaglia, L. Raimondi, L. Lay, L. Poletti, *Org. Biomol. Chem*., 2011, **9**, 3295; g) for imidazole-derived organocatalysts, see: D. Almasi, D. A. Alonso, E. Gomez-Bengoa, C. Najera, *J. Org. Chem*., 2009,**74**, 6163; h) for Rosin-derived organocatalysts, see: X. Jiang, R. Wang, *et al*, *J. Org. Chem*., 2009,**74**,5562.

II-4.2. Michael addition of 2-fluoro-1,3-diketones to nitroalkenes: reaction optimization

We began our investigation on a model Michael addition of 2-fluoro-1-phenyl-1,3-butadione (**II-4.7**, Table 6) to (*E*)-β-nitrostyrene (**I-189a**) catalyzed by *Cinchona* alkaloid-derived organocatalysts with different types of H-bonding moiety. *Quinine*-derived thiourea (**I-194a**) and urea (**I-194e**) catalysts were found superior to their guanidine analogue (**I-194f**), leading to the desired product in a clean reaction with full conversion of starting material to product and 90% - 91% ee for the major diastereomer obtained in a 2:1 diastereomeric ratio (entries 1 & 2), as compared to 28% ee and 1.5:1 dr, with low conversion of 40%, in the guanidine catalyzed reaction (entry 3). Therefore, the screening was continued with different thiourea-containing organocatalysts. In an attempt to increase the dr value, the highly stereoselective *Quinine*-derived catalyst **II-1.11** incorporating *L*-*tert*-leucine moiety which was utilized in other Michael additions was then tested. Unfortunately, disappointing results were obtained; even though the enantioselectivity was high (93% & 90% ee), a 1:1 mixture of diastereomers was obtained. Insignificant improvement of diastereoselectivity was observed when *Quinine*-derived dipeptide (*L*)-Val-(*L*)-Val-featuring catalyst (**II-4.9**) was employed - Michael adduct was obtained in 3:2 diastereomeric ratio with 84% / 85% ee in 60% conversion (entry 5). Next, other scaffolds besides *Cinchona* alkaloid-derived scaffolds were tested. The tryptophan-derived catalyst **Trp1** was found effective (100 conv.) and enantioselective (92% ee), however, the dr value was still low (2:1, entry 6). Similar result was obtained in reaction catalysed by tryptophan-thiourea catalyst **II-4.10** containing additional H-bonding hydroxyl group, albeit enantioselectivity was slightly lower (87%, entry 7). Further drop in enantioselectivity to 81% was found in the reaction catalysed by cyclohexyl-*tert*-amine-containing catalyst (**II-4.11**) derived from TBS-protected *L*-threonine (entry 8). Unable to improve diastereoselectivity with different thiourea-containing catalysts, attention was then turned to sulphonamide organocatalysts.

Table 6. Optimization of organocatalyzed Michael addition of 2-fluoro-1-phenyl-1,3-butadione (**II-4.7a**) to (*E*)-β-nitrostyrene (**I-189a**).[a]





Entry	Catalyst	Solvent	Temp. [°C]	Conv. (%)[b]	Ee (%)[c]	Dr[b]
1	**I-149b**	CH_2Cl_2	rt	100	90/87	2:1
2	**I-149c**	CH_2Cl_2	rt	100	91/87	2:1
3	**I-149d**	CH_2Cl_2	rt	40	28/30	1.5:1
4	**II-1.11**	CH_2Cl_2	rt	100	93/90	1:1
5	**II-4.9**	CH_2Cl_2	rt	60	84/85	1.5:1
6	**Trp1**	CH_2Cl_2	rt	100	92/87	2:1
7	**II-4.10**	CH_2Cl_2	rt	100	87/85	2:1
8	**II-4.11**	CH_2Cl_2	rt	100	81/79	2:1

9	**II-2.16**	CH_2Cl_2	rt	100	84	3:1
10	**II-4.12**	CH_2Cl_2	rt	100	-18/-22	1.5:1
11	**II-4.13**	CH_2Cl_2	rt	100	10/7	1.5:1
12	**II-4.14**	CH_2Cl_2	rt	40	25/10	2:1
13	**II-4.15**	CH_2Cl_2	rt	100	10/5	1:1
14	**II-2.16**	$CHCl_3$	rt	100	74/61	2:5
15	**II-2.16**	Toluene	rt	100	70/68	3:1
16	**II-2.16**	Et_2O	rt	100	85/76	3:1
17	**II-2.16**	CH_3CN	rt	100	76/61	3.3:1
18	**II-2.16**	Et_2O	0	100	88/81	3:1
19	**II-2.16**	Et_2O	-20	100	89/81	3:1
20	**II-2.16**	Et_2O	-70	95	92	6:1
21[d]	**II-2.16**	Et_2O	rt	100	67/33	3:1
22[e]	**II-2.16**	Et_2O	rt	100	81/72	3:1

[a] Reaction conditions: **II-4.7a** (0.05 mmol), the catalyst (0.005 mmol) in the solvent (0.5ml) with nitrostyrene **I-189a** (0.06 mmol) at the temp. indicated; [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.[c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction in the presence of 4Å molecular sieves (5 mg); [e] 20 mol% of catalyst was used.

Quinine-derived sulphonamide catalyst with *bis*-(trifluoromethyl)phenyl substituent (**II-2.16**) was found effective (100% conv.) and stereoselective 84% ee with highest diastereoselectivity of 3:1 so far. Following that finding, other sulphonamide catalysts were then tested. To our surprise, the pseudo-enantiomeric *Quinidine*-sulphonamide catalyst (**II-4.12**) led to the product with dramatically decreased enantioselectivity (-18% & -22% ee, the opposite enantiomers were obtained) and halved diastereoselectivity (1.5:1, entry 10). Even lower enantioselectivities were measured in reactions catalysed by *Quinine*-sulphonamide catalysts with pentafluoro- (**II-4.13**) or 2,4,6-trimethylphenyl substituents (**II-4.14**) - 10% & 7% and 25% & 10% ee respectively with 1.5:1 and 2:1 dr (entries 11&12), which indicated the importance of the sulphone aryl substituent for stereoselectivity. In the final attempt to

increase the diastereoselectivity of the reaction, the best *Quinine*-sulphonamide catalyst was modified by installing *L-tert*-leucine moiety (catalyst **II-4.15**); however, only low enantioselectivity (10% & 5%) with no diastereoselection was the end-result (entry 13). Therefore, the reaction with the best catalyst- *Quinidine-bis*(trimethyl)phenylsulphonamide **II-2.16** was then further optimized. First, solvents were screened (entries 14 – 17) and enantioselectivity was found to vary in the range of 70% - 85%, with the lowest value found for toluene, and highest for diethyl ether. Secondly, temperature was lowered and consistent increase in enantioselectivity with decrease of reaction temperature was measured – 88% at 0 ^{o}C, 89% ee at -20 ^{o}C and 92% ee at -70 ^{o}C (entries 18 – 20), with diastereoselectivity up to 6:1. The following experiments with additional molecular sieves or increased catalyst loading (entries 21 – 22) did not furnish better result. Therefore, the optimum conditions were found to be 10 mol% catalyst in diethyl ether at -70 ^{o}C, with absence of any additives.

To rationalize the observed importance of the *bis*-(trifluoromethyl)phenyl- group on the sulphone moiety in the structure of the best catalyst (**II-2.16**) on stereoselectivity, a ternary complex was proposed (Figure 29). The diketone enolate (black) is bound in an ionic interaction with ammonium cation of the catalyst. The nitro moiety of the nitroalkene (blue) interacts with the sulphonamide hydrogen, while the aryl substituent engages in π–π interactions with the phenylsulphonyl group of the catalyst. This resulting partial shielding of the reverse side of the nitroalkene directs the attack of the enolate from the ‘’top’’ side of the nitroolefin. The vitality of trifluoromethyl substituents (see entries 9, 11, 13, Table 6) may be rationalized by the known effect of fluorination on the quadrupol moment of aromatic rings affecting π–π interactions.[160] Additionally, trifluoromethyl substituents are sterically demanding.

[160] See for example: a) E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem. Int. Ed.*, 2003, **42**, 1210; b) K. Burger, L. Hennig, P. Tsouker, J. Spengler, F. Albericio, B. Koksch, *Amino Acids*, 2006, **31**, 55.

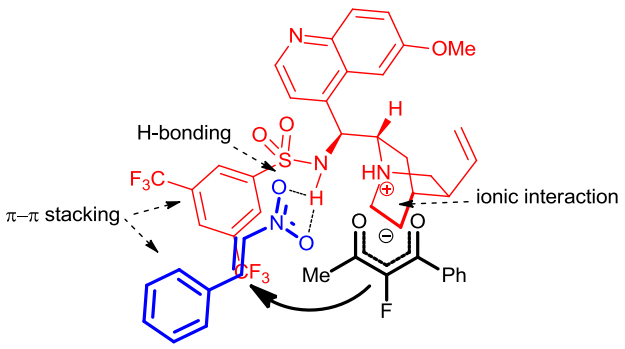
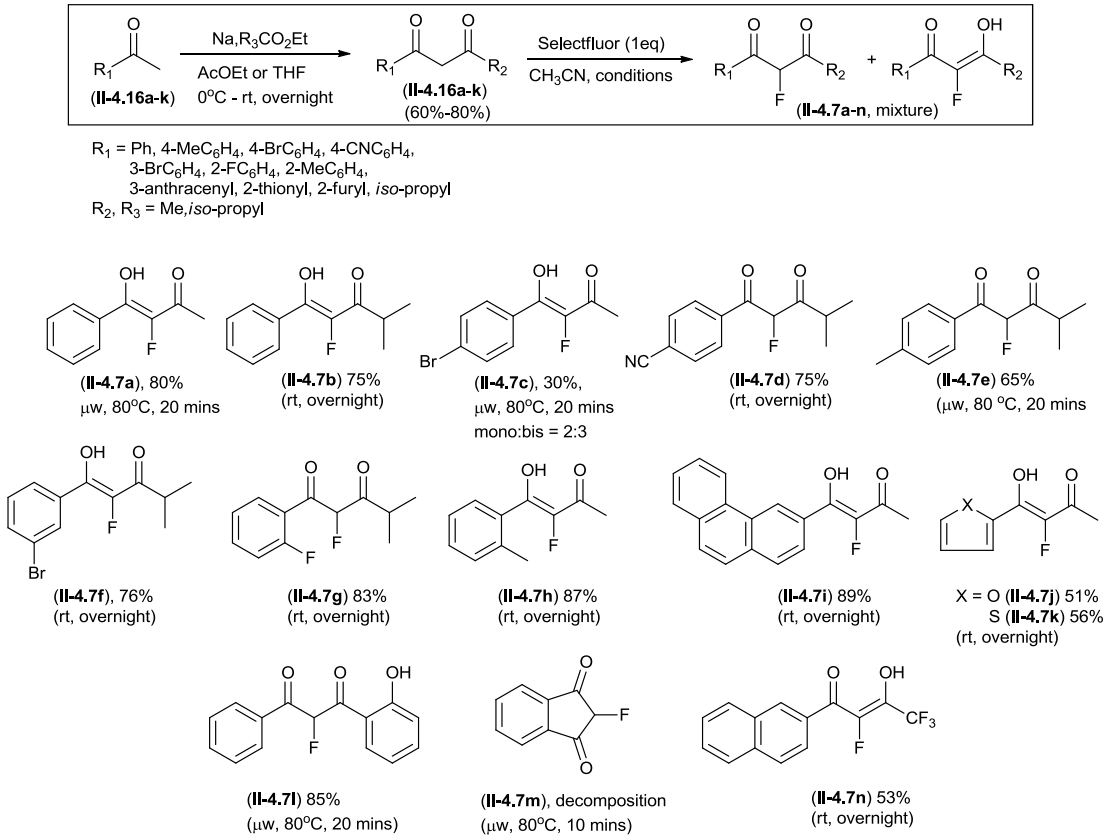


Figure 29. Ternary complex in the Michael addition promoted by catalyst **II-2.16** (in red).

II-4.3. Preparation of the substrates

In order to examine the reaction scope, different 2-fluoro-1,3-diketones were prepared in a two-step sequence (Claisen condensation and fluorination), starting from commercially available aryl(alkyl)-methylketones (Scheme 72). The Claisen condensation was generally easy to perform and a range of diketones was easily prepared in decent yields 60% - 80%. The trifluoromethyl- and phenol-featuring diketones were commercially available. The second step -fluorination - required optimization, as some diketones were less reactive, while others were prone to undergo *bis*-fluorination. The use of any base resulted in *bis*-fluorination, therefore neutral conditions were employed, with microwave irradiation required in some cases. The cyclic diketone **II-4.7m** was found unstable and attempts of purification either by column chromatography or distillation resulted in decomposition of the presumed product (as judged by TLC analysis). Notably, it was found that enantioselectivities were generally higher (by 5% on average) with substrates purified by reduced-pressure distillation than column chromatography, presumably due to the presence of a trace amount of impurities which in some cases could not be removed by chromatographic purification.



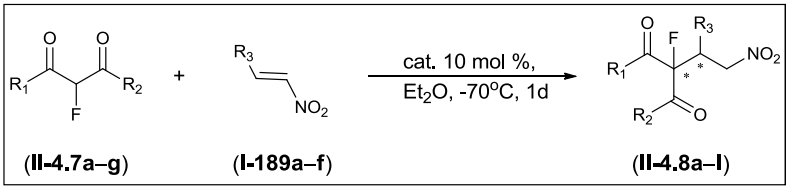
Scheme 72. Preparation of fluorinated diketones for Michael addition.

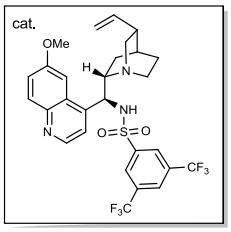
II-4.4. Scope of the reaction

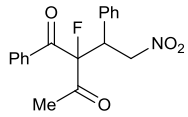
With substrates in hand, the reaction scope was examined (Table 7). As compared to phenyl-methyl diketone, phenyl-*iso*-propyl substrate was more stereoselective and consequently the corresponding product (**II-4.8b**) was obtained with higher enantio- and diastereoselectivity (96% ee & 8:1 dr versus 92% ee & 6:1 dr for **II-4.8a**), with good yield maintained. Diketone with halogen in *para*-position on aromatic ring was found equally reactive; however the corresponding product (**II-4.8c**) was isolated with slightly decreased enantioselectivity (89%) and diastereoselectivity (4:1). On the other hand, excellent enantioselectivities (96% - 97%) were achieved with diketones containing either a larger aryl ring (anthracene - **II-4.8d**) or heterocycle (furan - **II-4.9e**), albeit with decreased diastereoselectivities (9:2 – 5:2). Electron withdrawing substituent on aryl ring of nitroalkene in *para* orientation caused a drop in diastereoselectivity as the corresponding product (**II-4.8f**) was obtained as a 2:1 mixture of

diastereomers, while very high enantioselectivity (94%) and good yield (82%) were maintained. Electron donating group in *para* position on nitroalkene's aryl ring was especially favored as the corresponding product (**II-4.8g**) was over 99% optically pure, with the diastereoselectivity remaining at the moderate level (9:2). Nitroalkenes with halogen substituent in either *meta*- or *ortho*- orientations were well tolerated in the reaction system as the corresponding products (**II-4.8h** & **II-4.8i**, respectively) were obtained in very high yields (90% – 95%), enantioselectivities (95% ee) and moderate diastereoselectivities (3:1 – 9:2). On the other hand, alkyl nitroalkene was generally a difficult substrate as only a trace amount of product was obtained at low temperature. When reaction temperature was increased to 0 ^{o}C, the corresponding product (**II-4.8j**) was isolated in 50% yield as a 3:2 mixture of diastereomers. Further increase of reaction temperature to room temperature resulted in the increase in isolated yield to 67%, at the expense of diastereoselectivity (1:1). The enantioselectivity of the product could not be assessed to date, as suitable HPLC conditions have not been found to separate the enantiomers. Unfortunately, the phenol-containing diketone and trifluoromethyl-substituted diketone were both found unreactive in the reaction and the formation of the corresponding products (**II-4.8k**–**l**) was not observed. Generally the reaction was found quite tolerant with respect to diketones, while aromatic nitroalkenes were preferable. Further investigation of the reaction scope is necessary to assess the practicality of our methodology. Unfortunately, to date, no single crystal suitable for X-ray analysis has been obtained and consequently the configuration of the products remains unknown. Work will also continue on this aspect.

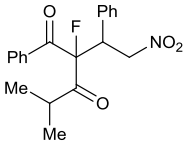
Table 7. Preliminary substrate scope in the Michael addition of fluorinated diketones to nitroalkenes.[a]



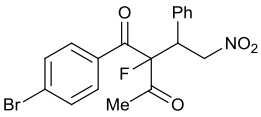




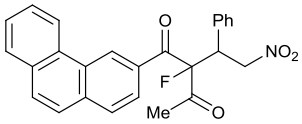
(**II-4.8a**)
80%,[b] 6:1 dr,[c] 92% ee[d]



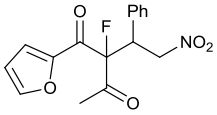
(**II-4.8b**)
81%, 8:1 dr, 96% ee



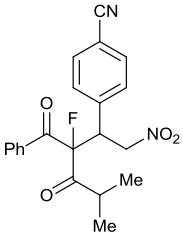
(**II-4.8c**)
76%, 4:1, 89% ee



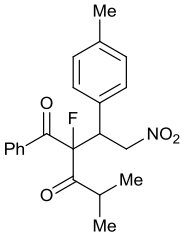
(**II-4.8d**)
95%, 9:2 dr, 96% ee



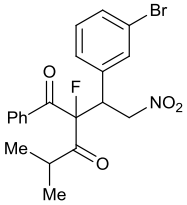
(**II-4.8e**)
94%, 5:2 dr, 97% ee



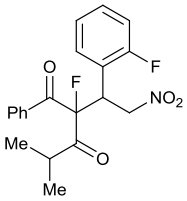
(**II-4.8f**)
82%, 2:1 dr, 94% ee



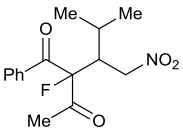
(**II-4.8g**)
70%, 9:2 dr, >99% ee



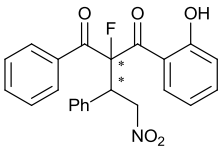
(**II-4.8h**)
95%, 3:1 dr, 95% ee



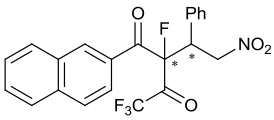
(**II-4.8i**)
90%, 9:2dr, 95% ee



(**II-4.8j**)
50%, 3:2 dr[e]
67%, 1:1 dr[f]



(**II-4.8k**) n.r.

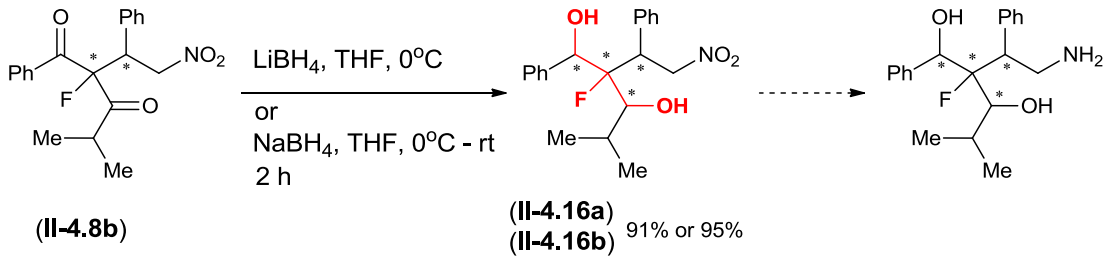


(**II-4.8l**) n.r.

[a] Reaction conditions: **Michael donor** (**II-4.7a-g**, 0.1 mmol), the catalyst (0.01 mmol) in diethyl ether (1ml) with nitroalkene (**I-189a-f**, 0.11 mmol) at -70 °C unless noted otherwise. [b] Isolated yield.[c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase; [e] reaction at 0 °C; [f] 20 mol% of catalyst used; reaction at room temperature.

II-4.5. Preparation of the glycerin analogue and further manipulations of the product

Simultaneously to the investigations of the reaction scope, work on assessing the synthetic utility of the Michael adducts was undertaken. The main goal of our methodology was to find effective routes to fluoro-isosteres of glycerine and such structures can be easily accessed from the Michael adducts (Scheme 73). Facile reduction of the product **II-4.8b** with either lithium or sodium borohydrides led to a separable mixture of three compounds, out of which the two major products (**II-4.16a** and **II-4.16b**) were isolated, characterized and confirmed to be the desired products in two diastereomeric forms. Further reduction of the nitro moiety to yield amino-diol was found feasible; however the product has not been isolated to date.



Scheme 73. Reduction of the carbonyl groups leading to glycerine fluoro-isostere.

Efforts were put to elucidate the absolute configuration of the two diols (**II-4.16**) and single crystals for X-ray analysis were obtained. Unfortunately, in both cases the only two suitable crystals contained both enantiomers, which may sometimes occur, since crystallization as a pair of enantiomers is in general easier than crystallization of a single enantiomer. This could perhaps be attributed to the sterically demanding and defined character of the diols containing three tertiary stereocenters adjacent to a quaternary stereocenter, and the facile H-bonding interactions between the hydroxyl and nitro moieties. The two crystal structures obtained are shown below (one enantiomer of each compound **II-4.16a**, Figure 30, **II-4.16b**, Figure 31). Notably, both samples were confirmed optically active by optical rotation measurement.

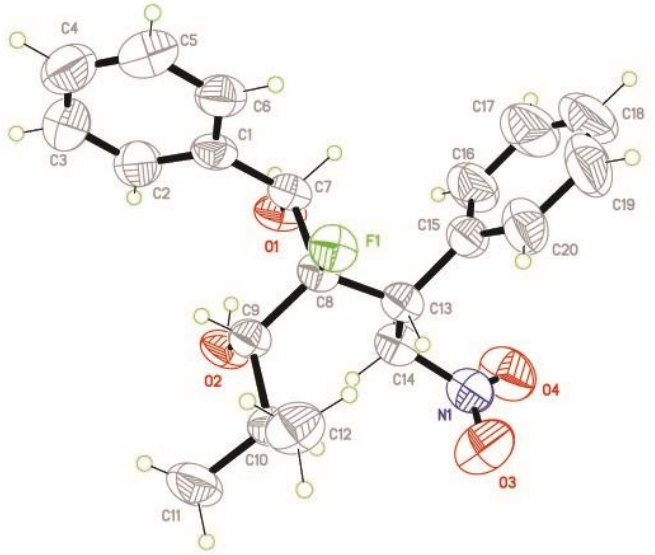


Figure 30. X-ray structure of arbitrary chosen enantiomer of diol **II-4.16a**.

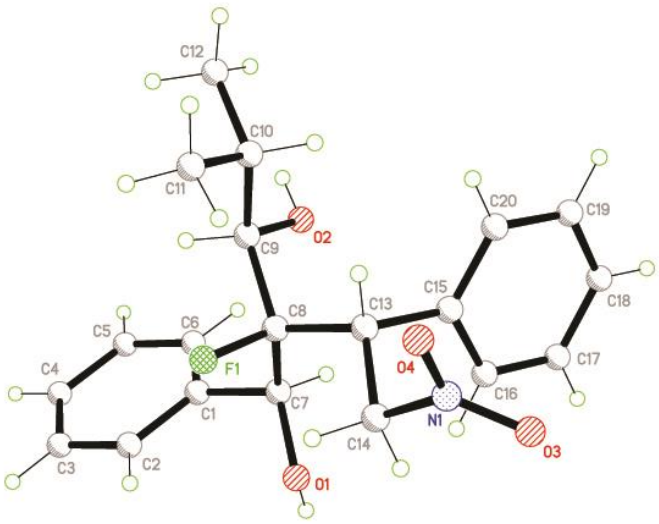
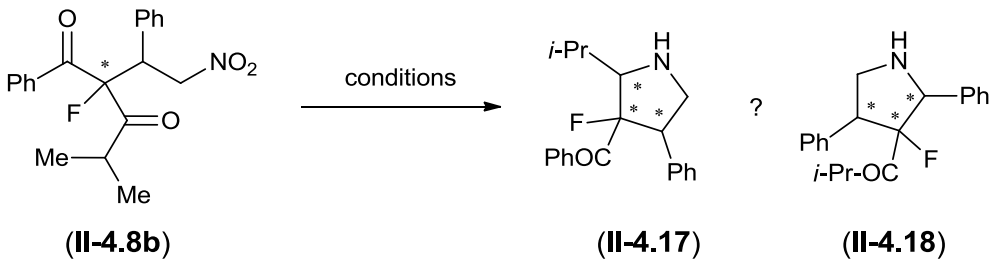


Figure 31. X-ray structure of arbitrary chosen enantiomer of diol **II-4.16a**.

In addition to carbonyl reduction, other manipulations of the Michael adduct were attempted, such as reduction of the nitro moiety with subsequent cyclization to pyrrolidine (Scheme 74).



Scheme 74. Reduction of nitro substituent leading to pyrrolidines.

Several common methods for nitro reduction were screened. The use of Zn/AcOH or nickel boride ($NiCl_2/NaBH_4$) led to complicated mixtures of products, while triphenylphosphine or iron were not effective in the reductions. On the other hand, prior experience with similar reductions of fluorinated 1,3-dicarbonyl compounds suggests that Pd/C would lead to defluorination. Therefore, less active palladium sources such as $Pd/BaSO_4$ will be tested in the future.

II-4.6. Summary and future perspective

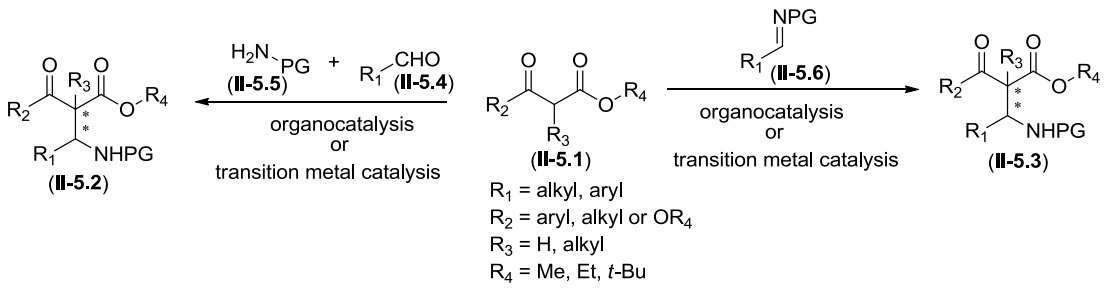
In conclusion, a highly enantioselective Michael addition of novel fluorinated 1,3-diketones to nitroalkenes was demonstrated with the use of simple and accessible *Quinine*-sulphonamide catalyst. Michael addition to aromatic nitroolefins led to products with high to excellent enantioselectivities (89% – >99%), low to good diastereoselectivities (2:1 – 8:1) in good to excellent yields (70% – 95%), while aliphatic nitroalkenes were found generally unreactive. Two diastereomeric glycerine fluoro-isosteres with four contiguous stereogenic centers were prepared from the model Michael adduct upon facile reduction. Future work will tackle expanding the substrate scope to other 2-fluoro-1,3-diketones and nitroalkenes, absolute configuration assessment and other manipulations of the addition products.

II-5. Asymmetric Mannich reaction - towards fluorinated amino acids, lactones and β-lactams

Following the successful development of enantioselective Mannich addition of α-fluoro-β-ketoesters we have focused on application of the Mannich adducts in preparation of fluorinated bioactive molecules and useful synthons. The following section details our synthetic efforts in preparation of α-fluoro-β-amino esters, α-fluoro-β-lactam and lactone. The methodology was extended to application of fluorinated malonates and subsequent tandem decarboxylation/protonation leading to linear α-fluoro-β-amino esters. Findings on this challenging process are presented in the second part of this chapter.

Background

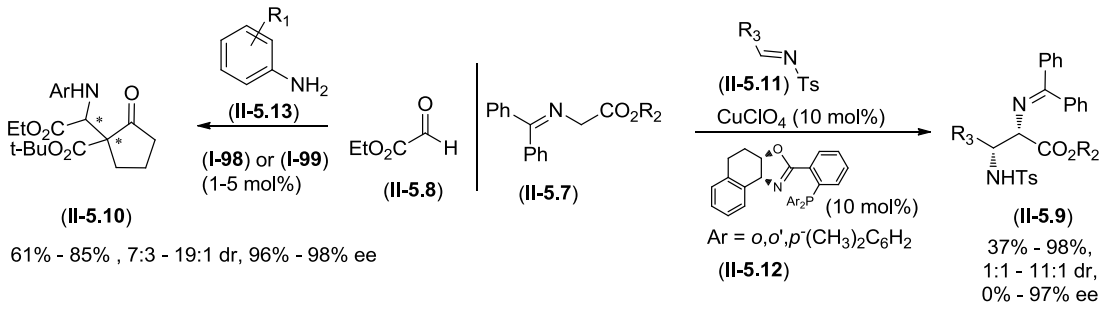
Mannich addition of carbonyl compounds to imines is an especially appealing C-C bond forming reaction, as it may lead to α- or β-amino esters. Several groups have reported successful use of organo- or metal-containing catalysts in enantioselective addition of ketoesters and malonates to preformed, protected imines or its three-component version, leading to β-amino esters (Scheme 75).[161]



Scheme 75. Mannich addition of 1,3-dicarbonyl compounds to imines leading to β-amino esters.

[161] a) For a recent review see: S. Kobayashi,Y. Mori, J. S. Fossey, M. M. Salter, *Chem. Rev*., 2011, **111**, 2626; b) Y. Hamashima, N. Sasamoto, D. Hotta, H. Somei, N. Umebayashi, M. Sodeoka, *Angew. Chem. Int. Ed*., 2005, **44**, 1525; c) L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* 2003, **68**, 2583.

Alternatively, addition to glyoxylate- or glycine-derived imines yields α-amino esters (Scheme 76).



Scheme 76. Mannich addition leading to α-amino esters.

II.5.1. Introduction: Development of organocatalytic Mannich addition of α-fluoro-β-ketoester to N-Boc aldimines

We envisioned that similar reaction between α-fluoro-β-ketoester would lead to potentially valuable compounds, α-fluoro-β-amino acids derivatives, *via* a general route.

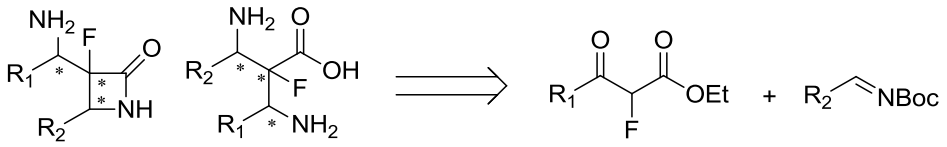
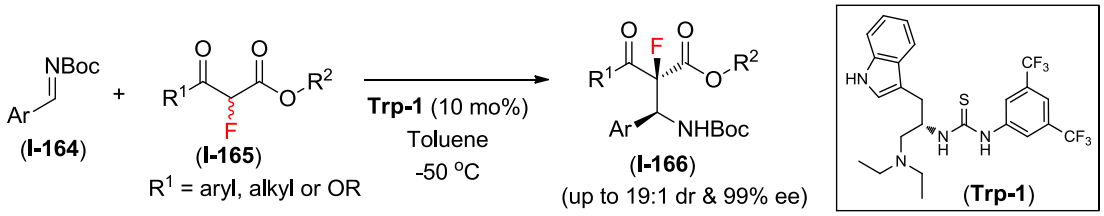


Figure 32. Hypothetical route towards α-fluoro-β,β-diaminoacids and α-fluoro-β-lactams.

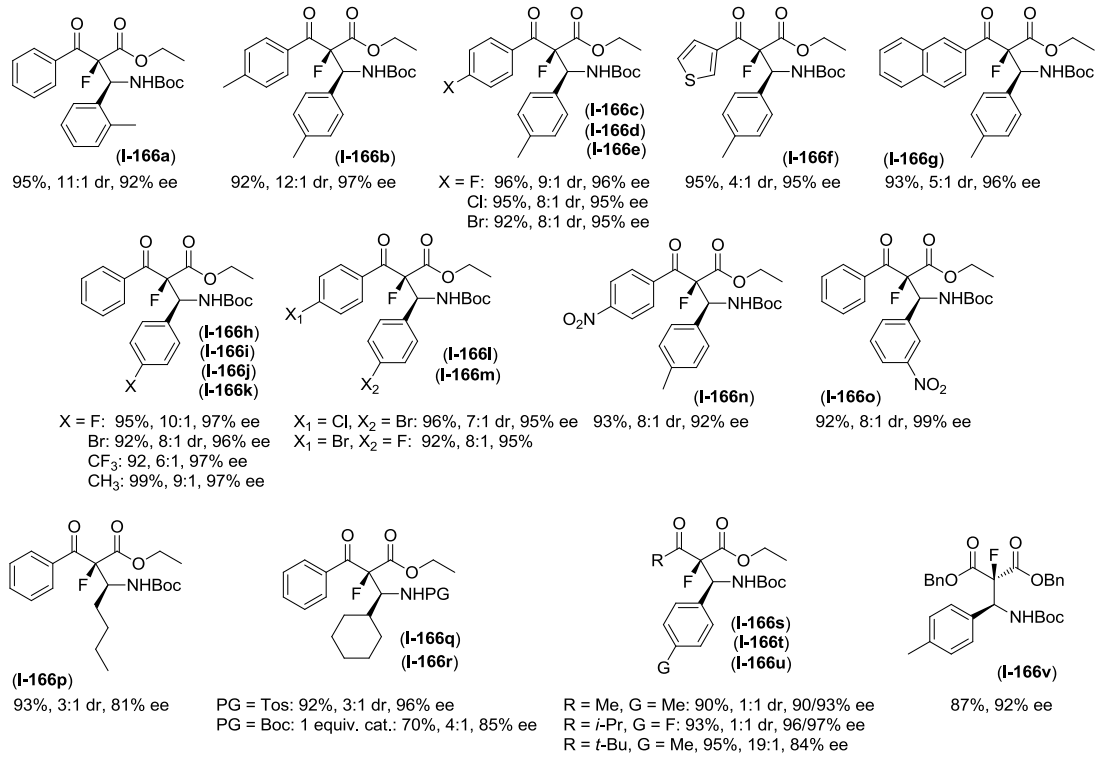
Upon catalyst screening and optimization, the novel tryptophan-derived catalyst (**Trp1**, Scheme 77) was found to be highly effective and stereo-selective in Mannich reaction between fluorinated ketoesters (**I-165**) and imines (**I-164**).[162]



Scheme 77. Asymmetric Mannich reaction catalyzed by tryptophan-derived organocatalyst Trp-1.

[162] X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.*, 2009, **48**, 7604; *Angew. Chem. Int. Ed.*, 2011, **50**, 2653.

Equally good results were obtained for a broad range of aromatic imines and aromatic and aliphatic ketoesters, as well as with very challenging substrates - aliphatic imines (**I-166a-v**, Scheme 78) with this general reaction.



Scheme 78. Structures of products attainable *via* **Trp1** catalyzed Mannich reaction.

To understand our catalytic system better, kinetic and computational studies (density functional theory) were performed. The reaction was found to be first rate with regards to both substrates and the catalyst. Computational modelling resulted in proposing plausible pre-transition state model for the formation of the product **I-166k**. The very good stereocontrol of the process was attributed to the formation several of H-bonding interactions (Figure 33).[163] After deprotonation of the ketoester, the *tert*-amine formed an iminium cation that in turn engaged into H-bonding interactions with the imine substrate. The fluorinated enolate substrate is bound by H-bonding interactions to the thiourea moiety, with additional assistance from non-classical C-H$^{\cdots}$O interactions.

[163] H. Xiao, R. Lee, T. Chen, J. Luo, Y. Lu, K.-W. Huang, *Scientific Reports*, 2013, DOI: 10.1038/srep02557.

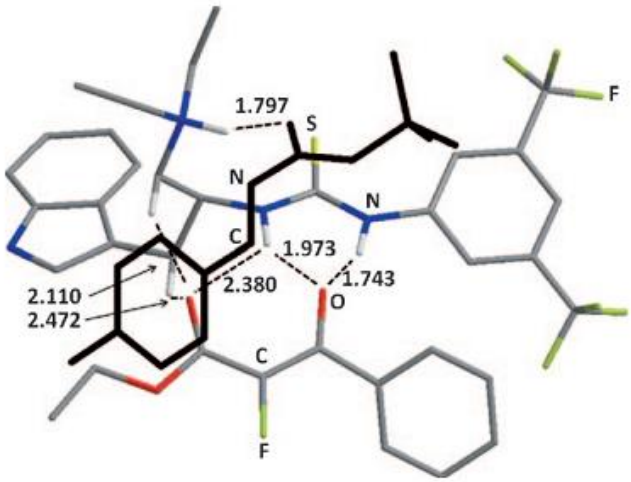
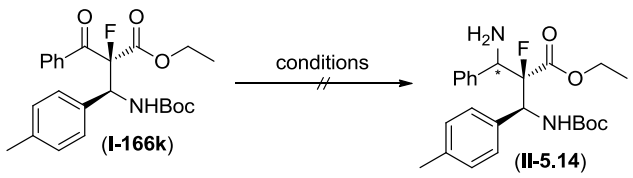


Figure 33. Proposed pre-transition state complex.

II.5.2. Manipulation of Mannich addition product - preparation of α-fluoro-β-lactam and lactone

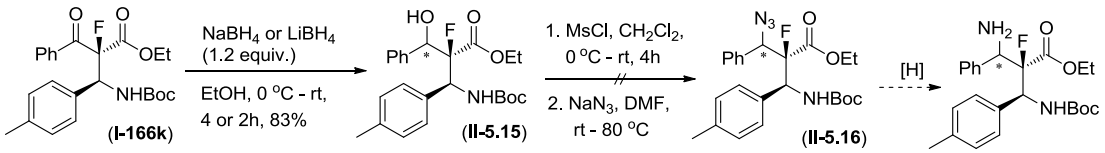
Being able to prepare a broad scope of Mannich adducts with excellent optical purity, we than explored their synthetic utility for the preparation of fluorinated precursors of bioactive compounds.

Firstly reductive amination on the model substrate to access α-fluoro-β,β-diamino ester (**II-5.14**, Scheme 79) *via* a one pot procedure was attempted. Benzyl or ethyl amines were used in combination with reducing agents such as sodium triacetoxyborohydride or sodium cyanoborohydride at pH = 5 in standard solvents: CH_2Cl_2, $(CH_2Cl)_2$ or THF. Unfortunately in all cases the reaction was messy, with no major product. Attempts to isolate the intermediate imine formed initially, evident by TLC analysis, were also unsuccessful. Presumably, the imine underwent facile hydrolysis during isolation, while the amine decomposed with release of HF and side products.



Scheme 79. Reductive amination of Mannich adduct.

We then decided to try a different route - reduction of ketone, followed by mesylation, displacement with azide and reduction (Scheme 80). Alcohol (**II-5.15**) could be obtained easily by reduction with either sodium or lithium borohydride in ethanol. Further mesylation of the alcohol was successful as well; however problems were encountered during the subsequent step - nucleophilic substitution with azide.

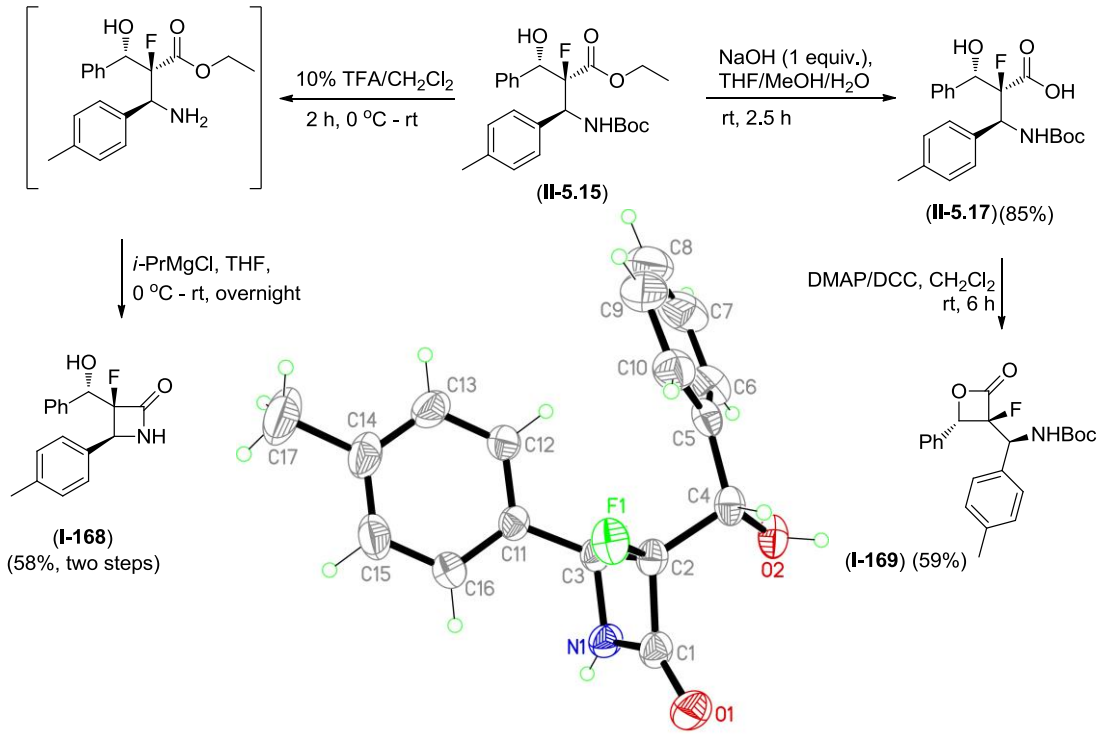


Scheme 80. Alternative route towards α-fluoro-β,β-diamino ester.

The reaction was sluggish at room temperature, but became messy at elevated temperatures (up to 80 °C), with no major spot. The observed reactivity was attributed to the presence of fluorine on the neighbouring carbon; the electron withdrawing effect could diminish the very good leaving ability of the mesyl group. On the other hand, the azide could attack the highly electron-positive fluorinated carbon atom at elevated temperatures in polar solvent (DMF).

We then decided to reduce the keto moiety to hydroxy in order to stabilize the molecule, and subsequently seek the routes towards free amino acid, β-lactam and β-lactone, as such compounds belong to the families of bioactive compounds (Scheme 81).[164]

[164] For the antibacterial activity and synthesis of β-lactam, see: a) J. D. Buynal, *Curr. Med. Chem.*, 2004, **11**, 1951; b) A. Brandi, S. Cicchi, F. C. Cordero, *Chem. Rev.*, 2008, **108**, 3988; c) R. Pal, S. C. Ghosh, K. Chandra, A. Basak, Synlett, 2007, 2321; for an example of drug candidate with lactone, see d) Z. Miao, C. Sheng, *et al*., *J. Med. Chem.*,2013, **56**, 7902, and references therein.



Scheme 81. Synthesis of a-fluoro-b-lactam and lactone; X-ray crystal structure of **I-148**.

The amine Boc protecting group in alcohol (**II-5.15**) was easily cleaved by TFA (10% in CH_2Cl_2). Common bases were tried to initiate lactamization, such as *n*-BuLi or LDA, both at -78 °C; however no desired product was obtained - the reactions were messy in both cases, with no major spot observed by TLC. Eventually, the resulting free amine was cyclised to β-lactam with the use of strong, non-nuclophilic base - freshly prepared *iso*-propyl-magnesium chloride (deprotonation of amino- moiety with its subsequent attack on the ester). The single crystal of the chiral α-fluoro-β-lactam was than analyzed by X-ray crystallography and the structure was unambiguously resolved. The result allowed for the assessment of configuration of all Mannich adducts (**I-166a-v**), alcohol (**II-5.15**) and lactone (**I-169**). The enantiopure α-fluoro-β-lactam can be screened for bioactivities, used as chiral building block *via* the lactam-opening methodologies or coupled with bioactive component to alter its properties, e.g. *via* ester or ether bond formed with the hydroxy moiety available on lactam's β-position.

In parallel to the preparation of lactam, efforts were also put to prepare lactone, as such motif is common in drug candidates.[164d] Ester (**II-5.15**) prepared as described above, was subjected

to hydrolysis by sodium hydroxide at room temperature, over 2.5 hours. The solvent mixture THF/MeOH/water (1/0.5/1) was developed to compensate for the somewhat poor solubility of the ester in MeOH/water, while reaction in THF/water was sluggish. The isolated hydroxyacid (**II-5.17**) was subsequently intramolecularly esterified by DCC and DMAP in CH_2Cl_2, at room temperature, over 6 h, yielding enantio-pure α-fluro-β-lactone (**I-149**), which is an interesting synthon that could be screened for bioactivities itself, or incorporated into macromolecular structure e.g. *via* the amino group handle installed in β-position.

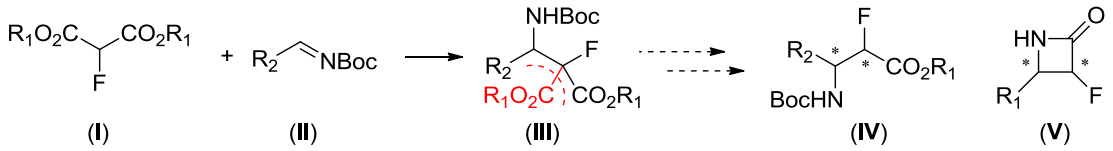
Summary

In conclusion, the Mannich addition of α-fluoro-β-ketoesters to N-Boc imines catalyzed by accessible tryptophan-derived organocatalysts was proven to be a short and effective route towards diverse α-fluoro-β-amino acids, α-fluoro-β-lactams and lactones. The fluorinated synthons prepared in such a way, possess tuneable substituents, as well as functional group (OH or NHBoc) in β-position for further functionalization or usage as a linker with macromolecules.

II.5.3. Decarboxylation/asymmetric protonation of Mannich malonate addition product

The development of enantioselective Mannich addition to imines, as describe in the previous section, provided an efficient route to α-fluoro-β-amino acids with a branched carbon chain. Construction of such molecules containing two tertiary stereocenters adjacent to a quaternary is a considerable challenge; however one may expect the effect of fluorination on the functional groups (pK_a, pK_b) diminished by electron donation from the aromatic and aliphatic hydrocarbon substituents. Moreover, the steric hindrance imparted by the substituents may affect negatively synthetic applications of such synthons. Therefore we were interested in devising methodology for the preparation of linear fluorinated amino acids precursors, with little steric hindrance and maximized effect of fluorine on neighbouring groups. Such

molecules would be close fluorinated β-amino-analogs of natural amino acids and precursors of simple β-lactams and could arise from Mannich addition of fluoromalonate to imines, followed by mono-decarboxylation (Scheme 82).



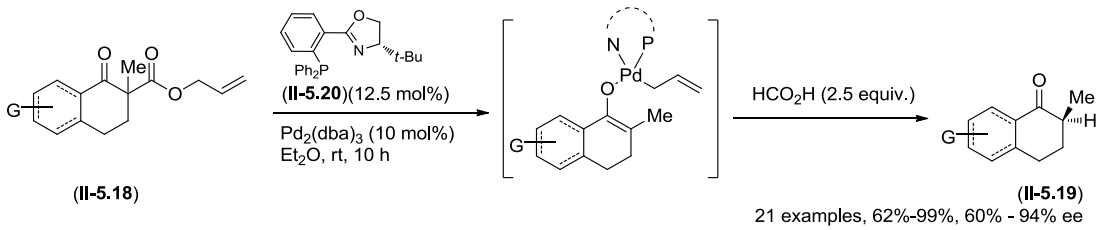
Scheme 82. Hypothetical route towards fluorinated analogs of proteinogenic amino acids and lactams.

It was expected that the methodology developed in the previous chapter would be general and applicable not only to ketoesters but malonates as well. The second step however, decarboxylation/asymmetric protonation, seemed rather challenging. This section will describe our efforts to tackle the transformation.

Introduction

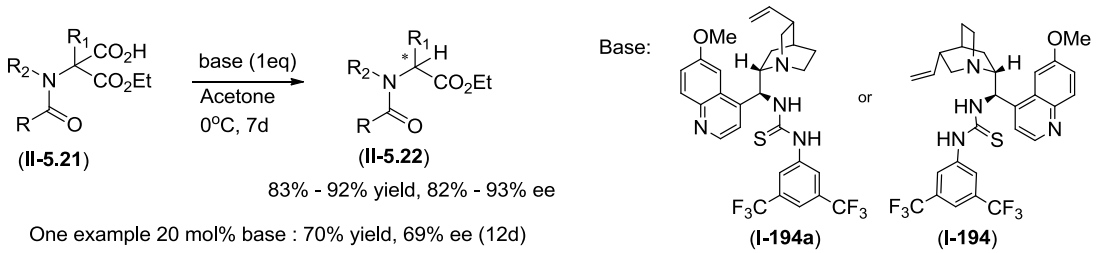
Asymmetric decarboxylation/protonation is a challenging transformation, and consequently the reports on the reaction are scarce, with metal-assisted processes more explored than those conducted under metal-free conditions. One of the best catalytic decarboxylation/asymmetric protonation was achieved by Stoltz and co-workers (Scheme 83).[165] The reaction is believed to proceed *via* the enolate intermediate - product of β-ketoester decarboxylation, stabilized by palladium-oxazoline complex; subsequent protonation by formic acid leads to formation of the corresponding products with good to excellent yields and enantioselectivities. Notably, β-ketoesters undergo decarboxylation very easily; additionally, only cyclic ketoesters were used as substrates (rigid, easier to control stereoselectivity as compared to acyclic ketoesters).

[165] J. T. Mohr, T. Nishimata, D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc*., 2006, **128**, 11348.



Scheme 83. Palladium-assisted decarboxylation/asymmetric protonation by Stoltz.

The best result based on the use of organocatalysts in the decarboxylation/protonation of malonate was achieved in Rouden's group [166a] (Scheme 84): up to 93% ee was achieved using stoichiometric amount of base over seven days, or 69% ee using 20 mol% of the base (in slightly less than two weeks of reaction time). It is also worth noticing, that most reports concern decarboxylation/protonation of α-amino malonates,[166] which may imply participation of the α-amino- group in the process, perhaps in stabilizing intermediate species. Up to date, there are no examples of the asymmetric decarboxylation/protonation of simple or α-fluorinated malonates.



Scheme 84. Asymmetric decarboxylation/protonation promoted by *Cinchona* alkaloid-derived base.

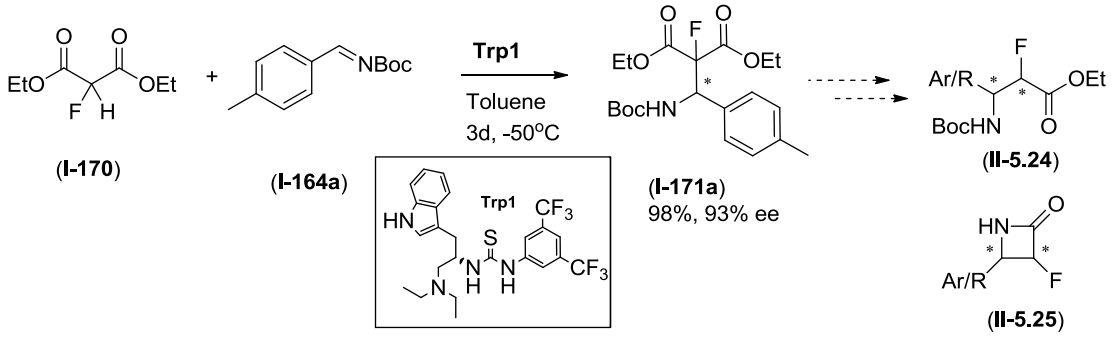
Research results

The previously developed protocol for asymmetric Mannich addition of α-fluoro-β-ketoesters to N-Boc imines was found applicable to malonates as well. The addition of diethylfluoromalonate to model N-Boc imine (**I-164a**, Scheme 85) proceeded smoothly and the corresponding product (**I-171a**) was obtained with very good yield and enantioselectivity (98% & 93% ee), which prompted us to pursue this reaction more thoroughly. Unfortunately,

166 a) M. Amere, M.-C. Lasne, J. Rouden, *Org. Lett.*, 2007, **9**, 2621; b) H. Brunner, M. A. Baur, *Eur. J. Org. Chem.*, 2003, 2854; c) L. M.-A. Rogers, J. Rouden, L. Lecomte, M.-C. Lasne, *Tetrahedron Letters*, 2003, **44**, 3047; d) T. Seitz *et al.*, *Tetrahedron*, 2006, **62**, 6155.

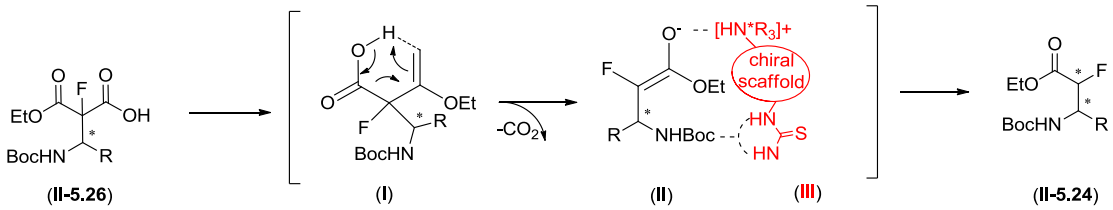
during the course of our research, another group has reported the same transformation.[167] Nevertheless, our main goal - decarboxylation/asymmetric protonation remained unchallenged.

We envisioned that if we succeed in the subsequent decarboxylation/asymmetric protonation of the product (**I-171a**), a simple and practical strategy towards unbranched and general α-fluoro-β-amino acids (**II-5.24**) and α-fluoro-β-lactams (**II-5-25**) from inexpensive, commercially available diethyl fluoromalonate could be achieved.



Scheme 85. Asymmetric Mannich and tandem decarboxylation/protonation reactions.

We hypothesized that the key to control the stereo-selectivity of the process is to engage the enolate (**II**, Scheme 86) in hydrogen bonding and ionic interactions (and any other weak to medium interactions) with chiral catalyst (**III**), which is also a donor of the proton, to form chiral complex. Eventually, the proton transfer would occur within the complex - from quaternary amine (catalyst) to enolate – in a stereo-controlled way due to the chiral environment.

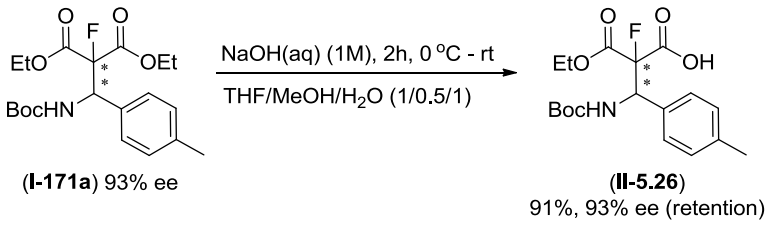


Scheme 86. Hypothesized mechanism of decarboxylation/protonation.

[167] J. H. Lee, D. Y. Kim, Synthesis, 2010, **11**, 1860.

Optimization of the decarboxylation/asymmetric protonation

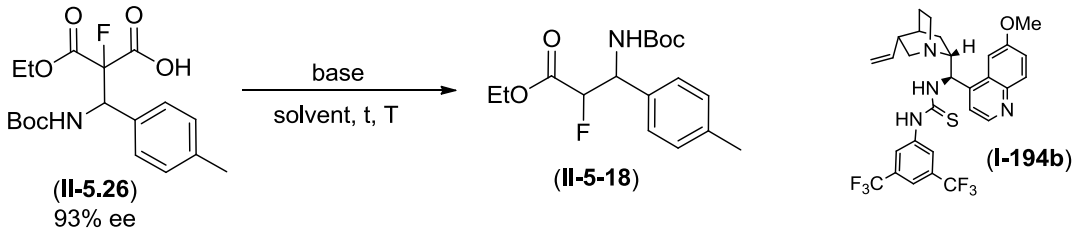
To validate the hypothesis, conditions for mono-hydrolysis of the model Mannich addition product (**I-171a**, Scheme 87) were developed and the immediate substrate for decarboxylation/protonation (**II-5.26**) was eventually obtained in very high yield, under simple conditions, as the only diastereomer (column purification).



Scheme 87. Monohydrolysis of Mannich fluoromalonate adduct.

With the substrate in hand, we then focused on the decarboxylation. After initial trials, it became obvious that the monoacid (**II-5.26**) is quite stable and does not undergo decarboxylation easily. Therefore, it was necessary to find the mildest possible conditions to carry out the decarboxylation before moving to catalyst screening. The major challenge was to find the balance between the need to increase the low reactivity of the substrate, and the threat of racemization of the chiral centre generated during the preceding Mannich addition, or even its decomposition through *retro*-Mannich mechanism. The landmark points of the optimization are summarized in Table 8. The halfester **II-5.26** did not undergo decarboxylation under the action of triethylamine (1.5 equiv.) at room temperature, even when polar DMF was used as solvent (entry 1, CH_3CN, acetone, and non-polar solvents did not result in any conversion as well; DMSO could also be used with the same result as DMF). However, at elevated temperature, 80% conversion to the desired product was observed (entry 2). To our satisfaction, the same result could be obtained when 0.2 equivalents of simple *Quinidine*-derived thiourea catalyst (**I-194b**) was used (entry 3). We then tried to lower the reaction temperature, which resulted in 80% conversion but over an extended reaction time of a week. When the chiral halfester (**II-5.26**) was subjected to the reaction conditions, the desired product (**II-5.18**) was obtained with 1:1.6 dr and 30% ee (entry 4).

Table 8. Optimization of decarboxylation/protonation.[a]



Entry	Base (equiv.)	Solvent	Temp [°C]	Time [h]	Conversion [%][b]	Dr[b]	Ee[c] [%]
1	**TEA** (1.5)	DMF	rt	20	n.r.	-	-
2	**TEA** (1.5)	DMF	65-75	20	80	-	-
3	**I-194b** (0.2)	DMF	55-60	24	80	1.4:1	-
4[d]	**I-194b** (0.2)	DMSO	40-50	7d	80	1.6:1	30
5[d]	**I-194b** (0.2)	DMSO	40-45	72	69	1:2.3	93
6	**I-194b** (0.1)	DCM	rt	22	-	-	-
7[d]	**I-194b** (0.1)	Acetone	70	20	40	n.d.	n.d.
8[d]	**I-194b** (0.2)	THF	70	72	70	1.5:1	53
9	**I-194b** (0.2)	DMSO	40-45	72	68	1:1	31

[a] Reaction conditions: **II-5.26** (0.05 mmol), the base in the solvent (1ml). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture; [c] Determined by HPLC analysis on a chiral stationary phase of purified product; [d] Chiral substrate was used.

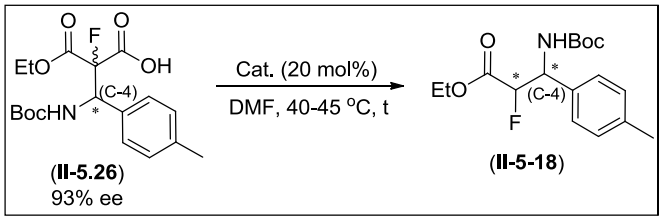
Evidently, some asymmetric protonation was achieved (dr value), however the low 30% ee value meant racemization of the stereogenic centre created during the preceding Mannich addition. Fortunately, we found that racemization can be avoided if the reaction time was shortened to 3 days, at the expense of reaction yield, assessed now as 69% (entry 5), with a higher dr value of 1:2.3. Lastly, several solvents were screened, but it was found that elevated temperature was necessary (entries 6-8). The reaction in the only other solvent found suitable - THF - required 70 °C to reach 70% conversion and the product was obtained with a lower dr value of 1.5:1 with partial racemization of the pre-installed asymmetric center (to 53% ee, entry 8). Therefore, we concluded that the optimum (preliminary) reaction conditions were as follows: DMSO, 40-45 °C, 0.2 equiv. of the catalyst, 72 h. To determine whether the protonation is an enantioselective (controlled by catalyst) or diastereoselective process

(controlled by the neighbouring, pre-installed in Mannich addition centre of asymmetry) the decarboxylation was performed using racemic halfester **II-5.26** (entry 9). The corresponding product was obtained with no dr (therefore no retro-Mannich reaction occurred) and with 31% ee on the newly generated asymmetric centre. This result proves that the protonation is controlled by catalyst; in fact the observed dr of 2.3:1 in reaction with chiral substrate corresponds well to 31% ee obtained in reaction with racemic halfester (31% ee is close to 2:1 ratio of enantiomers), which further proves that the influence of neighbouring chiral centre on protonation is not significant.

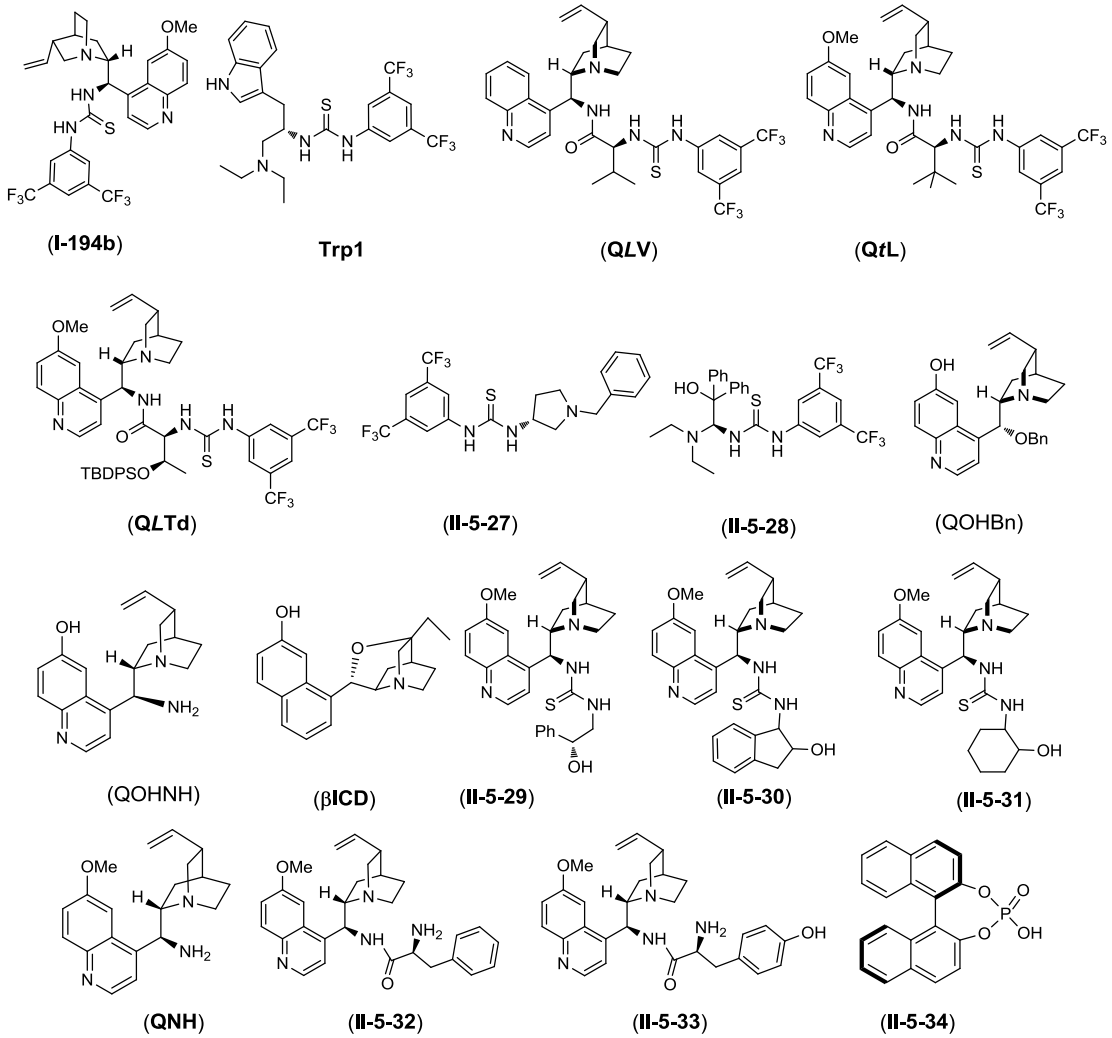
Catalyst screening in the decarboxylation/asymmetric protonation

With the preliminary conditions established, the organocatalysts were then screened using chiral substrate **II-5.26** (Table 9). The tryptophan-derived catalyst (**Trp1**) used for Mannich addition, displayed similar reactivity to the benchmark *Quinidine*-derived thiourea catalyst (**I-194b**), however the product was obtained as 1:1 mixture of diastereomers (entries 1 and 2). Next, the usually much more diastereoselective, *Quinine*-amino acid incorporating catalysts were trialed. All four catalysts were found more active, since the full conversion was achieved after 30 hours instead of 3 days; however, the best in the series - (*L*)-valine featuring catalyst **Q*L*V**, led to formation of the desired product with only 2:1 dr ratio; and diastereoselectivity was found to drop with the increase of the molecular volume of amino acid side chain (entries 3 – 5). Alternative catalysts **II-5.27** and **II-5.27** - devoid of quinuclidine *tert*-amine were than tested. Unfortunately, in both cases, drop in the enantioselectivity of the centre generated in Mannich addition (C-4) was observed (65% ee and 54% ee, entries 6 and 7). Next, *Cinchona* alkaloid-derived catalysts with additional functional groups were screened. It was found that *Quinine*-derived catalyst with de-methylated phenolic moiety was not only highly effective (reaction complete within 24 h) but also the most stereo-selective, with 2.6:1 dr ratio and untouched C-4 centre (93% ee, entry 7). Therefore, a series of catalysts with similar motif was than evaluated;

Table 9. Catalysts screening in the decarboxylation/enantioselective protonation of the Mannich adduct.[a]



Catalyst:



Entry	Catalyst	Time [h]	Conversion[b] [%]	Ee [%][c]	Dr[b]
1	**I-194b**	72	69	93	2.3:1
2	**Trp1**	72	65	93	1:1
3[d]	**QLV**	30	>99	92	2:1 (1:1.7)[d]
4	**QtL**	30	>99	93	1.5:1

5	**Q*L*Td**	30	>99	92	1.3:1
6	**II-5.27**	72	>99	65	1.4:1
7	**II-5.28**	72	>99	54	1.6:1
8	**QOHBn**	24	>99	93	2.6:1
9	**QOHNH**	22	>99	91	1.7:1
10	**βICD**	22	>99	92	2:1
11	**II-5.29**	72	>99	28	2:1
12	**II-5.30**	72	>99	57	2:1
13	**II-5.31**	72	>99	59	1.7:1
14	**QNH**	30	>99	91	2.2:1
15	**QNH** & **(+)CSA**	69	>99	90	2:1
16	**II-5.32**	51	>99	91	1.9:1
17	**II-5.33**	67	>99	91	1.6:1
18	**II-5.34**	n.d.	<10	n.d.	n.d.

[a] Reaction conditions: **II-5.26** (0.05 mmol), the base in the solvent (1ml). [b] Determined by 1H NMR analysis of the crude reaction mixture; [c] Determined by HPLC analysis on a chiral stationary phase of purified product; [d] Reaction with catalyst incorporating (*D*)-valine instead of (*L*)-valine.

Quinine-derived, phenol-containing catalyst **QOHNH** with additional primary amine was equally effective, but the dr ratio was lower (1.7:1, entry 8); similar result was also obtained with β-*iso*-Cupreine (**βICD**, entry 9). Subsequently, it was decided to explore the other hydroxyl-containing catalysts in the reaction (**II-5.29**–**31**, entries 10–12). Unfortunately, a decrease in ee value at C-4 asymmetric centre was observed in all three cases, with catalyst **II-5.29** containing benzylic hydroxyl group and flexible chain causing the most damage (only 28% ee detected, entry 11). Attention was then turned back to primary amine-containing catalysts in an effort to improve the previous result with phenolic and primary amine containing catalyst **QOHNH**. The primary *Quinine*-derived amine, with methylated phenolic moiety **QNH**, was as effective as **QOHNH** with diastereoselectivity improved to 2.2:1 (entry 14). Furthermore, addition of 1 equiv. of + CSA resulted in a slight decrease in reaction rate and diastereoselectivity (2:1 dr). Based on these results, it was reasoned that primary amine moiety may be as beneficial as phenolic OH, and subsequently two more primary amine-

containing catalysts were prepared and tested. Catalyst **II-5.32** displayed lower reactivity than **QNH** (reaction time extended to 51 h) and similar diastereoselectivity (1.9:1). The second catalyst - **II-5.33** - with an additional phenolic OH installed on the phenyl ring, was found to be even less reactive (67 h) and diastereoselective (1.6:1). Lastly, the general (*R*)-Binol-derived phosphoric acid was found ineffective in the reaction, yielding hardly any conversion of the malonate halfester.

The results obtained indicate that decarboxylation followed by enantioselective protonation took place, however despite extensive catalyst screening, we were unable to achieve practical levels of stereocontrol. Further understanding of the process and the relationship between catalyst and hypothetical enolate are necessary to envision suitable catalysts. Additionally, computational methods to approximate the protonation step and interactions between the catalyst and the enolate could aid catalyst design. Lastly, the use of external proton sources for the protonation step should also be considered in subsequent screenings.

II.5.4. Conclusion

The enantioselective Mannich addition to N-Boc imines led to preparation of diverse products with excellent optical purity. The model adduct was than transformed efficiently into α-fluoro-β-amino acid in 2 simple steps, α-fluoro-β-lactam and α-fluoro-β-lactone, both in 3 steps. The synthons prepared *via* this methodology possess two substituents easily tuneable by means of varying ketoesters and imines in the Mannich reaction. Furthermore, additional functional group present in the β-position of products (OH or NHBoc) is available for further modifications or may serve as a point of connection of the synthon to macromolecule.

The methodology for highly enantioselective Mannich addition was applicable to fluorinated malonate and the addition product to model N-Boc imine was obtained in 98% yield and with 93% ee. Subsequent tandem mono-decarboxylation/asymmetric protonation of the adducts was envisioned as an effective route towards unbranched α-fluoro-β-amino acids and was investigated. A large pool of organocatalysts was tested and found suitable for the

transformation and the enantioselective protonation was achieved with up to 2.6:1 diastereoselectivity ratio (or 31% ee). Further understanding of the reaction mechanism should be gained for the stereoselectivity of the process to be brought up to practical level.

III. Conclusion and future perspectives

III-1. Summary

III-2. Preliminary results and future perspective: decarboxylative additions of fluoromalonate halfester

III-1. Summary

Understanding the importance of fluorination as a tool for modifying the properties of bioactive molecules, studies in this thesis detail the efforts put toward the design and development of effective routes toward chiral selectively fluorinated compounds, focusing on nitrogen-containing species. Several new fluorinated donors were prepared and employed in Michael additions to representative acceptors - nitroalkenes.

Synthesis of compounds containing α-fluoro-α-amino core was achieved employing α-fluoro-α-nitro-containing prochiral donors. α-Fluoro-α-amino esters (**II-1.12**, Figure 34), α-fluoroesters (**II-1.14**) and precursors of α-fluoro-α,γ-diamines (**II-1.13**) were accessed *via* ethyl fluoronitroacetate (Chapter II-1). A practical route towards α-fluoro- mono- and diamines (**II-2.4**&**6**), as well as fluorinated heterocycles (tetrahydropyrimidines, **II-1.5**) was demonstrated with the use of 1-fluoro-1-nitro-1-arylmethanes (Chapter II-2).

Preparation of α-fluoro-β-amino-containing molecules was successfully carried out employing 2-fluoro-1,3-dicarbonyl prochiral donors. α-Fluoro-β-amino acid (**II-5.17**), β-lactam and lactone (**I-168**&**169**) were prepared through functional group manipulations performed on representative Mannich addition product (**II-5.15**, Chapter II-5). Analogical enantioselective Mannich additions of fluorinated malonate led to α-fluoro-β-amino malonate halfester (**II-5.26**) and the subsequent mono-decarboxylation/asymmetric protonation afforded linear α-fluoro-β-amino ester (**II-5.18a**). The latter challenging transformation was proven possible, however more work is necessary to increase stereoselectivity. The investigation also led to establishing a direct route toward the linear α-fluoro-β-amino esters *via* decarboxylative addition of malonate halfesters, which is detailed in future perspectives section.

The work above demonstrates a general methodology for Michael additions, applicable to other fluorinated acceptors as well. Addition of 2-fluoro-1,3-diketones was demonstrated as a method for the rapid generation of fluoro-isosteres of glycerines containing multiple asymmetric centers (**II-4.16a**&**b**, Chapter II-4); however more work is necessary to elucidate the absolute configuration of the products. Addressing the scarcity of methodologies for the preparation of fluorinated phosphorus-containing species, prochiral α-fluoro-β-ketophosphonates were synthesized and employed in Michael additions yielding branched and functionalized fluorinated phosphonates and pyrrolidines (**II-3.2**, **II-3.10** & **II-3.3** Chapter II-3).

Overall, the research presented in this thesis contributed several practical methodologies for the synthesis of precursors of fluorinated bioactive molecules *via* enantioselective Michael and Mannich additions, as well as decarboxylations. The uncommon α-fluoro-α-amino-containing species prepared for the first time (amino acid, amines and tetrahydropyrimidines), as well as novel fluorinated phosphonates and α-fluoro-β-amino-containing molecules (esters, lactams and lactones) represent potential targets for bioactivity screenings.

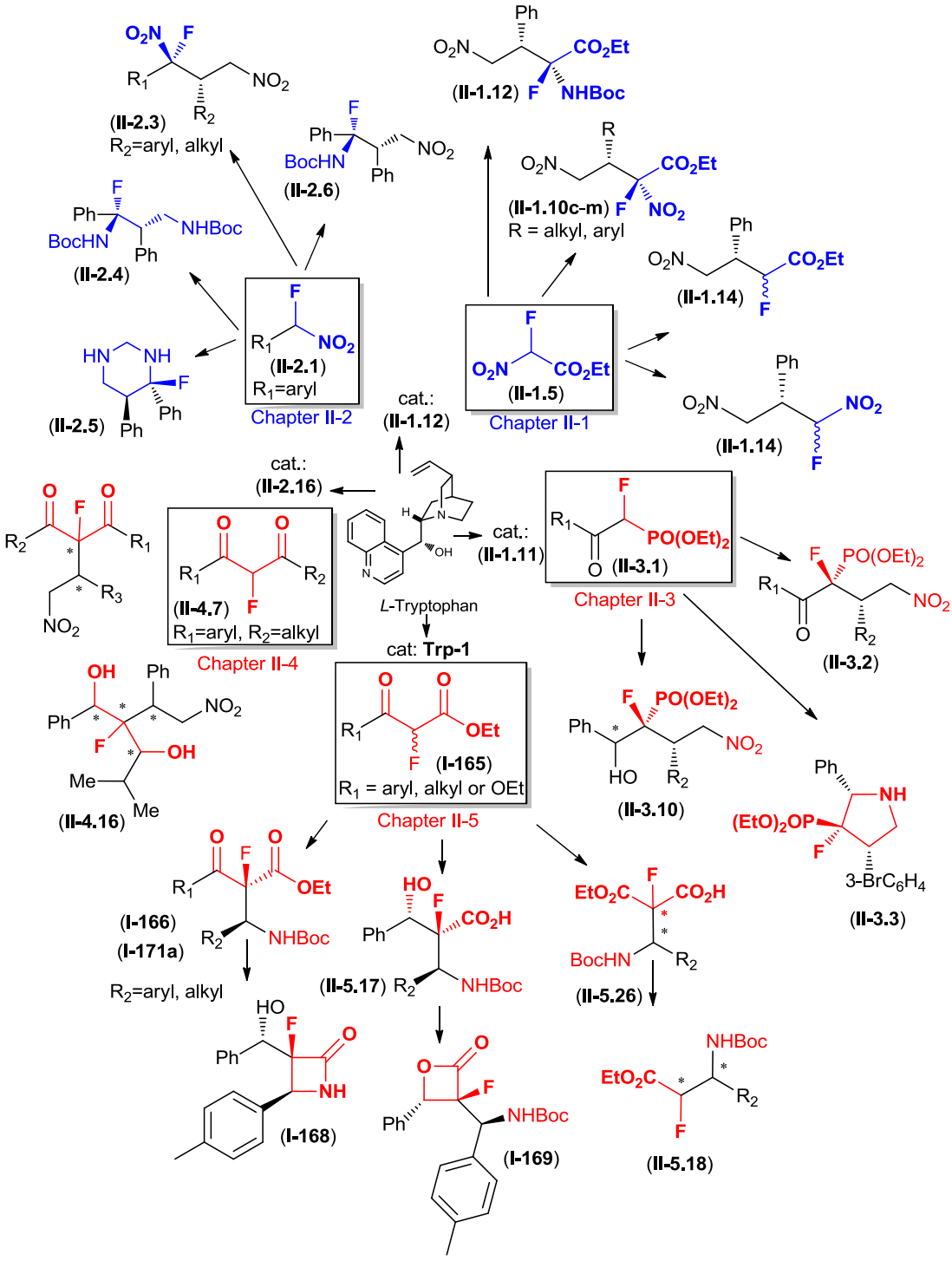
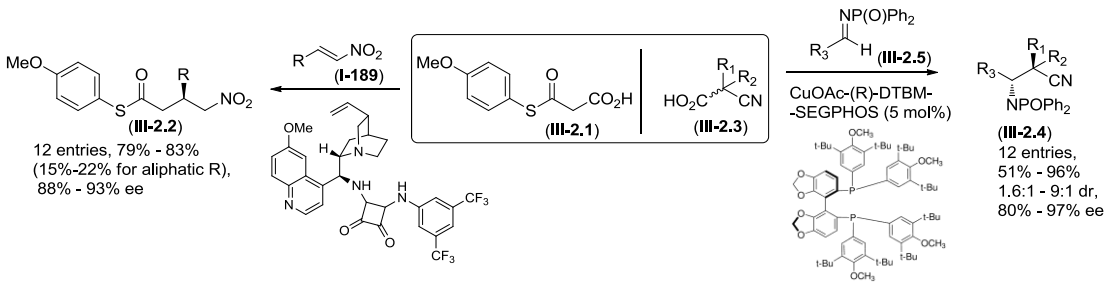


Figure 34. Synthetic methods towards chiral organofluorine molecules as precursors for bioactive compounds.

III-2. Preliminary results and future perspective: decarboxylative additions of fluoromalonate halfester

Introduction

Generation of nucleophilic enolate by decarboxylation (especially malonate half-thioesters MAHT) is a process common in biological systems,[168] less so in a synthetic laboratory.[169] Successful methodologies concern mainly decarboxylative additions of reactive acids such as malonate half-thioesters (**III-2.1**, Scheme 88),[170] α-cyanoacids (**III-2.3**)[171] or β-ketoacids.[172] However, no such reactions have been reported for malonic acid halfesters, probably due to low reactivity.

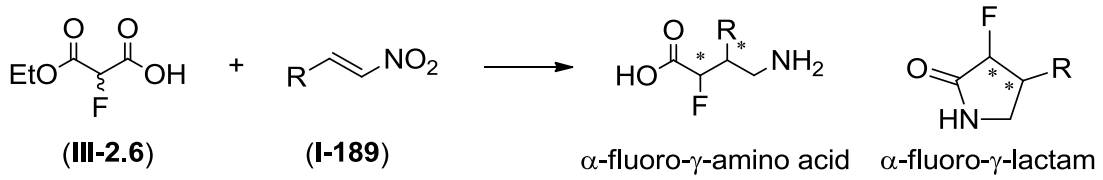


Scheme 88. Decarboxylative additions of halfesters.

We envisioned that fluorine substituent in the α position on malonic acid halfester would polarize the molecule and stabilize the resulting enolate, and as such, activate fluoromalonate halfester towards decarboxylation. Subsequent addition of the stabilized enolate to electrophiles would yield products of the formal addition of α-fluoroacetic acid ester synthon; utilizing nitroalkenes as Michael acceptor would yield products being direct precursors of α-

[168] a) A. Hill, *Nat. Prod. Rep*., 2006, **23**, 256; b) M. B. Austin, M. Izumikawa, M. E. Bowman, D. W. Udwary, J. L. Ferrer, B. S. Moore, J. P. Noel, *J. Biol. Chem*., 2004, **279**, 45162.
[169] For a recent review see: Z.-L. Wang, *Adv. Synth. Catal*., 2013, **355**, 2745.
[170] See for example: H. Y. Bae, S. Some, J. H. Lee, J. Y. Kim, M. J. Song, S. Lee, Y. J. Zhang, C. E. Song, *Adv. Synth. Catal*., 2011, **353**, 3196.
[171] L. Yin, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc*., 2009, **131**, 9610.
[172] F. R. Zhong, W. J. Yao, X. W. Dou, Y. X. Lu, *Org. Lett*., 2012, **14**, 4018.

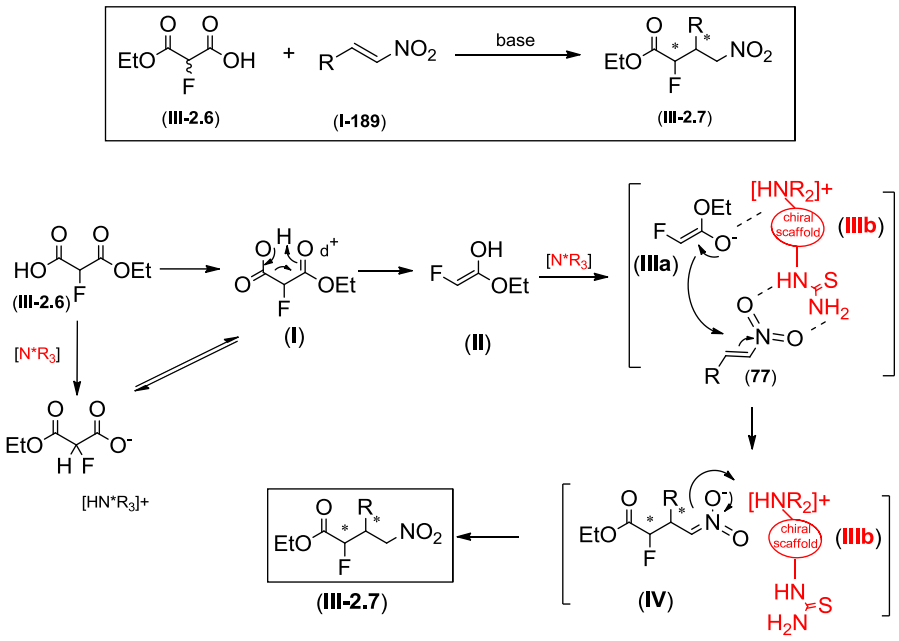
fluoro-γ-amino acids and lactams (Scheme 89) - biologically important molecules (analogues of GABA[173]) and synthons for further synthesis.



Scheme 89. Hypothetical route towards α-fluoro-γ-amino acids and α-fluoro-γ-lactams.

Preliminary results and future perspectives

Investigations on the possible mechanisms of the decarboxylation of Mannich adduct (see chapter 5) led us to the analogical hypothetical mechanism of decarboxylative addition of fluoromalonate halfesters to nitroalkenes (Scheme 90). We speculated that bifunctional catalyst (**IIIb**) would hold the two reaction partners in proximity – enolate (**IIIa**) *via* electrostatic interactions and nitroolefin (**I-189**) by the means of hydrogen-bonding of the nitro moiety to thiourea - a well proven interaction, while the chiral environment originating from chiral catalyst scaffold would enforce stereo-selectivity of the addition.

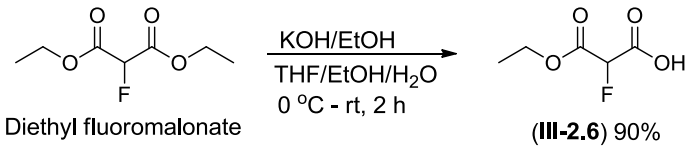


Scheme 90. Decarboxylative addition of malonate hemiester to nitroolefins.

[173] GABA - γ-aminobutyric acid - one of the most important neurotransmitters in mammalian central nervous system; compound frequently targeted in biochemical and pharmaceutical research.

Successful development of this methodology would be of great significance, as such simple general one step synthetic process from accessible fluorinated malonate hemiester and nitroolefins, yielding chiral fluorinated GABA analogues has not been reported to date.

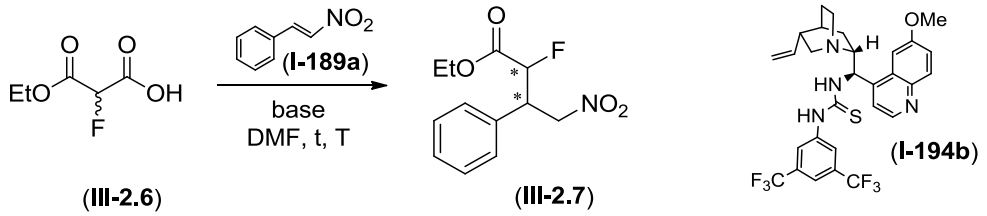
Ethyl fluoromalonate halfester was found to be easily accessible *via* monohydrolysis of commercially available diethyl fluoromalonate after optimizing the reaction conditions (Scheme 91).



Scheme 91. Monohydrolysis of diethyl fluoromalonate.

With the substrate in hand, we began to screen the reaction. It was found that the monoacid was quite stable and did not undergo decarboxylation easily under catalytic conditions; however 70% yield of the product was obtained at room temperature after 20 h when an excess of triethylamine (TEA) was used (entries 1 and 2, Table 10). Fortunately, in the absence of base, almost no reaction took place even at elevated temperature, therefore stereo-selective process would not be compromised by background racemic reaction at temperatures as high as 70 ^{o}C (entry 3). We then began searching for the mildest conditions in terms of temperature and catalyst loading in which the reaction would proceed with acceptable yield. It was found that a combination of 1 equiv. of TEA and 0.2 equiv. of chiral base **I-194b**, led to 50% conversion after 3 days at room temperature (entry 4). At elevated temperature, the reaction was found to proceed with catalytic amount of catalyst (entries 5-9); acceptable conversions can be achieved at 55 - 60 ^{o}C over 24 h (54%) or at 40 - 45 ^{o}C over 7 days (65%). In all cases, the observed diastereoselectivity was 1:1, while measurement of enantioselectivity was not yet carried out due to difficulties with separation of peaks on HPLC chromatogram.

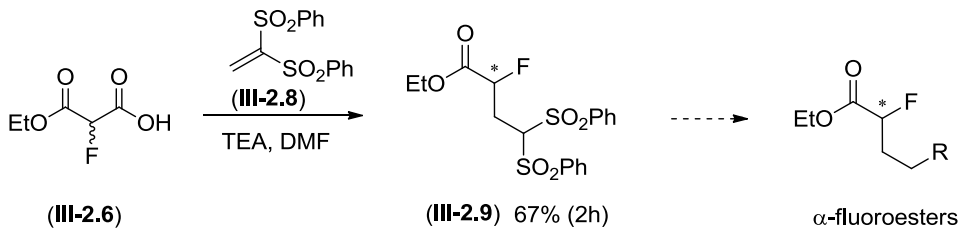
Table 10. Decarboxylative addition of nitroolefin to fluoromalonate hemiester.[a,b]



Entry	Base (equiv.)	Temp [°C]	Time [h]	Yield [%][c]	Dr[d]
1	TEA (1.5)	rt	20h	70%	1:1
2	**I-194b** (0.1)	rt	7d -	<10%	n.d.
3	----	65-70 °C	22h	<10%	n.d.
3	**I-194b** (0.2) + **TEA** (1)	rt	72h	50%	1:1
5	**I-194b** (0.2)	65-75 °C	20h	55%	1:1
6	**I-194b** (0.1)	65-75 °C	22h	44%	1:1
7	**I-194b** (0.2)	55-60 °C	24h	54%	…
9	**I-194b** (0.2), DMSO	40-45 °C	7d	65%	1:1

[a] Reaction conditions: **III-2.6** (0.05 mmol), nitroalkene (0.06 mmol), the base in the solvent (1ml). [b] The ee value was not determined, due to inability to separate peaks on HPLC to date; [c] Isolated yield; [d] Determined by ^{1}H NMR analysis of the crude reaction mixture.

Upon finding the conditions to measure the ee value, more catalysts will be screened for this transformation. Furthermore, the methodology is general and other acceptors can be employed, such as vinyl sulphones (Scheme 92).



Scheme 92. Decarboxylative addition of fluoromalonate hemiester to vinyl sulphone.

Such reaction would lead to general and linear α-fluoro-esters - a class of important yet under-investigated compounds in three steps, which would otherwise be difficult to synthesize *via* other methods.

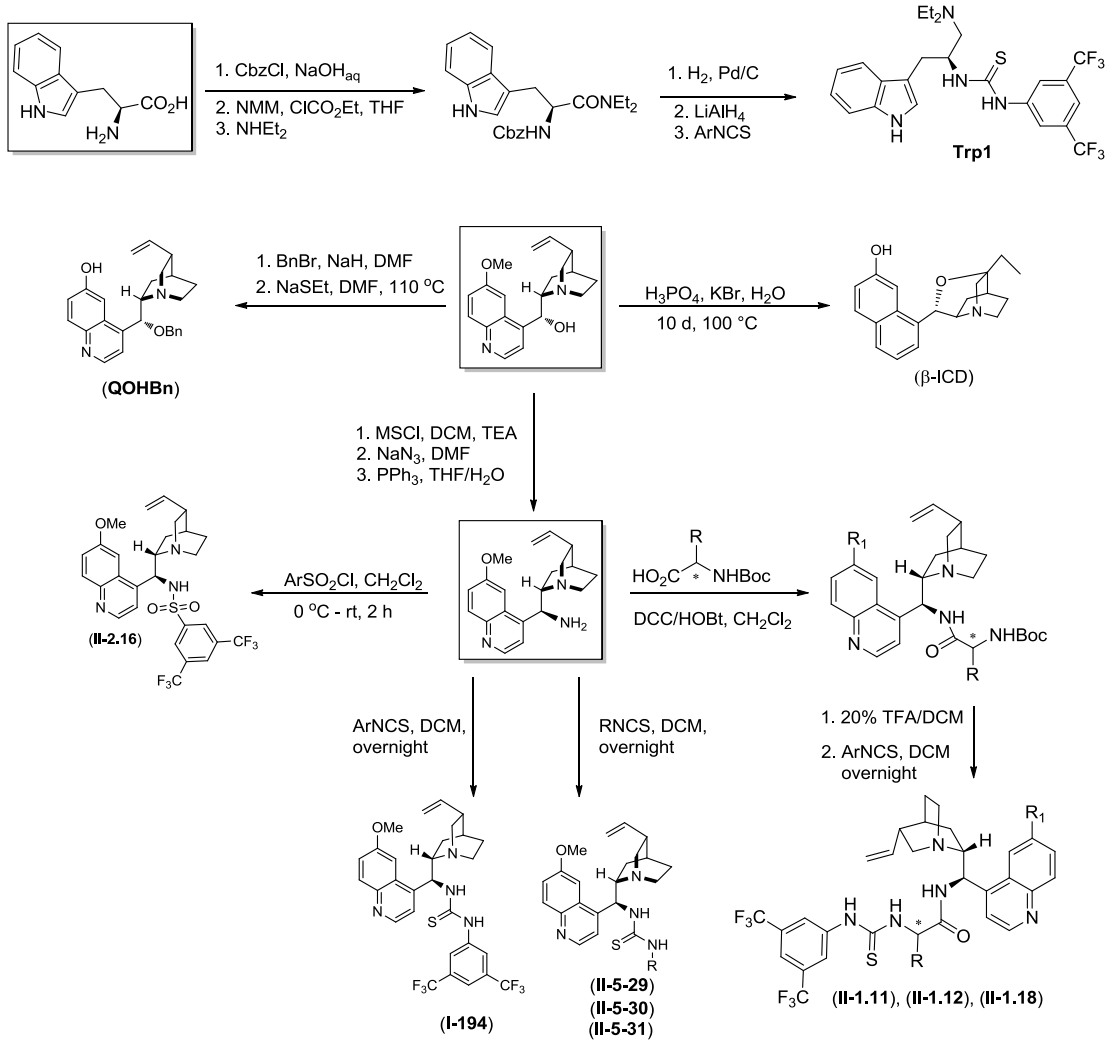
IV - Experimental

General Information

All the starting materials were obtained from commercial sources and used without further purification unless otherwise stated. Solvent purification system was used to dry and purify toluene, CH_2Cl_2 and diethyl ether while THF was dried and distilled from sodium benzophenone ketyl prior to use. $CHCl_3$ was distilled from CaH_2 prior to use. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker ACF300, AMX 400 or AMX500 (^1H and ^{13}C only) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0), fluorine $CFCl_3$ (AMX400) or TFA (ACF300). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), bs (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL- T mass spectrometer in FAB mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL- T spectrometer. For thin layer chromatography (TLC), Merck pre- coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with $KMnO_4$ aqueous solution or ninhydrine solution in ethanol, followed by heating with a heat gun. Flash chromatographic separations were performed on Merck 60 (0.040- 0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral-phase HPLC analysis. Optical rotations were recorded on Jasco DIP-1000 Digital Polarimeter with 10 mm cell and 589 nm sodium lamp.

All the catalysts used in screenings were prepared according to known procedures (see the general Scheme 93) and their data identical with reported data. 2-fluoro-1,3-diketones were prepared according to known procedures (scheme shown in chapter II-4) and their NMR characteristics were identical with reported data.[174] Nitroalkenes were prepared according to published procedures from corresponding aldehydes and nitromethane.

[174] a) N. Ahlsten, A. Bartoszewicz, S. Agrawal, B. Martin-Matute, *Synthesis*, 2011, **16**, 2600; b) S. Hara, N. Yoneda, *et. al.*, *J. Fluor. Chem.*, 1998, **87**, 189; c) T. Kitamura, S. Kuriki, M. H. Morshed, Y.



Scheme 93. General synthetic routes towards organocatalysts employed.[175]

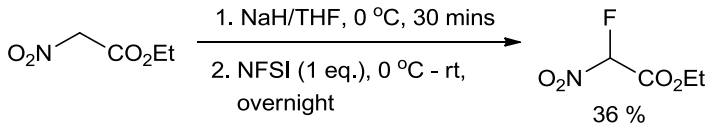
Hori, *Org. Lett.*, 2011, **13**, 2392; d) S. T. Purrington, C. L. Bumgardner, N. V. Lazaridis, P. Singh, *J. Org. Chem.*, 1987, **52**, 4307.

[175] a) X, Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.*, 2009, **48**, 7604; b) Q. Zhu, Y. Lu, *Org. Lett.*, 2009, **11**, 1721; c) X. Liu, Y. Lu, *Org. Lett.*, 2010, **12**, 5592; d) X. Liu, Y. Lu, *Org. Biomol. Chem.*, 2010, **8**, 4063; e) A. Nakano, S. Kawahara, S. Akamatsu, K. Morokuma, M. Nakatani, Y. Iwabuchi, K. Takahashi, J. Ishihara and S. Hatakeyama, *Tetrahedron*, 2006, **62**, 381.

IV-1. Towards the enantioselective synthesis of functionalized α-fluoro-α-amino acids: organocatalytic Michael addition / hydrogenation of ethyl fluoro -nitroacetate

IV-1.1. Preparation of Substrates

Nitroalkenes were prepared from respective aldehydes and nitromethane according to reported procedures. Ethyl fluoronitroacetate was prepared from commercially available ethyl nitroacetate. As the compound is unstable and decomposes over several hours it was freshly prepared before each batch of reactions. It can be stored for a week at -78 ^{o}C, however the trace impurities generated over that time would affect negatively the enantioselectivities of Michael addition products.



To a dried round bottom flask (heated under vacuum with heat gun) filled with argon was added freshly distilled THF (10 ml) and ethyl nitroacetate (2mmol, 266 mg). The flask was placed into cooling bath and 15 minutes later; NaH (60% dispersion in oil, 80 mg) was added in one portion, under the protection of argon. The reaction mixture was then stirred overnight at room temperature. After 12-16 h, TLC analysis or crude NMR indicated 40% - 50% conversion of ethyl nitroacetate into ethyl fluoronitroacetate. The reaction mixture was diluted with ethyl acetate (50 ml) and washed 3 times with 1M aqueous solution of HCl, followed by brine (1x). After drying over sodium sulphate, organic layer was evaporated and the crude product subjected to purification by column chromatography on silica get column eluting with Hexane/diethyl ether = 7/1. The product was obtained as a lively, pale yellow oil - 109 mg, 36% yield.[176] The analytical data was identical with previously reported data for that compound.

[176] The quality of ethyl fluoronitroacetate affects severely the enantioselectivities obtained in the Michael reaction. Impurities are difficult to spot on ^{1}H NMR spectrum due to overlapping peaks with

Ethyl fluoronitroacetate (**II-1.5a**)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (d, J = 48.6 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.0 Hz, 3H).

iso-Propyl fluoronitroacetate (**II-1.5b**)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.00 (d, J = 48.8 Hz, 1H), 5.21 (m, 1H), 1.36 (d, J = 6.3 Hz, 6H); ^{13}C NMR (100.62 MHz, $CDCl_3$): 158.56 (d, J = 24.9 Hz), 102.91 (d, J = 250.1), 73.43, 21.33, 21.29; ^{19}F NMR (376.46 MHz, $CDCl_3$): -150.00 (d, J = 48.9 Hz).

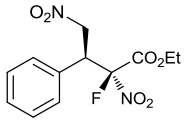
IV-1.2. Experimental procedure and the analytical data of the Michael reaction products

Michael addition of ethyl fluoronitroacetate to nitroalkenes - representative procedure:

To a sample vial containing the fluoronitroacetate (0.1 mmol, 15 mg) in toluene (1 ml), **II-1.11b** (0.01 mmol, 10 mg) was added. The vial was then capped and the reaction mixture was stirred for 5 minutes at 0 ^{o}C. Subsequently nitroalkene (0.11 mmol) was added at 0 ^{o}C under nitrogen protection, the vial was sealed and the reaction mixture was stirred at that temperature for one hour. Upon completion of the reaction, the mixture was passed through a short silica gel column to remove the catalyst (possible recovery of the catalyst), evaporated and analyzed by ^{1}H NMR. Lastly, the crude product was subjected to column chromatographic separation eluting with hexane/ethyl acetate (20 : 1 – 10 : 1) to afford the respective Michael products (**II-1.10a**–**m**).

the desired product but manifest themselves by colouring the ethyl fluoronitroacetate to a more intense yellow to orange.

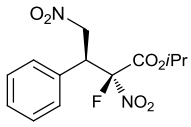
Ethyl (2*S*,3*S*)-2-fluoro-2,4-dinitro-3-phenylbutanoate (**II-1.10a**)



II-1.10a

$[\alpha]^{270}_{D}$ = +56.1 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 3H), 7.29 (m, 2H), 5.07 (dd, J = 13.2 Hz, 4.4 Hz, 1H), 4.96 – 4.82 (m, 3H), 4.42 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 160.28, 160.01, 129.86, 129.34, 129.10, 113.03 (d, J = 257.5 Hz), 74.57, 65.28, 47.09 (d, J = 18.1 Hz), 13.63; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -132.88 (d, J = 28.5 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{12}FN_2O_6$ $[M-H]^+$ = 299.0685, found = 299.0681; the ee value was 97%, t_R (major) = 17.5 min, t_R (minor) = 20.2 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

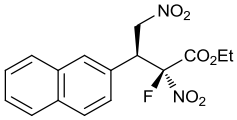
Isopropyl 3-(3-bromophenyl)-2-fluoro-2,4-dinitrobutanoate (**II-1.10b**)



II-1.10b

$[\alpha]^{270}_{D}$ = +56.7 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (m, 1H), 7.46 (s, 1H), 7.23 (d, J = 4.8 Hz, 2H), 5.22 (m, 1H), 5.06 (dd, J = 13.6 Hz, 5.2 Hz, 1H), 4.91 – 4.78 (m, 2H), 1.35 (d, J = 6.4 Hz, 3H), 1.33 (d, J – 6.4 Hz, 3H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 159.52, 159.26, 133.14, 132.15, 130.81, 127.79, 123.28, 112.79 (d, J = 257.99 Hz), 74.65, 74.33, 46.63 (d, J = 18.1 Hz), 21.24, 21.05 ; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ –132.50 (d, J = 27.85 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{14}FN_2O_6$ $[M-H]^-$ = 313.0857, found = 313.0853; the ee value was 86%, t_R (major) = 15.0 min, t_R (minor) = 9.2 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

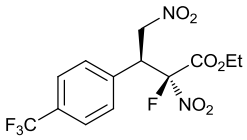
Ethyl 2-fluoro-3-(naphthalen-2-yl)-2,4-dinitrobutanoate (**II-1.10c**)



II-1.10c

$[\alpha]^{270}_{D}$ = +52.1 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 – 7.77 (m, 4H), 7.52 (m, 2H), 7.38 (d, J = 8.4 Hz, 1H), 5.18 – 4.94 (m, 3H), 4.63 – 4.41 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.47 Hz, $CDCl_3$) δ 160.17 (d, J = 26.4 Hz), 133.53, 133.03, 129.44, 129.39, 128.18, 127.69, 127.27, 127.21, 126.87, 125.37, 113.06 (d, J = 267.7 Hz), 74.62 (d, J = 3.5 Hz), 65.33, 47.22 (d, J = 18.3 Hz), 13.64; ^{19}F NMR (376.46 Hz, $CFCl_3$) δ -132.44 (d, J = 27.8 Hz); HRMS (ESI) m/z calcd for $C_{16}H_{14}FN_2O_6$ $[M-H]^-$ = 349.0837, found = 349.0841; the ee value was 82%, t_R (major) = 18.1 min, t_R (minor) = 14.2 min (Chiralcel IA, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

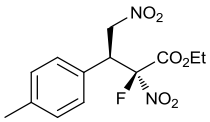
Ethyl 2-fluoro-2,4-dinitro-3-(4-(trifluoromethyl)phenyl)butanoate (**II-1.10d**)



II-1.10d

$[\alpha]^{270}_{D}$ = +54.4 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.24 (dd, J = 5.2 Hz, 0.80 Hz, 2H), 5.11 (dd, J = 13.6 Hz, 4.0 Hz, 1H), 5.98 (ddd, J = 28.0 Hz, 10.0 Hz 4.4 Hz, 1H), 4.84 (dd, J = 12.0 Hz, 9.2 Hz, 1H), 4.43 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 159.70, 133.97, 131.99, 129.72, 126.36, 124.82, 122.11, 112.62 (d, J = 258.14 Hz), 74.17, 65.57, 46.76 (d, J = 17.8 Hz), 13.61 ; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ 63.10, –132.62 (d, J = 27.8 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{11}F_4N_2O_6$ $[M]^-$ = 367.0559, found = 367.0541; the ee value was 96%, t_R (major) = 12.9 min, t_R (minor) = 26.1 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

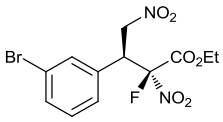
Ethyl 2-fluoro-2,4-dinitro-3-(*p*-tolyl)butanoate (**II-1.10e**)



II-1.10e

$[\alpha]^{270}_{D}$ = +75.1 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (m, 4H), 5.07 – 5.02 (m, 1H), 4.92 – 4.79 (m, 2H), 4.42 (m, 2H), 2.32 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 160.07, 139.91, 130.03, 128.94, 128.92, 126.74, 113.12 (d, J = 257.03 Hz), 74.62, 65.22, 46.81 (d, J = 17.7 Hz), 21.12, 13.63 ; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ −133.01 (d, J = 28.6 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{15}FNaN_2O_6$ $[M+Na]^+$ = 337.0806, found = 337.0812; the ee value was 82%, t_R (major) = 21.5 min, t_R (minor) = 22.8 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

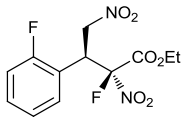
Ethyl 3-(3-bromophenyl)-2-fluoro-2,4-dinitrobutanoate (**II-1.10f**)



II-1.10f

$[\alpha]^{270}_{D}$ = +49.0 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (m, 1H), 7.47 (s, 1H), 7.24 (dd, J = 5.2 Hz, 0.80 Hz, 2H), 5.22 (m, 1H), 5.06 (dd, J = 13.6 Hz, 4.0 Hz, 1H), 4.92 – 4.77 (m, 2H), 4.42 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 160.03, 133.18, 132.14, 130.83, 127.80, 127.78, 123.30, 112.67 (d, J = 257.84 Hz), 74.26, 65.48, 74.33, 46.65 (d, J = 18.2 Hz), 13.63 ; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ −132.61 (d, J = 27.8 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{11}BrFN_2O_6$ $[M]^-$ = 376.9690, found = 376.9787; the ee value was >99%, t_R (major) = 17.8 min, t_R (minor) = 15.5 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

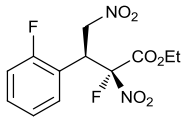
Ethyl 2-fluoro-3-(2-fluorophenyl)-2,4-dinitrobutanoate (**II-1.10g**)



II-1.10g

major diastereomer

$[\alpha]^{270}_{D}$ = +3.8 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.30 (m, 2H), 7.18 – 7.08 (m, 2H), 5.34 – 5.31 (m, 1H), 5.25 (dd, J = 8.0 Hz, 4.8 Hz, 1H), 5.11 (dd, J = 14.0 Hz, 4.8 Hz, 1H), 4.41 (qd, J = 7.2 Hz, 2.0 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 159.93 (d, J = 26.8 Hz), 131.90, 130.17, 125.04, 117.59, 116.72, 116.55, 112.68 (d, J = 258.8 Hz), 73.64 (d, J = 3.3 Hz), 65.38, 40.90 (d, J = 18.9 Hz), 13.62; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ –114.12, -131.42 (dd, J = 27.4 Hz, 15.8 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{12}F_2NaN_2O_6$ $[M]^+$= 341.0561, found = 341.0565; the ee value was 63%, t_R (major) = 17.1 min, t_R (minor) = 34.3 min (Chiralcel IB+IC, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

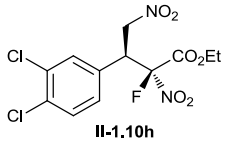


II-1.10g'

minor diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.38 (m, 1H), 7.37 – 7.30 (m, 1H), 7.21 – 7.11 (m, 2H), 5.39 – 5.30 (m, 1H), 4.93 (t, J = 8.4 Hz, 2H), 4.22 (q, J = 7.2 Hz, 1H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.47 Hz, $CDCl_3$) δ 159.10 (d, J = 27.2 Hz), 131.91, 129.52, 125.10, 117.53, 116.63, 116.32, 112.56 (d, J = 257.2 Hz), 73.16 (d, J = 4.4 Hz), 64.99, 40.12 (d, J = 19.5 Hz), 13.42; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ –114.22, –130.52 (dd, J = 22.9 Hz, 11.3 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{12}F_2NaN_2O_6$ $[M]^+$= 341.0561, found = 341.0567; the ee value was 26%, t_R (major) = 18.8 min, t_R (minor) = 30.8 min (Chiralcel IB+IC, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

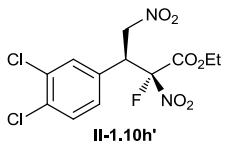
Ethyl 3-(3,4-dichlorophenyl)-2-fluoro-2,4-dinitrobutanoate (**II-1.10h**)



II-1.10h

major diastereomer

$[\alpha]^{270}_{D}$ = +59.8 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.4 Hz, 1H), 7.40 (s, 1H), 7.16 (d, J = 8.6 Hz, 1H), 5.06 (dd, J = 13.6 Hz, 4.0 Hz, 1H), 4.92 – 4.74 (m, 2H), 4.46 – 4.40 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 159.70 (d, J = 26.5 Hz), 134.72, 133.74, 131.36, 131.10, 129.97, 128.33, 112.48 (d, J = 257.9 Hz), 74.08 (d, J = 3.6 Hz), 65.60, 46.20 (d, J = 18.1 Hz), 13.62; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -132.65 (d, J = 27.4 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{10}Cl_2FN_2O_6$ $[M]^-$ = 366.9905, found = 366.9922; the ee value was 83%, t_R (major) = 25.4 min, t_R (minor) = 31.7 min (Chiralcel IB, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 1 mL/min).

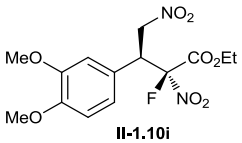


II-1.10h'

minor diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.19 (d, J = 8.0 Hz, 1H), 4.95 – 4.77 (m, 3H), 4.27 (qd, J = 7.2 Hz, 1.6 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 158.81 (d, J = 26.3 Hz), 134.70, 134.74, 131.37, 130.03, 128.35, 112.82 (d, J = 254.8 Hz), 73.59 (d, J = 5.3 Hz), 65.19, 46.27 (d, J = 18.4 Hz), 13.57; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -131.95 (d, J = 24.0 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{10}Cl_2FN_2O_6$ $[M]^-$ = 366.9905, found = 366.9922; the ee value was 17%, t_R (major) = 29.6 min, t_R (minor) = 36.4 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

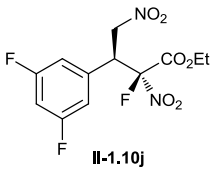
(2S,3S)-ethyl 3-(3,4-dimethoxyphenyl)-2-fluoro-2,4-dinitrobutanoate (**II-1.10i**)



II-1.10i

$[\alpha]^{270}_{D}$ = +37.4 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) (diastereomeric mixture 2:1): δ 6.87 - 6.72 (m, 6H), 5.05 – 5.02 (m, 1H), 4.89 – 4.77 (m, 5H), 4,41 (m, 2H, major dr), 4.19 (q, J = 7.0 Hz, 2H, minor dr), 3.86 (m, 12H), 1.36 (t, J = 7.0 Hz, 3H, major dr), 1.16 (t, J = 7.0 Hz, 3H, minor dr); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 160.37, 159.97, 150.12 (d, J = 3.6 Hz), 149.32 (d, J = 3.8 Hz), 121.75, 121.62, 112.15 (d, J = 20.3 Hz), 112.14 (d, J = 19.6 Hz), 111.45, 74.68 (d, J = 7.8 Hz), 74.24 (d, J = 8.6 Hz), 65.25, 64.75, 56.01, 55.82, 46.97 (d, J = 3.8 Hz), 46.73 (d, J = 3.5 Hz), 29.69, 29.35, 14.11, 13.65; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -56.652 (d, J = 33.8 Hz), -57.01 (d, J = 39.1 Hz); HRMS (ESI) m/z calcd for $C_{14}H_{16}FN_2O_8$ $[M]^-$ = 359.0891, found = 359.0894; the ee value was 85%, t_R (major) = 32.9 min, t_R (minor) = 36.4 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.2 mL/min).

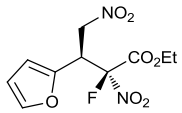
Ethyl 3-(3,5-difluorophenyl)-2-fluoro-2,4-dinitrobutanoate (**II-1.10j**)



II-1.10j

$[\alpha]^{270}_{D}$ = +54.8 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 – 6.83 (m, 3H), 5.08 (dd, J = 14.0 Hz, 4.4 Hz, 1H), 4.87 (ddd, J = 27.6 Hz, 9.6 Hz, 6.4 Hz, 1H), 4.78 (dd, J = 13.6 Hz, 10.0 Hz, 1H), 4.46 – 4.41 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.47 Hz, $CDCl_3$) δ 164.75 (d, J = 12.8 Hz), 161.45 (d, J = 12.4 Hz), 159.71 (d, J = 26.3 Hz), 133.30, 112.77, 112.39, 112.35 (d, J = 256.5 Hz), 74.05 (d, J = 3.6 Hz), 65.64, 46.52 (d, J = 17.6 Hz), 13.62; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ –106.72 (t, J = 7.1 Hz), -132.68 (d, J = 27.4 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{10}F_3N_2O_6$ $[M]^-$= 335.0491, found = 335.0498; the ee value was 77%, t_R (major) = 6.5 min, t_R (minor) = 9.5 min (Chiralcel IC, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

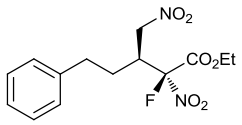
Ethyl 2-fluoro-3-(furan-2-yl)-2,4-dinitrobutanoate (**II-1.10k**)



II-1.10k

$[\alpha]^{270}_{D}$ = +36.9 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) (diastereomeric mixture): δ 7.44 – 7.42 (m, 2H), 6.45 (dd, J = 3.3 Hz, 0.3 Hz, 1H), 6,41 – 6.36 (m, 3H), 517 – 5.04 (m, 2H), 5.01 – 4.93 (m, 3H), 4.85 – 4.80 (m, 1H), 4.42 (q, J = 7.0 Hz, 2H, minor dr), 4.32 (q, J = 7.2 Hz, 2H, major dr), 1.37 (t, J = 7.0 Hz, 3H, minor dr), 1.28 (t, J = 7.2 Hz, 3H, major dr); ^{13}C NMR (75 Hz, $CDCl_3$) δ 159.94, 159.59, 144.53, 144.46, 143.11, 143.03, 112.07, 112.00 (d, J = 255.5 Hz), 111.99, 111.76 (d, J = 254.3 Hz), 111.11, 111.07, 72.12, 72.09, 65.34, 65.09, 41.73, 41.46, 13.63; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -129.78 (d, J = 24.8 Hz), –132.04 (d, J = 28.2 Hz); HRMS (ESI) m/z calcd for $C_{10}H_{11}FNaN_2O_7$ $[M+Na]^+$ = 313.0443, found = 313.0450; the ee value was 81% for major diastereomer, t_R (major) = 13.3 min, t_R (minor) = 17.2 min (Chiralcel IA, λ = 254 nm, 2% *i*PrOH/hexanes, flow rate = 1 mL/min); the ee value was 27% for the minor diastereomer, t_R (major) = 11.9 min, t_R (minor) = 15.5 min (Chiralcel IA, λ = 254 nm, 2% *i*PrOH/hexanes, flow rate = 1 mL/min).

Ethyl 2-fluoro-2-nitro-3-(nitromethyl)-5-phenylpentanoate (**II-1.10l**)

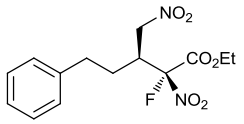


II-1.10l

major diastereomer

$[\alpha]^{270}_{D}$ = +11.7 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, J = 6.8 Hz, 2H), 7.24 (d, J = 7.2 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 4.73 (dd, J = 14.8 Hz, 5.6 Hz, 1H), 4.49 (dd, J = 14.4 Hz, 5.2 Hz, 1H), 4.36 (qd, J = 7.2 Hz, 2.0 Hz, 2H), 3.73 – 3.64 (m, 1H), 2.82 – 2.64 (m, 2H), 1.91 – 1.85 (m, 1H), 1.81 – 1.76 (m, 1H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 160.05 (d, J = 26.8 Hz), 139.13, 128.81, 128.24, 126.79, 114.05 (d, J = 254.1 Hz), 73.19 (d, J = 2.9 Hz),

65.03, 40.83 (d, J = 19.9 Hz), 32.65, 28.89, 13.58; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -131.08 (d, J = 22.3 Hz); HRMS (ESI) m/z calcd for $C_{14}H_{16}FN_2O_6$ $[M-H]^-$ = 327.0998, found = 327.0985; the ee value was 81%, t_R (major) = 19.9 min, t_R (minor) = 17.9 min (Chiralcel IB, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

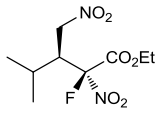


II-1.10l'

minor diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, J = 6.8 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 7.14 (d, J = 7.2 Hz, 2H), 4.78 (dd, J = 14.4 Hz, 4.8 Hz, 1H), 4.45 (dd, J = 14.8 Hz, 6.0 Hz, 1H), 4.38 (qd, J = 7.2 Hz, 2.0 Hz, 2H), 3.65 – 3.59 (m, 1H), 2.82 – 2.66 (m, 2H), 2.07 – 1.98 (m, 1H), 1.84 – 1.74 (m, 1H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.47 Hz, $CDCl_3$) δ 159.90 (d, J = 26.9 Hz), 139.25, 128.79, 128.24, 126.77, 114.03 (d, J = 276.5 Hz), 73.64 (d, J = 4.5 Hz), 65.04, 40.82 (d, J = 20.7 Hz), 32.68, 29.62, 13.66; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -127.88 (d, J = 18.4 Hz); HRMS (ESI) m/z calcd for $C_{14}H_{16}FN_2O_6$ $[M-H]^-$ = 327.0998, found = 327.0985; the ee value was 14%, t_R (major) = 14.7 min, t_R (minor) = 15.9 min (Chiralcel IB, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

Ethyl 2-fluoro-4-methyl-2-nitro-3-(nitromethyl)pentanoate (**II-1.10m**)

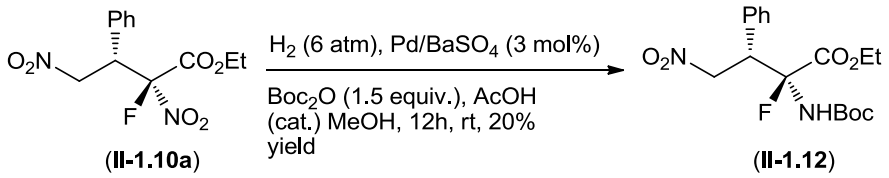


II-1.10m

$[\alpha]^{270}_D$ = +21.4 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (diastereomeric mixture): δ 4.61 (td, J = 15.2 Hz, 6.0 Hz, 2H), 4.50 (ddd, J = 15.2 Hz, 4.0 Hz, 2.0 Hz, 2H), 4.42 (q, J = 7.2 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.82 – 3.79 (m, 1H), 3.78 – 3.73 (m, 1H), 2.20 – 2.16 (m, 1H, minor dr), 2.01 – 1.97 (m, 1H, major dr), 1.37 (m, 6H), 1.09 (dd, J = 6.8 Hz, 5.2 Hz, 6H), 0.96 (m, 6H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 160.30 (d, J = 34.3 Hz), 160.15 (d, J = 33.6 Hz), 115.13

(d, J = 255.2 Hz), 114.89 (d, J = 255.9 Hz), 70.33, 70.30, 65.04, 64.93, 45.45 (d, J = 17.9 Hz), 45.26 (d, J = 17.8 Hz), 27.72, 27.41, 21.40, 21.36, 17.41, 17.35, 13.69, 13.51; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -129.75 (d, J = 24.5 Hz), –132.00 (d, J = 28.2 Hz); HRMS (ESI) m/z calcd for $C_9H_{14}FN_2O_6$ $[M-H]^-$ = 265.0841, found = 265.0833; the ee value for the major diastereomer was 78%, t_R (major) = 6.9 min, t_R (minor) = 8.3 min (Chiralcel ID, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

IV-1.3. Catalytic hydrogenation and analytical data of α-fluoro-α-amino ester



Experimental procedure:

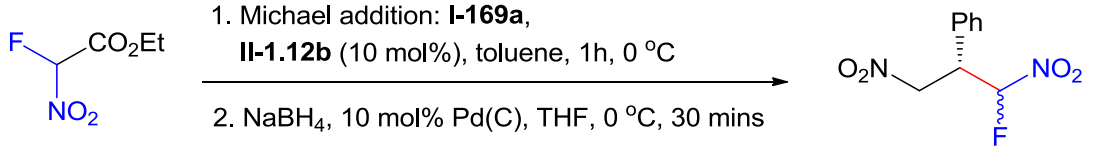
Michael adduct (**II-1.10a**, 0.2 mmol, 60 mg) was dissolved in MeOH (2 ml). Boc anhydride was then added (1.5 equiv. 65.5 mg), followed by 2 drops of glacial acetic acid, $Pd/BaSO_4$ (3 mol% Pd, 0.006 mmol, 12.8 mg of 5 wt% $Pd/BaSO_4$). The reaction mixture was placed in autoclave and stirred for 12 h at 6 atm H_2 with stirring at room temperature. After that time, the reaction mixture was filtered through cellite and the volatiles were removed *in vacuo*, below 20 °C.[177] The crude reaction mixture was purified on silica gel column eluting with hexane/ethyl acetate (20/1 – 10/1). The pure product was obtained as a white solid (15 mg, 20%).

$[\alpha]^{270}_D$ = -15.0 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 - 7.33 (m, 5H), 5.39 – 5.31 (m, 2H), 4.99 (dd, J = 12.0 Hz, 7.2 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.98 (s, 1H), 1.56 (s, 9H), 1.32

[177] Heating should be avoided and it is recommended to remove acetic acid together with solvent to avoid defluorination - thus the use of vaccum; other work-up procedures resulted in lower isolated yield of product.

(t, J = 7.2 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 162.34, 154.24, 133.45, 129.22, 128.40, 118.22, 85.43, 75.12, 62.99, 41.8, 27.63, 13.90; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -132.82 (d, J = 28.2 Hz); HRMS (ESI) m/z calcd for $C_{17}H_{26}FN_2O_7$ $[M+H_3O]^+$ = 389.1336, found = 389.1348.

IV-1.4. Decarboethoxylation and analytical data of fluoro-dinitro compounds

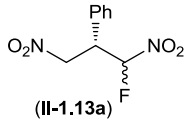


(**II-1.5a**) (**II-1.13a**,**b**) 96%, 3:1 dr

Experimental procedure:

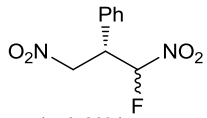
The Michael addition reaction mixture was filtered through a short column of silica gel to remove the catalyst and concentrated. The crude residue (approx. 0.1 mmol of product) was dissolved in dry THF (1.5 ml) and Pd/C was added (10 mol%, 0.01 mmol, 10.6 mg of 10 w% Pd/C). The reaction mixture was capped, placed in 0 °C cooling bath and stirred for 10 mins. Then, 1.5 equiv. of sodium borohydride was added in one portion (6 mg, 0.15 mmol) and the reaction mixture was stirred at 0 °C for additional 30 mins. Upon completion (TLC analysis), the reaction was quenched with satd. aqueous ammonium chloride (2 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The organic phases were combined, dried over sodium sulphate and evaporated. The residue was purified on silica gel column eluting with hexane/ethyl acetate (20/1 - 10/1) and both diastereomers were separated and collected as pure products - pale yellow oils in 3:1 ratio. Total yield was 96% (21.8 mg).

((2S)-1-fluoro-1,3-dinitropropan-2-yl)benzene, ***major*** **(II-1.13a)**



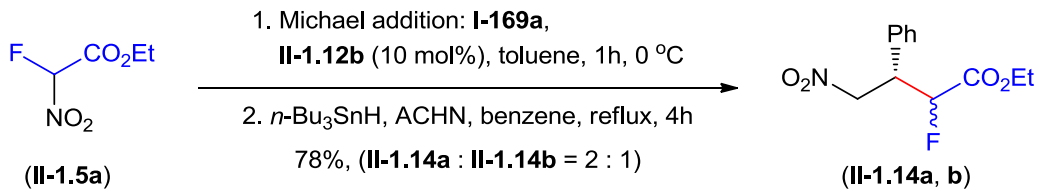
(**II-1.13a**) $[\alpha]^{270}_{D}$ = +19.0 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 - 7.36 (m, 3H), 7.21 (m, 2H), 6.22 (dd, J = 50.5 Hz, 3.0 Hz, 1H), 4.98 (dd, J = 14.5 Hz, 5.5 Hz, 1H), 4.79 (dd, J = 14.5 Hz, 6.6 Hz, 1H), 4.51 – 4.42 (m, 1H), ; ^{13}C NMR (125 Hz, $CDCl_3$) δ 129.89, 129.53, 128.69, 108.90 (d, J = 242.9 Hz), 73.84, 46.13; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -155.50 (dd, J = 50.4 Hz, 27.8 Hz); HRMS (ESI) m/z calcd for $C_9H_8FN_2O_4$ $[M-H]^-$ = 227.0474, found = 227.0474.

((2S)-1-fluoro-1,3-dinitropropan-2-yl)benzene, ***minor*** **(II-1.13b)**



(**II-1.13b**) $[\alpha]^{270}_{D}$ = -13.7 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 - 7.41 (m, 3H), 7.28 (m, 2H), 6.07 (dd, J = 49.5 Hz, 4.5 Hz, 1H), 4.89 (d, J = 9.0 Hz, 2H), 4.44 – 4.34 (m, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 130.97, 129.83, 129.72, 128.17, 110.33 (d, J = 242.9 Hz), 73.33, 46.30; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -133.34 (dd, J = 49.3 Hz, 20.6 Hz); HRMS (ESI) m/z calcd for $C_9H_8FN_2O_4$ $[M-H]^-$ = 227.0474, found = 227.0467.

IV-1.5. Denitration and analytical data of α-fluoroesters

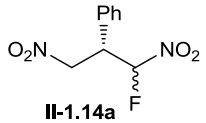


Experimental procedure:

The Michael addition reaction mixture was filtered through a short column of silica gel to remove the catalyst and concentrated. The crude residue (approx. 0.1 mmol of product) was dissolved in dry benzene (1.5 ml) and (n-Bu)$_3$SnH was added (1.5 equiv., 0.15 mmol, 43.6

mg), followed by 0.5 equiv. of ACHN (1,1'-Azobis(cyclohexanecarbonitrile) (0.05 mmol, 12 mg). The reaction mixture was flushed with argon, and refluxed under argon for 4 h. After this time only trace amount of starting material was detected (TLC analysis) and the reaction was cooled to room temperature. After removing benzene *in vacuo*, the residue was purified on silica gel column eluting with hexane/ethyl acetate (20/1 - 10/1) and both diastereomers were separated and collected as pure products - white solids in 2:1 ratio. Total yield was 78% (20 mg).

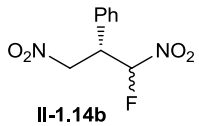
((2S)-1-fluoro-1,3-dinitropropan-2-yl)benzene, major (**II-1.14a**)



II-1.14a

$[\alpha]^{270}_{D}$ = +5.0 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 - 7.33 (m, 3H), 7.27 (m, 2H), 5.28 (dd, J = 48.5 Hz, 3.0 Hz, 1H), 4.95 (dd, J = 14.0 Hz, 8.5 Hz, 1H), 4.75 (dd, J = 13.5 Hz, 7.0 Hz, 1H), 4.17 – 4.05 (m, 3H), 1.08 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 166.93 (d, J = 22.5), 133.08, 129.03, 128.76, 88.33 (d, J = 191.5 Hz), 75.48, 61.88, 45.76 (d, J = 18.3 Hz), 13.91; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -200.30 (dd, J = 48.9 Hz, 31.2 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{13}FNO_4$ $[M-H]^-$ = 254.0834, found = 254.0833.

((2S)-1-fluoro-1,3-dinitropropan-2-yl)benzene, minor (**II-1.14b**)



II-1.14b

$[\alpha]^{270}_{D}$ = -0.6 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 - 7.34 (m, 3H), 7.30 – 7.26 (m, 2H), 5.10 (dd, J = 48.0 Hz, 5.0 Hz, 1H), 4.89 (dd, J = 19.5 Hz, 5.5 Hz, 1H), 4.80 (dd, J = 13.5 Hz, 9.0 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 4.17 – 4.09 (m, 1H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 167.39 (d, J = 23.6 Hz), 133.74, 133.23, 129.21, 128.78, 128.18, 128.11, 89.76 (d, J = 190.4 Hz), 75.04, 62.21, 46.06, 13.90; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -194.49 (dd, J = 48.1 Hz, 22.3 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{13}FNO_4$ $[M-H]^-$ = 254.0834, found = 254.0832.

IV-1.6. X-ray crystallographic analysis and determination of configurations of Products

Absolute configuration of all Michael addition product was assigned is analogy to configuration of **II-1.10a** found from X-ray analysis of a single crystal.

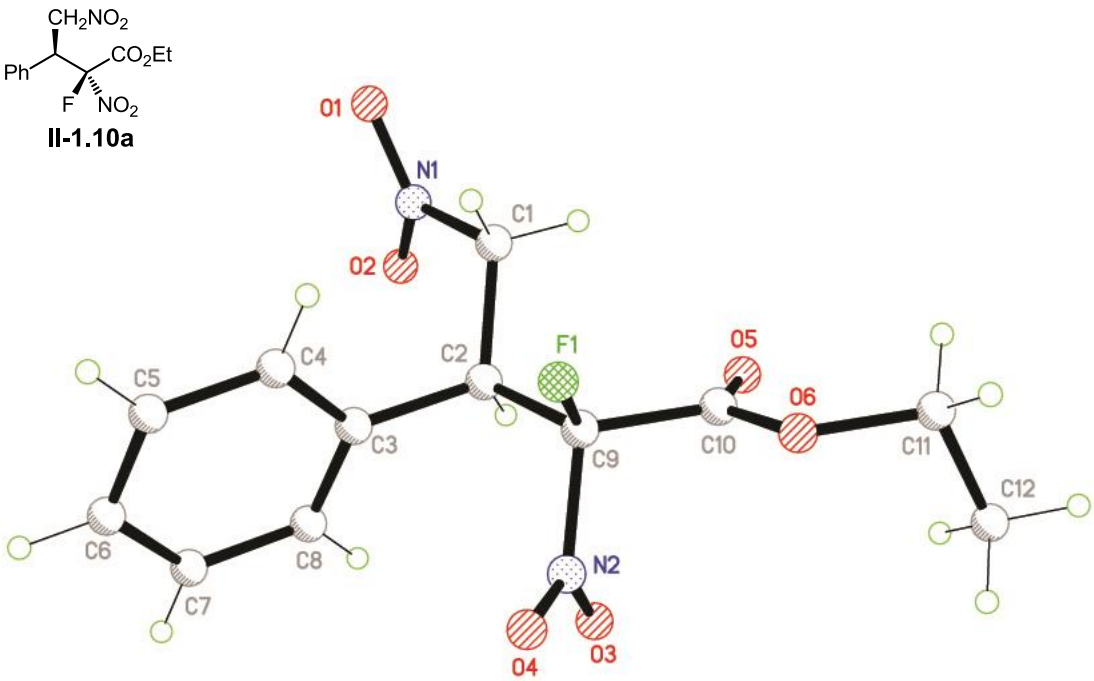


Table 1. Crystal data and structure refinement for D610.

Identification code	D610	
Empirical formula	C12 H13 F N2 O6	
Formula weight	300.24	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.5351(6) Å	α= 90°.
	b = 11.2034(12) Å	β= 90°.
	c = 21.678(2) Å	γ = 90°.
Volume	1344.3(3) $Å^3$	
Z	4	
Density (calculated)	1.483 Mg/m^3	
Absorption coefficient	1.117 mm^{-1}	
F(000)	624	

Crystal size	0.280 x 0.150 x 0.130 mm^3
Theta range for data collection	4.078 to 72.323°.
Index ranges	-6<=h<=6, -13<=k<=13, -26<=l<=26
Reflections collected	22572
Independent reflections	2637 [R(int) = 0.0240]
Completeness to theta = 67.679°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.753 and 0.6796
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2637 / 0 / 191
Goodness-of-fit on F^2	1.094
Final R indices [I>2sigma(I)]	R1 = 0.0250, wR2 = 0.0655
R indices (all data)	R1 = 0.0253, wR2 = 0.0658
Absolute structure parameter	0.05(2)
Extinction coefficient	n/a
Largest diff. peak and hole	0.167 and -0.248 e.$Å^{-3}$

Full data can be obtained from the Cambridge Crystallographic Data Centre under the number: CCDC 975749

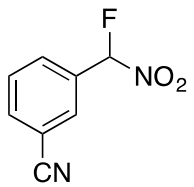
IV-2. Organocatalytic Michael addition of α-fluoro-α-nitro benzyls to nitroalkenes: facile preparation of fluorinated amines and pyrimidines

IV-2.1. Preparation of Substrates and analytical data of new α-fluoro-α-nitrobenzyls

Nitroalkenes were prepared from respective aldehydes and nitromethane according to reported procedures.

The α-fluoro-α-nitro benzyls were prepared form respective benzyl bromides in reaction with sodium nitrite and urea in DMF at -20°C, according to previously reported procedure.[178] The fluorination was performed using selectfluor in acetonitrile/water (1/1) at rt over 12h and KOH as base according to the reported procedure.[179]

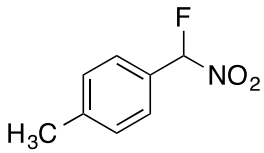
3-(Fluoro(nitro)methyl)benzonitrile (**II-2.1b**)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 4.8 Hz, 1H), 7.71 – 7.68 (m, 2H), 6.95 (d, J = 47.6 Hz, 1H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 133.62, 133.52, 132.68, 132.41, 132.40, 126.72,115.49, 112.69, 106.65 (d, J = 241.3 Hz); ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -140.26 (d, J = 47.4 Hz); HRMS (ESI) m/z calcd for $C_8H_5FN_2O_2$ $[M]^-$=179.0257, found = 179.0251.

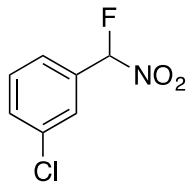
[178] *N. Kornblum , W. M. Weaver , J. Am. Chem. Soc.*, 1958 , **80** , 4333.
[179] W. Peng, J. M. Shreeve, *Tetrahedron Letters*, 2005, **46**, 4905.

1-(Fluoro(nitro)methyl)-4-methylbenzene (**II-2.1c**)



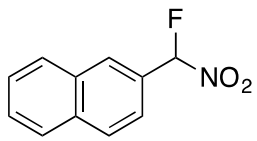
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 7.6 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.59 (d, J = 48.8 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 142.47, 129.75, 127.54, 127.33, 126.51, 126.45, 111.38, 109.00, 21.41; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ −138.93 (d, J = 48.5 Hz); HRMS (ESI) m/z calcd for $C_8H_8FNO_2$ $[M]^+$= 168.0461, found = 168.0458.

1-Chloro-3-(fluoro(nitro)methyl)benzene (**II-2.1d**)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.52 (d, J = 9.6 Hz, 2H), 7.43 (m, 1H), 6.58 (d, J = 48.4 Hz, 1H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 135.31, 132.19, 130.48, 126.72, 126.65, 124.69, 124.63; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ −141.29 (d, J = 48.1 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{14}FN_3O_4$ $[M]^-$=187.9915, found = 187.9899.

2-(Fluoro(nitro)methyl)naphthalene (**II-2.1e**)



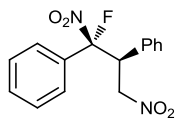
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.96 – 7.88 (m, 3H), 7.65 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.62 – 7.58 (m, 2H), 6.77 (d, J = 48.8 Hz, 1H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 135.43, 134.38, 131.82, 129.41, 128.00, 127.92, 127.77, 127.54, 126.83; ^{19}F NMR (376.46

Hz, $CDCl_3$) δ -139.08 (d, J = 48.6 Hz); HRMS (ESI) m/z calcd for $C_{11}H_8FNO_2$ $[M]^-$ = 204.0461, found = 204.0532.

IV-2.2. General procedure and analytical data of the Michael reaction products

Michael addition of ethyl fluoronitroacetate to nitroalkenes - representative procedure: to a sample vial containing the α-fluoro-α-nitro substrate (0.1 mmol, **II-2.1a**–**f**) in toluene (1 ml), the catalyst **II-1.12b** (0.01 mmol, 10 mg) was added. The vial was then capped and the reaction mixture was stirred for 5 minutes at 0 °C. Subsequently nitroalkene (0.11 mmol) was added in one portion, under nitrogen protection, the vial was sealed and the reaction mixture was stirred at 0 °C for the time indicated. Upon completion of the reaction, the mixture was passed through a short silica gel column to remove the catalyst (possible recovery of the catalyst), evaporated and analyzed by ^{1}H NMR. The crude product was then subjected to column chromatographic separation eluting with hexane/ethyl acetate (20:1 – 10:1) to afford the pure Michael product (**II-2.3a**–**n**).

((1S,2S)-1-fluoro-1,3-dinitropropane-1,2-diyl)dibenzene (**II-2.3a**)

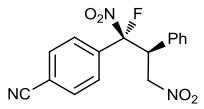


(**II-2.3a**)

$[\alpha]^{270}_D$ = +51.6 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 – 7.87 (m, 2H), 7.58 – 7.54 (m, 3H), 7.44 – 7.42 (m, 2H), 7.39 – 7.37 (m, 3H), 5.10 (ddd, J = 38.4 Hz, 10.8 Hz, 4.0 Hz, 1H), 4.77 (dd, J = 13.6 Hz, 10.8 Hz, 1H), 4.49 (dd, J = 13.2 Hz, 3.6 Hz, 1H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 131.91, 131.01, 130.78, 130.71, 129.62, 129.61, 129.59, 129.53, 129.51, 129.19, 125.41, 12 5.31, 118.90 (d, J = 244.1 Hz), 75.33 (d, J = 2.1 Hz), 50.14 (d, J = 18.3 Hz); ^{19}F NMR (376.46 Hz, $CDCl_3$) δ −136.63 (d, J = 31.6 Hz); HRMS (ESI) m/z calcd for $C_{15}H_{12}FN_2O_4$ $[M-H]^-$ = 303.8787,

found = 383.8789; the ee value was 90%, t_R (major) = 12.1 min, t_R (minor) = 10.6 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

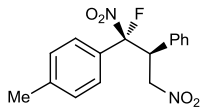
4-((1*S*,2*S*)-1-Fluoro-1,3-dinitro-2-phenylpropyl)benzonitrile (**II-2.3b**)



(**II-2.3b**)

$[\alpha]^{270}_{D}$ = +68.2 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.40 (s, 5H), 5.05 (ddd, J = 31.6 Hz, 10.4 Hz, 4.4 Hz, 1H), 4.75 (dd, J = 13.6 Hz, 10.0 Hz, 1H); 4.44 (dd, J = 13.6 Hz, 4.4 Hz, 1H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 135.19, 134.95, 133.21, 133.19, 130.07, 129.95, 129.37, 129.34, 126.55, 126.44 117.94 (d, J = 245.9 Hz), 117.09, 116.22, 74.89, 50.14 (d, J = 18.4 Hz) ; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -136.70 (d, J = 31.2 Hz); HRMS (ESI) m/z calcd for $C_{32}H_{22}F_2NaN_6O_8$ $[2M-2H+Na]^-$ = 679.1370, found = 679.1342; the ee value was 88%, t_R (major) = 17.3 min, t_R (minor) = 16.4 min (Chiralcel IB+ID, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

1-((1*S*,2*S*)-1-fluoro-1,3-dinitro-2-phenylpropyl)-4-methylbenzene (**II-2.3c**)

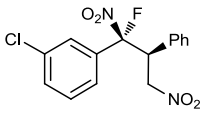


(**II-2.3c**)

$[\alpha]^{270}_{D}$ = +95.1 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, J = 8.4 Hz, 1.6 Hz, 2H), 7.42 (m, 2H), 7.38 – 7.34 (m, 5H), 5.08 (ddd, J = 31.2 Hz, 10.8 Hz, 3.6 Hz, 1H), 4.75 (dd, J = 13.6 Hz, 10.8 Hz, 1H); 4.50 (dd, J = 13.2 Hz, 3.6 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 142.45, 130.84, 130.23, 130.22, 129.55, 129.53, 129.50, 129.15, 128.14, 127.91, 125.33, 12 5.23, 119.11 (d, J = 243.7 Hz), 75.44, 50.10 (d, J = 18.3 Hz), 21.29; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -136.54 (d, J = 31.2 Hz); HRMS (ESI) m/z calcd for $C_{32}H_{28}F_2NaN_4O_8$ $[2M-2H+Na]^-$ =

657.1778, found = 657.1794; the ee value was 90%, t_R (major) = 30.6 min, t_R (minor) = 20.6 min (Chiralcel IB, λ = 254 nm, 2% *i*PrOH/hexanes, flow rate = 1 mL/min).

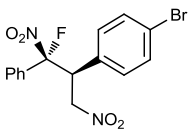
1-Chloro-3-((1*S*,2*S*)-1-fluoro-1,3-dinitro-2-phenylpropyl)benzene (**II-2.3.d**)



(**II-2.3d**)

$[\alpha]^{270}_{D}$ = +81.3 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (m, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 2Hz, 1H), 7.40 – 7.26 (m, 5H), 5.03 (ddd, J = 31.2 Hz, 10.8 Hz, 4.0 Hz, 1H), 4.78 (dd, J = 13.6 Hz, 10.8 Hz, 1H), 4.48 (dd, J = 13.6 Hz, 4.0 Hz, 1H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 135.95, 132.76, 132.53, 132.22, 130.94, 130.93, 130.35, 129.78, 129.46, 129.44, 129.27, 125.80, 123.70, 118.07 (d, J = 245.36 Hz), 75.10, 50.19 (d, J = 18.40 Hz); ^{19}F NMR (376.46 Hz, $CDCl_3$) δ −136.29 (d, J = 31.2 Hz); HRMS (ESI) m/z calcd for $C_{15}H_{11}ClFN_2O_4$ $[M-H]^-$ = 337.0397, found = 337.0392; the ee value was 87%, t_R (major) = 15.8 min, t_R (minor) = 11.4 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

1-Bromo-4-((1*S*,2*S*)-1-fluoro-1,3-dinitro-1-phenylpropan-2-yl)benzene (**II-2.3e**)

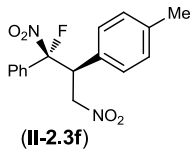


(**II-2.3e**)

$[\alpha]^{270}_{D}$ = +22.2 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, J = 7.6 Hz, 1.2 Hz, 2H), 7.58 – 7.51 (m, 5H), 7.31 (dd, J = 8.4 Hz, 1.6 Hz, 2H), 5.07 (ddd, J = 30.8 Hz, 10.8 Hz, 3.6 Hz, 1H), 4.72 (dd, J = 13.2 Hz, 10.8 Hz, 1H); 4.47 (dd, J = 13.6 Hz, 3.6 Hz, 1H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 132.48, 132.07, 131.14, 131.1, 130.07, 130.42, 129.70, 129.68, 125.31, 125.21, 124.16, 118.64 (d, J = 244.2 Hz), 75.08, 49.65 (d, J = 18.5 Hz); ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -136.77 (d, J = 30.9 Hz); HRMS (ESI) m/z calcd for $C_{15}H_{11}BrFN_2O_4$ $[M-H]^-$ = 380.9892, found =

380.9880; the ee value was 90%, t_R (major) = 22.6 min, t_R (minor) = 18.4 min (Chiralcel AD-H, λ = 254 nm, 2% *i*PrOH/hexanes, flow rate = 1 mL/min).

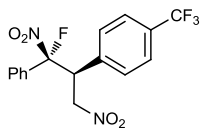
1-((1*S*,2*S*)-1-fluoro-1,3-dinitro-1-phenylpropan-2-yl)-4-methylbenzene (**II-2.3f**)



(**II-2.3f**)

$[\alpha]^{270}_{D}$ = +65.4 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, J = 8.4 Hz, 1.6 Hz, 2H), 7.55 (m, 3H), 7.30 (dd, J = 8.4 Hz, 1.6 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 5.06 (ddd, J = 31.6 Hz, 10.8 Hz, 4.0 Hz, 1H), 4.75 (dd, J = 11.2 Hz, 10.8 Hz, 1H); 4.47 (dd, J = 13.2 Hz, 3.6 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 131.85, 131.09, 130.86, 129.89, 129.57, 129.55, 129.35, 128.71, 127.55, 125.42, 118.98 (d, J = 244.2 Hz), 75.40, 49.85 (d, J = 18.5 Hz), 21.13 ; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -136.70 (d, J = 31.5 Hz); HRMS (ESI) m/z calcd for $C_{16}H_{15}FN_2O_4$ $[M-H]^-$ = 317.0943, found = 317.0949; the ee value was 88%, t_R (major) = 25.7 min, t_R (minor) = 20.8 min (Chiralcel IA, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

1-((1S,2S)-1-Fluoro-1,3-dinitro-1-phenylpropan-2-yl)-4-(trifluoromethyl)benzene (**II-2.3g**)

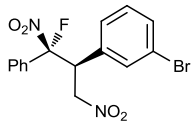


(**II-2.3g**)

$[\alpha]^{270}_{D}$ = +61.9 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, J = 7.6 Hz, 1.6 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.59 (m, 5H), 5.19 (ddd, J = 31.2 Hz, 11.2 Hz, 3.6 Hz, 1H), 4.77 (dd, J = 13.6 Hz, 10.8 Hz, 1H); 4.51 (dd, J = 13.6 Hz, 3.8 Hz, 1H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 134.83, 132.18, 131.73, 130.51, 130.28, 130.07, 129.77, 126.21, 126.17, 125.29, 125.19, 124.93, new 118.62 (d, J = 244.7 Hz), 75.00, 49.85 (d, J = 18.6 Hz) ; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ –63.02, -136.54 (d, J = 30.8 Hz); HRMS (ESI) m/z calcd for $C_{16}H_{13}F_4N_2O_5$ $[M-H]^-$ = 371.0660, found =

371.0650; the ee value was 91%, t_R (major) = 15.1 min, t_R (minor) = 10.9 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

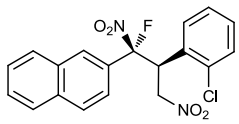
1-bromo-3-((1*S*,2*S*)-1-fluoro-1,3-dinitro-1-phenylpropan-2-yl)benzene (**II-2.3h**)



(**II-2.3h**)

$[\alpha]^{270}_D$ = +53.1 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, J = 7.6 Hz, 1.6 Hz, 2H), 7.61 – 7.53 (m, 5H), 7.39 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 5.08 (ddd, J = 30.8 Hz, 10.8 Hz, 3.6 Hz, 1H), 4.74 (dd, J = 13.6 Hz, 10.8 Hz, 1H); 4.49 (dd, J = 14.0 Hz, 4.0 Hz, 1H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 132.92, 132.51, 132.08, 130.68, 130.41, 128.27, 128.25, 125.30, 125.20, 123.17, 118.64 (d, J = 244.3 Hz), 75.09, 49.65 (d, J = 18.4 Hz); ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -136.55 (d, J = 30.8 Hz); HRMS (ESI) m/z calcd for $C_{15}H_{11}BrFN_2O_4$ $[M-H]^-$ = 380.0892, found = 380.9873; the ee value was 90%, t_R (major) = 16.0 min, t_R (minor) = 11.5 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

2-((1*S*,2*S*)-2-(2-Chlorophenyl)-1-fluoro-1,3-dinitropropyl)naphthalene (**II-2.3i**)

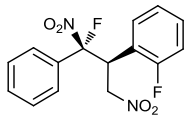


(**II-2.3i**)

$[\alpha]^{270}_D$ = +77.1 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J = 2.0 Hz, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.96 (dd, J = 6.8, 2.4 Hz, 1H), 7.91 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 7.85 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.65 -7.62 (m, 2H), 7.46 (d, J = 1.6 Hz, 1H), 6.49 (d, J = 3.6 Hz, 1H), 6.39 (d, J = 2.0 Hz, 1H), 5.49 (ddd, J = 29.6 Hz, 10.4 Hz, 3.2 Hz, 1H), 4.90 (dd, J = 13.6 Hz, 10.4 Hz, 1H); 4.43 (dd, J = 13.6 Hz, 3.6 Hz, 1H); ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -134.94 (d, J = 29.7 Hz); HRMS (ESI) m/z calcd for $C_{19}H_{13}ClFN_2O_4$ $[M-H]^-$ = 387.0553, found = 387.0548; the ee value was 70%, t_R

(major) = 16.0 min, t_R (minor) = 11.5 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

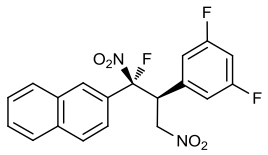
1-Fluoro-2-((1*S*,2*S*)-1-fluoro-1,3-dinitro-1-phenylpropan-2-yl)benzene (**II-2.3j**)



(**II-2.3j**)

$[\alpha]^{270}_{D}$ = +45.0 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, J = 7.6 Hz, 1.6 Hz, 2H), 7.57 – 7.52 (m, 3H), 7.48 – 7.40 (m, 1H), 7.39 – 7.34 (m, 1H), 7.21 – 7.10 (m, 2H), 5.53 (ddd, J = 30.0 Hz, 10.0 Hz, 3.6 Hz, 1H), 4.80 (dd, J = 13.6 Hz, 10.4 Hz, 1H); 4.52 (dd, J = 14.0 Hz, 4.0 Hz, 1H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 162.39, 132.02, 131.60, 131.51, 129.84, 129.59, 128.04, 125.44, 125.34, 124.93, 118.75 (d, J = 245.7 Hz), 116.67, 116.44, 74.52 (d, 2.0 Hz), 43.43 (d, J = 18.8 Hz); ^{19}F NMR (376.46 Hz, $CDCl_3$) δ –114.29, -135.93 (dd, J = 31.2 Hz, 14.7 Hz); HRMS (ESI) m/z calcd for $C_{15}H_{11}F_2N_2O_4$ $[M-H]^-$ = 321.0692, found = 321.0687; the ee value was 85%, t_R (major) = 18.8 min, t_R (minor) = 17.7 min (Chiralcel IB, λ = 254 nm, 2% *i*PrOH/hexanes, flow rate = 1 mL/min).

2-((1*S*,2*S*)-2-(3,5-Difluorophenyl)-1-fluoro-1,3-dinitropropyl)naphthalene (**II-2.3k**)

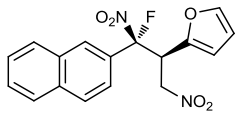


(**II-2.3k**)

$[\alpha]^{270}_{D}$ = +58.1 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 2.0 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.95 (dd, J = 6.8 Hz, 3.6 Hz, 2H), 7.88 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.65 (m, 2H), 7.04 (dd, J = 5.6 Hz, 1.2 Hz, 2H), 6.90 – 6.84 (m, 1H), 5.23 (ddd, J = 30.0 Hz, 10.8 Hz, 3.6 Hz, 1H), 4.73 (dd, J = 14.0 Hz, 11.2 Hz, 1H); 4.50 (dd, J = 13.6 Hz, 3.6 Hz, 1H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 164.35 (d, J = 12.6 Hz), 161.85 (d, J = 12.5 Hz), 134.48, 134.33, 132.51, 130.22,

128.92, 128.76, 127.87, 127.38, 127.15, 126.17, 126.06, 118.67 (d, J = 244.9 Hz), 113.14, 112.85, 105.56, 75.00, 49.65 (d, J = 18.5 Hz); ^{19}F NMR (376.46 Hz, $CDCl_3$) δ –107.20, -135.87 (d, J = 30.1 Hz); HRMS (ESI) m/z calcd for $C_{19}H_{12}F_3N_2O_4$ $[M-H]^-$ = 389.0755, found = 389.0757; the ee value was 96%, t_R (major) = 7.7 min, t_R (minor) = 9.1 min (Chiralcel AD-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

2-((1*S*,2*R*)-1-Fluoro-1-(naphthalen-2-yl)-1,3-dinitropropan-2-yl)furan (**II-2.3l**)

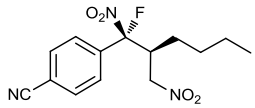


(**II-2.3l**)

$[\alpha]^{270}_D$ = +40.1 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 1.6 Hz, 1H), 8.08 – 7.92 (m, 3H), 7.67 – 7.61 (m, 3H), 7.48 (dd, J = 6.8 Hz, 1.6 Hz, 1H), 7.36 – 7.32 (m, 2H), 6.12 – 6.01 (m, 1H), 4.83 – 4.71 (m, 1H), 4.59 (dd, J = 13.2 Hz, 4.0 Hz, 1H); ^{13}C NMR (100.62

Hz,$CDCl_3$)δ 134.43, 132.42, 130.71, 130.41, 129.93, 128.94, 128.77, 128.58, 127.83, 127.72, 127.62, 126.31, 121.32, 118.67 (d, J = 245.6 Hz), 75.50, 45.16 (d, J = 18.0 Hz) ; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -134.92 (d, J = 30.8 Hz); HRMS (ESI) m/z calcd for $C_{17}H_{12}FN_2O_5$ $[M-H]^-$ = 343.0736, found = 343.0738; the ee value was 88%, t_R (major) = 15.4 min, t_R (minor) = 34.5 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

4-((1S,2S)-1-fluoro-1-nitro-2-(nitromethyl)hexyl)benzonitrile (**II-2.3m**)

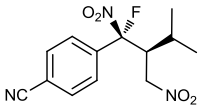


(**II-2.3m**)

$[\alpha]^{270}_D$ = +72.0 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 – 7.70 (m, 4H), 4.33 – 4.20 (m, 2H), 3.94 (dd, J = 30.4 Hz, 5.2 Hz, 1H), 1.62 – 1.34 (m, 7H), 0.91 (m, 2H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 135.22, 132.95, 126.50, 119.36 (d, J = 244.5 Hz), 117.17, 115.99, 74.03 (d, J = 4.2

Hz), 43.90 (d, J = 20.6 Hz), 28.32, 26.99, 22.32, 13.60; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ –139.01 (d, J = 31.6 Hz); HRMS (ESI) m/z calcd for $C_{14}H_{15}FN_3O_4$ $[M-H]^-$ = 308.1052, found = 308.1053; the ee value was 82%, t_R (major) = 12.5 min, t_R (minor) = 11.4 min (Chiralcel ID, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

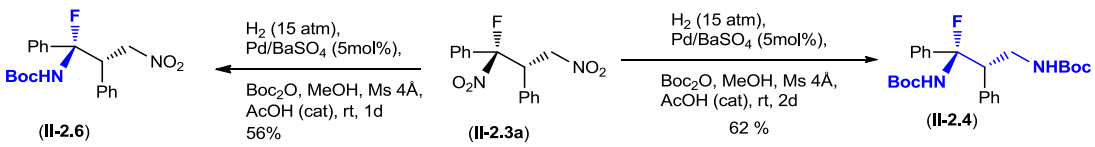
4-((1*S*,2*S*)-1-fluoro-3-methyl-1-nitro-2-(nitromethyl)butyl)benzonitrile (**II-2.3n**)



(**II-2.3n**)

$[\alpha]^{270}_D$ = +45.5 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 7.8 Hz, 2H), 7.77 (t, J = 7.6 Hz, 2H), 4.43 (dd, J = 14.4 Hz, 4.8 Hz, 1H), 4.16 (dd, J = 14.4 Hz, 5.6 Hz, 1H), 3.99 (dtd, J = 34.0 Hz, 5.2 Hz, 2.4 Hz, 1H), 2.06 (m, 1H), 1.10 (d, J = 6.8 Hz, 3H), 1.05 (dd, J = 6.8 Hz, 2.0 Hz, 3H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 135.42, 132.83, 127.21, 126.60, 126.49, 120.29 (d, J = 247.98 Hz), 117.20, 115.96, 70.76, 48.20 (d, J = 19.1 Hz), 27.86, 21.88, 17.56; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ –137.87 (d, J = 33.8 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{13}FN_3O_4$ $[M-H]^-$ = 294.0896, found = 294.0893; the ee value was 82%, t_R (major) = 17.1 min, t_R (minor) = 19.8 min (Chiralcel AD-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

IV-2.3. Catalytic hydrogenation and analytical data of fluoroamines

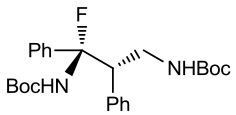


Experimental procedure for catalytic hydrogenation leading to *bis*-amine:

Michael adduct (**II-2.3a**, 0.2 mmol, 61 mg) was dissolved in MeOH (2 ml). Boc anhydride was then added (2.5 equiv. 109 mg), followed by 2-3 drops of glacial acetic acid, $Pd/BaSO_4$ (5 mol% Pd, 0.01 mmol, 21.3 mg of 5 wt% $Pd/BaSO_4$) and freshly activated MS 4Å (~20

mg). The reaction mixture was placed in autoclave and stirred for 48 h at 15 atm H_2 with stirring at room temperature. After that time, the reaction mixture was filtered through cellite and the volatiles were removed *in vacuo*, below 20 ^{o}C.[180] The crude reaction mixture was purified on silica gel column eluting with hexane/chloroform (10/1). The pure product was obtained as a pale yellow oil (55 mg, 62%).

di-tert-butyl ((1R,2S)-1-fluoro-1,2-diphenylpropane-1,3-diyl)dicarbamate;



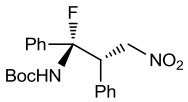
(**II-2.4**) $[\alpha]^{270}_{D}$ = -52.0 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (m, 2H), 7.49 (m, 3H), 7.42 (m, 2H), 7.36 - 7.30 (m, 3H), 4.59 (ddd, J = 32.8 Hz, 10.4 Hz, 3.6 Hz, 1H), 4.13 (m, 1H), 3.73 (m, 1H), 1.44 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 151.72, 151.70, 133.27, 132.30, 132.11, 131.12, 129.98, 120.06, 128.60, 128.55, 125.59, 125.51, 120.24, (d, *J* = 246.2 Hz), 85.17, 82.62, 50.52, 49.76 (d J = 18.1 Hz), 27.83, 27.54; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -137.84 (d, J = 32.7 Hz); HRMS (ESI) m/z calcd for $C_{25}H_{34}FN_2O_4$ $[M+H]^+$ = 445.2503, found = 445.2504.

Experimental procedure for catalytic hydrogenation leading to *mono*-amine:

The experimental procedure is the same as the above procedure for bis-reduction, except that 2 equiv. of Boc_2O were used (87 mg) and the reaction was stopped after 12h. The pure product was obtained after chromatography on silica gel column eluting with hexane/ethyl acetate (10/1 - 5:1) as a pale yellow oil (42 mg, 56%).

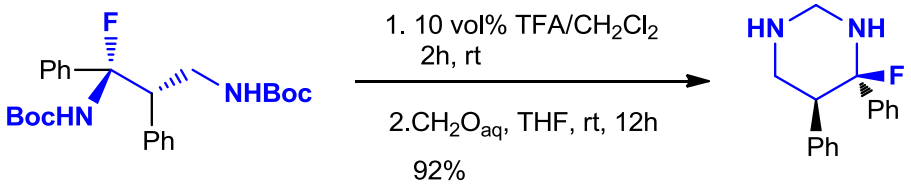
[180] Heating should be avoided and it is recommended to remove acetic acid together with solvent to avoid defluorination - thus the use of vaccum; other work-up procedures resulted in lower isolated yield of product.

tert-butyl ((1R,2S)-1-fluoro-3-nitro-1,2-diphenylpropyl)carbamate;



(**II-2.6**) $[\alpha]^{270}_{D}$ = +98.0 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (m, 2H), 7.51 (m, 3H), 7.43 (m, 2H), 7.32 (m, 3H), 5.98 (bs, 1H), 4.72 (ddd, J = 33.2 Hz, 10.4 Hz, 4.4 Hz, 1H), 4.06 (dd, J = 14.4 Hz, 10.4 Hz, 1H), 3.57 (dd, J = 14.4 Hz, 4.4 Hz, 1H), 1.24 (s, 9H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 155.37, 133.36, 132.34, 132.15, 131.15, 129.96, 129.94, 129.08, 129.07, 128.66, 125.55, 125.47, 120.29 (d, J = 242.6 Hz), 82.31, 49.88 (d, J = 3.1 Hz), 48.96 (d, J = 18.5 Hz), 27.95; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -137.32 (d, J = 32.7 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{22}FN_2O_4$ $[M-H]^-$ = 373.1569, found = 373.1664.

IV-2.4. Preparation of tetrahydropyrimidine and analytical data



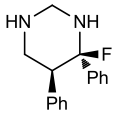
(**II-2.4**) (**II-2.5**)

Experimental procedure:

The bis-amine (**II-2.4**, 0.1 mmol, 44 mg) was dissolved in CH_2Cl_2 (2ml) and 0.2 ml of TFA was added dropwise while stirring at room temperature. Even though deprotection seemed to proceed fast, the reaction was stirred for additional 2 h to ensure complete deprotection of both amino functionalities. After that time, the reaction was quenched by addition of water (2ml), diluted with CH_2Cl_2 and brought to pH 10 by a dropwise addition of satd. aqueous $NaHCO_3$. Then, the crude product was extracted with CH_2Cl_2 (3x 10 ml) and the organic phase was dried over sodium sulphate and evaporated. The crude free diamine was then dissolved in THF (1 ml) and 37 wt% aqueous formaldehyde was added dropwise at room

temperature (1 equiv., 8 mg). The reaction was then stirred at room temperature for 12 h to ensure full conversion and heterocyclic ring formation.[181] Upon completion, the reaction mixture was diluted with CH_2Cl_2 (2ml), dried over sodium sulphate and concentrated. The pure product was obtained after column chromatography on silica gel eluting with toluene/chloroform (10/1 - 5/1) as a pale yellow oil (23.5 mg, 92%).

(4R,5S)-4-fluoro-4,5-diphenylhexahydropyrimidine



(**II-2.5**) $[\alpha]^{270}_{D}$ = +65.6 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (m, 2H), 7.53 (dd, J = 5.5 Hz, 2.0 Hz, 3H), 7.48 – 7.45 (m, 2H), 7.38 – 7.34 (m, 3H), 6.10 (d, J = 7.2 Hz, 1H), 5.82 (d, J = 7.2 Hz, 1H), 5.22 (ddd, J = 33.5 Hz, 10.5 Hz, 3.7 Hz, 1H), 4.08 (dd, J = 11.8 Hz, 10.7 Hz, 1H), 3.97 (dd, J = 12.0 Hz, 3.7 Hz, 1H), ; ^{13}C NMR (125 Hz, $CDCl_3$) δ 132.22, 131.52, 131.39, 129.53, 129.51, 129.32, 129.08, 129.03, 128.20, 125.72, 125.64, 124.94, 119.98 (d, J = 243.6 Hz), 65.75, 49.06, 48.92; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -59.15 (d, J = 44.7 Hz); HRMS (ESI) m/z calcd for $C_{16}H_{16}FN_2$ $[M-H]^-$ = 255.2330, found = 255.2336.

IV-2.5. X-Ray Crystallographic analysis and determination of configurations of products

Configuration of all Michael addition products was assigned as analogical to configuration of product **II-2.3e**.

[181] The change of ninhydrine stain color on TLC suggested that the reaction proceeded fast - within 0.5 h; however it is difficult to distinguish product and starting material spot on TLC and therefore the reaction was stirred for additional time.

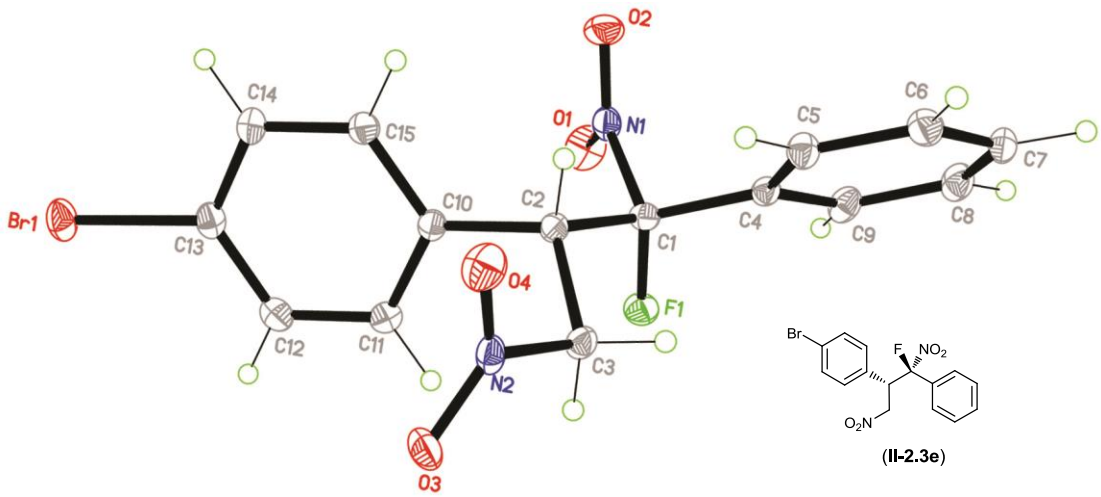


Table 1. Crystal data and structure refinement for D345.

Identification code	d345	
Empirical formula	C15 H12 Br F N2 O4	
Formula weight	383.18	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 5.6907(11) Å	α= 108.137(3)°.
	b = 7.4227(14) Å	β= 100.781(3)°.
	c = 9.3653(18) Å	γ = 90.415(3)°.
Volume	368.39(12) $Å^3$	
Z	1	
Density (calculated)	1.727 Mg/m^3	
Absorption coefficient	2.823 mm^{-1}	
F(000)	192	
Crystal size	0.52 x 0.50 x 0.20 mm^3	
Theta range for data collection	2.34 to 27.50°.	
Index ranges	-7<=h<=7, -9<=k<=9, -12<=l<=12	
Reflections collected	4816	
Independent reflections	3338 [R(int) = 0.0145]	
Completeness to theta = 27.50°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8372 and 0.5831	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3338 / 3 / 208	

Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0379, wR2 = 0.0946
R indices (all data)	R1 = 0.0379, wR2 = 0.0947
Absolute structure parameter	0.000(6)
Largest diff. peak and hole	0.455 and -0.338 e.$Å^{-3}$

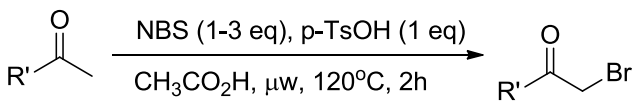
Full data can be obtained from the Cambridge Crystallographic Data Centre under the number: CCDC 975748.

IV-3. Enantioselective synthesis of functionalized fluorinated phosphonates *via* Michael addition of α-fluoro-β-ketophosphonates to nitroalkenes

IV-3. 1. Preparation of the substrates and analytical data

Bromination

Commercially available bromides were purchased, while others were synthesized with the use of microwave initiator.

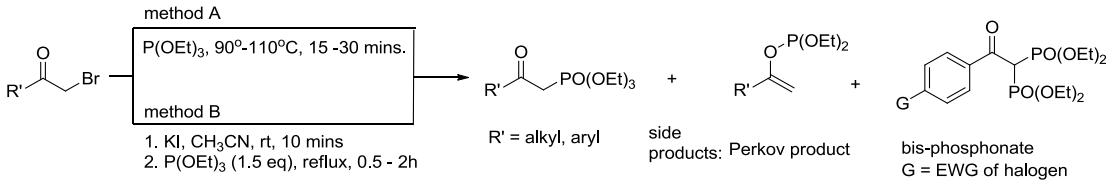


General procedure:

To a microwave vial containing ketone (3 mmol), 10 ml of glacial acetic acid was added followed by *p*-toluenesulphonic acid monohydrate (*p*-TsOH x H_2O, 3 mmol, 570 mg) and N-bromo succinimide (NBS, 3 mmol, 534 mg). The vial was than capped and placed in the microwave initiator (40 minutes at 120°C). In certain cases, ketones were difficult to brominate (TLC control) and therefore, the reaction was repeated up to 2 more times (to the reaction mixture from previous step was added: NBS (3 mmol) and *p*-TsOH (3 mmol) and the reaction mixture was subjected to microwave irradiation for additional 40 minutes at 120°C). Upon completion of the reaction (TLC) the reaction mixture was evaporated, dissolved in Ethyl Acetate (50 ml) and washed carefully with aqueous $NaHCO_3$ saturated solution (3-times), followed by brine. The Organic layer was than dried over sodium sulfate and evaporated to yield crude bromide, which was used in subsequent Arbuzov reaction without purification.

Arbuzov Reaction

Phosphonates were synthesized according to method A or B. In all cases starting materials (bromides) were fully consumed, while the low yields of desired phosphonates are the result of the generation of side products: Perkov products (in all cases) and bis-phosphonates (in the reactions of acetophenone-derived bromides with halogen or electron-withdrawing group at the *para*- position in the phenyl ring).



Method A:

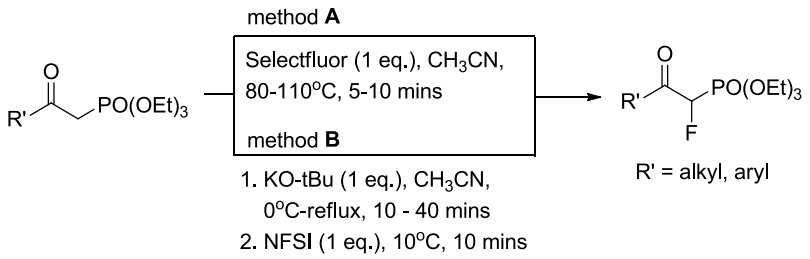
To triethyl phosphite (3 mmol, 498 mg) stirred at 90°C under argon, was carefully added the crude bromide (dropwise, dissolved in minimum amount of CH_2Cl_2) and the reaction was stirred for 15-30 minutes (TLC control, CH_2Cl_2 was allowed to evaporate through needle). Upon consumption of the bromide, the excess of triethyl phosphite was removed over vacuum equipped with cold trap. The crude product was than purified by flash chromatography on silica gel using hexane/ethyl acetate as eluent (solvent ratio: 6/1 to 2/1).

Method B:

To a solution of crude bromide (~2.7 mmol) in CH_3CN (15 ml) was added KI (3 mmol, 498 mg) in one portion. The reaction was then stirred for 10 minutes at room temperature. Next, to the reaction mixture $P(OEt)_3$ was added (4.5 mmol, 747 mg) in one portion and the reaction mixture was then brought to reflux and stirred for 0.5 – 2h. Upon consumption of the bromide (TLC), the reaction mixture was evaporated, dissolved in ethyl acetate (50 ml) and washed with water (2x) and brine (1x). The organic layer was then dried over sodium sulfate and evaporated. The crude product was than purified by flash chromatography on silica gel using hexane/ethyl acetate as eluent (solvent ratio: 6/1 to 2/1).

Fluorination

Fluorination[182] was performed according to method A or B. In all cases, *bis*-fluorination was also observed, which contributed to lowered yields of the desired mono-fluorinated phosphonates.



General procedures:

Method A:

To the solution of β-ketophosphonate (1 mmol) in CH_3CN (5 ml, microwave vial) was added Selectfluor (1 mmol, 354 mg). The capped vial was subjected to microwave irradiation for 5-10 minutes at 80 to 110°C. The reaction has to be stopped when optimum ratio of product to smarting material to byproduct is achieved (TLC analysis). Longer reaction times lead to increased amount of bis-fluorinated by-product whereas higher temperatures resulted in decomposition of the desired mono-fluorinated product. The reaction mixture was than evaporated and dissolved in ethyl acetate (20 ml). The organic layer was washed with aqueous $NaHCO_3$ saturated solution (2- times), followed by brine. The Organic layer was than dried over sodium sulfate and evaporated. The desired product was then isolated using column chromatography on silica gel, using hexane/ethyl acetate as eluent (solvent ratio: 5/1 to 2/1).

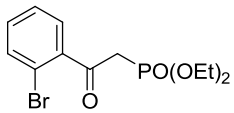
[182] During preparation of this manuscript an alternative preparation of a narrow scope of racemic mono-fluorinated ketophosphonates was reported: K. Radwan-Olszewska, F. Palacios, P. Kafarski, *J. Org. Chem*., 2011, **76**, 1170.

Method B:

To the solution of β-ketophosphonate (1 mmol) in CH_3CN (15 ml) was added potassium *tert*-butoxide (1.1 mmol, 123 mg) in one portion at 0°C. The reaction mixture was then brought to reflux over 30 minutes and then cooled down again to about 10°C. Next, N-Fluorobenzenesulfonmide (NFSI, 1 mmol, 315 mg) was added in one portion. The reaction was stirred for 10 minutes at 10°C. Upon consumption of the starting material (TLC) the reaction mixture was evaporated, dissolved in ethyl acetate (20 ml). The organic layer was then washed with aqueous HCl (1M), 2 times), followed by brine, dried over sodium sulfate and evaporated. The desired product was then isolated from byproducts (bis-fluorination and condensations) using column chromatography on silica gel, using hexane/ethyl acetate as eluent (solvent ratio: 5/1 to 2/1).

NMR Data of Novel Phosphonates[183]

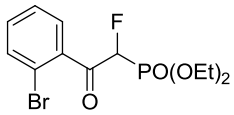
Diethyl (2-(2-bromophenyl)-2-oxoethyl)phosphonate



A pale yellow oil; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.24-1.29 (t, J = 14.0 Hz, 6H), 3.66 (s, 1H), 3.73 (s, 1H), 4.10-4.27 (m, 4H), 7.29-7.41 (m, 2H), 7.53-7.68 (m, 2H); ^{13}C NMR (75.48 Hz, $CDCl_3$) δ 16.19 (d, J = 6.6 Hz), 41.05, 42.75, 62.66 (d, J = 6.0 Hz), 118.94, 127.41, 129.75, 132.13, 133.65, 140.74, 195.01; ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 19.59; HRMS (ESI) m/z calcd for $C_{12}H_{16}BrO_4P$ $[M+H]^+$ = 333.9970 (279.0762 – Br), found = 279.0759.

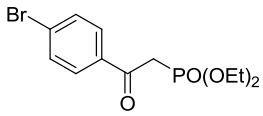
[183] NMR analysis of other phosphonates was identical with the published data; for details see: a) R' = *p*-OMe-C_6H_4-: Luke, G. P.; Seekamp, C. K.; Wang, Z.-Q.; Chenard, B. L. *J.Org. Chem.* **2008**, *73*, 6397; Kim, D. Y.; Choi, Y. J. *Synth. Comm.* **1998**, *28*, 1491; b) R' = *p*-Br-C_6H_4-: Moorhoff, C. M. *Synth. Comm.* **2003**, *33*, 2069; c) R' = Et : Loreto, M. A.; et al., *J. Org. Chem.* **2006**, *71*, 2163; Coutrot, P.; Grison, C. *Tetrahedron: lett.* **1988**, *29*, 2655; d) R' = *t*-Bu : Sampson, P.; Hammond, G. B.; Wiemer, D. F. *J.Org. Chem.* **1986**, *51*, 4342; e) R' = C_6H_5-: Radwan-Olszewska, K.; Palacios, F.; Kafarski, P. *J. Org. Chem.* **2011**, *76*, 1170; f) R' = *p*-F-C_6H_4-: Yuen, C.; Xie, R. *Phosphorus, Sulfur and Silicon and the Related Elements* **1994**, *1-4*, 47-51.

Diethyl (2-(2-bromophenyl)-1-fluoro-2-oxoethyl)phosphonate;



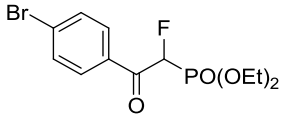
A pale yellow oil; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.23-1.27 (t, J = 7.0 Hz, 3H), 1,31-1.36 (t, J = 7.0 Hz, 3H), 4.10-4.27 (m, 4H), 5.89-5.6.09 (dd, J = 13.3 Hz, 47.4 Hz, 1H), 7.46 (t, J = 15.3 Hz, 2H), 7.59-7.64 (d, J = 7.6 Hz, 1H), 8.01-8.04 (d, J = 7.6 Hz, 2H); ^{13}C NMR (75.48 Hz, $CDCl_3$) δ 16.15 (d, J = 6.0 Hz), 16.25 (d, J = 6.0 Hz), 64.25 (d, J = 7.1 Hz), 87.93, 90.24 (d, J = 43.9 Hz), 92.56, 128.57, 129.27, 129.31, 134.24, 191.18 (d, J = 16.5 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 10.66 (d, J = 71.1 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ –131.86 (d, J = 47.3 Hz), -131.61 (d, J = 47.3 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{15}BrFNaO_4P$ $[M+Na]^+$ = 374.9773, found = 374.9764.

Diethyl (2-(4-bromophenyl)-2-oxoethyl)phosphonate



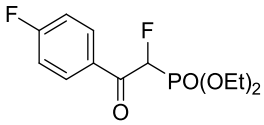
A pale yellow oil; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.19-1.24 (t, J = 7.0 Hz, 6H), 3.50 (s, 1H), 3.58 (s, 1H), 4.04-4.09 (m, 4H), 7.53-7.56 (d, J = 8.6 Hz, 2H), 7.80-7.83 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75.48 Hz, $CDCl_3$) δ 16.05 (d, J = 6.0 Hz), 37.51, 39.23, 62.62 (d, J = 6.0 Hz), 128.85, 130.41, 131.73, 135.04, 135.06, 190.74 (d, J = 6.6 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 20.11.

Diethyl (2-(4-bromophenyl)-1-fluoro-2-oxoethyl)phosphonate;



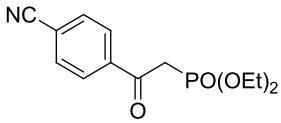
A pale yellow oil; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.33 (t, J = 7.7 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 4.19-4.31 (m, 4H), 5.93 (dd, J = 13.5 Hz, 47.4 Hz, 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 8.0 Hz, 2H); ^{13}C NMR (75.48Hz) δ: 16.26 (t, J = 5.5 Hz), 64.34, 64.43, 91.18 (dd, J = 152.1 Hz, 197.1 Hz), 129.76, 130.84, 130.89, 131.97, 132.89, 190.46 (d, J = 17.0 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 10.42 (d, J = 71.1 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ –131.05 (dd, J = 47.4 Hz, 71.1 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{15}BrFNaO_4P$ $[M+Na]^+$ = 374.9773, found = 374.9761.

Diethyl (1-fluoro-2-(4-fluorophenyl)-2-oxoethyl)phosphonate;



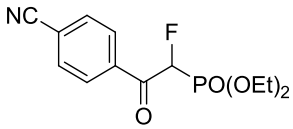
A pale yellow oil; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.24 (t, J = 7.4 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 4.11-4.21 (m, 4H), 5.90, (dd, J = 13.5 Hz, 47.4 Hz, 1H), 7.12 (t, J = 8.85 Hz, 2H), 8.03-8.08 (m, 2 H); ^{13}C NMR (75.48 Hz, $CDCl_3$) δ 16.11 (t, J = 5.5 Hz), 64.16 (d, J = 2.2 Hz), 64.25 (d, J = 2.7 Hz), 90.35 (dd, J = 152.1 Hz, 197.1 Hz), 115.72 (d, J = 22.0 Hz), 130.54, 132.11 (d, J = 3.3 Hz), 132.24 (d, J = 3.8 Hz), 164.54, 167.95, 189.62 (d, J = 17.0 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 10.56 (d, J = 72.6 Hz) ; ^{19}F NMR (282.38 Hz, $CDCl_3$) δ –26.71-(-26.68)(m), -130.98 (dd, J = 47.4 Hz, 72.2 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{16}F_2O_4P$ $[M+H]^+$ = 293.0676, found = 293.0741.

Diethyl (2-(4-cyanophenyl)-2-oxoethyl)phosphonate;



A pale-yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J = 7.0 Hz, 6H), 3.60 (d, J = 22.8 Hz), 4.06-4.11 (m, 4H), 7.74 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75.48 Hz, $CDCl_3$) δ 16.08 (d, J = 6.0 Hz), 37.98, 39.69, 62.76 (d, J = 6.6 Hz), 116.66, 117.65, 129.33, 132.29, 139.23, 190.65 (d, J = 6.6 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 19.24; HRMS (ESI) m/z calcd for $C_{13}H_{17}NO_4P$ $[M+H]^+$ = 282.0817, found = 282.0878.

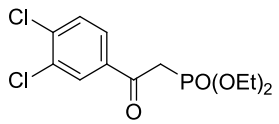
Diethyl (2-(4-cyanophenyl)-1-fluoro-2-oxoethyl)phosphonate;



A pale-yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25-1.38 (m, 6H), 4.18-4.25 (m, 4H), 5.87 (dd, J = 14.0 Hz, 47.5 Hz, 1H), 7.79 (d, J = 8.7 Hz, 2H), 8.15 (d, J = 8.04, 2H); ^{13}C NMR (75.48Hz) δ: 16.20 (d, J = 3.3 Hz), 16.28 (d, J = 3.3 Hz), 64.49 (d, J = 2.7 Hz), 64.59 (d, J = 3.3 Hz), 90.93 (dd, J = 152.1 Hz, 198.2 Hz), 117.29, 117.64, 129.82, 129.87, 132.30, 137.17 (d, J = 1.6 Hz), 190.76 (d, J = 18.1 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 9.92 (d, J = 71.1 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -

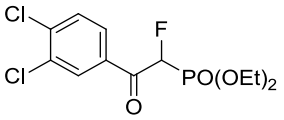
131.04 (dd, J = 47.4 Hz, 71.1 Hz); HRMS (ESI) m/z calcd for $C_{13}H_{16}FNO_4P$ $[M+H]^+$ = 300.0723, found = 300.0783.

Diethyl (2-(3,4-dichlorophenyl)-2-oxoethyl)phosphonate



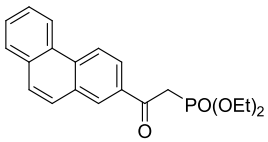
A colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, J = 7.0 Hz, 6H), 3.57 (d, J = 23.0 Hz, 1H), 4.08-4.18 (m, 4H), 7.55 (d, J = 8.4 Hz, 1H), 7.84 (dd, J = 2.0 Hz, 8.4 Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 15.97 (d, J = 6.4 Hz), 37.95, 38.94, 62.53, 127.95, 130.42, 130.69, 132.97, 135.69, 137.93, 137.98, 189.52 (d, J = 7.3 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 19.46; HRMS (ESI) m/z calcd for $C_{12}H_{16}Cl_2O_4P$ $[M+H]^+$ = 325.0085, found = 325.0158.

Diethyl (2-(3,4-dichlorophenyl)-1-fluoro-2-oxoethyl)phosphonate



A white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26-1.31 (t, J = 7.2 Hz, 3H), 1.31-1.36 (t, J = 7.1 Hz, 3H), 4.13-4.28 (m, 4H), 5.75-5.95 (dd, J = 13.7 Hz, 47.4 Hz, 1H), 7.54-7.56 (d, J = 8.4 Hz, 1H), 7.86-7.89 (dd, J = 2.0 Hz, 8.4 Hz, 1H), 8.11 (d, J = 1.7, 1H); ^{13}C NMR (75.48 Hz, $CDCl_3$) δ 16.16 (d, J = 3.8), 16.24 (d, J = 3.3 Hz), 64.36 (d, J = 3.3 Hz), 64.45 (d, J = 2.7 Hz), 88.28, 90.60 (d, J = 45.0 Hz), 92.92, 128.47 (d, 3.8 Hz), 130.65, 131.18, 131.23, 133.30, 133.52, 138.92, 189.43 (d, J = 17.6 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 10.09 (d, J = 71.0 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ –131.08 (dd, J = 47.3 Hz, 71.7 Hz); HRMS (ESI) m/z calcd for $C_{12}H_{15}Cl_2FO_4P$ $[M+H]^+$ = 342.9991, found = 343.0051.

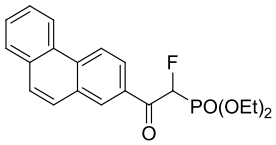
Diethyl (2-oxo-2-(phenanthren-2-yl)ethyl)phosphonate;



An orange oil; ^{1}H NMR (300 MHz) δ: 1.23 (t, J = 6.9 Hz, 6H), 3.76 (d, J = 22.7 Hz, 2H), 4.08-4.17 (m, 4H), 7.56-7.82 (m, 6H), 8.08 (d, J = 8.2 Hz, 1H), 8.68 (d, J = 6.2 Hz, 1H), 9.29 (s, 1H); ^{13}C NMR (75.48Hz) δ: 16.00, 16.08, 37.76, 39.48, 62.49, 62.57, 122.50, 124.86, 125.43, 125.87, 127.00, 127.16, 127.75, 128.54, 128.57, 129.84, 130.35, 131.84, 133.76, 134.97, 191.63 (d, J = 6.6 Hz); ^{31}P

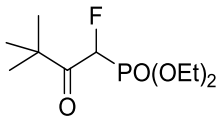
NMR (121.49 Hz) δ: 20.94; HRMS (ESI) m/z calcd for $C_{20}H_{22}O_4P$ $[M+H]^+$ = 357.1177, found = 357.1246.

Diethyl (1-fluoro-2-oxo-2-(phenanthren-2-yl)ethyl)phosphonate;



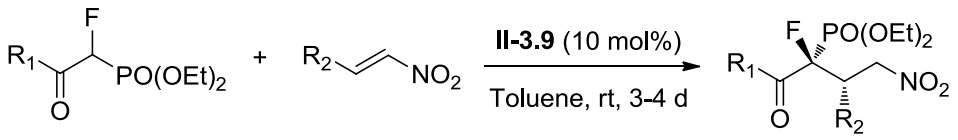
A white solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24-1.27 (t, J = 7.5 Hz, 3H), 1.34-1.37 (t, J = 7.0, 3H), 4.16-4.28 (m, 2H), 4.29-4.31 (m, 2H), 6.12-6.24 (dd, J = 13.2 Hz, 47.3 Hz, 1H), 7.65-7.68 (m, 1H), 7.74-7.76 (m, 2H), 7.87-7.96 (m, 3H), 8.19-8.20 (d, J = 8.2 Hz, 1H), 8.78-8.80 (d, J = 8.2 Hz, 1H), 9.48 (s, 1H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.24 (d, J = 5.5 Hz), 16.34 (d, J = 6.4 Hz), 64.33 (d, J = 6.4 Hz), 64.41 (d, J = 6.4 Hz), 89.40, 90.78 (d, J = 44.0 Hz), 92.17, 122.89, 125.71, 126.16, 127.39, 127.61, 128.84, 128.87, 130.53, 132.17, 135.71, 191.05 (d, J = 17.4 Hz); ^{31}P NMR (202.45 Hz, $CDCl_3$) δ 11.10 (d, J = 71.9 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ −130.76 (dd, J = 47.4 Hz, 72.2 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{21}FO_4P$ $[M+H]^+$ = 375.1083, found = 375.1156.

Diethyl (1-fluoro-3,3-dimethyl-2-oxobutyl)phosphonate



A pale yellow oil; ^{1}H NMR (300 MHz) δ: 1.24 (s, 9H), 1.33 (t, J = 4.6 Hz, 3H), 1.37 (t, J = 4.6 Hz, 3H), 4.17-4.28 (m, 4H), 5.45 (dd, J = 14.1 Hz, 47.4 Hz, 1H); ^{13}C NMR (75.48Hz) δ: 16.26 (d, J = 1.6Hz), 16.34 (d, J = 1.1 Hz), 25.67 (d, J = 2.7 Hz), 44.64, 63.85 (d, J = 6.6 Hz), 64.06 (d, J = 7.1 Hz), 88.05, 90.11, 90.70, 92.76, 207.35 (d, J = 15.9 Hz); ^{31}P NMR (121.49 Hz) δ: 11.83 (d, J = 71.1 Hz); ^{19}F NMR (282.38 Hz) δ: -128.54 (dd, J = 47.3 Hz, 71.7 Hz); HRMS (ESI) m/z calcd for $C_{10}H_{21}FO_4P$ $[M+H]^+$ = 255.1083, found = 255.1146.

IV-3.2. Representative procedure for Michael addition

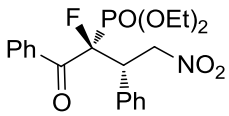


(**II-3.1a-k**) (**I-189a-n**) (**II-3.2ab-ke**)

To a sample vial containing the α-fluoro-β-ketophosphonate (0.05 mmol), toluene (0.5 ml) was added, followed by the catalyst **II-3.9** (0.005 mmol, 3.5 mg) (or **II-3.8**, 0.005 mmol, 3.4 mg). The vial was then capped and the reaction mixture was stirred for 5 minutes. Next, the nitroalkene (0.06 mmol) was added and the reaction mixture was stirred at room temperature for a given period (Table **3**). At the end of the reaction, the mixture was subjected directly to flash column chromatographic separation using a mixture of hexane/ethyl acetate (10 : 1 to 7 : 1) as the eluent to afford the Michael addition products (**II-3.2ab-ke**).

IV-3.3. Analytical data of the Michael Reaction Products

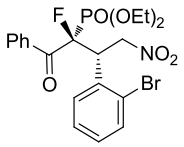
Diethyl (2-fluoro-4-nitro-1-oxo-1,3-diphenylbutan-2-yl)phosphonate (**II-3.2aa**)*;*



A pale-yellow oil; $[\alpha]^{27}_{D}$ = -18.0 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12-1.17 (t, J = 7.1 Hz, 3H), 1.25-1.29 (t, J = 7.0 Hz, 3H), 3.91-4.12 (m, 4H), 4.55-4.70 (m, 1H), 5.02-5.05 (m, 2H), 7.25-7.42 (m, 7H), 7.53-7.58 (m, 1H), 7.78-7.80 (m, 2H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.07 (d, J = 5.5 Hz), 16.34 (d, J = 5.5 Hz), 48.56 (dd, J = 2.7 Hz, 21.1 Hz), 64.40 (d, J = 7.3 Hz), 64.8 (d, J = 6.4 Hz), 75.6 (t, J = 7.3 Hz), 102.72 (dd, J = 48.6 Hz, 158.6 Hz), 128.29, 128.63, 128.77, 129.76, 129.83, 129.92, 133.70, 197.66 (dd, J = 1.8 Hz, 22.9 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.57 (d, J = 78.5 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -97.28 (dd, J = 24.8 Hz, 78.4 Hz); HRMS

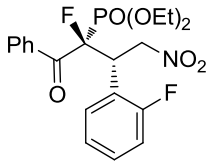
(ESI) m/z calcd for $C_{20}H_{23}FNO_6P$ $[M+H]^+$ = 424.1247, found = 424.1322; the ee value was 99%, t_R (major) = 32.8 min, t_R (minor) = 34.9 min (Chiralcel IA-H, λ = 220 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

Diethyl (3-(2-bromophenyl)-2-fluoro-4-nitro-1-oxo-1-phenylbutan-2-yl)phosphonate ***(II-3.2ab);***



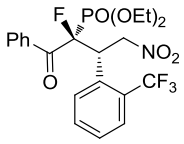
A pale-yellow oil; $[\alpha]^{27}_D$ = -71 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 (t, J = 6.9 Hz, 3H), 1.39 (t, J = 6.9 Hz, 3H), 4.09-4.26 (m, 2H), 4.27-4.32 (m, 2H), 5.03-5.08 (m, 1H), 5.04-5.44 (m, 2H), 7.11-7.14 (m, 1H), 7.17-7.20 (m, 1H), 7.26-7.27 (m, 1H), 7.36 (t, J = 7.5 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.61-7.63 (m, 1H), 7.74 (d, J = 8.1 Hz, 2H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.21 (d, J = 5.5 Hz), 16.47 (d, J = 5.5 Hz), 46.09 (d, J = 22.0 Hz), 64.80 (d, J = 6.4 Hz), 65.35 (d, J = 7.3 Hz), 75.90 (d, J = 6.4 Hz), 102.34 (dd, J = 156.7 Hz, 206.2 Hz), 127.54, 127.76, 128.22, 128.89, 129.83, 129.90, 130.00, 133.59, 133.70, 133.80, 135.66, 197.80 (d, J = 22.9 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.41 (d, J = 78.5 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -94.72 (dd, J = 13.7 Hz, 79.3 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{22}BrFNO_6P$ $[M+H]^+$ = 502.0352, found = 502.0429; the ee value was 97%, t_R (major) = 21.4 min, t_R (minor) = 19.3 min (Chiralcel IA-H, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

*Diethyl (2-fluoro-3-(2-fluorophenyl)-4-nitro-1-oxo-1-phenylbutan-2-yl)phosphonate (***II-3.2ac***);*



A pale-yellow oil; $[\alpha]^{27}_{D}$ = -28.1 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16-1.19 (t, J = 13.85 Hz, 3H), 1.32-1.35 (t, J = 14.5 Hz, 3H), 4.01-4.24 (m, 4H), 5.03-5.08 (m, 2H), 5.14-5.16 (m, 1H), 7.04-7.09 (m, 2H), 7.27-7.33 (m, 2H), 7.38-7.41 (m, 2H), 7.54-7.57 (m, 1H), 7.82-7.83 (d, J = 1.9 Hz, 2H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.07 (d, J = 5.51 Hz), 16.28 (d, J = 5.5 Hz), 29.67, 41.23 (d, J = 21.98 Hz), 64.69 (d, J = 6.4 Hz), 65.09 (d, J = 7.3 Hz), 74.82 (t, J = 5.5 Hz), 102.39 (dd, J = 157.6 Hz, 206.2 Hz), 116.00 (d, J = 22.9 Hz), 124.28 (d, J = 3.7 Hz), 128.30, 129.82, 129.88, 130.11, 130.45, 130.52, 133.78, 135.40, 160.51, 162.50, 197.48 (d, J = 24.8 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.22 (d, J = 80.0 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -38.23 (m), -97.09 (m). HRMS (ESI) m/z calcd for $C_{20}H_{22}F_2NO_6P$ $[M+H]^+$ = 442.1153, found = 442.1236; the ee value was 98%, t_R (major) = 32.5 min, t_R (minor) = 35.3 min (Chiralcel IA-H + OD-H, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

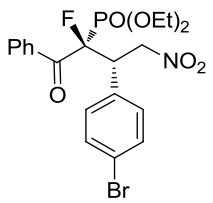
*Diethyl (2-fluoro-4-nitro-1-oxo-1-phenyl-3-(2-(trifluoromethyl)phenyl)butan-2-yl)phosphonate (***II-3.2*ad***);*



A pale-yellow oil; $[\alpha]^{27}_{D}$ = -33.8 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23–1.26 (t, J = 14.5 Hz, 3H), 1.41-1.43 (t, J = 14.5 Hz, 3H), 4.08-4.23 (m, 2H), 4.31-4.37 (m, 2H), 5.09-5.14 (d, J = 8.8 Hz, 2H), 5.74-5.76 (d, J = 8.8 Hz, 1H), 7.31-7.40 (m, 5H), 7.49-7.52 (m, 1H), 7.65-7.66 (d, J = 7.6, 2H), 7.72-7.71 (m, 1H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.13 (d, J = 6.4 Hz), 16.34 (d, J =

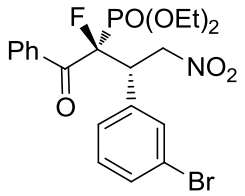
5.5 Hz), 43.38 (d, J = 23.8 Hz), 64.96 (d, J = 7.3 Hz), 65.52 (d, J = 7.3 Hz), 76.69, 101.10 (dd, J = 155.8 Hz, 207.13 Hz), 122.77, 124.96, 127.30, 128.20 (d, J = 1.8 Hz), 128.85, 129.88 (d, J = 8.2 Hz), 131.15 (d, J = 29.3 Hz), 132.15, 133.00 (d, J = 11.9 Hz), 133.73, 135.93 (d, J = 3.7 Hz), 198.41 (d, J = 23.8 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.68 (d, J = 77.0 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ 19.12 (d, J = 13.4 Hz), -91.44 (m); HRMS (ESI) m/z calcd for $C_{21}H_{22}F_4NO_6P$ $[M+H]^+$ = 492.1121, found = 492.1205; the ee value was 96%, t_R (major) = 52.7 min, t_R (minor) = 57.3 min (Chiralcel IA-H + OD-H, λ = 220 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

*Diethyl (3-(4-bromophenyl)-2-fluoro-4-nitro-1-oxo-1-phenylbutan-2-yl)phosphonate (***II-3.2*af*)***;*



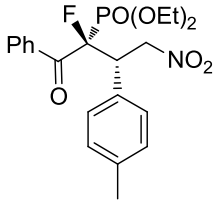
A pale-yellow oil; $[\alpha]^{27}_D$ = -28.5 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13-1.16 (t, J = 6.9 Hz, 3H), 1.26-1.29 (t, J = 6.9 Hz, 3H), 3.96-4.02 (m, 2H), 4.04-4.14 (m, 2H), 4.56-4.65 (m, 1H), 4.96-4.98 (m, 2H), 7.23-7.25 (d, J = 8.2 Hz, 2H), 7.41-7.45 (m, 4H), 7.56-7.59 (t, J = 7.6 Hz, 1H), 7.85-7.86 (m, 2); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.05 (d, J = 5.5 Hz), 16.30 (d, J = 5.5 Hz), 48.05 (d, J = 2.75), 48.21 (d, J = 2.75 Hz), 64.57 (d, J = 6.4 Hz), 64.88 (d, J = 6.4 Hz), 75.37, 102.64 (dd, J = 49.5 Hz, 158.6 Hz), 123.02, 128.41, 129.91, 129.87, 131.56, 131.58, 131.75, 132.28, 132.33, 133.95, 197.25 (d, J = 22.9 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.24 (d, J = 77.0 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -98.23 (dd, J = 25.8 Hz, 78.3 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{22}BrFNO_6P$ $[M+H]^+$ = 524.0250, found = 524.0254; 526.0242; the ee value was 99%, t_R (major) = 24.0 min, t_R (minor) = 29.9 min (Chiralcel IA-H, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

*Diethyl (3-(3-bromophenyl)-2-fluoro-4-nitro-1-oxo-1-phenylbutan-2-yl)phosphonate (**II-3.2ae**);*



A pale-yellow oil; $[\alpha]^{27}_{D}$ = -10.0 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13–1.15 (t, J = 14.5 Hz, 3H), 1.27-1.29 (t, J = 13.8 Hz, 3H), 3.96-4.03 (m, 2H), 4.05-4.13 (m, 2H), 4.56-4.64 (m, 1H), 4.95-4.96 (m, 2H), 7.15-7.18 (t, J = 8.2 Hz, 1H), 7.28-7.30 (d, J = 7.6 Hz, 1H), 7.40-7.43 (m, 2H), 7.53-7.58 (m, 2H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 15.97-16.02 (d, J = 6.4 Hz), 16.23-16.28 (d, J = 5.5 Hz), 48.11-48.27 (d, J = 20.2 Hz), 64.51-64.56 (d, J = 6.4 Hz), 64.79-64.85 (d, J = 7.3 Hz), 75.28-75.39 (t, J = 6.4 Hz, 14.7 Hz), 102.67 (dd, J = 157.6 Hz, 208.1 Hz), 122.45, 128.34, 128.59, 129.78-129.84 (d, J = 8.3 Hz), 130.01, 131.81, 132.92, 133.88, 135.27, 135.57-135.62 (d, J = 6.4 Hz), 197.11-197.30 (d, J = 23.8 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.11 (d, J = 78.5 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -98.53 (dd, J = 25.9 Hz, 77.8 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{22}BrFNNaO_6P$ $[M+Na]^+$= 524.0250, found = 524.0242; the ee value was 99%, t_R (major) = 43.6 min, t_R (minor) = 40.9 min (Chiralcel IA-H, λ = 220 nm, 5% *i*PrOH/hexanes, flow rate = 0.75 mL/min).

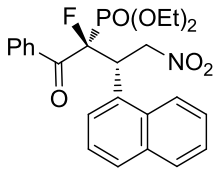
*Diethyl (2-fluoro-4-nitro-1-oxo-1-phenyl-3-(p-tolyl)butan-2-yl)phosphonate (**II-3.2ag**);*



A pale-yellow oil; $[\alpha]^{27}_{D}$ = -27.8 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14-1.17 (t, J = 14.5 Hz, 3H), 1.26-1.29 (t, J = 16.4 Hz, 3H), 2.29 (s, 3H), 3.92-4.14 (m, 4H), 4.53-4.60 (m, 1H), 4.99-5.07 (m, 2H), 7.09-7.10 (d, J = 7.6 Hz, 2H), 7.22-7.23 (d, J = 7.6 Hz, 2H), 7.37-7.40 (m, 2H),

7.53-7.56 (m, 1H), 7.79-7.80 (m, 2H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.06 (d, J = 6.4 Hz), 16.32 (d, J = 5.5 Hz), 21.06, 48.25 (dd, J = 2.7 Hz, 21.0 Hz), 64.38 (d, J = 7.3 Hz), 64.77 (d, J = 7.3 Hz), 75.70, 102.73 (dd, J = 48.6 Hz, 158.6Hz), 128.25, 129.30, 129.70, 129.75, 129.82, 129.97, 130.03, 133.64, 138.64, 197.73 (d, J = 21.0 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.69 (d, J = 78.5 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -97.03 (dd, J = 23.7 Hz, 77.3 Hz); HRMS (ESI) m/z calcd for $C_{21}H_{25}FNNaO_6P$ $[M+Na]^+$= 460.1401, found = 460.1302; the ee value was 99%, t_R (major) = 17.1 min, t_R (minor) = 18.6 min (Chiralcel IA-H, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

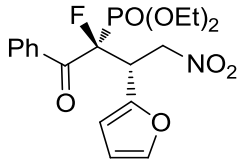
*Diethyl (2-fluoro-3-(naphthalen-1-yl)-4-nitro-1-oxo-1-phenylbutan-2-yl)phosphonate (***II-3.2*ah***);*



A pale-yellow oil; $[\alpha]^{27}_D$ = -69.5 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15–1.18 (t, J = 13.9 Hz, 3H), 1.29-1.31 (t, J = 13.9 Hz, 3H), 3.96-4.14 (m, 4H), 5.20-5.25 (dd, J = 10.8 Hz, 13.9 Hz, 1H), 5.40-5.44 (dd, J = 3.2 Hz, 13.9 Hz, 1H), 5.71-5.79 (m, 1H), 7.34-7.38 (m, 3H), 7.39-7.56 (m, 3H), 7.64-7.67 (m, 1H), 7.71-7.72 (d, J = 7.6 Hz, 2H), 7.81-7.83 (d, J = 8.2 Hz, 1H), 7.86-7.88 (d, J = 8.2 Hz, 1H), 8.34-8.35 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.09 (d, J = 6.4 Hz), 16.30 (d, J = 5.5 Hz), 41.29 (d, J = 22.0 Hz), 64.52 (d, J = 7.3 Hz), 64.88 (d, J = 7.3 Hz), 76.38 (t, J = 5.5 Hz), 103.03 (dd, J = 157.64 Hz, 206.2 Hz), 123.70, 124.87, 125.82 (d, J = 1.8 Hz), 126.00, 126.63, 128.19, 128.67, 129.42, 129.85 (d, J = 8.2 Hz), 130.34 (d, J = 8.2 Hz), 133.08, 133.62, 133.92, 135.67 (d, J = 2.8 Hz), 198.14 (d, J = 22.9 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.77 (d, J = 79.5 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ 95.83 (dd, J = 18.3 Hz, 79.3 Hz); HRMS (ESI) m/z calcd for $C_{24}H_{25}FNNaO_6P$ $[M+Na]^+$= 496.1301, found = 496.1303; the ee value

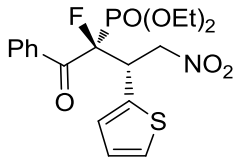
was 98%, t_R (major) = 40.1 min, t_R (minor) = 35.4 min (Chiralcel IA-H, λ = 220 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

*Diethyl (2-fluoro-3-(furan-2-yl)-4-nitro-1-oxo-1-phenylbutan-2-yl)phosphonate (***II-3.2ai***);*



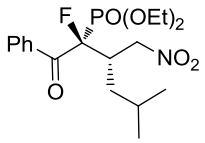
A pale-yellow oil; $[\alpha]^{27}_{D}$ = -7.1 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26-1.29 (t, J = 13.8Hz, 3H), 1.37-1.40 (t, J = 14.5 Hz, 3H), 4.12-4.30 (m, 4H), 4.70-4.77 (m, 1H), 5.04-5.10 (dd, J = 13.9 Hz, 1H), 5.19-5.22 (dd, J = 3.8 Hz, 13.9 Hz, 1H), 6.31-6.32 (d, J = 3.8 Hz, 1H), 6.38-6.39 (d, J = 3.8 Hz, 1H), 7.32 (s, 1H), 7.42-7.45 (t, J = 15.8 Hz, 2H), 7.57-7.60 (t, J = 15.1 Hz, 1H), 7.84-7.85 (d, J = 6.3 Hz, 2H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.16-16.22 (d, J = 6.4 Hz), 16.34-16.38 (d, J = 5.5 Hz), 29.67, 42.99, 64.79-64.84 (d, J = 7.3 Hz), 65.10-65.16 (d, J = 7.3 Hz), 74.24, 100.94 (dd, J = 48.6 Hz, 158.6 Hz), 110.73, 111.17, 128.25, 129.69, 129.75, 133.66, 143.10, 146.83, 146.92, 196.94-197.13 (d, J = 22.9 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.41 (d, J = 78.5 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -93.68 (dd, J = 18.6 Hz, 78.4 Hz); HRMS (ESI) m/z calcd for $C_{18}H_{22}FNO_7P$ $[M+H]^+$= 414.1040, found = 414.1112; the ee value was 99%, t_R (major) = 15.0 min, t_R (minor) = 17.2 min (Chiralcel IA-H, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

Diethyl (2-fluoro-4-nitro-1-oxo-1-phenyl-3-(thiophen-2-yl)butan-2-yl)phosphonate (**II-3.2aj***);*



A pale-yellow oil; $[\alpha]^{27}_{D}$ = -30.1 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22-1.25 (t, J = 13.9 Hz, 3H), 1.33-1.36 (t, J = 13.9 Hz, 3H), 4.04-4.24 (m, 4H), 4.93-4.95 (m, 1H), 4.98-5.05 (m, 1H), 5.13-5.16 (m, 1H), 6.95-6.96 (d, J = 1.85 Hz, 1H), 7.08-7.09 (d, J = 3.8 Hz, 1H), 7.27-7.28 (d, J = 5.1 Hz, 1H), 7.42-7.45 (m, 2H), 7.57-7.60 (t, J = 7.6 Hz, 1H), 7.88-7.90 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75.48 Hz, $CDCl_3$) δ 16.11 (d, J = 6.0 Hz), 16.36 (d, J = 5.5 Hz), 29.67, 44.45 (d, J = 2.7 Hz), 44.74 (d, J = 2.7 Hz), 64.81 (q, J = 7.1 Hz, 26.9 Hz), 102.06 (dd, J = 156.4 Hz, 207.0 Hz), 126.58, 126.80, 128.30, 128.32, 129.01, 129.85 (d, J = 8.2 Hz), 133.82, 134.91 (d, J = 8.8 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.38 (d, J = 78.5 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ 94.47 (dd, J = 21.6 Hz, 77.3 Hz); HRMS (ESI) m/z calcd for $C_{18}H_{22}FNO_6PS$ $[M+H]^+$= 430.0811, found = 430.0889; the ee value was 99%, t_R (major) = 32.1 min, t_R (minor) = 36.6 min (Chiralcel IA-H, λ = 220 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

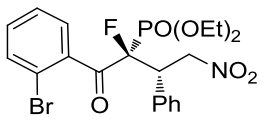
*Diethyl (2-fluoro-5-methyl-3-(nitromethyl)-1-oxo-1-phenylhexan-2-yl)phosphonate (***II-3.2*ak***);*



A pale-yellow oil; $[\alpha]^{27}_{D}$ = 4.6 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85-0.86 (d, J = 6.3 Hz, 3H), 0.88-0.90 (d, J = 6.3 Hz, 3H), 0.91-0.94 (m, 1H), 1.30-1.32 (t, J = 7.0 Hz, 3H), 1.34-1.36 (t, J = 13.8 Hz, 3H), 3.36-3.46 (m, 1H), 4.17-4.28 (m, 4H), 4.41-4.45 (dd, J = 6.3 Hz, 14.5 Hz, 1H), 5.18-5.22 (dd, J = 3.8 Hz, 13.8 Hz, 1H), 7.46-7.49 (m, 2H), 7.59-7.60 (m, 1H), 8.02-8.04

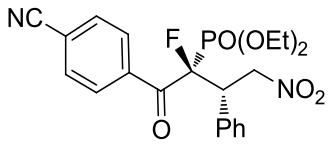
(d, J = 8.2 Hz, 1H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.27 (d, J = 7.33), 16.35, 21.31, 23.33, 25.51, 38.11 (d, J = 6.4 Hz), 41.11 (d, J = 21.1 Hz), 64.63 (d, J = 7.3 Hz), 64.88 (d, J = 7.3 Hz), 103.05 (dd, J = 157.6 Hz, 202.6 Hz), 128.42, 129.86, 129.93, 133.81, 197.37 (d, J = 25.7 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 12.63 (d, J = 80.0 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ 94.25 (dd, J = 16.8Hz, 80.9 Hz); HRMS (ESI) m/z calcd for $C_{18}H_{28}FNO_6P$ $[M+H]^+$= 404.1560, found = 404.1637; the ee value was 96%, t_R (major) = 49.1 min, t_R (minor) = 38.7 min (Chiralcel IC, λ = 220 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

Diethyl ((2R,3S)-1-(2-bromophenyl)-2-fluoro-4-nitro-1-oxo-3-phenylbutan-2-yl)phosphonate **(II-3.2ba)**;



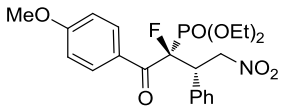
A pale-yellow oil; $[\alpha]^{27}_D$ = -16.5 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13-1.16 (t, J = 7.0 Hz, 3H), 1.26-1.28 (t, J = 7.0 Hz, 3H), 3.89-4.12 (m, 4H), 4.58-4.66 (m, 1H), 5.03-5.06 (m, 2H), 7.29-7.30 (m, 2H), 7.35-7.40 (m, 4H), 7.53-7.56 (m, 1H), 7.78-7.80 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.05 (d, J = 5.5 Hz), 16.32 (d, J = 5.5 Hz), 48.57 (dd, J = 2.74 Hz, 21.1 Hz), 64.39 (d, J = 6.4 Hz), 64.77 (d, J = 7.3 Hz), 75.60 (t, J = 7.3 Hz), 102.71 (dd, J = 158.6 Hz, 207.1 Hz), 128.27, 128.61, 128.74, 129.75, 129.82, 129.91, 133.68, 197.63 (d, J = 22.9 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.57 (d, J = 77.0 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -97.23 (dd, J = 24.74 Hz, 78.4 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{22}BrFNNaO_6P$ $[M+Na]^+$= 524.0250, found = 524.0242; the ee value was 99%, t_R (major) = 20.3 min, t_R (minor) = 23.1 min (Chiralcel IB, λ = 220 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

Diethyl ((2R,3S)-1-(4-cyanophenyl)-2-fluoro-4-nitro-1-oxo-3-phenylbutan-2-yl)phosphonate (**II-3.2ea**);



A pale-yellow oil; $[\alpha]^{27}_{D}$ = -29.9 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12-1.17 (t, J = 7.1 Hz, 3H), 1.26-1.30 (t, J = 7.0 Hz, 3H), 3.91-4.17 (m, 4H), 4.45-4.60 (m, 1H), 4.96-5.11 (m, 2H), 7.26 (s, 5H), 7.60-7.63 (d, J = 8.7 Hz, 2H), 7.72-7.74 (m, 2 H); ^{13}C NMR (75.48 Hz, $CDCl_3$) δ 16.13 (d, J = 6.0 Hz), 16.38 (d, J = 6.0 Hz), 22.68, 31.23, 48.41 (dd, J = 2.2 Hz, 21.4 Hz), 64.67 (d, J = 7.1 Hz), 65.24 (d, J = 7.1 Hz), 75.21, 101.12 (dd, J = 157.6 Hz, 204.22 Hz), 117.18 (d, J = 70.3 Hz), 128.83, 129.02, 129.69, 129.98, 130.09, 131.93, 132.81, 132.92, 138.70, 197.28 (d, J = 24.7 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.01 (d, J = 78.5 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ –96.25 (dd, J = 22.7 Hz, 78.4 Hz); HRMS (ESI) m/z calcd for $C_{21}H_{22}FN_2NaO_6P$ $[M+Na]^+$= 471.1097, found = 471.1104; the ee value was 99%, t_R (major) = 24.1 min, t_R (minor) = 23.1 min (Chiralcel IB, λ = 220 nm, 20% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

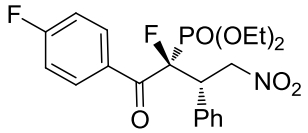
Diethyl ((2R,3S)-2-fluoro-1-(4-methoxyphenyl)-4-nitro-1-oxo-3-phenylbutan-2-yl)phosphonate (**II-3.2fa**);



Colourless oil; $[\alpha]^{27}_{D}$ = -30.5 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11-1.16 (t, J = 7.0 Hz, 3H), 125-1.29 (t, J = 7.0, 3H), 3.85 (s, 3H), 3.91-4.11 (m, 4H), 4.54-4.69 (m, 1H), 5.01-5.04 (m, 2H), 6.85-6.88 (d, J = 9.0 Hz, 2H), 7.26-7.36 (m, 5H), 7.86-7.87 (d, J = 2.0 Hz); ^{13}C NMR (75.48 Hz, $CDCl_3$) δ 16.09 (d, J = 6.0 Hz), 16.34 (d, J = 5.5 Hz), 48.57 (d, J = 18.7 Hz), 55.49, 64.32 (d, J = 7.7 Hz), 64.62 (d, J = 7.1 Hz), 75.75, 100.43, 113.62, 113.64, 128.54, 128.66, 129.95, 129.97, 132.57, 132.70, 133.31, 164.14, 194.95 (d, J = 22.0 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.96

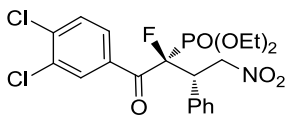
(d, J = 77.0 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -96.56 (dd, J = 24.8 Hz, 78.4 Hz); HRMS (ESI) m/z calcd for $C_{21}H_{26}FNO_7P$ $[M+H]^+$= 454.1353, found = 454.1434; the ee value was 98%, t_R (major) = 51.5 min, t_R (minor) = 62.6 min (Chiralcel IA, λ = 220 nm, 5 % *i*PrOH/hexanes, flow rate = 1 mL/min).

Diethyl ((2R,3S)-2-fluoro-1-(4-fluorophenyl)-4-nitro-1-oxo-3-phenylbutan-2-yl)phosphonate **(II-3.2da)**;



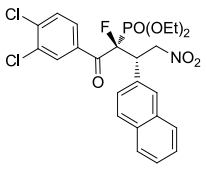
A pale-yellow oil; $[\alpha]^{27}_D$ = -24.2 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13-1.18 (t, J = 7.0 Hz, 3H), 1.27-1.32 (t, J = 7.0 Hz, 3H), 3.98-4.11 (m, 4H), 4.54-4.65 (m, 1H), 5.02-5.07 (m, 2H), 7.02-7.08 (t, J = 8.7 Hz, 2H), 7.28-7.31 (m, 5H), 7.83-7.84 (m, 2H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.08 (d, J = 5.5 Hz), 16.36 (d, J = 5.5 Hz), 48.48 (t, J = 21.1 Hz), 64.45 (d, J = 6.41 Hz), 64.90 (d, J = 7.3 Hz), 75.51 (t, J = 6.4 Hz), 102.67 (dd, J = 157.65 Hz, 206.2 Hz), 115.55 (d, J = 11.0 Hz), 128.66, 128.82, 129.83, 132.76, 132.83, 132.90, 165.99 (d, J = 128.3 Hz), 195.92 (d, J = 22.9 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.52 (d, J = 77.7 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -27.00 (m), -96.25 (dd, J = 23.7 Hz, 78.4 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{23}F_2NO_6P$ $[M+H]^+$= 442.1153, found = 442.1225; the ee value was %, t_R (major) = 30.3 min, t_R (minor) = 32.6 min (Chiralcel, IA, λ = 220 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

Diethyl ((2R,3S)-1-(3,4-dichlorophenyl)-2-fluoro-4-nitro-1-oxo-3-phenylbutan-2-yl)phosphonate (**II-3.2ca**);



A pale beige solid; $[\alpha]^{27}_{D}$ = -32.6 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16–1.21 (t, J = 7.1 Hz, 3H), 1.29-1.34 (t, J = 7.1 Hz, 3H), 3.92-4.19 (m, 4H), 4.50-4.64 (m, 1H), 4.99-5.13 (m, 2H), 7.31 (s, 5H), 7.44-7.46 (d, J = 8.6 Hz, 1H), 7.57-7.80 (m, 1H), 7.81 (s, 1H); ^{13}C NMR (75.48 Hz, $CDCl_3$) δ 16.11 (d, J = 6.1 Hz), 16.37 (d, J = 6.1 Hz), 48.41 (dd, J = 2.3 Hz, 21.3 Hz), 64.57 (d, J = 7.1 Hz), 65.10 (d, J = 7.1 Hz), 75.28 (t, J = 6.3 Hz), (dd, J = 158.1 Hz, 205.9 Hz), 128.78, 128.90, 128.97, 129.74 (d, J = 1.1 Hz), 130.41, 131.65, 131.77, 132.83, 132.94, 134.78 (d, J = 3.8 Hz), 138.54, 195.69 (d, J = 24.1 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.16 (d, J = 77.0 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -96.13 (dd, J = 22.7 Hz, 77.3 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{22}Cl_2FNO_6P$ $[M+H]^+$= 492.0468, found = 492.0540; the ee value was %, t_R (major) = 33.6 min, t_R (minor) = 31.6 min (Chiralcel, ID, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

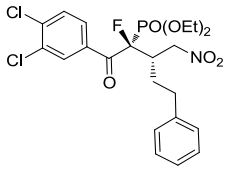
*Diethyl ((2R,3S)-1-(3,4-dichlorophenyl)-2-fluoro-3-(naphthalen-2-yl)-4-nitro-1-oxobutan-2-yl)phosphonate (***II-3.2im***);*



A pale beige solid; $[\alpha]^{27}_{D}$ = -24.2 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10-1.13 (t, J = 6.9 Hz, 3H), 1.25-1.28 (t, J = 6.9 Hz, 3H), 3.93-4.12 (m, 4H), 4.71-4.80 (m, 1H), 5.15-5.16 (d, J = 7.5 Hz, 2H), 7.40-7.43 (t, J = 7.5 Hz, 2H), 7.47-7.49 (m, 2H), 7.63-7.65 (d, J = 8.8 Hz, 1H), 7.78-7.80 (d, J = 8.2 Hz, 4H), 7.88 (s, 1H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.02 (d, J = 6.4 Hz), 16.31

(d, J = 5.5 Hz), 48.59 (d, J = 21.1 Hz), 64.60 (d, J = 6.4 Hz), 65.11 (d, J = 7.3 Hz), 75.43 (t, J = 6.4 Hz), 103.53 (dd, J = 188.8 Hz, 205.3 Hz, 126.60 (d, J = 8.2 Hz), 126.74, 127.58, 127.98, 128.52, 128.89 (d, J = 8.2 Hz), 129.58, 130.24, 130.30, 130.41, 131.72, 131.79, 132.99, 133.20, 134.68, 138.58, 195.64 (d, J = 26.6 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.16 (d, J = 78.5 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -96.23 (dd, J = 22.7 Hz, 77.3 Hz); HRMS (ESI) m/z calcd for $C_{24}H_{23}Cl_2FNNaO_6P$ $[M+Na]^+$= 564.0522, found = 564.0527; the ee value was 99%, t_R (major) = 35.3 min, t_R (minor) = 25.7 min (Chiralcel, AD-H, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

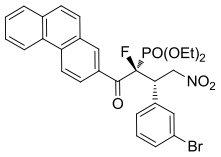
Diethyl (1-(3,4-dichlorophenyl)-2-fluoro-3-(nitromethyl)-1-oxo-5-phenylpentan-2-yl)phosphonate (**II-3.2in**);



A pale-yellow oil; $[\alpha]^{27}_D$ = -8.5 (c 1, $CHCl_3$); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.29-1.32 (t, J = 7.0 Hz, 3H), 1.32-1.35 (t, J = 7.0 Hz, 3H), 1.75-1.89 (m, 1H), 2.09-2.20 (m, 1H), 2.56-2.66 (m, 1H), 2.69-2.79 (m, 1H), 3.27-3.44 (m, 1H), 4.12-4.30 (m, 4H), 4.52-4.59 (dd, J = 6.1 Hz, 13.5 Hz, 1H), 5.07-5.13 (dd, J = 3.9 Hz, 14.1 Hz, 1H), 7.10-7.13 (m, 2H), 7.17-7.19 (m, 1H), 7.23-7.27 (m, 2H), 7.52-7.55 (d, J = 8.6 Hz, 1H), 7.81-7.89 (dt, J = 1.8 Hz, 14.5 Hz, 1H), 8.10-8.11 (t, J = 1.5 Hz, 1H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.26 (d, J = 5.5 Hz), 16.35 (d, J = 5.5 Hz), 30.10, 30.46 (q, J = 2.8 Hz, 5.5 Hz), 33.12 (d, J = 11.9 Hz), 42.43 (d, J = 22.9 Hz), 64.87 (d, J = 7.3 Hz), 65.13 (d, J = 7.3 Hz), 75.37, 103.24 (dd, J = 351.9 Hz, 454.8 Hz), 126.34, 128.26 (d, J = 22.9 Hz), 128.55 (d, J = 6.4 Hz), 129.11 (d, J = 4.6 Hz), 130.57, 131.96 (d, J = 9.2 Hz), 133.15, 134.64 (d, J = 3.7 Hz), 138.76, 140.19, 195.0 (d, J = 23.8 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 12.0 (d, J = 81.5 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ - 95.43 (dd, J = 18.3 Hz, 80.9 Hz); HRMS (ESI) m/z calcd for $C_{22}H_{26}Cl_2FNO_6P$ $[M+H]^+$= 520.0781, found = 520.0871; the ee value was 98%, t_R

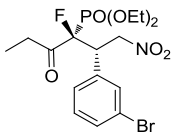
(major) = 11.8 min, t_R (minor) = 15.1 min (Chiralcel, IA, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

Diethyl (3-(3-bromophenyl)-2-fluoro-4-nitro-1-oxo-1-(phenanthren-2-yl)butan-2-yl)phosphonate **(II-3.2ge);**



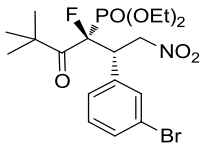
A white solid; $[\alpha]^{27}_{D}$ = -44.7 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18-1.20 (t, J = 6.9 Hz, 3H), 1.32-1.35 (t, J = 6.9, 3H), 4.05-4.21 (m, 4H), 4.65-4.74 (m, 1H), 5.04-5.09 (dd, J = 11.4 Hz, 14.0 Hz, 1H), 5.16-5.19 (dd, J = 10.1 Hz, 13.9 Hz, 1H), 7.15-7.18 (m, 1H), 7.32-7.34 (d, J = 7.6 Hz, 1H), 7.42-7.43 (d, J = 8.2, 1H), 7.63-7.66 (m, 2H), 7.73-7.75 (m, 2H), 7.88-7.92 (m, 3H), 8.04-8.06 (d, J = 2.1 Hz, 1H), 8.60-8.61 (d, J = 8.2 Hz, 1H), 9.17 (s, 1H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.16 (d, J = 5.5 Hz), 16.41 (d, J = 5.5 Hz), 29.68, 48.30 (d, J = 23.8 Hz), 64.69 (d, J = 6.4 Hz), 64.99 (d, J = 7.3 Hz), 75.29, 122.70 (d, J = 12.8 Hz), 126.05, 126.17 (d, J = 10.1 Hz), 126.37 (d, J = 7.3 Hz), 127.37, 127.57, 128.39, 128.63, 128.85, 129.41, 130.19, 130.59, 130.64, 132.02, 132.09, 133.21, 135.36, 135.65 (d, J = 7.3 Hz), 197.14 (d, J = 22.9 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.19, 11.82; ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -95.67 (dd, J = 22.9 Hz, 77.8 Hz); HRMS (ESI) m/z calcd for $C_{28}H_{27}BrFNO_6P$ $[M+H]^+$= 602.0665, found = 602.0743; the ee value was 99%, t_R (major) = 25.8 min, t_R (minor) = 21.3 min (Chiralcel, IA, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

Diethyl ((2S,3R)-2-(3-bromophenyl)-3-fluoro-1-nitro-4-oxohexan-3-yl)phosphonate (**II-3.2ke**);



A pale yellow oil; $[\alpha]^{27}_{D}$ = 14.0 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01-1.06 (t, J = 7.1 Hz, 3H), 1.20-1.25 (t, J = 7.0 Hz, 3H), 1.31-1.35 (t, J = 7.2 Hz, 3H), 2.69-2.83 (m, 1H), 3.99-4.08 (m, 3H), 4.10-4.16 (m, 2H), 4.90-4.93 (d, J = 7.7 Hz, 2H), 7.18-7.21 (m, 2H), 7.30-7.44 (m, 2H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 6.53 (d, J = 2.8 Hz), 16.15 (d, J = 5.5 Hz), 16.38 (d, J = 5.5 Hz), 33.46, 46.97 (dd, J = 1.4 Hz, 20.2 Hz), 64.45 (d, J = 6.4 Hz), 64.92 (d, J = 6.4 Hz), 74.89 (t, J = 6.9 Hz), 101.03 (dd, J = 156.7 Hz, 201.6 Hz), 122.62, 128.12, 130.13, 131.93, 132.64 (d, J = 1.8 Hz), 135.50 (d, J = 7.3 Hz), 207.69 (d, J = 25.7 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 10.69 (d, J = 80.0 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ 103.88 (dd, J = 22.7 Hz, 79.4 Hz); HRMS (ESI) m/z calcd for $C_{16}H_{23}BrFNO_6P$ $[M+H]^+$= 454.0352, found = 454.0412; the ee value was 96% for the major diastereomer, t_R (major) = 19.0 min, t_R (minor) = 17.2 min (Chiralcel, IA, λ = 220 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min); the ee value was 84% for the minor diastereomer, t_R (major) = 13.3 min, t_R (minor) = 10.3 min (Chiralcel, IC, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

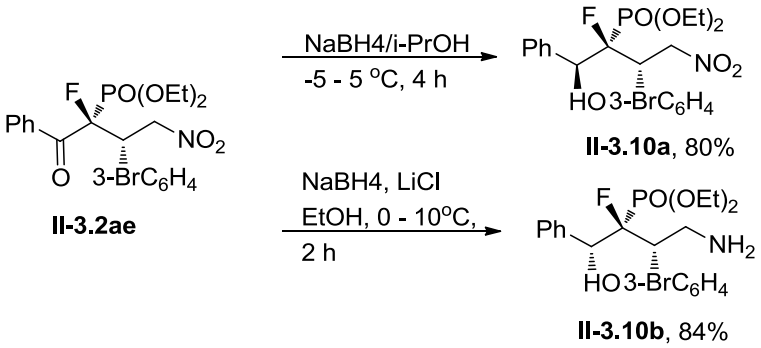
Diethyl ((2S,3R)-2-(3-bromophenyl)-3-fluoro-5,5-dimethyl-1-nitro-4-oxohexan-3-yl)phosphonate (**II-3.2je**);



A pale-yellow oil; $[\alpha]^{27}_{D}$ = -8.7 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.22-1.25 (t, J = 6.9 Hz, 3H), 1.33-1.36 (t, J = 6.9 Hz, 3H), 4.06-4.17 (m, 4H), 4.36-4.42 (m, 1H), 4.88-5.04

(m, 2H), 7.16-7.23 (m, 2H), 7.40-7.45 (m, 2 H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.15 (t, J = 5.5 Hz), 16.38 (d, J = 5.5 Hz), 48.50 (t, J = 29.3 Hz), 64.30 (d, J = 7.3 Hz), 64.95 (d, J = 6.4 Hz), 75.37 (t, J = 7.3 Hz), 103.64 (dd, J = 155.8 Hz, 295.1 Hz), 122.44, 128.88, 130.07 (d, J = 32.1 Hz), 131.95 (d, J = 8.2 Hz), 133.12, 135.47 (d, J = 7.3 Hz), 211.03 (d, J = 21.1 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 12.00 (d, J = 80.0 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ 99.87 (dd, J = 22.9 Hz, 79.3 Hz); HRMS (ESI) m/z calcd for $C_{18}H_{27}BrFNO_6P$ $[M+H]^+$= 482.0665, found = 482.0732; the ee value was 99% for the major diastereomer, t_R (major) = 9.5 min, t_R (minor) = 7.5 min (Chiralcel, IA, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min);

IV-3.4. Synthesis of α-fluoro-β-hydroxy-γ-nitro phosphonate

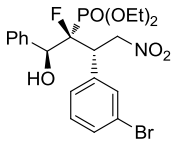


To a flask containing **II-3.2ae** (0.1 mmol) in *i*-PrOH (1ml) $NaBH_4$ (0.3 mmol, 11.4 mg) was added in one portion at -5 - 0°C, under argon. The reaction was then stirred at this temperature for 4h. After the starting material was fully converted (TLC), 2 ml of aqueous saturated NH_4Cl was added, followed by10 ml of ethyl acetate. The product was then extracted using ethyl acetate (3x 10 ml). Combined organic organic phases were than dried over Na_2SO_4 and evaporated. The crude product (**9**) was then purified by flash chromatography on silica gel using ethyl acetate/hexane = 5:1 as eluent.

Reduction of **3ae** leading to **10** was performed analogically, with slight modifications: EtOH was used as solvent; LiCl (3 mol equivalents, 0.3 mmol) was added prior to addition of

$NaBH_4$; the reaction temperature was slightly higher 0 – 10°C and time shorter (2h). **9** and **10** are very close on TLC.

Diethyl ((1S,2R,3S)-3-(3-bromophenyl)-2-fluoro-1-hydroxy-4-nitro-1-phenylbutan-2-yl)phosphonate (**II-3.10a**);



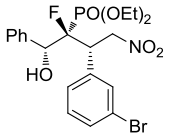
There are several rotamers of α-hydroxyphosphonates, which is reflected on NMR spectrums, where the ester group (here - ethyl) differentiates with population proportional to the lifetime of each rotamer.[184] Additionally, both ester groups are not equivalent. In the case of (**II-3.10a**), the hydrogen bonding between –OH and the phosphonate oxygen (as evidenced by X-ray analysis, see the respective chapter) is the cause of noticeable coupling between –OH hydrogen and -3'-Br-C_6H_4-C**H**- proton (J~4.5 Hz) and non-equivocality of -CH_2-NO_2 protons.

A white solid; $[\alpha]^{27}_D$ = -22.5 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86-0.89 (t, J = 13.8 Hz, 3H), 1.05-1.08 (t, J = 14.5 Hz, 3H), 2.73-2.74 (d, J = 4.4 Hz, 1H, O**H**), 3.67-3.72 (m, 1H, C**H**$_2$-CH_3, rotamer), 3.81-3.92 (m, 3H, C**H**$_2$-CH_3, rotamer), 4.68-4.73 (d, J = 25.9 Hz, 1H, -C**H**OH), 4.90-5.00 (ddt, J = 4.1 Hz, 10.1 Hz, 29.0 Hz, 1H, 3'-Br-C_6H_4-C**H**), 5.09-5.12 (dd, J = 4.1 Hz, 13.9 Hz, 1H, -C**H**$_2$$NO_2$), 5.31-5.36 (dd, J = 10.1 Hz, 13.9 Hz, 1H, -C**H**$_2$$NO_2$), 7.21-7.24 (m, 1H), 7.32-7.34 (m, J = 8.2 Hz, 5H), 7.46-7.47 (d, J = 7.6 Hz, 1H), 7.56-7.58 (d, J = 7.6 Hz, 1H), 7.80 (s, 1H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 15.74 (d, J = 6.4 Hz), 15.87 (d, J = 6.4 Hz), 45.70 (d, J = 23.8 Hz), 62.17 (d, J = 7.3 Hz), 63.98 (d, J = 6.4 Hz), 72.84 (t, J = 9.2 Hz), 75.77 (d, J = 7.3 Hz), 99.65 (dd, J = 32.1 Hz, 166.8 Hz), 122.36, 128.11, 128.53 (d, J = 1.83 Hz), 128.76, 129.17, 129.88, 131.54, 133.04; ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 15.21 (d, J = 88.9 Hz); ^{19}F NMR (282.38 Hz,

[184] M. P. Belciug, A. M. Modro, T. A. Modro, P. L. Wessels, *J. Phys. Org. Chem.*, 1992, **5**, 787.

$CDCl_3$) δ -112.88 (ddd, J = 10.7, 26.0 Hz, 90.0 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{24}BrFNNaO_6P$ $[M+Na]^+$= 526.0406, found = 526.0399.

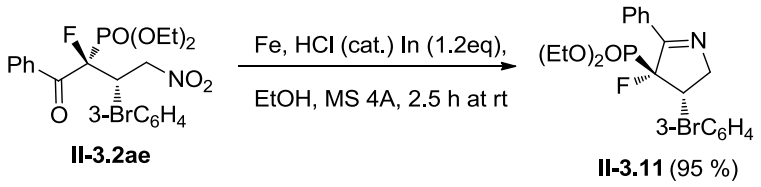
Diethyl ((1R,2R,3S)-3-(3-bromophenyl)-2-fluoro-1-hydroxy-4-nitro-1-phenylbutan-2-yl)phosphonate (**II-3.10b**);



A white solid; $[\alpha]^{27}_D$ = 26.6 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92-0.95 (t, J = 6.9 Hz, 3H), 1.36-1.39 (t, J = 6.9 Hz), 3.31-3.39 (m, 1H, C**H**$_2$-CH_3, rotamer), 3.67-3.75 (m, 1H, C**H**$_2$-CH_3, rotamer), 3.90-3.92 (d, J = 10.1 Hz, 1H, O**H**), 4.16-4.25 (m, 2H, C**H**$_2$-CH_3, rotamer), 4.28-4.35 (dtd, J = 2.5 Hz, 10.7 Hz, 18.3 Hz, 1H, -C**H**OH), 4.77-4.86 (dt, J = 10.7 Hz, 25.9 Hz, 1H, 3'-Br-C_6H_4-C**H**), 5.25-5.28 (dd, J = 2.5 Hz, 14.5 Hz, 1H, C**H**$_2NO_2$), 5.37-5.42 (dd, J = 10.7 Hz, 14.5 Hz, -C**H**$_2NO_2$), 7.24-7.28 (m, 2H), 7.32-7.33 (m, 5H), 7.40-7.42 (d, J = 8.2 Hz, 1H), 7.49-7.50 (d, J = 8.2 Hz, 1H), 7.59 (s, 1H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 15.85 (d, J = 6.4 Hz), 16.18 (d, J = 5.5 Hz), 48.86 (dd, J = 5.5 Hz, 23.8 Hz), 63.72 (d, J = 8.2 Hz), 64.04 (d, J = 7.3 Hz), 72.46 (dd, J = 3.7 Hz, 22.0 Hz), 75.49 (d, J = 8.2 Hz), 96.85(dd, J = 158.5 Hz, 196.1 Hz), 122.74, 127.48 (d, J = 3.7 Hz), 128.12, 128.41, 128.52, 130.11, 131.89, 133.54, 135.38, 135.46, 137.34 (d, J = 3.7 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 16.03 (d, J = 77.0 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -94.29 (d, J = 76.3 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{24}BrFNNaO_6P$ $[M+Na]^+$= 526.0406, found = 526.0404.

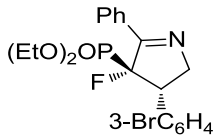
IV-3.5. Synthesis of fluorinated pyrrolidine

Imine Formation



To **II-3.2ae** (0.1 mmol, 50 mg) in EtOH (absolute, 2 ml) Indium was added (0.12 mmol, 11.4 mg)[185] followed by 4Å powdered molecular sieves (freshly activated), Fe (1 mmol, 56 mg) and a small drop of HCl (2M aq. solution, strongly acidic conditions or excess of acid must be avoided due to de-fluorination; in absence of any acid reaction is slow). The reaction mixture was then stirred for 2.5 h at room temperature. Upon completion (TLC), reaction mixture was diluted with ethyl acetate (15 ml) and filtered through a pad of cellite. Then the solution was washed with $NaHCO_3$ (satd., aq.), followed by brine, dried over Na_2SO_4 and evaporated to yield crude product. Pure **II-3.11** was obtained after flash chromatography on silica gel using ethyl acetate/hexane as eluent (5:1 – 4:1).

Diethyl ((3S,4R)-3-(3-bromophenyl)-4-fluoro-5-phenyl-3,4-dihydro-2H-pyrrol-4-yl)phosphonate; (**II-3.11**);

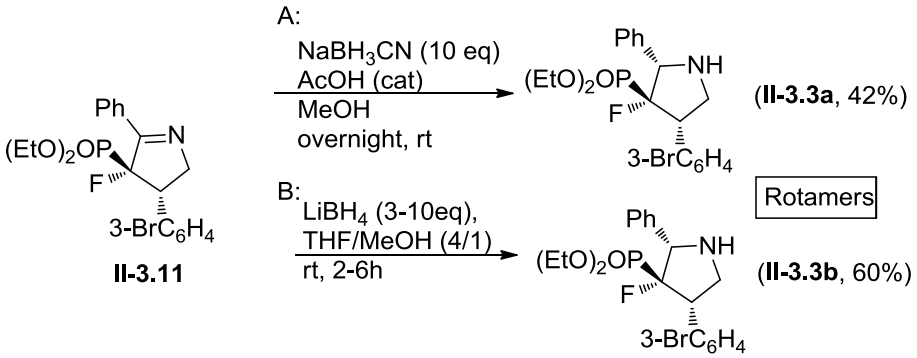


A colourless oil; $[\alpha]^{27}_{D}$ = 46.2 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19-1.22 (t, J = 7.0 Hz, 3H), 1.25-1.28 (t, J = 7.4 Hz, 3H), 3.87-3.92 (m, 1H), 4.07-4.14 (m, 3H), 4.19-4.21 (m, 1H), 4.34-4.38 (m, 1H), 4.43-4.48 (m, 1H), 7.13-7.17 (m, 2H), 7.35 (s, 1H), 7.39-7.46 (m, 4H), 8.06-

[185] Addition of indium is unnecessary and can be avoided (e.g. from economic reasons), however it does facilitate the reaction yield by supressing the formation of hydroxypyrrolidines byproducts (partial reduction of NO_2 moiety). See also: S. Cicchi, M. Bonanni, F. Cardona, J. Revuelta, A. Goti, *Org. Lett.* 2003, **5**, 1773.

8.07 (d, J = 7.0 Hz); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 16.26 (d, J = 5.5 Hz), 51.01 (dd, J = 6.4 Hz, 18.3 Hz), 63.94 (d, J = 3.7 Hz), 63.99 (d, J = 2.7 Hz), 104.11 (dd, J = 171.4 Hz, 209.0 Hz), 122.43, 127.36, 128.16, 128.87 (d, J = 3.7 Hz), 129.99, 130.65, 131.00, 131.93, 132.28, 132.29, 138.64, 138.70, 167.40 (d, J = 16.5 Hz); ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 15.39 (d, J = 99.2 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ -98.53 (dt, J = 6.1 Hz, 99.2 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{23}BrFNO_3P$ $[M+H]^+$= 454.0661, found = 454.0582.

Reduction of Cyclic Imine to Pyrrolidine

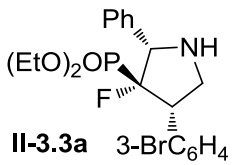


Procedure ***A***:

To MeOH (dry, 1.5 ml) solution of imine (**II-3.11**, 0.1 mmol, 45 mg) $NaBH_3CN$ (1 mmol, 63 mg) was added in 3 portions in 30 minutes intervals. The reaction mixture was then stirred overnight (16-18 h) at room temperature. After that time, despite only partial conversion (longer reaction times or larger excess of reducing agent resulted in formation of byproducts), reaction was quenched by addition of 1 ml of ice water and diluted with ethyl acetate (15 ml). The solution was then washed with $NaHCO_3$ (satd., aq.), followed by brine, dried over Na_2SO_4 and evaporated to yield crude product. Pure **II-3.3a** was obtained after flash chromatography on silica gel using ethyl acetate/hexane as eluent (5:1 – 4:1).

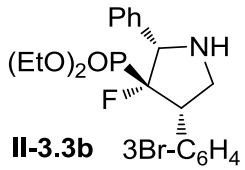
Procedure ***B***:

To THF/MeOH (4/1, total of 2 ml, dry solvents) solution of imine (**II-3.11**, 0.1 mmol, 45 mg) $LiBH_4$ (1 mmol, 22 mg) was added in 3 portions in 30 minutes intervals. The reaction mixture was then stirred for 4h at room temperature. After that time, despite only partial conversion (similarly, longer reaction times or larger excess of reducing agent resulted in formation of byproducts), reaction was quenched by addition of 1 ml of ice water and diluted with ethyl acetate (15 ml). The solution was then washed with $NaHCO_3$ (satd., aq.), followed by brine, dried over Na_2SO_4 and evaporated to yield crude product. Pure **II-3.3b** was obtained after flash chromatography on silica gel using ethyl acetate/hexane as eluent (5:1 – 4:1).



II-3.3a

A white solid; $[\alpha]^{27}_{D}$ = -14.3 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84-0.86 (t, J = 7.0 Hz, 3H), 0.88-0.91 (t, J = 6.9 Hz, 3H); 3.46-3.51 (m, 1H), 3.62-3.73 (m, 4H), 3.85-3.92 (dd, J = 2.7 Hz, 4.8 Hz), 4.04-4.16 (m, J = 30.2 Hz, 1H), 4.51-4.59 (dd, J = 9.5 Hz, 31.5 Hz, 1H), 5.88 (bs, 1H), 7.24-7.26 (m, 1H), 7.38-7.41 (m, 3H), 7.47-7.48 (m, 4H), 7.60 (s, 1H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 15.76 (d, J = 3.7 Hz), 49.02, 56.86 (d, J = 11.00), 63.62 (d, J = 6.4 Hz), 63.76 (d, J = 7.3 Hz), 74.68 (t, J = 16.5 Hz), 103.51, 122.41, 128.00, 128.67, 128.89, 129.99, 130.03, 130.27, 131.52, 133.02, 135.44; ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.21 (d, J = 78.5 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ 116.51 (dt, J = 32.0 Hz, 79.3 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{23}BrFNO_3P$ $[M+H]^+$= 456.0661, found = 456.0717.



II-3.3b

A white solid; $[\alpha]^{27}_{D}$ = -1.0 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, J = 6.9 Hz, 3H), 0.93 (t, J = 6.9 Hz, 3H), 3.53-3.62 (m, 1H), 3.64-3.90 (m, 4H), 4.12-4.23 (m, 1H), 4.53 (bs, 1H), 4.59-4.67 (dd, J = 8.2 Hz, 32.2 Hz, 1H), 7.23-7.26 (m, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.42-7.47 (m, 6H), 7.61 (s, 1H); ^{13}C NMR (125.77 Hz, $CDCl_3$) δ 15.82 (d, J = 7.7 Hz), 49.13 (d, J = 22.0 Hz), 58.34 (d, J = 12.8 Hz), 63.51, 76.12, 101.28, 122.46, 128.62, 128.80, 129.69, 129.72, 130.0, 131.43, 131.88, 132.81, 135.63; ^{31}P NMR (121.49 Hz, $CDCl_3$) δ 11.77 (d, J = 81.5 Hz); ^{19}F NMR (282.38 Hz, $CDCl_3$) δ −116.49 (dt, J = 32.0 Hz, 33.6 Hz, 79.3 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{23}BrFNO_3P$ $[M+H]^+$= 456.0661, found = 456.0739.

IV-3.6. X-Ray crystallographic analysis and determination of configurations of products

The crystal is orthorhombic, space group P2(1)2(1)2(1). The asymmetric unit contains one molecule of the compound $C_{20}H_{24}NO_6FPBr$. As the absolute structure parameter is 0.001 with esd 0.010, the reported structure is the correct absolute configuration. Final R values are R1=0.0496 and wR2=0.0715 for 2-theta up to 55º.

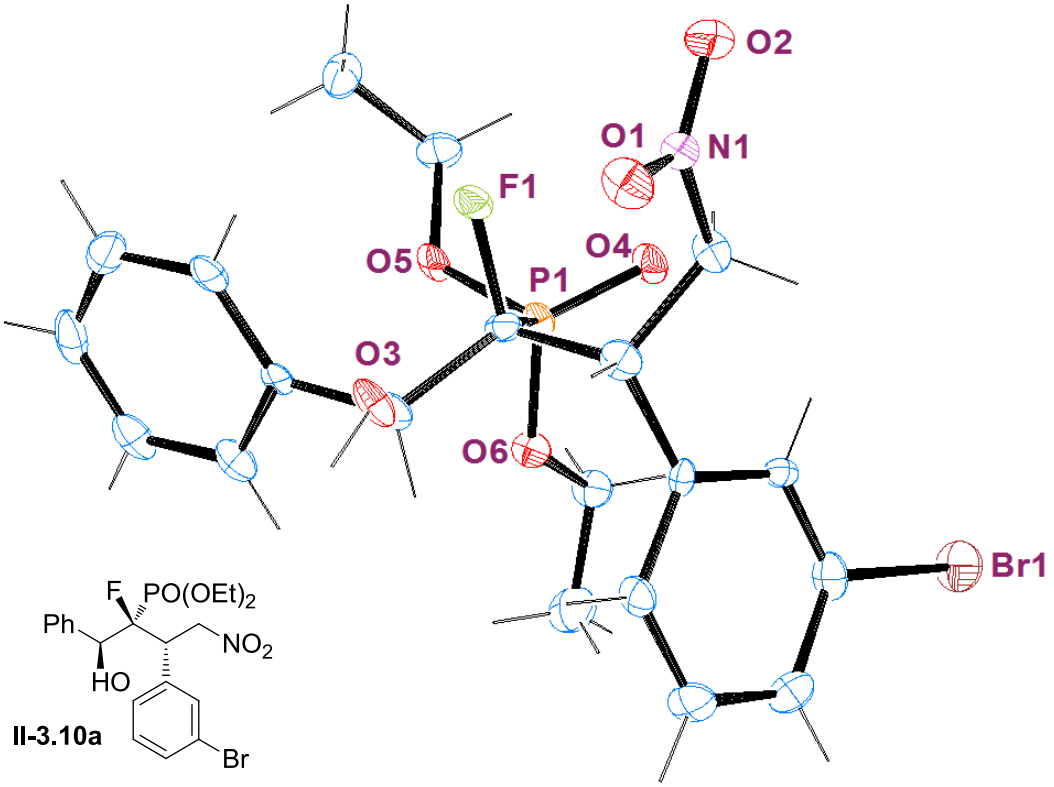


Table 1. Crystal data and structure refinement for C016.

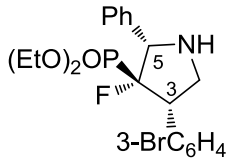
Identification code	c016	
Empirical formula	$C_{20}H_{24}BrFNO_6P$	
Formula weight	504.28	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.6675(8) Å	α= 90°.
	b = 16.0614(16) Å	β= 90°.
	c = 17.4809(18) Å	γ = 90°.
Volume	2152.8(4) $Å^3$	
Z	4	

Density (calculated)	1.556 Mg/m^3
Absorption coefficient	2.029 mm^{-1}
F(000)	1032
Crystal size	0.24 x 0.10 x 0.08 mm^3
Theta range for data collection	1.72 to 27.50°.
Index ranges	-9<=h<=9, -20<=k<=17, -22<=l<=22
Reflections collected	15621
Independent reflections	4938 [R(int) = 0.1000]
Completeness to theta = 27.50°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7457 and 0.5979
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4938 / 0 / 274
Goodness-of-fit on F^2	0.983
Final R indices [I>2sigma(I)]	R1 = 0.0496, wR2 = 0.0715
R indices (all data)	R1 = 0.0767, wR2 = 0.0766
Absolute structure parameter	0.001(10)
Largest diff. peak and hole	0.731 and -0.753 $e.Å^{-3}$

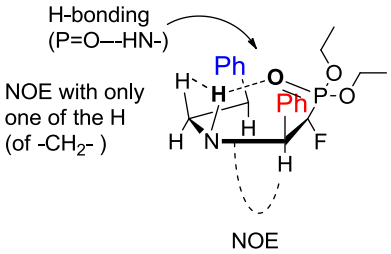
Full data can be obtained from the Cambridge Crystallographic Data Centre under the number: CCDC-924624

IV-3.7. Determination of configuration of pyrrolidines

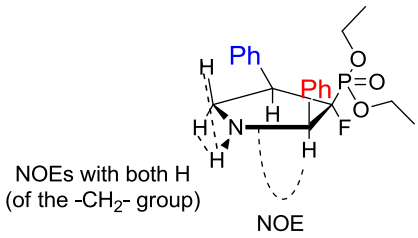
To assess the configuration of new chiral centre, HMBC, QC and NOESY experiments were performed for the pyrrolidines (**II-3.3a**&**b**). It was found that in both pyrrolidines, the proton at the newly generated chiral centre (C-5) gave positive Overhauser effect with the proton at C-3 of known configuration. Therefore, the relationship of C-5 and C-3 protons was determined to be *cis* and configuration of C-5 was assigned as *S*.



(**II-3.3a**) & (**II-3.3b**): rotamers



(**II-3.3a**)



(**II-3.3b**)

Li^+ complexation during reduction; results in no NH—O=P H-bonding in the product **b**

The rotation of the phosphonate moiety may be inhibited by the steric hindrance due to the presence of the two phenyl groups on the same side of the pyrrolidine ring, perhaps involved in π-π interactions. During the reduction of the imine, the formation of intramolecular H-bonding between phosphonate and pyrrolidine NH could result in orientation like in **II-3.3a**. On the other hand, Li^+, present during the reduction step, would coordinate to phosphonate and prevent it from forming H-bond with pyrrolidine NH, resulting in the configuration observed in **II-3.3b**.

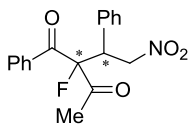
IV-4. Organocatalytic Michael addition of 2-fluoro-1,3-diketones to nitroalkenes: towards fluoro-isosteres of glycerine

IV-4.1. General procedure and analytical data of the Michael reaction products

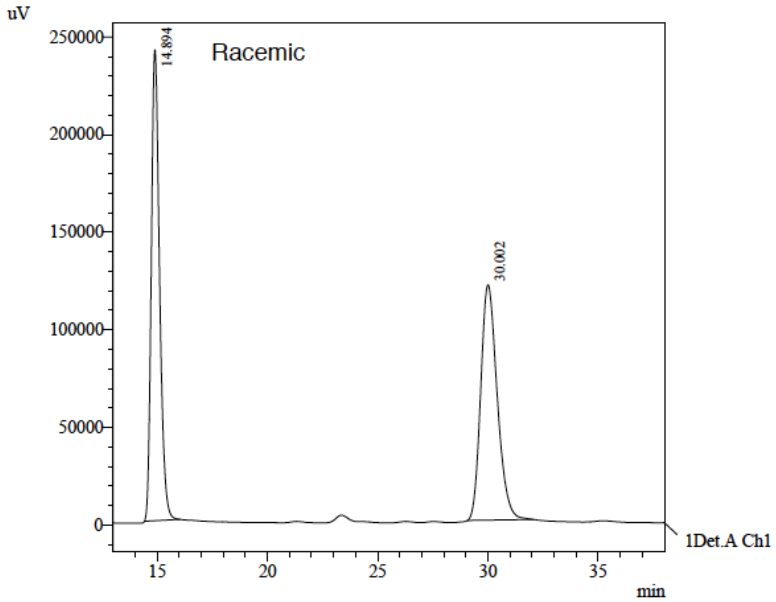
Michael addition of 2-fluoro-1,3-diketones to nitroalkenes - representative procedure:

To a sample vial containing the fluoroketone (0.1 mmol, **II-4.7a**–**g**) in diethyl ether (1 ml), the catalyst **II-2.16** (0.01 mmol, 6 mg) was added. The vial was then capped and the reaction mixture was stirred for 5 minutes at -70 ^{o}C. Subsequently nitroalkene (0.11 mmol) was added in one portion, under nitrogen protection, the vial was sealed and the reaction mixture was stirred at -70 ^{o}C for the time indicated. Upon completion of the reaction, the mixture was passed through a short silica gel column to remove the catalyst (possible recovery of the catalyst), evaporated and analyzed by ^{1}H NMR. The crude product was then subjected to column chromatographic separation eluting with hexane/ethyl acetate (20:1 – 5:1) to afford the pure Michael product (**II-4.8a**–**j**).

2-fluoro-2-(2-nitro-1-phenylethyl)-1-phenylbutane-1,3-dione (**II-4.8a**)



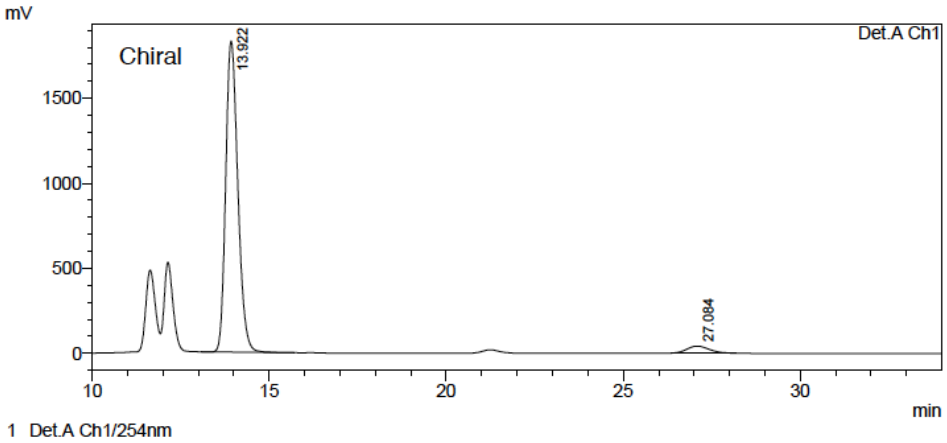
$[\alpha]^{270}_{D}$ = +47.7 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, J = 7.2 Hz, 1.6 Hz, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 2H), 7.25 – 7.20 (m, 5H), 4.87 – 4.75 (m, 3H), 2.37 (d, J = 4.0 Hz, 3H); ^{13}C NMR (100.62 Hz, $CDCl_3$) δ 199.77, 192.80, 134.50, 133.83, 132.86, 129.51, 129.49, 129.13, 129.08, 128.84, 128.68, 128.45, 107.48 (d, J = 206.4 Hz), 75.17, 47.82 (d, J = 18.3 Hz), 26.27; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -137.34 (d, J = 31.2 Hz); HRMS (ESI) m/z calcd for $C_{18}H_{15}FNO_4$ $[M-H]^-$ = 328.0991, found = 328.0981; the ee value was 92%, t_R (major) = 13.9 min, t_R (minor) = 27.1 min (Chiralcel IC, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.894	6266375	241202	50.005	66.676
2	30.002	6265226	120550	49.995	33.324
Total		12531601	361752	100.000	100.000

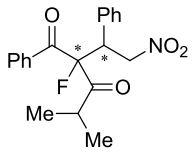


PeakTable

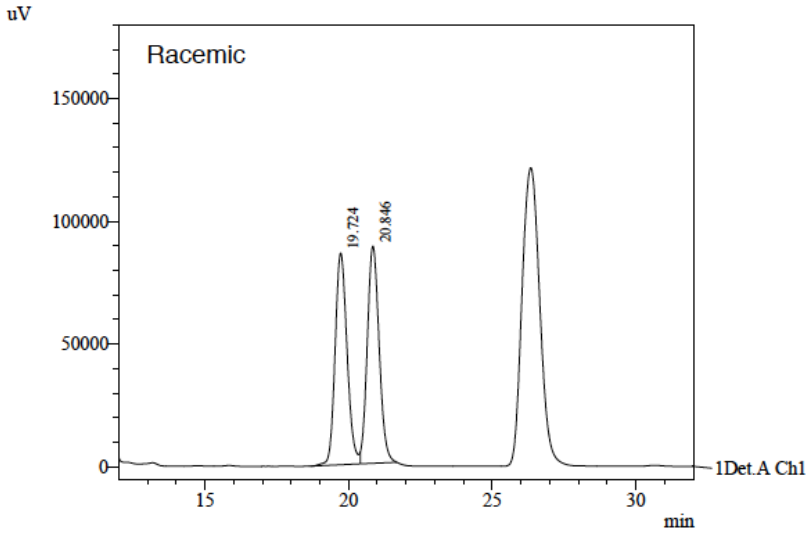
Detector A Ch1 254nm

Peak#	Ret. Time	Area %
1	13.922	96.013
2	27.084	3.987
Total		100.000

2-fluoro-4-methyl-2-(2-nitro-1-phenylethyl)-1-phenylpentane-1,3-dione (**II-4.8b**)



$[\alpha]^{270}_{D}$ = +82.9 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 6.7 Hz, 2H), 7.50 (m, 1H), 7.31 (m, 2H), 7.22 – 7.18 (m, 5H), 4.91 – 4.66 (m, 3H), 3.14 (m, 1H), 1.09 (d, J = 6.4 Hz, 3H), 1.02 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 206.15 (d, J = 23.4 Hz), 192.65 (d, J = 23.8 Hz), 134.70, 134.41, 133.66, 132.73, 129.95, 129.83, 129.54, 129.12, 129.07, 128.79, 128.65, 128.38, 108.02 (d, J = 206.5 Hz), 75.29 (d, J = 5.9 Hz), 48.03 (d, J = 18.1 Hz), 36.63, 18.66; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -170.95 (d, J = 30.8 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{19}FNO_4$ $[M-H]^-$ = 356.1304, found = 356.1304; the ee value was 96%, t_R (major) = 20.8 min, t_R (minor) = 19.8 min (Chiralcel IE, λ = 254 nm, 15% *i*PrOH/hexanes, flow rate = 1 mL/min).

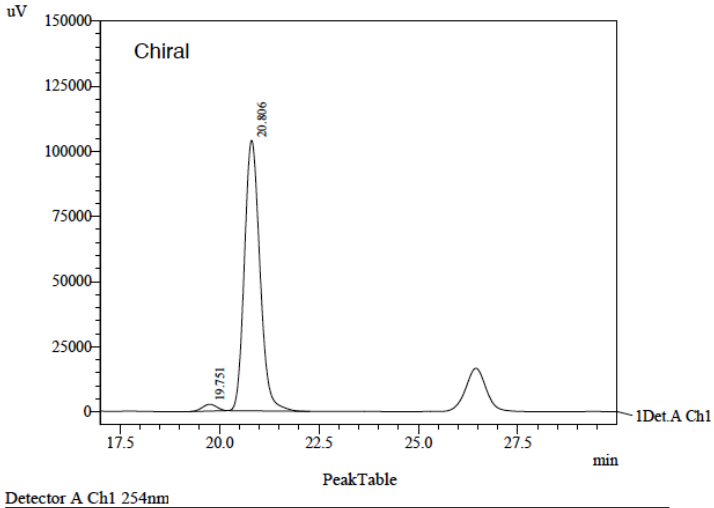


1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.724	2503939	86222	49.751	49.350
2	20.846	2528988	88493	50.249	50.650
Total		5032927	174715	100.000	100.000

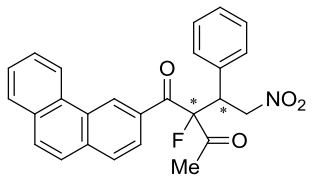


PeakTable

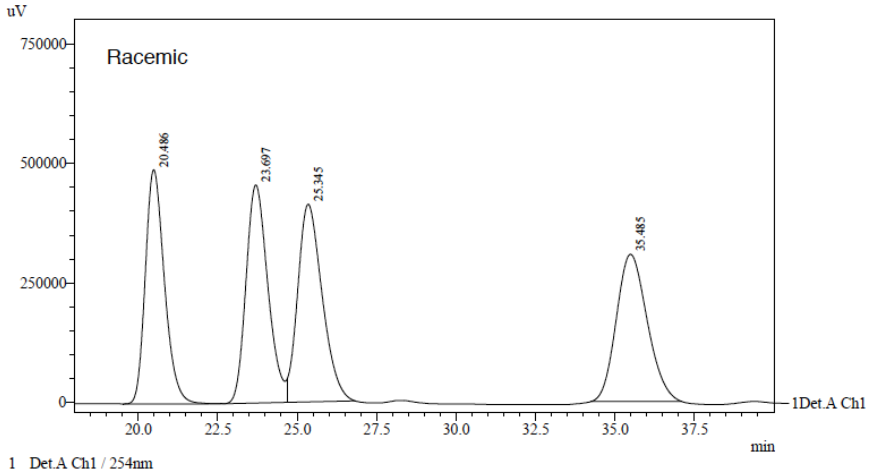
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.751	64931	2580	2.249	2.426
2	20.806	2822757	103788	97.751	97.574
Total		2887689	106369	100.000	100.000

2-fluoro-2-(2-nitro-1-phenylethyl)-1-(phenanthren-3-yl)butane-1,3-dione (**II-4.8c**)

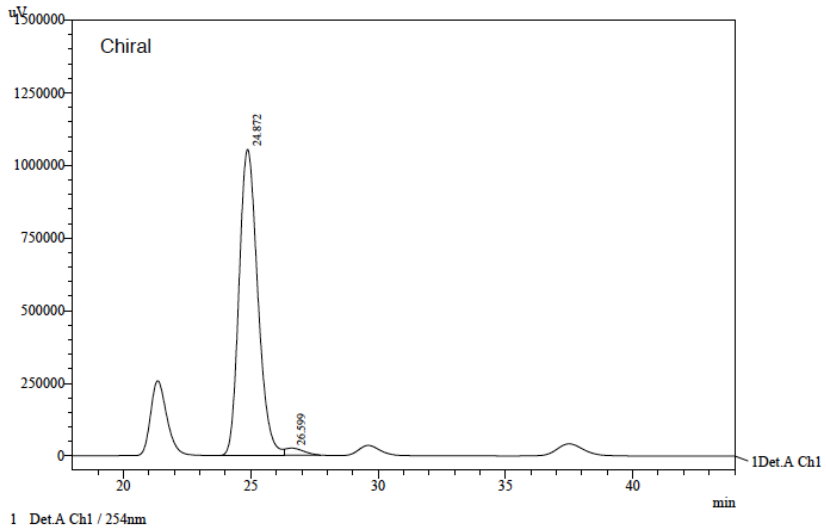


$[\alpha]^{270}_{D}$ = +9.3 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (s, 1H), 8.70 (d, J = 8.4 Hz, 1H), 8.15 (dt, J = 8.4 Hz, 1.6 Hz, 1H), 7.93 (m, 2H), 7.77 – 7.66 (m, 3H), 7.48 – 7.22 (m, 6H), 5.11 – 4.95 (m, 1H), 4.89 (m, 2H), 2.02 (d, J = 3.6 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 200.01, 192.52, 138.99, 135.22, 132.99, 132.07, 131.02, 130.61, 129.52, 129.34, 129.08, 128.86, 128.68, 127.55, 127.41, 125.96, 125.69, 125.64, 125.46, 125.40, 122.61, 107.78 (d, J = 206.1 Hz), 75.19, 47.94 (d, J = 18.8 Hz), 26.34; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -166.30 (d, J = 32.3 Hz); HRMS (ESI) m/z calcd for $C_{26}H_{19}FNO_4$ $[M-H]^-$ = 428.1304, found = 428.1302; the ee value was 96% major diastereomer, t_R (major) = 24.8 min, t_R (minor) = 26.6 min (Chiralcel IC, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).



PeakTable
Detector A Ch1 254nm

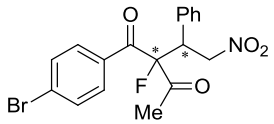
Peak#	Ret. Time	Area %
1	20.486	23.999
2	23.697	25.680
3	25.345	25.945
4	35.485	24.376
Total		100.000



PeakTable
Detector A Ch1 254nm

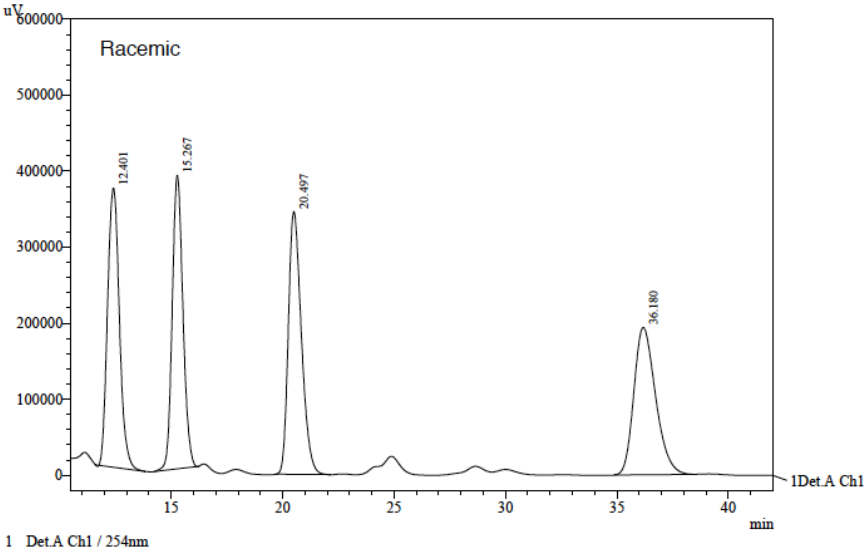
Peak#	Ret. Time	Area %
1	24.872	97.876
2	26.599	2.124
Total		100.000

<u>1-(4-bromophenyl)-2-fluoro-2-(2-nitro-1-phenylethyl)butane-1,3-dione (**II-4.8d**)</u>



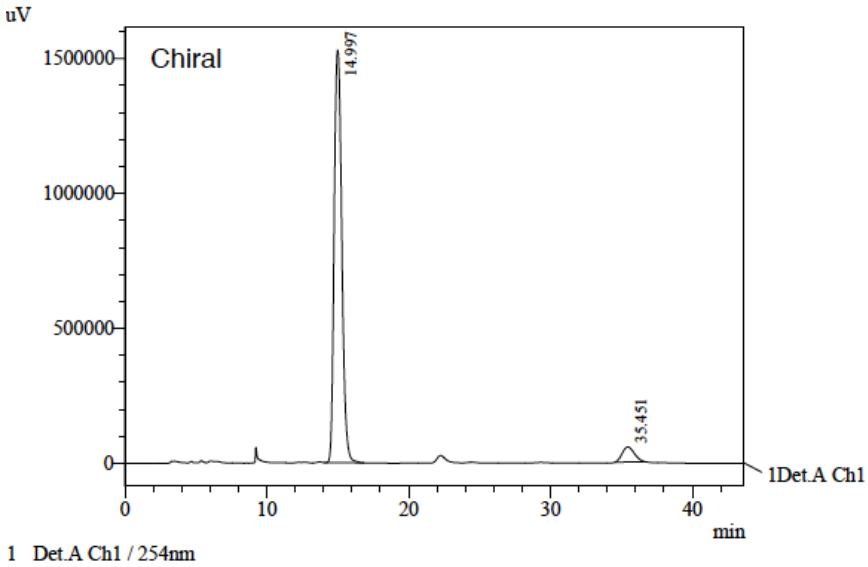
$[\alpha]^{270}_{D}$ = +64.8 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (s, 4H), 7.24 – 7.21 (m, 5H), 4.85 – 4.73 (m, 3H), 2.36 (d, J = 4.0 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 199.37, 192.20, 133.15, 133.12, 132.70, 131.82, 130.62, 130.56, 129.45, 128.94, 128.82, 107.67 (d, J = 206.5 Hz),

74.98, 47.85 (d, J = 18.9 Hz), 26.24; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -167.98 (d, J = 31.9 Hz); HRMS (ESI) m/z calcd for $C_{18}H_{14}BrFNO_4$ $[M-H]^-$ = 406.0096, found = 406.0098; the ee value was 89% major diastereomer, t_R (major) = 14.9 min, t_R (minor) = 35.5 min (Chiralcel IC, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).



PeakTable
Detector A Ch1 254nm

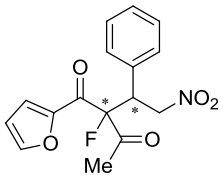
Peak#	Ret. Time	Area %
1	12.401	25.279
2	15.267	23.999
3	20.497	26.204
4	36.180	24.517
Total		100.000



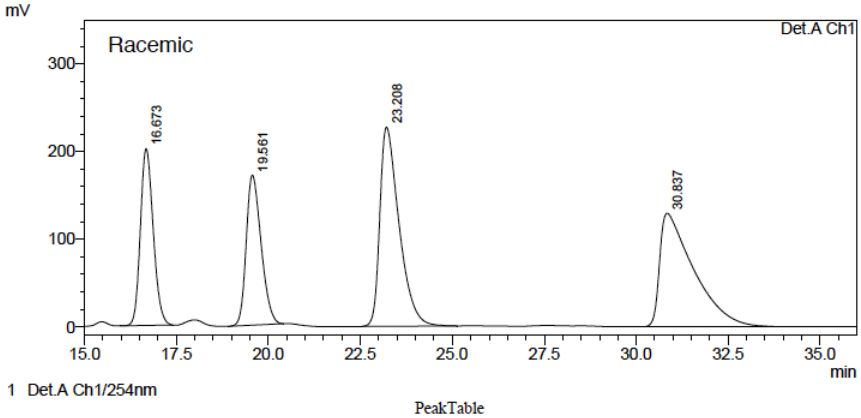
PeakTable
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.997	57183603	1529657	94.499	96.469
2	35.451	3328501	55997	5.501	3.531
Total		60512104	1585653	100.000	100.000

2-fluoro-1-(furan-2-yl)-2-(2-nitro-1-phenylethyl)butane-1,3-dione (**II-4.8e**)

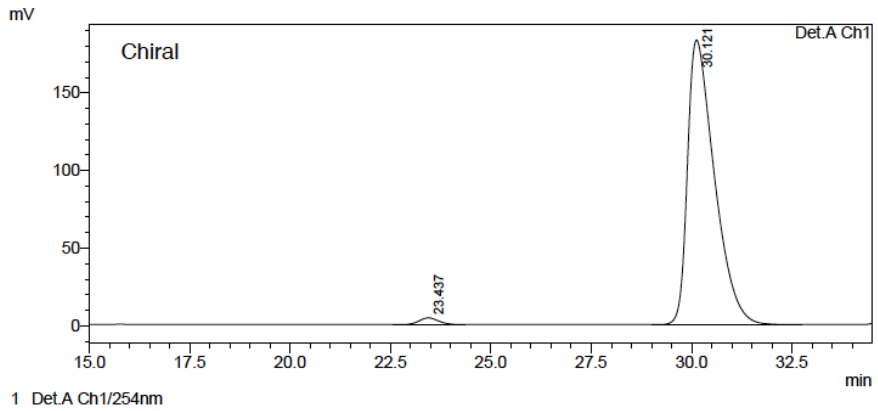


$[\alpha]^{270}_{D}$ = +134.2 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.38 (m, 1H), 7.32 – 7.25 (m, 5H), 6.53 (dd, J = 5.0 Hz, 2.5 Hz, 1H), 4.92 – 4.85 (m, 3H), 2.40 (d, J = 4.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 199.53, 178.48, 148.53, 132.59, 129.27, 129.09, 128.82, 128.70, 122.90, 122.80, 112.73, 105.68 (d, J = 204.6 Hz), 75.05, 47.25, 26.18; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -171.43 (d, J = 31.2 Hz); HRMS (ESI) m/z calcd for $C_{16}H_{13}FNO_5$ $[M-H]^-$ = 318.0783, found = 318.0778; the ee value was 95%, t_R (major) = 30.1 min, t_R (minor) = 23.4 min (Chiralcel ID, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).



PeakTable
Detector A Ch1 254nm

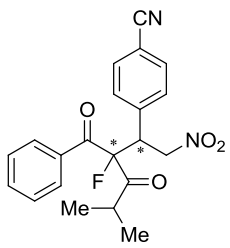
Peak#	Ret. Time	Area %
1	16.673	18.631
2	19.561	18.354
3	23.208	31.447
4	30.837	31.568
Total		100.000



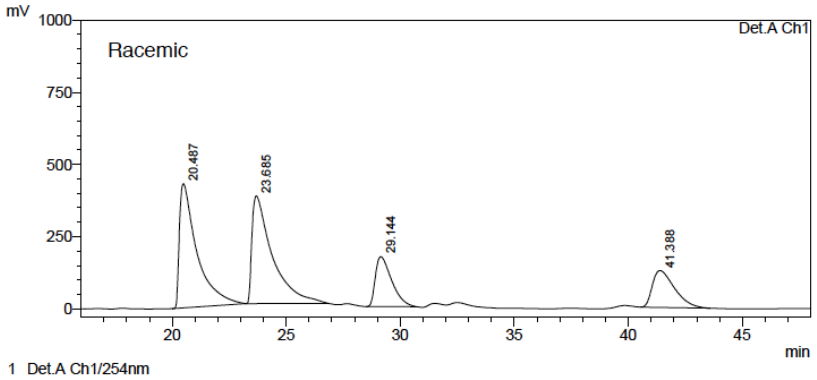
PeakTable
Detector A Ch1 254nm

Peak#	Ret. Time	Area %
1	23.437	1.671
2	30.121	98.329
Total		100.000

4-(3-benzoyl-3-fluoro-5-methyl-1-nitro-4-oxohexan-2-yl)benzonitrile (**II-4.8f**)

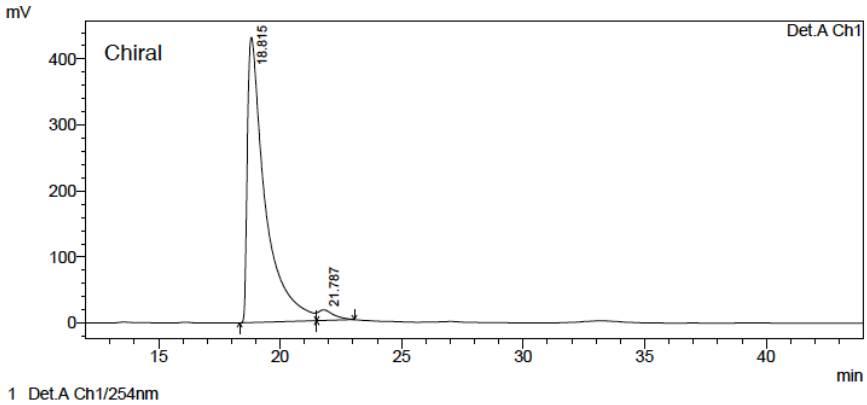


$[\alpha]^{270}_{D}$ = +46.8 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 – 7.61 (m, 3H), 7.53 – 7.57 (m, 4H), 7.36 (d, J = 7.6 Hz, 2H), 4.97 – 4.76 (m, 2H), 4.72 – 4.66 (m, 1H), 3.16 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 205.83, 191.60, 138.37, 134.35, 132.63, 132.46, 130.40, 129.98, 129.88, 129.17, 129.08, 128.74, 117.95, 112.81, 108.11 (d, J = 198.5 Hz), 74.89, 47.80 (d, J = 18.1 Hz), 36.57, 18.78, 18.32; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -170.58 (d, J = 31.2 Hz); HRMS (ESI) m/z calcd for $C_{21}H_{18}FN_2O_4$ $[M-H]^-$ = 381.1256, found = 381.1255; the ee value was 94%, t_R (major) = 18.8 min, t_R (minor) = 21.8 min (Chiralcel IB, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).



PeakTable
Detector A Ch1 254nm

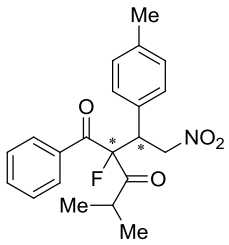
Peak#	Ret. Time	Area %
1	20.487	36.239
2	23.685	36.625
3	29.144	13.574
4	41.388	13.561
Total		100.000



PeakTable
Detector A Ch1 254nm

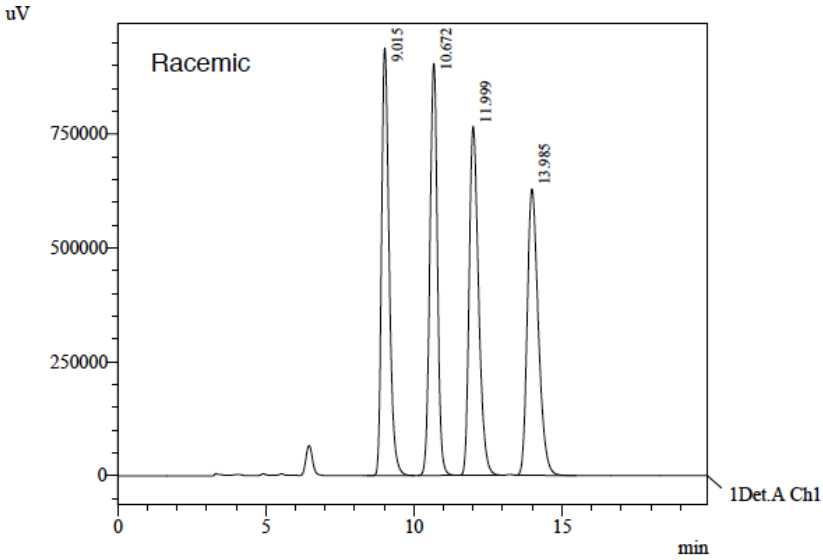
Peak#	Ret. Time	Area %
1	18.815	96.828
2	21.787	3.172
Total		100.000

2-fluoro-4-methyl-2-(2-nitro-1-(p-tolyl)ethyl)-1-phenylpentane-1,3-dione (**II-4.8g**)



$[\alpha]^{270}_{D}$ = +53.1 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (m, 2H), 7.50 (m, 1H), 7.32 (t, J = 8.0 Hz, 2H), 7.10 (d, J = 6.8 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 4.91 – 4.64 (m, 3H), 3.14 (m, 1H), 2.22 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 206.41, 192.71, 138.45, 134.75, 134.36, 133.60, 129.96, 129.90, 129.70, 129.60, 129.47,

129.38, 129.19, 128.36, 108.05 (d, J = 206.3 Hz), 75.45, 47.75 (d, J = 18.4 Hz), 36.60, 20.98, 18.69; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -170.78 (d, J = 30.5 Hz); HRMS (ESI) m/z calcd for $C_{21}H_{21}FNO_4$ $[M-H]^-$ = 370.1460, found = 370.1462; the ee value was >99% major diastereomer, t_R (major) = 8.9 min, t_R (minor) = 12.3 min (Chiralcel IC, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

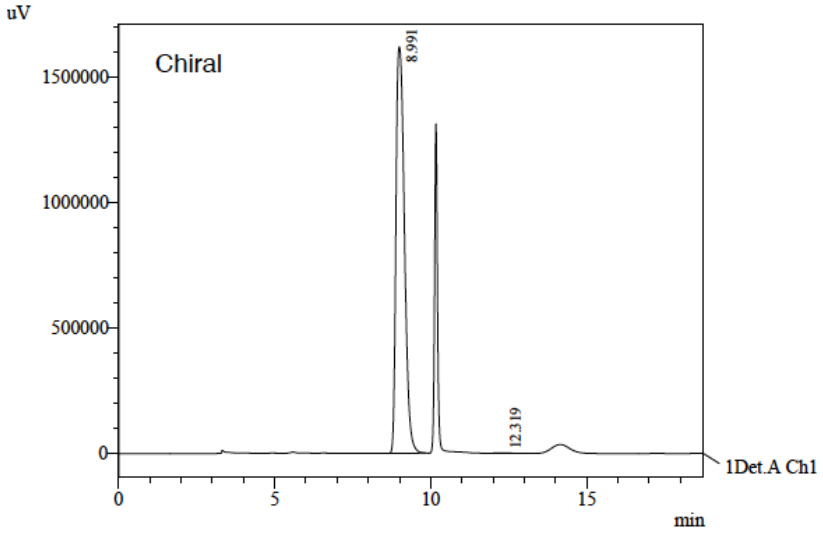


1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.015	16703488	938252	25.316	28.991
2	10.672	16001892	903917	24.253	27.930
3	11.999	16904928	765594	25.621	23.656
4	13.985	16370014	628567	24.810	19.422
Total		65980322	3236330	100.000	100.000



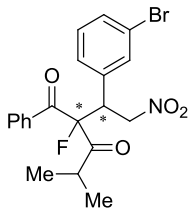
1 Det.A Ch1 / 254nm

PeakTable

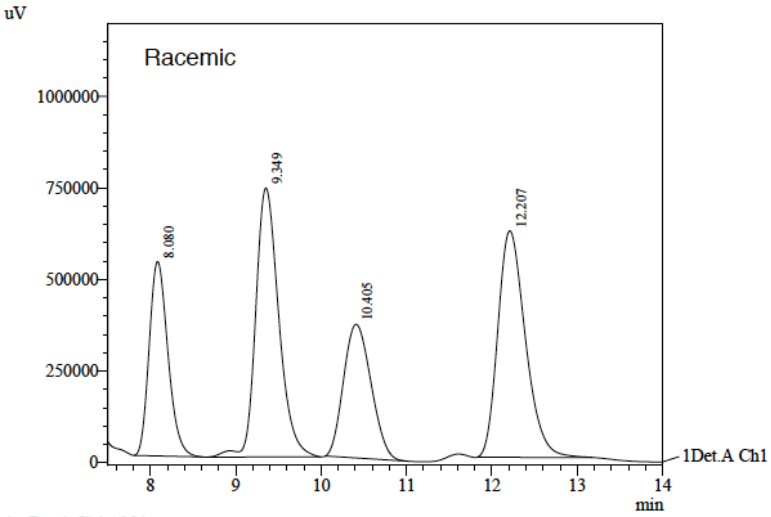
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.991	30582428	1619743	99.835	99.916
2	12.319	50652	1358	0.165	0.084
Total		30633080	1621100	100.000	100.000

2-(1-(3-bromophenyl)-2-nitroethyl)-2-fluoro-4-methyl-1-phenylpentane-1,3-dione (**II-4.8h**)



$[\alpha]^{270}_{D}$ = +100.0 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 8.4 Hz, 2H), 7.53 (m, 1H), 7.38 – 7.30 (m, 4H), 7.16 (d, J = 6.8 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 4.85 – 4.65 (m, 3H), 3.15 (m, 1H), 1.09 (d, J = 6.8 Hz, 3H) 1.02 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 205.99, 192.28, 135.16, 134.59, 133.96, 132.54, 131.86, 130.27, 129.90, 129.17, 129.11, 128.89, 128.56,122.75, 107.78 (d, J = 207.3 Hz), 75.07, 47.50 (d, J = 18.9 Hz), 36.66, 18.73, 18.35; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -170.75 (d, J = 30.8 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{18}BrFNO_4$ $[M-H]^-$ = 434.0409, found = 434.0409; the ee value was 95%, t_R (major) = 7.8 min, t_R (minor) = 9.6 min (Chiralcel IC, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

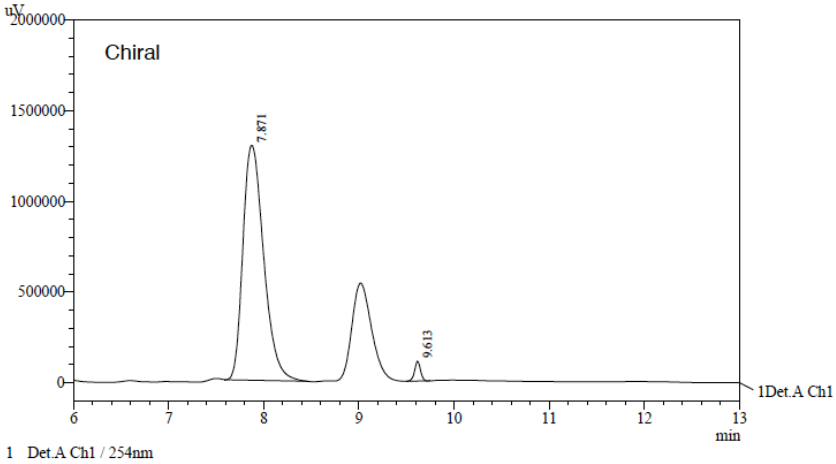


1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

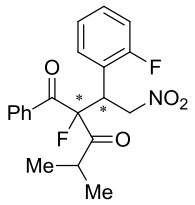
Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.080	8099335	531217	18.399	23.615
2	9.349	13843214	734674	31.446	32.659
3	10.405	8181616	365004	18.585	16.226
4	12.207	13897445	618604	31.570	27.500
Total		44021611	2249498	100.000	100.000



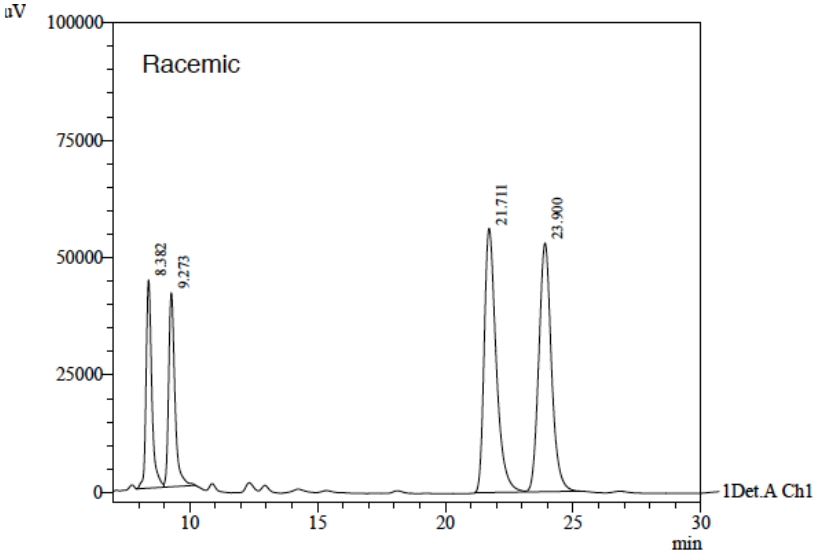
PeakTable
Detector A Ch1 254nm

Peak#	Ret. Time	Area %
1	7.871	97.673
2	9.613	2.327
Total		100.000

2-fluoro-2-(1-(2-fluorophenyl)-2-nitroethyl)-4-methyl-1-phenylpentane-1,3-dione (**II-4.8i**)



$[\alpha]^{270}_{D}$ = +100.3 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 10.5 Hz, 2H), 7.53 (t, J = 9.5 Hz, 1H), 7.35 (m, 3H), 7.22 – 7.15 (m, 1H), 7.03 (t, J = 9.5 Hz, 1H), 6.93 (t, J = 10.5 Hz, 1H), 5.24 (ddd, J = 36.5 Hz, 13.5 Hz, 5.0 Hz, 1H), 4.97 (dd, J = 17.0 Hz, 13.0 Hz, 1H), 4.73 (dd, J = 18.5 Hz, 5.0 Hz, 1H), 3.15 (m, 1H), 1.06 (d, J = 8.0 Hz, 3H) 1.02 (d, J = 8.0 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 206.17, 192.22, 162.03, 160.04, 133.99, 130.62, 130.55, 130.20, 129.31, 129.26, 128.53, 124.61, 116.11, 115.93, 107.27 (d, J = 206.8 Hz), 74.58, 36.71, 35.92, 18.72, 18.67; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -168.73 (dd, J = 28.6 Hz, 12.0 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{18}F_2NO_4$ $[M-H]^-$ = 374.1209, found = 374.1206; the ee value was 95%, t_R (major) = 8.1 min, t_R (minor) = 8.9 min (Chiralcel IB, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1 mL/min).

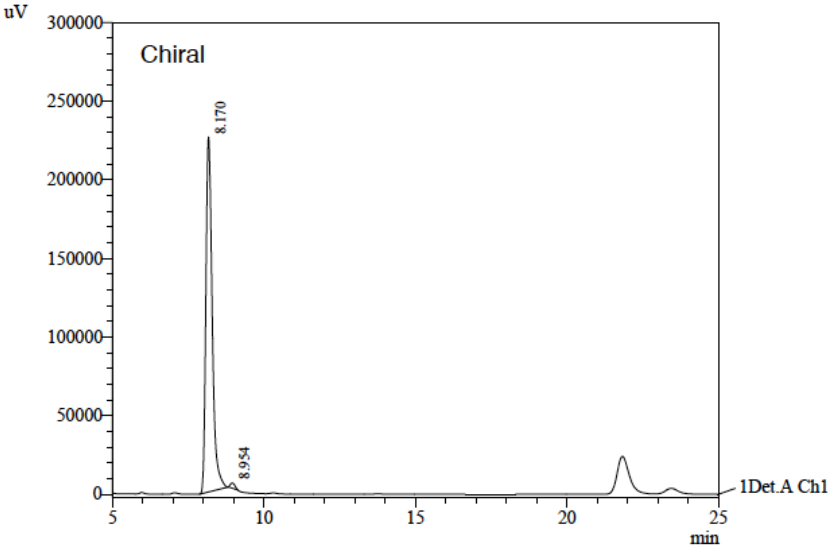


1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.382	693151	44300	13.734	22.743
2	9.273	706631	41300	14.001	21.202
3	21.711	1832148	56252	36.302	28.879
4	23.900	1815057	52936	35.963	27.176
Total		5046986	194787	100.000	100.000



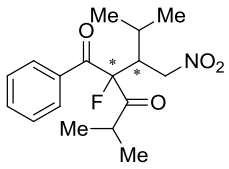
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

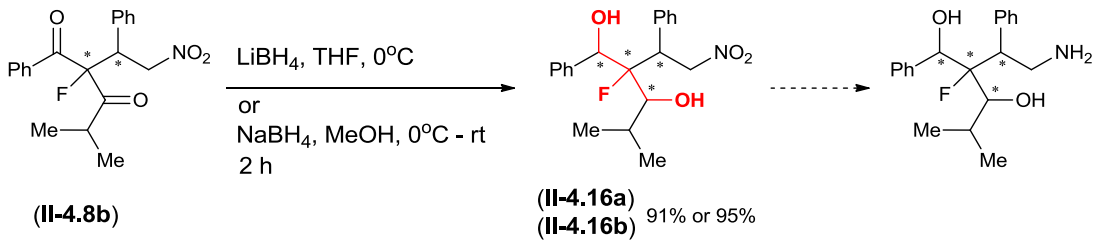
Peak#	Ret. Time	Area	Height	Area %
1	8.170	3274900	225821	98.950
2	8.954	34752	3322	1.050
Total		3309652	229143	100.000

2-fluoro-2-(3-methyl-1-nitrobutan-2-yl)-1-phenylbutane-1,3-dione (**II-4.8j**)



$[\alpha]^{270}_{D}$ = +142 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (diastereomeric mixture): δ 7.99 (m, 4H), 7.65 – 7.60 (m, 2H), 7.51 – 7.46 (m, 4H), 4.63 – 4.59 (m 2H), 4.45 (dd, J = 11.2 Hz, 5.2 Hz, 1H, CH_2NO_2 diastereomer 1), 4.41 (dd, J = 10.8 Hz, 5.2 Hz, 1H, CH_2NO_2 diastereomer 2), 3.60 – 3.48 (m, 2H), 3.20 – 3.11 (m, 2H), 1.31 – 1.22 (m, 2H), 1.09 – 1.06 (m, 4H), 0.98 (d, J = 6.8 Hz, 2H), 0.92 – 0.83 (m, 6H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 207.33 (d, J = 28.3 Hz), 207.11 (d, J = 29.8 Hz), 193.57 (d, J = 24.6 Hz), 193.26 (d, J = 24.5 Hz), 134.62, 134.59, 134.45, 134.42, 134.28, 134.18, 129.79, 129.74, 129.68, 128.78, 108.16 (d, J = 203.0 Hz), 108.05 (d, J = 203.9 Hz), 75.50 (d, J = 3.5 Hz), 75.19 (d, J = 3.6 Hz), 41.03 (d, J = 18.1 Hz), 40.85 (d, J = 14.5 Hz), 37.34, 37.31, 36.81, 36.48, 25.40, 25.39, 23.53, 23.41, 21.08, 21.05, 19.15, 18.80, 18.62, 18.49; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -166.52 (d, J = 21.8 Hz), -168.68 (d, J = 24.8 Hz); HRMS (ESI) m/z calcd for $C_{15}H_{17}FNO_4$ $[M-H]^-$ = 294.1174, found = 294.1172.

IV-4.2. Reduction and analytical data of fluoroglycerines

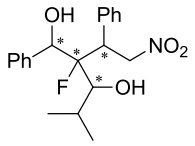


Experimental procedure:

To the Michael addition product **II-4.8b** (0.2 mmol, 35.5 mg) in MeOH (4 ml) at 0 °C was added sodium borohydride (0. 5 mmol, 19 mg). The reaction mixture was allowed to warm to room temperature, and stirring was continued for additional 1.5 h. The reaction was then

placed in an ice bath and quenched by adding saturated aqueous solution of ammonium chloride (5 mL). The mixture was extracted with ethyl acetate (3 x 10 ml), and the combined organic layers were dried over Na_2SO_4. After filtration and concentration, the residue was purified by column chromatography (hexane/chloroform = 5:1 to 2:1) to yield **II-4.16a** as a white solid (41 mg, 57%) and **II-4.16b** as a white solid (27 mg, 38%).

2-fluoro-4-methyl-2-(2-nitro-1-phenylethyl)-1-phenylpentane-1,3-diol (**II-4.16a**)



$[\alpha]^{270}_{D}$ = - 108.4 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J = 7.0 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.35 – 7.25 (m, 6H), 5.42 (dd, J = 13.9 Hz, 12.0 Hz, 1H), 5.25 (m, 1H), 4.80 (m, 1H), 4.34 (ddd, J = 14.8 Hz, 11.9 Hz, 2.9 Hz, 1H), 3.76 (m, 1H), 3.34 (td, J = 9.0 Hz, 3.4 Hz, 1H), 2.81 (m, 1H), 2.09 (dt, J = 8.1 Hz, 6.6 Hz, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.94 (m, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 138.50, 134.53, 129.97, 128.58, 128.23, 128.16, 128.06, 126.89, 126.87, 95.66 (d, J = 181,0 Hz), 78.80 (d, J = 27.8 Hz), 75.55 (d, J = 6.8 Hz), 75.40 (d, J = 12.0 Hz), 48.13 (d, J = 23.4 Hz), 29.75, 20.02, 19.12; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -154.83 (bs); HRMS (ESI) m/z calcd for $C_{20}H_{23}FNO_4$ $[M-H]^-$ = 360.1617, found = 360.1619.

X-ray analysis

The crystal is triclinic, space group P-1. The asymmetric unit contains one molecule of the compound C20h23FNO4. As P-1 is a centro space group, the crystal is a racemic mixture. Final R values are R1=0.0358 and wR2=0.0903 for 2-theta up to 55º.

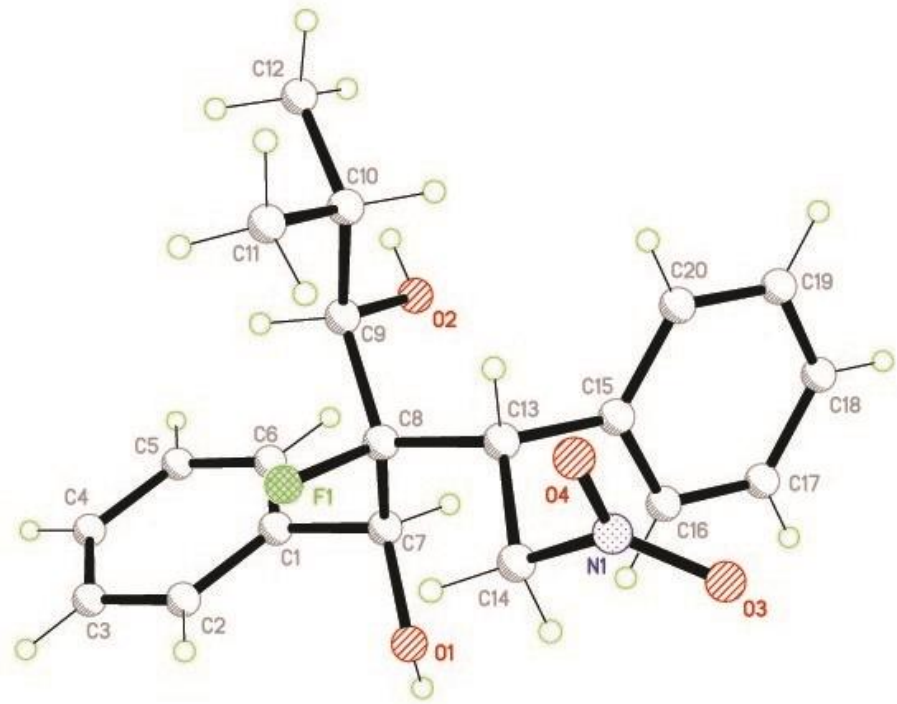
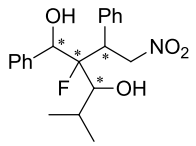


Table 1. Crystal data and structure refinement for D652.

Identification code	D652	
Empirical formula	C20 H24 F N O4	
Formula weight	361.40	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.5306(7) Å	α= 98.5360(10)°.
	b = 10.0139(7) Å	β= 106.7890(10)°.
	c = 10.8100(8) Å	γ = 108.1950(10)°.
Volume	905.46(11) $Å^3$	
Z	2	
Density (calculated)	1.326 Mg/m^3	
Absorption coefficient	0.817 mm^{-1}	
F(000)	384	
Crystal size	0.400 x 0.360 x 0.200 mm^3	
Theta range for data collection	4.427 to 68.222°.	

Index ranges	-10<=h<=11, -12<=k<=12, -13<=l<=13
Reflections collected	22331
Independent reflections	3284 [R(int) = 0.0160]
Completeness to theta = 67.679°	99.3 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3284 / 2 / 243
Goodness-of-fit on F^2	1.089
Final R indices [I>2sigma(I)]	R1 = 0.0358, wR2 = 0.0901
R indices (all data)	R1 = 0.0360, wR2 = 0.0903
Extinction coefficient	n/a
Largest diff. peak and hole	0.243 and -0.329 e.$Å^{-3}$

2-fluoro-4-methyl-2-(2-nitro-1-phenylethyl)-1-phenylpentane-1,3-diol (**II-4.16b**)



$[\alpha]^{270}_{D}$ = + 24.6 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 2.0 Hz, 2H), 7.40 – 7.33 (m, 3H), 7.33 – 7.25 (m, 5H), 5.33 (dd, J = 12.9 Hz, 3.5 Hz, 1H), 4.86 (dd, J = 12.8 Hz, 11.3 Hz, 1H), 4.51 (bs, 1H), 4.45 (ddd, J = 32.0 Hz, 10.8 Hz, 3.2 Hz, 1H), 3.96 (dt, J = 14.7 Hz, 4.8 Hz, 1H), 2.27 (m, 1H), 2.08 (m, 1H), 1.22 (m, 1H), 0.83 (d, J = 6.8 Hz, 3H), 0.52 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 137.90, 136.68, 129.87, 128.81, 128.14, 127.83, 127.00, 126.96, 100.22 (d, J = 189.9 Hz), 78.02 (d, J = 7.7 Hz), 74.87 (d, J = 22.7 Hz), 73.60 (d, J = 30.6 Hz), 47.13, 29.55, 21.02, 16.92; ^{19}F NMR (376.46 Hz, $CDCl_3$) δ -173.23 (dd, J = 29.7 Hz, 13.5 Hz); HRMS (ESI) m/z calcd for $C_{20}H_{23}FNO_4$ $[M-H]^-$ = 360.1617, found = 360.1619.

X-ray analysis

The crystal is triclinic, space group P-1. The asymmetric unit contains one molecule of the compound C20H23FNO4. NO2 group of one of the molecules was disordered into two positions with occupancy ratio=66:34. Restraints in bond length and thermal parameters were

applied to the disordered atoms. As P-1 is a centro space group, the crystal is a racemic mixture. Final R values are R1=0.0763 and wR2=0.2693 for 2-theta up to 55º.

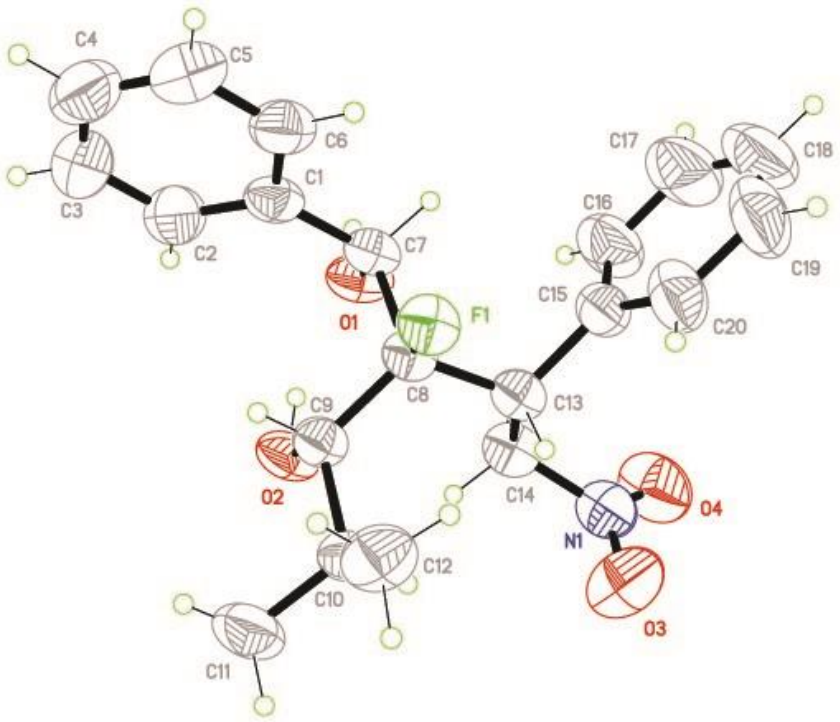


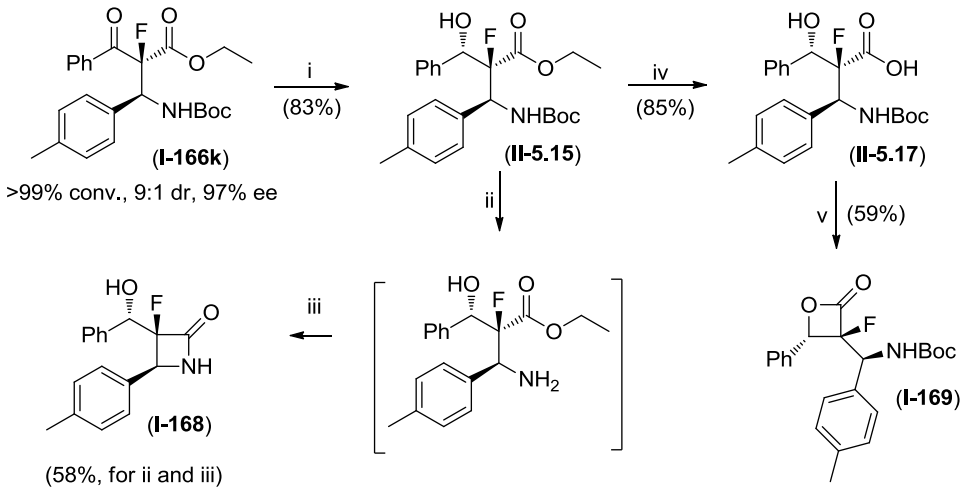
Table 1. Crystal data and structure refinement for D687.

Identification code	D687	
Empirical formula	C20 H24 F N O4	
Formula weight	361.40	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.1094(6) Å	α= 89.156(2)°.
	b = 11.3084(8) Å	β= 88.332(3)°.
	c = 18.2603(14) Å	γ = 88.251(2)°.
Volume	1879.2(2) $Å^3$	
Z	4	
Density (calculated)	1.277 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	768	

Crystal size	0.26 x 0.16 x 0.08 mm^3
Theta range for data collection	2.106 to 27.499°.
Index ranges	-11<=h<=11, -14<=k<=14, -23<=l<=23
Reflections collected	35873
Independent reflections	8618 [R(int) = 0.0549]
Completeness to theta = 25.242°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7457 and 0.6930
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8618 / 65 / 513
Goodness-of-fit on F^2	1.081
Final R indices [I>2sigma(I)]	R1 = 0.0763, wR2 = 0.2397
R indices (all data)	R1 = 0.1525, wR2 = 0.2693
Extinction coefficient	n/a
Largest diff. peak and hole	0.666 and -0.455 e.$Å^{-3}$

IV-5. Asymmetric Mannich reaction - towards fluorinated amino acids, lactones and β-lactams

IV-5.1. Preparation and analytical data of acid, lactam and lactone



i) $NaBH_4$/EtOH; ii) 10% TFA/CH_2Cl_2; iii) *i*-PrMgCl, THF; iv) NaOH, THF/MeOH/H_2O; v) DMAP/DCC, CH_2Cl_2

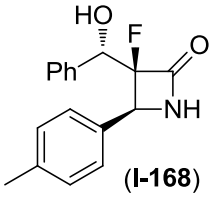
(2S, 3S)-Ethyl 3-(tert-butoxycarbonylamino)-2-fluoro-2-((S) hydroxy(phenyl) methyl)-3-p-tolylpropanoate (**II-5.15**)

To a solution of Mannich product **I-166k** (100 mg, 0.23 mmol) in absolute EtOH (8 mL) at 0 ^{o}C was added sodium borohydride (0.56 mmol, 34 mg). The reaction mixture was allowed to warm to room temperature, and stirring was continued for additional 1.5 h. The reaction was then placed in an ice bath and quenched by adding saturated aqueous solution of ammonium chloride (25 ml). The mixture was extracted with ethyl acetate (3 x 15 ml), and the combined organic layers were dried over Na_2SO_4. After filtration and concentration, the residue was purified by column chromatography (hexane:ethyl acetate = 9:1 to 4:1) to yield 5 as a white solid (83 mg, 83%).

^{1}H NMR (300 MHz, CDCl3) δ 0.63-0.68 (t, 3H), 1.38 (s, 9H), 2.19 (s, 3H), 3.62-3.73 (m, 2H), 4.66 (bs, 1H), 4.99-5.07 (d,1H), 5.24-5.30 (t, J = 9.5 Hz, 1H), 5.86-5.89 (d, J = 10.5 Hz, 1H), 6.99-7.07 (m, 4H), 7.15-7.17 (m, 3H), 7.26-7.28 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ

13.36, 20.91, 28.18, 54.72 (d, J = 31.29 Hz), 61.28, 73.68 (d, J = 18.67 Hz), 81.23, 97.34, 100.10, 127.33, 127.35, 127.70, 127.71, 127.86, 128.18, 128.99, 132.56, 136.87, 137.93, 156.52, 169.04 (d, J = 21.96 Hz).

(3S, 4S)-3-Fluoro-3-((S)-hydroxy(phenyl)methyl)-4-p-tolylazetidin-2-one (**I-168**).



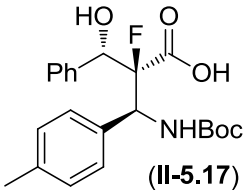
(**I-168**)

To a solution of **II-5.15** (60 mg, 0.14 mmol) in dichloromethane (4 mL) at 0 ^{o}C was added trifluoroacetic acid (0.4 mL). The ice bath was then removed and the reaction mixture was allowed to warm up to room temperature and stirred for 2 h. Saturated aqueous ammonium chloride (10 mL) was added to quench the reaction, and the resulting mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, after filtration, the filtrate was concentrated to yield the crude free amine, which was used directly for the next step without further purification. Grignard reagent was prepared from isopropyl chloride (5 mmol, 392 mg) and magnesium (10 mmol, 240 mg) in dry THF (10 mL), initiated with a few crystals of iodine. To a solution of the crude amine in dry THF (2 mL) at 0 ^{o}C, freshly prepared Grignard reagent was added (10 eqiv., 2.5 ml of THF solution). The reaction mixture was then allowed to warm to room temperature and stirred overnight. The reaction was quenched with the addition of saturated aqueous ammonium chloride (10 mL). The mixture was extracted with ethyl acetate (3 x 10 mL), and the organic extracts were combined, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (hexane:ethyl acetate = 9:1 to 4:1) to afford the β-lactam as a white solid (20 mg, 58%).

$[\alpha]D^{25}$ = 43.2 (c = 0.6, CHCl3); ^{1}H NMR (300 MHz, CDCl3) δ 2.31 (s, 3H), 3.37 (s, 1H), 5.04-5.07 (d, J = 4.92 Hz, 1H), 5.27-5.29 (d, J = 8.22 Hz, 1.0H), 6.59-6.61 (d, J = 6.06 Hz,

1H), 6.79-6.82 (d, J = 8.07 Hz, 2H), 7.06-7.09 (d, J = 7.89 Hz, 2H), 7.37-7.46 (m, 3H), 7.53-7.56 (d, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 20.99, 29.61, 58.35 (d, J = 23.46 Hz), 70.33 (d, J = 27.82 Hz), 104.2 (d, J = 226.4 Hz), 126.66 (d, J = 1.64 Hz), 126.77, 128.35, 128.52, 129.02, 130.88 (d, J = 1.64 Hz), 137.35, 138.14, 166.86 (d, J = 35.45 Hz); HRMS (IT-TOF) m/z calcd for $C_{17}H_{16}FNO_2$ $[M+Na]^+$ = 308.1063, found = 308.0962. Crystal obtained for X-ray diffraction was recrystallized from a mixture of EtOAc/Hexane.

(2S,3S)-3-(tert-Butoxycarbonylamino)-2-fluoro-2-((S)-hydroxy(phenyl)methyl)-3-p-tolylpropanoic acid (**II-5.17**)

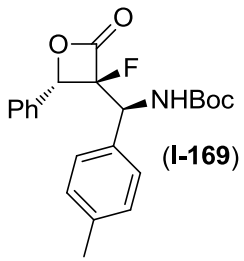


(**II-5.17**)

To a solution of **II-5.15** (100 mg, 0.232 mmol) in THF (2 mL) and MeOH (1 mL), 3M aqueous NaOH was added (2 mL). The reaction mixture was stirred at room temperature for 2.5 h. Upon completion, ethyl acetate (10 mL) was added to the reaction mixture, followed by slow addition of 2M aqueous solution of HCl until pH 1-2 was reached. The phases were then separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to yield crude product, which was purified by chromatography (ethyl acetate/hexane = 1:4 to 1:1) to afford acid **II-5.17** as a white solid (80 mg, 85%)

^{1}H NMR (300 MHz, CDCl3) δ 1.53 (s, 9H), 2.36 (s, 3.0 H), 5.15-5.23 (d, J = 24 Hz, 1H), 5.38-5.44 (t, J = 9.0 Hz, 1H), 5.98-6.01 (d, J = 9.0 Hz, 1H), 6.82 (bs, 1H), 7.14-7.22 (m, 4H), 7.30-7.34 (m, 3H), 7.42-7.43 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 21.01, 28.23, 54.88 (d, J = 30.9 Hz), 73.53 (d, J = 18.1 Hz), 81.73, 99.1 (d, J = 203.8 Hz), 127.44, 127.74, 128.11, 128.42, 129.28, 132.15, 136.38, 138.22, 156.69, 171.4 (d, J = 24.1Hz); HRMS m/z calcd for $C_{22}H_{26}FNO_5$ $[M+Na]^+$ = 426.1693, found = 426.1511.

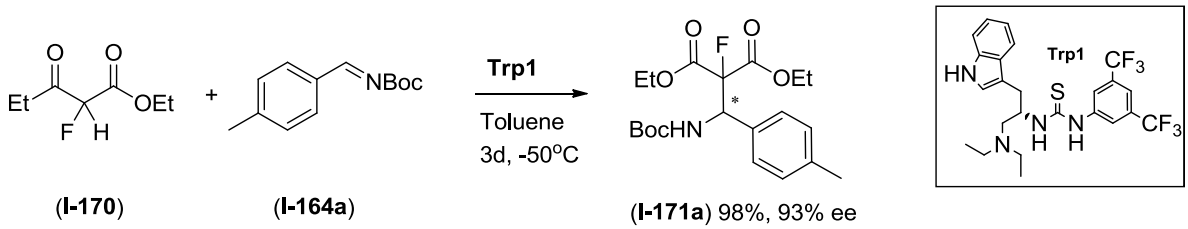
tert-Butyl (S)-((3S, 4S)-3-fluoro-2-oxo-4-phenyloxetan-3-yl)(p-tolyl)methylcarbamate (**I-169**)



To a solution of acid **II-5.17** (77 mg, 0.19 mmol) in dry CH_2Cl_2 (3.5 mL), DMAP was added (0.02 mmol, 4.9 mg), followed by a solution of DCC (59 mg, 0.3 mmol) in dry CH_2Cl_2 (1.5 mL). The reaction mixture was stirred at room temperature for 6 hours. Upon completion (judged by TLC), DCU was removed by filtration, and the filtrate was washed with CH_2Cl_2 and the organic layers were combined and concentrated. The crude product was purified by chromatography using silica gel (ethyl acetate/hexane = 1:10) to afford lactone **I-169** as white solid (43 mg, 59%).

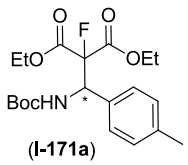
^{1}H NMR (300 MHz, CDCl3) δ 1.46 (s, 9H), 2.29 (s, 3.0 H), 5.07-5.24 (m, 2H), 5.57-5.61 (d, J = 12.0 Hz, 1H), 6.54-6.57 (d, J = 7.08 Hz, 2H), 6.90-6.92 (d, J = 7.89 Hz, 2H), 7.20-7.23 (d, J = 7.41 Hz, 2H), 7.32-7.45 (m, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 20.94, 28.16, 52.47 (d, J = 19.76 Hz), 80.48, 82.75 (d, J = 24.7 Hz), 105.48 (d, J = 226.70 Hz), 126.65, 128.09, 128.13, 128.67, 128.86, 129.60, 130.90, 131.52, 131.56, 138.03, 154.54, 164.29 (d, J = 25.24 Hz); HRMS m/z calcd for $C_{22}H_{24}FNO_4$ $[M+Na]^+$ = 408.1587, found = 408.1408.

IV-5.2. Experimental procedure for Mannich addition of fluoromalonate and analytical data of the product



Ethyl fluoromalonate **I-170** (18 mg, 0.1 mmol) was added to a mixture of the catalyst **Trp-1** (5 mg, 0.01 mmol) and imine **I-164a** (16.43 mg, 0.15 mmol) in toluene (2.0 - 1.0 mL) in a sample vial. The vial was then capped and the reaction mixture was stirred at -50 ^{o}C for 72 h. The reaction mixture was than filtered through short silica gel column to remove the catalyst. Solvent was evaporated and the crude product was purified by column chromatography on silica gel (hexane: ethyl acetate = 30:1 to 10: 1) to afford **I-171a** as a pale yellow oil (39 mg, 98%). The enantiomeric excess of product was determined by chiral HPLC analysis.

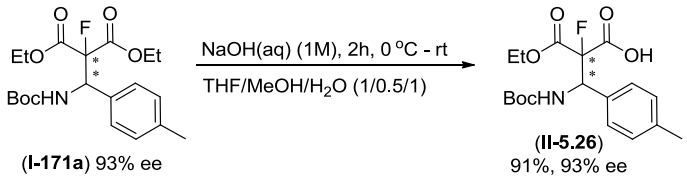
Diethyl 2-(((tert-butoxycarbonyl)amino)(p-tolyl)methyl)-2-fluoromalonate;



colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): d= 7.31–7.20 (m, 2 H), 7.17–7.07 (m, 2 H), 5.71 (d, J= 10.2 Hz, 1 H), 5.55 (dd, J= 10.2, 10.0 Hz, 1 H), 4.38–4.21 (m, 2 H), 4.21–4.02 (m, 2 H), 2.30 (s, 3 H), 1.38 (s, 9 H), 1.31 (t, J= 7.0 Hz, 3 H), 1.13 (t, J= 7.0 Hz, 3 H). The ee value was determined as 93% (Chiralcel AD-H, λ= 220 nm, 10% iPrOH/hexane, flow rate = 1 mL/min, t_R = 15.0 min, 17.2 min).

The analytical data was identical with the reported data.[167]

IV-5.3. Preparation of malonate Mannich adduct halfester and analytical data

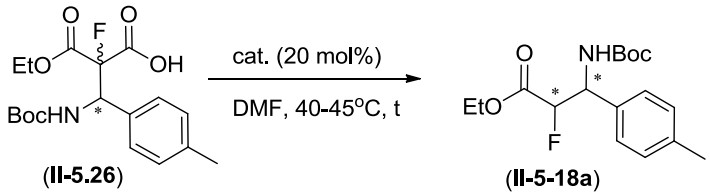


To a stirred solution of **I-171a** in mixed solvent (0.5 mmol, 195 mg in 10 ml of solvent: THF/MeOH/H_2O = 1/0.5/1), was added 1M aqueous solution of NaOH (0.5 ml) dropwise at 0 ^oC. The reaction was then allowed to warm to room temperature and stirred for additional 1.5 h - 2 h. Upon completion (TLC analysis), slight excess of solid citric acid was added until pH reached 3-4. The reaction mixture was then extracted with CH_2Cl_2 (4x 10 ml), dried over Na_2SO_4 and evaporated. The crude product was purified on silica gel column, eluting with hexane/ethyl acetate = 5/1 - 2/1. Pure product was obtained as white solid, 167 mg, 91% yield.

3-((tert-butoxycarbonyl)amino)-2-(ethoxycarbonyl)-2-fluoro-3-(p-tolyl)propanoic acid (**II-5.26**)

^{1}H NMR (400 MHz, $CDCl_3$, diastereomeric mixture 1:1): δ = 10.0 (s, 1H), 7.72 - 7.69 (m, 1H), 7.54 - 7.52 (m, 1H), 7.36 - 7.35 (m, 1H), 7.12 - 7.10 (m, 6H), 5.63 - 5.53 (m, 3H), 4.96 (dd, J = 16 Hz, 28Hz, 0.5H, CHArN), 4.95 (dd, J = 16 Hz, 28Hz, 0.5H, CHArN), 4.30 (m, 2H, CH_2O), 4.26 (m, 2H, CH_2O), 2.31 (s, 1.5 H, $PhCH_3$), 2.30 (1.5 H, 1.5 H, $PhCH_3$), 1.33 (s, 4.5 H, *t*-Bu), 1.28 (s, 4.5 H, *t*-Bu), 0.92 (t, *J* = 7.0 Hz, 1.5 H, CH_3), 0.90 (t, *J* = 7.0, 1.5 H, CH_3); ^{13}C NMR (125 Hz, $CDCl_3$): δ = 186, 184, 172, 171, 130.9, 129.0, 128.8, 128.1, 126.1, 125.8, 124.4, 124.0, 119.0, 77.2, 68.2, 68.0, 53.4, 53.2, 31.9, 31.4, 23.7, 23.0, 14.0, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ = 173.8 (d, *J* = 28 Hz), 174.1 (d, *J* = 28 Hz).

IV-5.4. Representative procedure for decarboxylation/protonation and analytical data of the product.

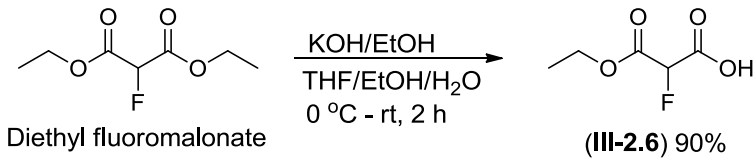


To a solution of halfester **II-5.26** (0.05 mmol, 18.4 mg) in DMF (0.5 ml) was added the base (0.01 mmol) at room temperature. The reaction mixture was then stirred at 40 - 45 ^{o}C the duration indicated in the table. Upon completion (TLC analysis) the reaction mixture was diluted with ethyl acetate (10 ml) and washed with water (10 ml x 3), brine (10 ml), dried over sodium sulphate and evaporated. The crude product was then analyzed by ^{1}H NMR and subsequently purified by column chromatography on silica gel, eluting with hexane/ethyl acetate (30:1 - 20/1) to yield the product as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 2:1 mixture of diastereomers): δ = 7.24 – 7.12 (m, 6 H), 5.37 – 5.04 (m, 3H), 4.30 – 4.24 (m, 1H, OCH_2 minor dr), 4.14 – 4.06 (m, 2H, OCH_2 major dr), 2.34 (s, 1.5 H, $PhCH_3$ minor dr), 2.32 (s, 3H, $PhCH_3$ major dr), 1.30 (t, J = 7.1 Hz, 1.5 H, CH_3 minor dr), 1.14 (t, *J* = 7.1 Hz, 3H, major dr); ^{13}C NMR (): δ 167.54 (d, *J* = 25.1 Hz), 167.01 (d, *J* = 23.7 Hz), 138.3, 137.8, 129.4, 129.3, 127.6, 126.6, 90.29 (dd, *J* = 191.1, 76.6 Hz, 80.2, 80.1, 61.76 (d, *J* = 51.2 Hz, major), 55.65 (d, *J* = 18.7 Hz, minor), 28.3 (major), 28.2 (minor), 21.1 (major), 21.0 (minor), 14.0 (minor), 13.9 (major); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -203.4 (dd, *J* = 27.4, 49.8 Hz, major), -203.5 (dd, *J* = 26.8, 48.8 Hz, minor); the ee value was determined as 93% (Chiralcel IA, λ= 220 nm, 1% *i*PrOH/hexane, flow rate = 1 mL/min, t_R (first diastereomer) = 25.3 min, 28.2 min; t_R (second diastereomer) = 31.3 min, 39.3 min).

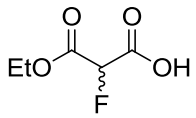
IV-6. Preliminary results and future perspective: decarboxylative additions of fluoromalonate halfester

IV-6.1. Preparation of malonic acid half-ester



To a solution of diethyl fluoromalonate (1 mmol, 178 mg) in a mixed solvent system THF/EtOH/H_2O (1/0.5/1, 5 ml total) was added 1 M solution of KOH in EtOH (1 equiv., 1 ml) dropwise at 0 ^oC under vigorous stirring. The reaction was then allowed to warm up to room temperature gradually and was stirred for an additional 1.5 - 2 h. Upon completion, the reaction mixture was cooled to 0 ^oC and the pH was adjusted to 2 with 1 M aqueous solution of HCl. The product was than extracted with CH_2Cl_2 (4 x 10 ml); the organic phase was dried and evaporated to yield the pure desired product as pale-yellow oil.

3-Ethoxy-2-fluoro-3-oxopropanoic acid (**III-2.6**)

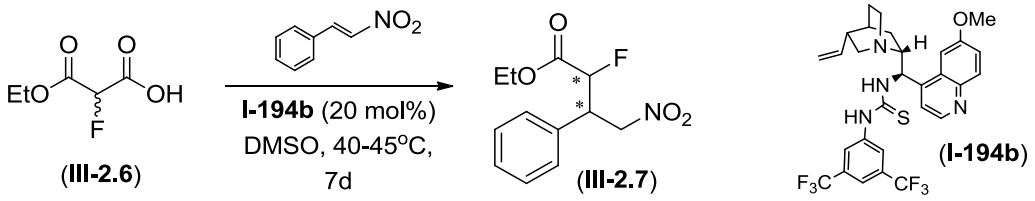


^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J = 7.1 Hz, 3H), 4.33 (d, J =7.0 Hz, 2H), 5.41 (d, J = 40.0 Hz, 1H), 10.16 (bs).

The analytical data was identical with reported.[186]

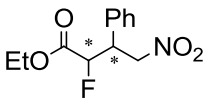
[186] T. Kitazume, T. Sato, T. Kobayashi, J. T. Lin, *J. Org. Chem*., 1986, **51**, 1003.

IV-6.2. Experimental procedure for decarboxylative addition to nitroalkene and analytical data of the product



To a solution of malonate half-ester (**III-2.6**, 0.1 mmol, 15 mg) in DMSO (1 ml) was added the catalyst (**I-194b**, 0.2 equiv., 6 mg), followed by nitroalkene (1.2 equiv., 18 mg). The reaction vial was flushed with argon, capped and stirred at 40 - 45 ^{o}C for 7 days, with occasional TLC analysis. After 7 days, the reaction mixture was cooled to room temperature and quenched with satd. aqueous NH_4Cl solution (2 ml) and extracted with ethyl acetate (2 x 5 ml). The organic layer was then washed with water (3 x 10 ml) dried over Na_2SO_4 and evaporated to yield the crude product. After ^{1}H NMR analysis of the crude reaction mixture, the product was purified on silica gel column eluting with hexane:ethyl acetate (40:1 - 10:1) to yield pure product as a pale-yellow oil.

Ethyl 2-fluoro-4-nitro-3-phenylbutanoate (**III-2.7**)



(**III-2.7**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 - 7.22 (m, 5H), 4.74 (dd, *J* = 7.0, 12.5 Hz, 1H), 4.64 (dd, *J* = 7.7, 12.5 Hz, 1H), 4.08 (q, *J* = 7.0, 14.3 Hz, 2H), 4.01 - 3.96 (m, 1H), 2.76 (d, *J* = 7.2 Hz, 1H), 1.17 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 138.3, 129.0, 128.0, 127.3, 79.5, 64.3 (d, J = 231 Hz), 60.9, 40.2, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ -108.8 – (-108.9) m.