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Access to Unprotected β-Fluoroalkyl β-Amino Acids and Their α-Hydroxy Derivatives

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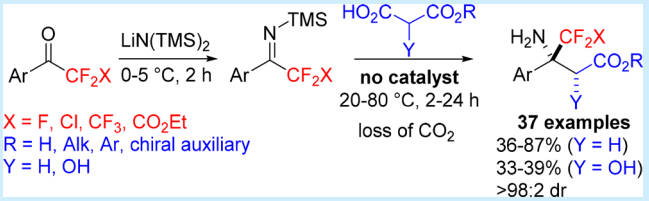
Supporting Information

ABSTRACT: Unprotected β-(het)aryl-β-fluoroalkyl β-amino acids and their α-hydroxy derivatives can be readily obtained using a decarboxylative Mannich-type reaction without protection/deprotection steps. This protocol utilizes lithium hexamethyldisilazide and (het)arylfluoroalkyl ketones to generate NH-ketimine intermediates. The mild reaction conditions allow the preparation of original fluorinated β-amino acids as useful building blocks in a practical and scalable manner.



The β-amino acids are the most prominent nonproteinogenic amino acids[1] and are found as a structural motif in many natural products[2] or biologically active molecules such as β-lactam antibiotics (Figure 1).[3] They are key synthetic precursors for important marketed pharmaceutical products (i.e., sitagliptin, paclitaxel).[4] Fluorinated analogues of amino acids have received considerable attention in recent years due to their potential in preparing bioactive molecules with remarkable properties.[5−7] β-Amino acids bearing a fluoroalkyl group at β-position are of particular interest as unique intermediates in the design of bioactive peptide mimetics or enzyme inhibitors. 3-Amino-4,4,4-trifluorobutanoic acid[8] has been incorporated into partially modified retropeptides exhibiting a β-turn-like conformation[9] into peptidomimetics, which inhibit MMP,[10] and more recently, into oligo-β-peptides, which are able to form significantly more stable helices due to the effects of CF_3 groups.[11] β-Substituted derivatives of β-fluoroalkyl-β-amino acids are scarce.[12] The synthesis of racemic 3-amino-4,4,4-trifluoro-3-phenylbutanoic acid was first described in 1991 by Kukhar's group via a hetero Diels−Alder cycloaddition using ketene (Scheme 1a).[13] However, harsh reaction conditions or substrate scope limitations call for the development of new routes.

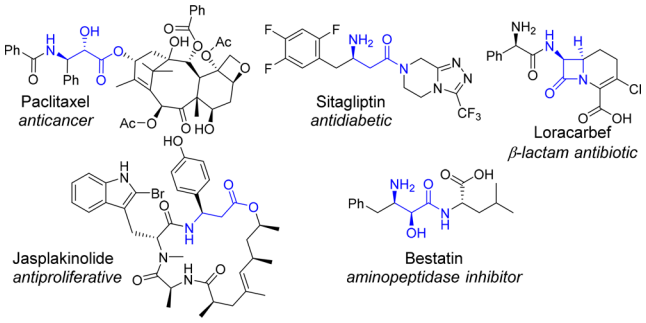


Figure 1. β-Amino acids in bioactive compounds.

In 2013, Grellepois[14] published the first diastereo- and enantioselective synthesis of β-alkyl(aryl)-β-trifluoromethyl-β-amino acid derivatives based on a CuI-catalyzed Reformatsky reaction (Scheme 1b). Enantiopure *N*-*tert*-butanesulfinyl trifluoromethyl ketimines generated in situ from stable precursors were thus advantageously used. Similar reports, using lithium enolate, gave rise to promising MGAT2 inhibitors[15] or modulators of mGluR4.[16] Recently, Ohshima and co-workers investigated a catalytic Mannich-type reaction with various (di)ketones and dialkyl malonates using trifluoromethyl NH-ketimines as electrophiles (Scheme 1c).[17] However, it required a strong metal-based Lewis acid catalyst and isolation of NH-ketimines that are not readily accessible, weakening its synthetic potential. Furthermore, this group also reported a catalytic enantioselective decarboxylative Mannich-type reaction of N-unprotected ketimines from

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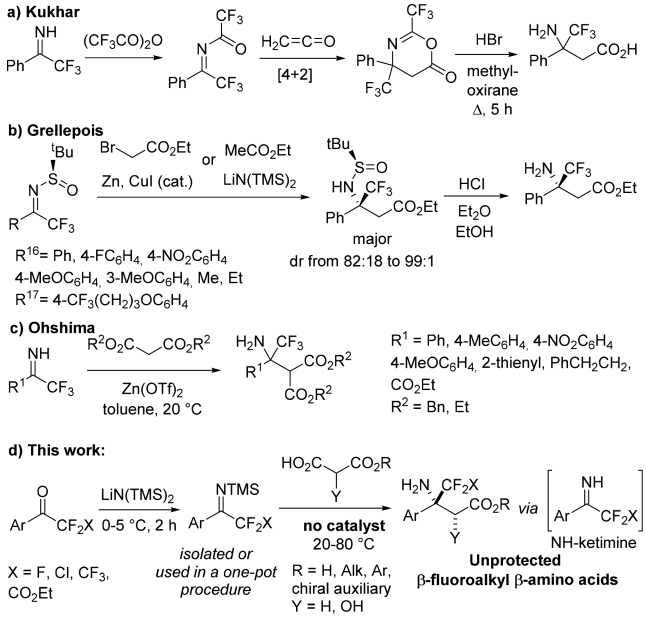
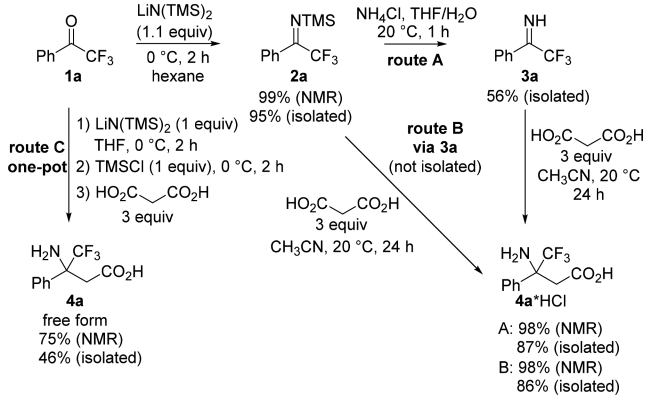
Scheme 1. Preparation of β-Substituted β-Trifluoromethyl-β-Amino Acids



Scheme 2. Prelminary Synthesis of β-Amino Acid 4a from Ketone 1a Using LiHMDS



isatins, providing N-unprotected 3-tetrasubstituted 3-amino-oxindole derivatives.[18]

The literature survey clearly pointed out the lack of simple and flexible protocols for accessing β-(het)aryl-β-fluoroalkyl-β-amino acids, which may limit their broader synthetic application. Despite the above-mentioned existing methods, only the simplest β-amino acid possessing a β-phenyl substituent has been characterized so far.[13] This is in striking contrast to β-substituted analogues, which are readily available in one step by the Rodionov reaction,[19] a three-component decarboxylative reaction of aldehydes, malonic acid (MA), and ammonium acetate. However, this approach suffers from limitations, providing a major challenge to develop sustainable alternatives.[20] In the context of our studies on trifluoromethyl NH-ketimines,[21] we present herein the first decarboxylative addition of malonic acids to generate in situ fluoroalkyl NH-ketimines as an attractive and direct access to unprotected β-fluoroalkyl-β-amino acids that has heretofore remained unexplored. Our approach complements the mechanistically similar Rodionov reaction, postulated to proceed via formation of the NH-aldimines,[19a] by introducing a new class of substrates challenging fluoroalkyl ketones.

Initially, we attempted to synthesize the starting NH-ketimine **3a**, used as a model substrate, from the corresponding trifluoromethyl ketone **1a** via the N-TMS derivative **2a** to avoid the use of highly toxic trifluoroacetonitrile or of triphenylphosphine imine, which is not readily available (Scheme 2, route A).[22] Compound **2a** was isolated in almost quantitative yield according to the known procedure using lithium hexamethyldilazide (LiHMDS).[23] Removal of the TMS group was achieved upon acidic treatment affording **3a** in 56% isolated yield after distillation. Then, we first studied the reaction of **3a** with MA. To our delight, the addition of MA (3 equiv) in anhydrous acetonitrile proceeded smoothly to full completion in 24 h at room temperature. The concurrent decarboxylation of the initially formed MA adduct (not shown in Scheme 2, but see the mechanism discussion below) occurred much faster since it could not be detected in the reaction mixture by ^{19}F NMR monitoring. In these conditions, 3-amino-4,4,4-trifluoro-3-phenylbutanoic acid **4a** was formed in quantitative NMR yield and precipitated from acetonitrile. After a simple workup, **4a** was isolated as hydrochloride salt in 87% yield.

We also demonstrated that 3-amino-4,4,4-trifluoro-3-phenylbutanoic acid **4a** could be obtained in higher overall yield directly from **2a** (route B). In this case, the cleavage of the N-TMS bond is likely to quickly occur in the presence of malonic acid leading to the in situ formation of the reactive NH-ketimine **3a**. It is worth noting that a one-pot procedure can also be advantageously used (route C). In this case, the equimolar amount of TMSOLi, resulting from the transformation of ketone to ketimine, was quenched with TMSCl before MA addition to prevent the formation of TMSOH. Its dimerization with concomitant water release may result in hydrolysis of **3a**.[24] Gratifyingly, the one-pot protocol directly led to the unprotected amino acid **4a**, which precipitates from the reaction mixture. However, in this case, the yield of pure isolated product **4a** dropped to 46% due to the still poorly controlled partial hydrolysis of in situ formed **3a** to ketone **1a** (see the Supporting Information). Since the best yield of unprotected β-amino acid **4a** was observed using method B, various conditions were then screened from N-TMS ketimine **2a** (see the Supporting Information). A series of common solvents were next examined, revealing that briefly heating the reaction mixture in acetonitrile (2 h at 80 °C) in the presence of 2 equiv of MA was best suited to the reaction.

With the optimized conditions in hand, the scope of this two-step reaction was examined with respect to the ketone derivatives **1a−y** (Scheme 3). The reaction proceeded smoothly with a wide functional group tolerance. Initially, the effect of the substituents on the aromatic ring of arylfluoroalkyl ketone (**1a−u**) was investigated. Both electron-donating (i.e., alkoxy, alkyl, or dialkylamino groups) and withdrawing groups (i.e., halogen, trifluoroalkyl, or nitro groups) with different substitution patterns were tolerated, thus giving the corresponding quaternary β-(het)aryl-β-fluoroalkyl-β-amino acids in good yields (**4a−u**). In addition, heteroaryl substituted ketones **1v−w** were also suitable for this reaction, providing the original β-hetaryl β-trifluoromethyl β-amino acids **4v−w**. Introduction of the $CClF_2$ and C_2F_5 groups led to the hitherto unknown β-fluoroalkyl β-amino acids **4x−y**. Additionally, the alternative one-pot procedure (method C) was applied to ketones **1b,j** affording the attempted products **4b,j** in lower yields. A variety of original unprotected β-

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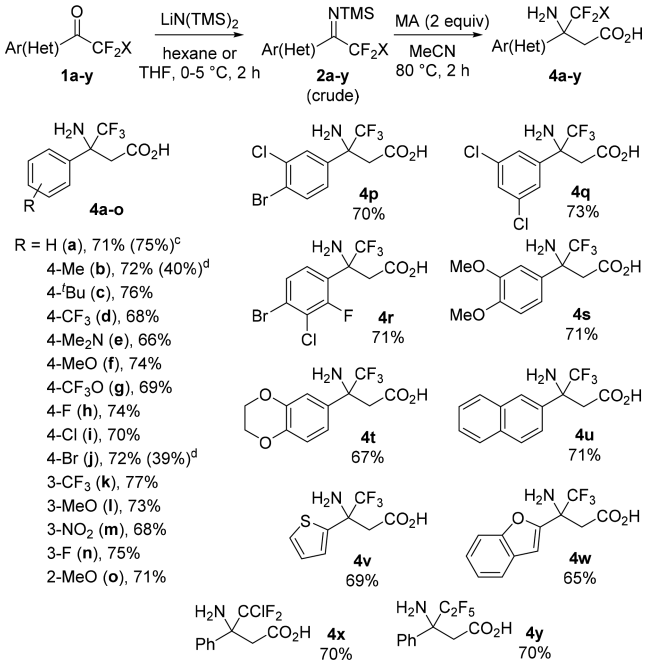
Scheme 3. Scope of Ketones 1a–y in the Synthesis of β-Fluoroalkyl β-Amino Acids 4a–y[a,b]

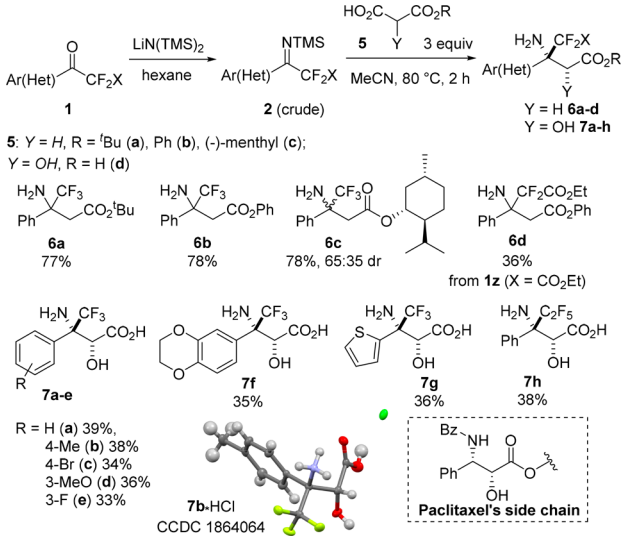


[a]Reaction conditions: Method B was used with isolation of crude N-TMS ketimines **2a–y** unless otherwise specified; syntheses were performed on a 1.5 mmol scale in 1 mL of CH_3CN. [b]Isolated yields were calculated on the basis of the corresponding starting ketones **1a–y**. [c]The reaction was performed on a 10 mM scale. [d]One-pot procedure C was used with addition of TMSCl (1 equiv, 0–5 °C, 2 h at rt) before addition of MA (see the Supporting Information for experimental details).

fluoroalkyl β-amino acids were thus readily furnished in synthetically useful yields without any chromatographic purification steps and in a convenient and easy way for scale-up (preparation of **4a** was achieved in 75% yield under optimal conditions on a 10 mM scale). There are also a great many uses for β-fluoroalkyl β-amino acids, which can be transformed to a variety of useful compounds.

Subsequently, we explored the use of substituted MA in this decarboxylative Mannich-type reaction with ketimines **2** (Scheme 4). To our delight, a range of malonic acid half esters **5a–d** were suitable for the reaction leading to β-amino esters **6a–d** (Y = H) in moderate to good yield, which demonstrated the remarkable scope of this method. Installation of a chiral auxiliary derived from optically pure (−)-menthol in the starting compound **5c** led to β-amino esters **6c** with 65:35 dr. Compound **6d** featuring an ethoxycarbonyldifluoromethyl group was obtained in moderate yield from the corresponding ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate **1z**. Noticeably, α-hydroxy-β-amino acids are important naturally occurring compounds primarily known as components of the taxane family of anticancer drugs.[25] Their corresponding β-aryl-β-fluoroalkyl derivatives remain elusive and represent an attractive synthetic target owing to the presence of the fluorinated functional group. We attempted to further confirm the broad generality and effectiveness of the developed method by involving commercially available hydroxymalonic (tartronic) acid **5d** (Scheme 4, Y = OH) as substrate. **5d** (3 equiv) reacted smoothly with the corresponding crude N-TMS ketimines **2** under the reaction conditions and afforded the

Scheme 4. Synthesis of β-Fluoroalkyl β-Amino Esters 6a–d and α-Hydroxy-β-Amino Acids 7a–h[a]

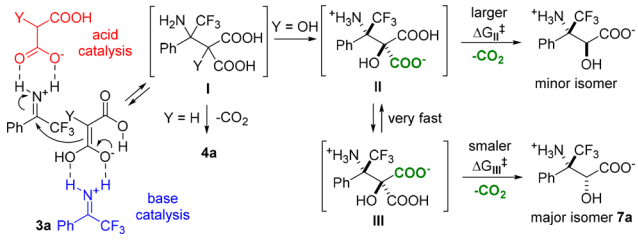


[a]Isolated yields were calculated from the corresponding starting ketones **1**. For compounds **7**, the structures and yields refer to isolated major diastereomers with >98:2 dr.

desired products **7a–h** as single diastereomers (>98:2 dr), albeit in lower yields, directly upon simple workup of the reaction mixture and crystallization. ^{19}F NMR analysis revealed that in the reaction of **2a** with **5d** a mixture of diastereomeric products (83:17 dr) was initially formed in 80% NMR yield (see the Supporting Information). The (2*R**,3*S**) relative configurations of the chiral centers in products **7a–h** were unambiguously proved by the XRD study of **7b**. Consequently, the obtained compounds **7** are the first racemic β-fluoroalkyl analogues of Paclitaxel's side chain amino acid, (2*R*,3*S*)-α-hydroxy β-phenylalanine.[7c,26]

In agreement with the previously reported literature results,[27] a proposed mechanism for the decarboxylative addition of MA and tartronic acid to NH-ketimine **3a** is outlined in Scheme 5. First, it should be noted that the rate of

Scheme 5. Proposed Mechanistic Pathways for the Decarboxylative Addition of Malonic or Tartronic Acid to 3a



4a formation is not sensitive to the presence of organic acid or base catalysts (TFA, TfOH, pyridine, Et_3N, etc., including chiral organocatalysts). We assume that in this case a mutual substrate catalysis is observed since **3a** itself is a weak organic base while MA is mildly acidic (pK_a^1 = 2.83). Therefore, both substrates are capable of activating each other's corresponding electrophilic (C=N bond) or nucleophilic (CH_2 group) centers, thus causing externally added catalyst inefficiency. The reactive C-nucleophilic species generated from malonic

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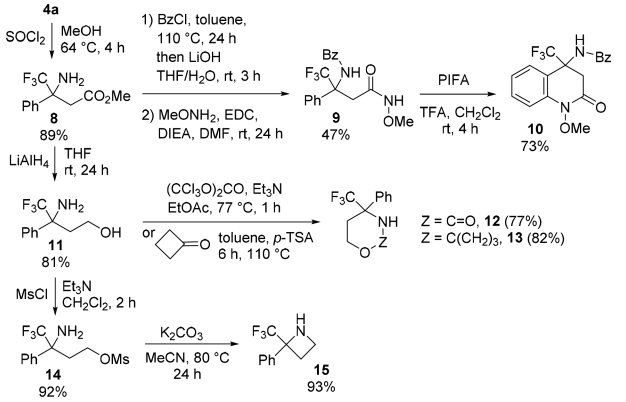
(tartronic) acid is assumed to be enolate monoanion (approximate pK_a^{CH} = 13−14 for MA).[28] In the first step, its reversible addition to protonated ketimine **3a** gives rise to intermediate **I**. Then, irreversible decarboxylation of **I** leads to **4a** (Y = H). In the case of tartronic acid addition (Y = OH), preferential formation of the major diastereomer **7a** is determined, according to the classic Curtin−Hammett principle, by the relatively large difference in $\Delta G_{II}^{\ddagger}$ and $\Delta G_{III}^{\ddagger}$ energies of the transition states derived from the respective most populated conformers **II** and **III**, which are stabilized by the intramolecular electrostatic interaction and hydrogen bonding between *syn*-clinal NH_3^+ and COO^-/COOH groups. These mechanistic assumptions imply that intermediates **II** and **III** should undergo rapid reversible interconversion by proton transfer and slower irreversible decarboxylation (presumably via the leaving CO_2^- group and the formation of a noncyclic anionic transition state)[29] into diastereomeric products.

To demonstrate the utility of this reaction and gain access to molecular diversity, we performed a short-step synthesis of the novel relevant 4-amino-4-(trifluoromethyl)-3,4-dihydroquinolin-2(1H)-one derivative **10** as an attractive scaffold for medicinal chemistry (Scheme 6).[30] The key cyclization step

Scheme 6. Application of β-Amino Acid 4a to the Synthesis of Original Heterocyclic Systems



of the *N*-methoxy amide **9** in the proposed synthetic sequence was achieved with phenyliodine bis(trifluoroacetate) (PIFA) in good yield.[31] In addition, reduction of the methyl ester **8** into amino alcohol **11** and its subsequent cyclocondensation with triphosgene or cyclobutanone provided derivatives of 1,3-oxazinan-2-one **12** and 5-oxa-9-azaspiro[3.5]nonane **13**, respectively. 2-Phenyl-2-(trifluoromethyl)azetidine **15** can be readily prepared from the corresponding mesylate **14** in excellent yield.

In summary, we reported a new and simple method for the preparation of a range of original β-aryl(hetaryl)-β-fluoroalkyl β-amino acids and their analogous α-hydroxy derivatives with high diastereoselectivity. The generality of this approach was demonstrated, and it opens the way to organofluorine building blocks that are otherwise challenging to prepare. The reaction occurred smoothly and without any chromatographic purification steps via a decarboxylative Mannich-type reaction involving an NH-ketimine intermediate which could be isolated. Further experiments are in progress to study the scope of this process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00622.

Experimental procedures, NMR data, and crystal structure of the products (PDF)

Accession Codes

CCDC 1864064 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Juaristi, E., Soloshonok, V. A., Eds. *Enantioselective Synthesis of Beta-Amino Acids*, 2nd ed.; John Wiley & Sons, Inc., 2005. (b) Weiner, B.; Szymański, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. Recent advances in the catalytic asymmetric synthesis of β-amino acids. *Chem. Soc. Rev.* **2010**, *39*, 1656−1691. (c) Kiss, L.; Fülöp, F. Synthesis of Carbocyclic and Heterocyclic β-Amino-carboxylic Acids. *Chem. Rev.* **2014**, *114*, 1116−1169. (d) Seebach, D.; Beck, A. K.; Capone, S.; Deniau, G.; Groselj, U.; Zass, E. Enantioselective Preparation of β^2-Amino Acid Derivatives for β-Peptide Synthesis. *Synthesis* **2009**, *2009*, 1−32. (e) Seebach, D.; Gardiner, J. β-Peptidic Peptidomimetics. *Acc. Chem. Res.* **2008**, *41*, 1366−1375.

(2) (a) Lelais, G.; Seebach, D. β^2-amino acids—syntheses, occurrence in natural products, and components of β-peptides. *Biopolymers* **2004**, *76*, 206−243. (b) Kudo, F.; Miyanaga, A.; Eguchi, T. Biosynthesis of natural products containing β-amino acids. *Nat. Prod. Rep.* **2014**, *31*, 1056−1073.

(3) Drawz, S. M.; Bonomo, R. A. Three decades of beta-lactamase inhibitors. *Clin. Microbiol. Rev.* **2010**, *23*, 160−201.

(4) (a) Savile, C. K.; Janey, J. M.; Mundorff, E. C.; Moore, J. C.; Tam, S.; Jarvis, W. R.; Colbeck, J. C.; Krebber, A.; Fleitz, F. J.; Brands, J.; Devine, P. N.; et al. Biocatalytic Asymmetric Synthesis of Chiral Amines from Ketones Applied to Sitagliptin Manufacture. *Science* **2010**, *329*, 305−309. (b) Sakai, T.; Kawamoto, Y.; Tomioka, K. Asymmetric Synthesis of Intermediates for Otamixaban and

DOI: 10.1021/acs.orglett.9b00622
Org. Lett. XXXX, XXX, XXX−XXX

Premafloxacin by the Chiral Ligand-Controlled Asymmetric Conjugate Addition of a Lithium Amide. *J. Org. Chem.* **2006**, *71*, 4706−4709.

(5) (a) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822−5880. (b) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315−8359. (c) Müller, C.; Faeh, C.; Diederich, F. Fluorine in pharmaceuticals: looking beyond intuition. *Science* **2007**, *317* (5846), 1881−1886. (d) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J.; Soloshonok, V.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II−III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422−518.

(6) (a) Groult, H., Leroux, F., Tressaud, A., Eds. *Modern Synthesis Processes and Reactivity of Fluorinated Compounds, Progress in Fluorine Science*; Elsevier, 2017; pp 427−464. (b) Salwiczek, M.; Nyakatura, E. K.; Gerling, U. I.; Ye, S.; Koksch, B. Fluorinated amino acids: compatibility with native protein structures and effects on protein−protein interactions. *Chem. Soc. Rev.* **2012**, *41*, 2135−2171. (c) Buer, B. C.; Marsh, E. N. Fluorine: A new element in protein design. *Protein Sci.* **2012**, *21*, 453−462. (d) Marsh, E. N. Fluorinated Proteins: From Design and Synthesis to Structure and Stability. *Acc. Chem. Res.* **2014**, *47*, 2878−2886. (e) Bandak, D.; Babii, O.; Vasiuta, R.; Komarov, I. V.; Mykhailiuk, P. K. Design and Synthesis of Novel ^{19}F-Amino Acid: A Promising ^{19}F NMR Label for Peptide Studies. *Org. Lett.* **2015**, *17*, 226−229. (f) Tkachenko, A. N.; Mykhailiuk, P. K.; Afonin, S.; Radchenko, D. S.; Kubyshkin, V. S.; Ulrich, A. S.; Komarov, I. V. A ^{19}F NMR Label to Substitute Polar Amino Acids in Peptides: A CF_3-Substituted Analogue of Serine and Threonine. *Angew. Chem., Int. Ed.* **2013**, *52*, 1486−1489. (g) Cametti, M.; Crousse, B.; Metrangolo, P.; Milani, R.; Resnati, G. The fluorous effect in biomolecular applications. *Chem. Soc. Rev.* **2012**, *41*, 31−42. (h) Tressler, C. M.; Zondlo, N. J. Synthesis of Perfluoro-tert-butyl Tyrosine, for Application in ^{19}F NMR, via a Diazonium-Coupling Reaction. *Org. Lett.* **2016**, *18*, 6240−6243. (i) Chaume, G.; Simon, J.; Lensen, N.; Pytkowicz, J.; Brigaud, T.; Miclet, E. Homochiral versus Heterochiral Trifluoromethylated Pseudoproline Containing Dipeptides: A Powerful Tool to Switch the Prolyl-Amide Bond Conformation. *J. Org. Chem.* **2017**, *82*, 13602−13608. (j) Zheng, B.; D'Andrea, S.; Sun, L.; Wang, A.; Chen, Y.; Hrnciar, P.; Friborg, J.; Falk, P.; Hernandez, D.; Yu, F.; et al. Potent Inhibitors of Hepatitis C Virus NS3 Protease: Employment of a Difluoromethyl Group as a Hydrogen-Bond Donor. *ACS Med. Chem. Lett.* **2018**, *9*, 143−148.

(7) (a) March, T. L.; Johnston, M. R.; Duggan, P. J.; Gardiner, J. Synthesis, Structure, and Biological Applications of α-Fluorinated β-Amino Acids and Derivatives. *Chem. Biodiversity* **2012**, *9*, 2410−2441. (b) Kuznetsova, L. V.; Pepe, A.; Ungureanu, I. M.; Pera, P.; Bernacki, R. J.; Ojima, I. Syntheses and Structure-Activity Relationships of Novel 3′-Difluoromethyl and 3′-Trifluoromethyl-Taxoids. *J. Fluorine Chem.* **2008**, *129* (9), 817−828. (c) Mikami, K.; Fustero, S.; Sánchez-Roselló, M.; Aceña, J. L.; Soloshonok, V.; Sorochinsky, A. Synthesis of Fluorinated β-Amino Acids. *Synthesis* **2011**, *2011*, 3045−3079.

(8) Shibata, N.; Nishimine, T.; Shibata, N.; Tokunaga, E.; Kawada, K.; Kagawa, T.; Aceña, J. L.; Sorochinsky, A. E.; Soloshonok, V. A. Asymmetric Mannich reaction between (S)-N-(*tert*-butanesulfinyl)-3,3,3-trifluoroacetaldimine and malonic acid derivatives. Stereodivergent synthesis of (R)- and (S)-3-amino-4,4,4-trifluorobutanoic acids. *Org. Biomol. Chem.* **2014**, *12*, 1454−1462.

(9) Volonterio, A.; Bellosta, S.; Bravin, F.; Bellucci, M. C.; Bruche, L.; Colombo, G.; Malpezzi, L.; Mazzini, S.; Meille, S. V.; Meli, M.; Ramirez de Arellano, C.; Zanda, M. Synthesis, Structure and Conformation of Partially-Modified Retro- and Retro-Inverso ψ-[NHCH(CF_3)]Gly Peptides. *Chem. - Eur. J.* **2003**, *9*, 4510−4522.

(10) Volonterio, A.; Bellosta, S.; Bravo, S.; Canavesi, M.; Corradi, E.; Meille, S. V.; Monetti, M.; Moussier, N.; Zanda, M. Solution/Solid-Phase Synthesis of Partially Modified Retro- and Retro-Inverso-ψ[NHCH(CF_3)]-Peptidyl Hydroxamates and Their Evaluation as MMP-9 Inhibitors. *Eur. J. Org. Chem.* **2002**, *2002*, 428−438.

(11) (a) Cho, J.; Sawaki, K.; Hanashima, S.; Yamaguchi, Y.; Shiro, M.; Saigo, K.; Ishida, Y. Stabilization of β-peptide helices by direct attachment of trifluoromethyl groups to peptide backbones. *Chem. Commun.* **2014**, *50*, 9855−9858. (b) Cho, J.; Nishizono, N.; Iwahashi, N.; Saigo, K.; Ishida, Y. Stereo-regulated synthesis of peptides containing a β-trifluoromethyl-β-amino acid. *Tetrahedron* **2013**, *69*, 9252−9260.

(12) For the synthesis of β-alkyl substituted β-fluoroalkyl-β-amino acids, see: (a) Fustero, S.; del Pozo, C.; Catalan, S.; Aleman, J.; Parra, A.; Marcos, V.; Ruano, J. L. G. A New Strategy for the Synthesis of Optically Pure β-Fluoroalkyl β-Amino Acid Derivatives. *Org. Lett.* **2009**, *11*, 641−644. α-Trifluoromethyl-β-hydroxyaspartic acid: (b) Bravo, P.; Fustero, S.; Guidetti, M.; Volonterio, A.; Zanda, M. Stereoselective Mannich-Type Reaction of an Acyclic Ketimine with a Substituted Chlorotitanium Enolate: Efficient Approach to D-erythro-α-Trifluoromethylβ-hydroxyaspartic Units. *J. Org. Chem.* **1999**, *64*, 8731−8735.

(13) Kolycheva, M. T.; Gerus, I. I.; Yagupol'ski, Yu.L.; Kukhar, V. P. Synthesis of 3-amino-4,4,4-trifluoro-3-phenylbutyric acid (3-phenyl-3-trifluoromethyl- β-alanine). *J. Org. Chem. USSR (Eng. Transl.)* **1991**, *27*, 101−104; *Zh. Org. Khim.* **1991**, *27*, 117−121.

(14) Grellepois, F. Enantiopure Trifluoromethylated $\beta^{3,3}$-Amino Acids: Synthesis by Asymmetric Reformatsky Reaction with Stable Analogues of Trifluoromethyl N-tert-Butanesulfinylketoimines and Incorporation into α/β-Peptides. *J. Org. Chem.* **2013**, *78*, 1127−1137.

(15) Meng, W.; Zhao, G. Preparation of dihydropyridinone MGAT2 inhibitors for use in the treatment of metabolic disorders. WO 2015134701 A1, 2015.

(16) Vieira, E.; Jaeschke, G.; Guba, W.; Ricci, A.; Rueher, D.; Biemans, B.; Plancher, J.-M.; O'Hara, F. Preparation of ethynyl derivatives of phenyl(or pyridinyl)pyrimidinedione as positive allosteric modulators (PAMs) of metabotropic glutamate receptor 4 (mGluR4). WO 2015128307 A1, 2015.

(17) Sawa, M.; Morisaki, K.; Kondo, Y.; Morimoto, H.; Ohshima, T. Direct Access to N-Unprotected α- and/or β-Tetrasubstituted Amino Acid Esters via Direct Catalytic Mannich-Type Reactions Using N-Unprotected Trifluoromethyl Ketimines. *Chem. - Eur. J.* **2017**, *23*, 17022−17028.

(18) Sawa, M.; Miyazaki, S.; Yonesaki, R.; Morimoto, H.; Ohshima, T. Catalytic Enantioselective Decarboxylative Mannich-Type Reaction of N-Unprotected Isatin-Derived Ketimines. *Org. Lett.* **2018**, *20*, 5393−5397.

(19) (a) Rodionow, W. M.; Postovskaja, E. A. The mechanism of formation of beta-aryl-beta-amino fatty acids by the condensation of aromatic aldehydes with malonic acid and its derivatives. *J. Am. Chem. Soc.* **1929**, *51*, 841−847. (b) Lebedev, A. V.; Lebedeva, A. B.; Sheludyakov, V. D.; Kovaleva, E. A.; Ustinova, O. L.; Kozhevnikov, I. B. Competitive Formation of β-Amino Acids, Propenoic, and Ylidenemalonic Acids by the Rodionov Reaction from Malonic Acid, Aldehydes, and Ammonium Acetate in Alcoholic Medium. *Russ. J. Gen. Chem.* **2005**, *75*, 1113−1124.

(20) We did not detect the formation of β-amino acids when the Rodionov protocol was applied to 1-phenyl-2,2,2-trifluoroethanone (see ref 19b). This fact may be attributed to the insufficient formation of NH-ketimine in the condensation of ketone and ammonia. The well documented electronic effect of the geminal trifluoromethyl group that prevents dehydration of the intermediate hemiaminal-type compounds into NH-ketimines may be responsible for this observation. See also: Kelly, C. B.; Mercadante, M. A.; Leadbeater, N. E. Trifluoromethyl ketones: properties, preparation, and application. *Chem. Commun.* **2013**, *49*, 11133−11148.

(21) (a) Sukach, V. A.; Golovach, N. M.; Pirozhenko, V. V.; Rusanov, E. B.; Vovk, M. V. Convenient enantioselective synthesis of β-trifluoromethyl-β-aminoketones by organocatalytic asymmetric Mannich reaction of aryl trifluoromethyl ketimines with acetone. *Tetrahedron: Asymmetry* **2008**, *19*, 761−764. (b) Bentya, A. V.; Mel'nichenko, N. V.; Vovk, M. V. Synthesis of 2-aryl-2-(trifluor-

DOI: 10.1021/acs.orglett.9b00622
Org. Lett. XXXX, XXX, XXX−XXX

omethyl)-2,5-dihydro-1,3-thiazoles. *Russ. J. Org. Chem.* **2016**, *52*, 292−293.
(22) (a) Vovk, M. V.; Bol'but, A. V.; Lebed, P. S.; Mel'nichenko, N. V. Synthesis of 2-aryl-2,4,6-tris(trifluoromethyl)-1,2-dihydro-1,3,5-triazines by Reaction of Arylmagnesium Bromides with Trifluoroacetonitrile. *Russ. J. Org. Chem.* **2007**, *43*, 928−929. (b) Morisaki, K.; Morimoto, H.; Ohshima, T. Direct access to N-unprotected tetrasubstituted propargylamines via direct catalytic alkynylation of N-unprotected trifluoromethyl ketimines. *Chem. Commun.* **2017**, *53*, 6319−6322. (c) Koos, M.; Mosher, H. S. α-Amino-α-trifluoromethylphenylacetonitrile: A potential reagent for ^{19}F NMR determination of enantiomeric purity of acids. *Tetrahedron* **1993**, *49*, 1541−1546.
(23) Gosselin, F.; O'Shea, P. D.; Roy, S.; Reamer, R. A.; Chen, C.-Y.; Volante, R. P. Unprecedented Catalytic Asymmetric Reduction of N−H Imines. *Org. Lett.* **2005**, *7*, 355−358.
(24) Astruc, D. *Organometallic Chemistry and Catalysis*; Springer Science & Business Media, 2007; p 331.
(25) Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M. In *Taxane Anticancer Agents: Basic Science and Current Status*; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1999.
(26) For fluorine-containing taxoid anticancer agents, see: (a) Seitz, J.; Vineberg, J. G.; Zuniga, E. S.; Ojima, I. Fluorine-containing taxoid anticancer agents and their tumor-targeted drug delivery. *J. Fluorine Chem.* **2013**, *152*, 157−165. (b) Ojima, I. Strategic incorporation of fluorine into taxoid anticancer agents for medicinal chemistry and chemical biology studies. *J. Fluorine Chem.* **2017**, *198*, 10−23.
(27) (a) Blaquiere, N.; Shore, D. G.; Rousseaux, S.; Fagnou, K. Decarboxylative Ketone Aldol Reactions: Development and Mechanistic Evaluation under Metal-Free Conditions. *J. Org. Chem.* **2009**, *74*, 6190−6198. (b) Yuan, H. N.; Li, S.; Nie, J.; Zheng, Y.; Ma, J. A. Highly Enantioselective Decarboxylative Mannich Reaction of Malonic Acid Half Oxyesters with Cyclic Trifluoromethyl Ketimines: Synthesis of β-Amino Esters and Anti-HIV Drug DPC 083. *Chem. - Eur. J.* **2013**, *19*, 15856−15860.
(28) Bruckner, R. *Advanced Organic Chemistry. Reaction Mechanisms*; Elsevier, 2002; pp 420−422.
(29) Thanassi, J. W. Aminomalonic acid. Spontaneous decarboxylation and reaction with 5-deoxypyridoxal. *Biochemistry* **1970**, *9*, 525−532.
(30) Patel, M.; McHugh, R. J.; Cordova, T.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Rodgers, J. D. Synthesis and evaluation of novel quinolinones as HIV-1 reverse transcriptase inhibitors. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1943−1945.
(31) (a) Romero, A. G.; Darlington, W. H.; McMillan, M. W. Synthesis of the Selective D_2 Receptor Agonist PNU-95666E from D-Phenylalanine Using a Sequential Oxidative Cyclization Strategy. *J. Org. Chem.* **1997**, *62*, 6582−6587. (b) Zou, M. F.; Keck, T. M.; Kumar, V.; Donthamsetti, P.; Michino, M.; Burzynski, C.; Schweppe, C.; Bonifazi, A.; Free, R. B.; Sibley, D. R.; Janowsky, A.; Shi, L.; Javitch, J. A.; Newman, A. H. Novel Analogues of (R)-5-(Methylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2(1H)-one (Sumanirole) Provide Clues to Dopamine D_2/D_3 Receptor Agonist Selectivity. *J. Med. Chem.* **2016**, *59*, 2973−2988.

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