# Diastereoselective Synthesis of $\alpha$-Fluoro-$\gamma$-Lactams via Difluorocarbene-Triggered Cyclization and Rearrangement

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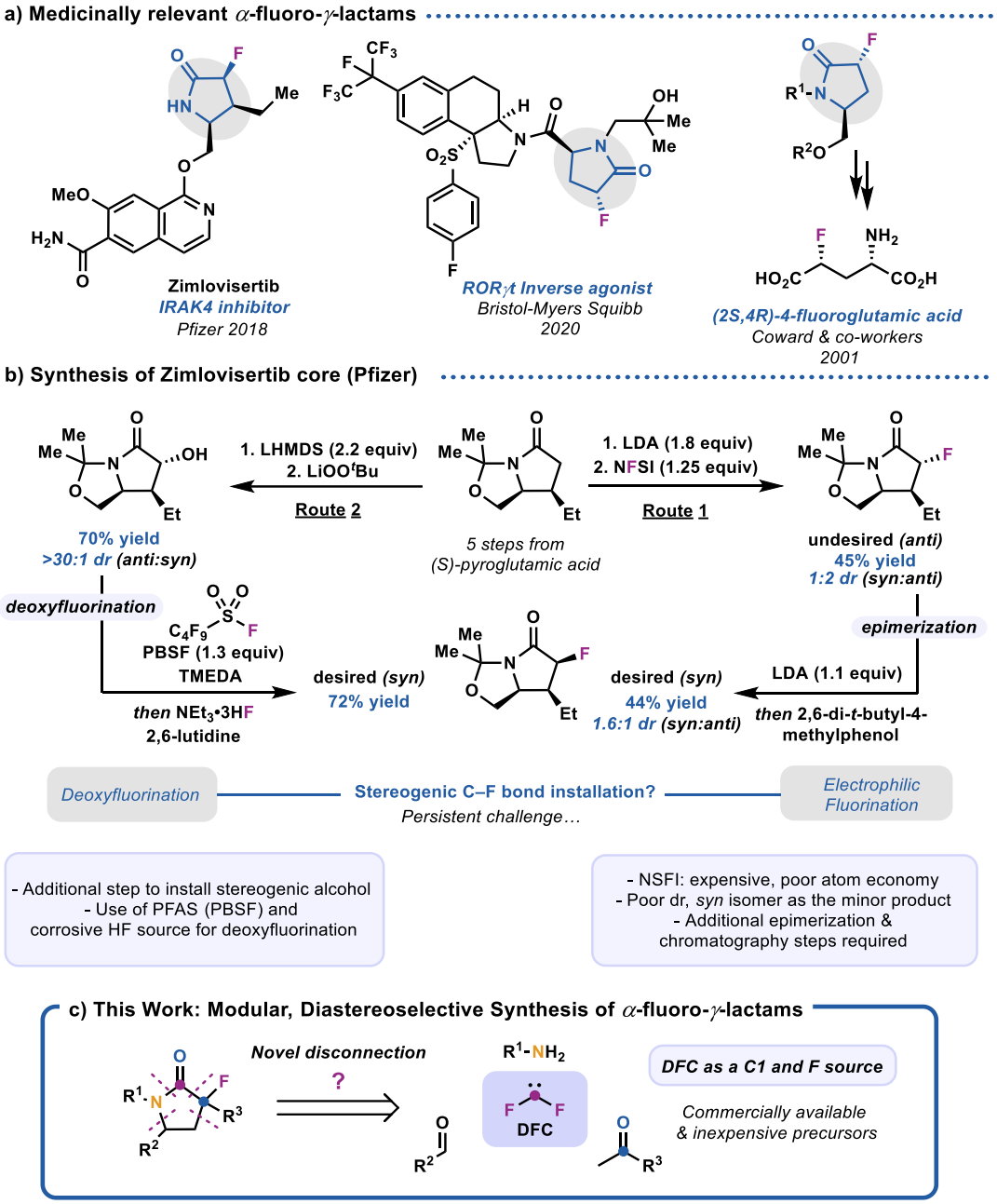
**Abstract:** We report a difluorocarbene-enabled, diastereoselective synthesis of *α*-fluoro-*γ*-lactams from readily accessible *β*-aminoketones and inexpensive, commercially available ethyl bromodifluoroacetate (EBDFA). Compared to established routes to this medicinally relevant motif, our strategy avoids the use of costly electrophilic fluorinating or deoxyfluorinating reagents, highlighting difluorocarbene as a versatile C1 and F building block. Density functional theory (DFT) calculations reveal that cyclization is the stereodetermining step, with observed diastereomeric ratios governed by Curtin-Hammett kinetics. In addition to activating EBDFA, the $K_2CO_3$ base enables the favourable formation of a transient hemiaminal epoxide intermediate, with subsequent C–F bond formation proceeding through a nucleophilic fluoride ring-opening pathway. Overall, this work not only delivers a direct and modular route to stereodefined *α*-fluoro-*γ*-lactams but more broadly expands our mechanistic understanding of difluorocarbene-mediated amine-carbonyl coupling reactions.

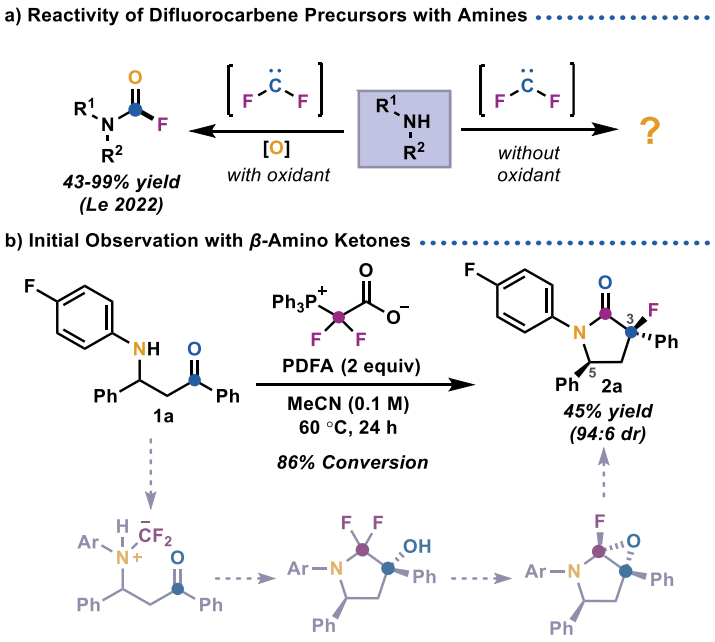
Fluorinated compounds are prevalent in pharmaceuticals and agrochemicals owing to the ability of fluorine to fine-tune essential physiochemical properties, including metabolic stability and bioavailability.[1] Accordingly, the field of organofluorine chemistry has seen remarkable progress in the last decade, particularly towards the design and synthesis of novel fluorinated motifs.[2] The *γ*-lactam core is a privileged structure in medicinal chemistry,[3,4] with *α*-fluorinated derivatives represented in several lead compounds and active pharmaceutical ingredients (APIs) (Scheme 1a).[5–9] Additionally, enantioenriched fluorinated *γ*-lactams have been employed as starting materials for the preparation of chiral NHCs and ligands for transition metal catalysts.[10,11] The *α*-fluorination of amides is typically carried out by generating the corresponding enolate with an organolithium base, followed by treatment with an electrophilic fluorine source, under cryogenic conditions. However, this approach often affords poor diastereoselectivities with substituted *γ*-lactams, and over-fluorination can occur, creating byproducts that require column chromatography and complicating purification on scale.[12] These challenges are exemplified in Pfizer's early discovery route towards the *α*-fluoro-*γ*-lactam core of Zimlovisertib bearing three contiguous stereocenters.[6] Specifically, the electrophilic fluorination step using *N*-fluorobenzensulfonimide (NFSI) proceeded with less than 2:1 diastereomeric ratio (dr) in favour of the undesired isomer, thus necessitating an additional epimerization step to access the targeted API intermediate, albeit in moderate yields (Scheme 1b). Despite the broad utility of electrophilic *N*–F based reagents, many derivatives are costly, exhibit poor atom economy, and may be highly oxidizing, thus limiting their application to densely functionalized targets in industry.[13] To address these issues, a process chemistry team at Pfizer developed an alternative route to the Zimlovisertib precursor, which featured a highly diastereoselective electrophilic hydroxylation step, followed by stereoinvertive deoxyfluorination with perfluorobutanesulfonyl fluoride (PBSF) and $NEt_3 \cdot 3HF$.[14] A similar deoxyfluorination strategy was employed by researchers at Bristol-Meyers-Squibb to access an advanced intermediate (BMT-415200) of an *α*-fluoro-*γ*-lactam-containing drug candidate currently under investigation.[7] Considering the recent regulatory challenges surrounding per- and polyfluoroalkylsubstances (PFAS), such as PBSF, and the use of a corrosive HF source,[15] there is certainly room for improvement in the process.[16] It is worth mentioning that other common deoxyfluorinating reagents present other limitations, such as shock-sensitivity (e.g., DAST) and high costs (e.g., XtalFluor-E/M).[17] Overall, the presented issues underscore the challenges of highly stereoselective, direct fluorination strategies that are amenable to industrially relevant targets. Modern methods for the synthesis of fluorinated *γ*-lactams under photoredox or transition metal catalysis have been disclosed, but most are only applicable to the synthesis of *α,α*-difluoro-derivatives.[18–24] Therefore, the development of an efficient strategy that enables the stereoselective synthesis of *α*-fluoro-*γ*-lactams under mild conditions with inexpensive and easy-to-handle reagents is highly desirable.




**Scheme 1.** Strategies for the Synthesis of α-Fluoro-γ-Lactams.

In 2022, we reported that secondary amines react with difluorocarbene (DFC) precursors such as (triphenylphosphonio)difluoroacetate (PDFA) in the presence of pyridine-*N*-oxides to deliver carbamoyl fluorides (Scheme 2a).[25] However, β-amino carbonyl derivatives showed no product formation, which prompted us to investigate the reaction without the oxidant. To our surprise, when compound **1a** was treated with PDFA under oxidant-free conditions, an unexpected product was detected in the crude reaction mixture by $^{19}F$ NMR spectroscopy with a notable signal at -142 ppm (Scheme 2b). Subsequent purification and structural elucidation by 1D and 2D NMR, HRMS and X-ray analysis revealed that the product was *cis*-α-fluoro-γ-lactam **2a**, obtained in moderate yield with good diastereoselectivity (CCDC 2515294, see SI for full details). Note that we have designated the relative *"cis* configuration" in reference to the stereogenic α-fluorine atom at C3 and the β-substituent at C5 on the γ-lactam core. The chemistry of DFC as a $CF_2$ synthon is well-established, and many precursors are commercially available or easily synthesized in the laboratory.[26,27] In recent years, unconventional reactions of DFC with tertiary amines have been reported, providing entry to novel fluorinated motifs via transient $R_3N$-$CF_2$ ylide species.[28–30] For example, Hu explored the fluorination-aminocarbonylation of aldehydes using DFC sources to form α-fluoroamides.[31] Subsequently, Lan and Song reported the formation of fluorinated oxindoles from α-aminoarylketones enabled by DFC and the reaction mechanism was explored using DFT studies.[32] However, to the best of our knowledge, our observation represents the first diastereoselective synthesis of α-fluoro-γ-lactams from DFC precursors. Importantly, this approach introduces a fundamentally new disconnection that unites all parts of α-fluoro-γ-lactam motif from readily prepared or commercial building blocks in a highly modular fashion. Moreover, β-aminoketones are easily accessible

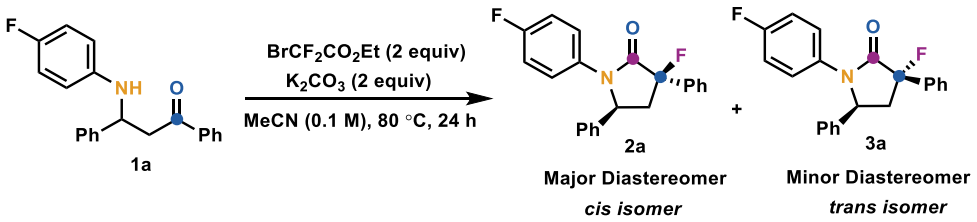
through well-established and even asymmetric routes (e.g., Mannich or aza-Michael reactions), allowing a wide variety of derivatives to easily be prepared.[33–35]




**Scheme 2.** Initial Observations on the Reactivity of Amines toward Difluorocarbene Precursors.

Our initial hit with PDFA revealed the presence of decomposition products resulting from the retro-aza-Michael addition of the starting material, leading to the formation of chalcone and 4-fluoroaniline, which largely accounted for the low efficiency. In addition, minor amounts (≤5%) of the corresponding *gem*-difluoroalkene (Wittig product) were detected, thus prompting further optimization. We observed that *cis*-α-fluoro-γ-lactam **2a** can be obtained in markedly higher yields using ethylbromodifluoroacetate (EBDFA) as the DFC source with $K_2CO_3$ at slightly elevated temperature (Table 1, entry 1). Notably, these conditions reduced the formation of undesired byproducts and minimized the decomposition of the starting material through the retro-aza Michael reaction, while preserving the high diastereoselectivity. EBDFA offers further benefits as it is commercially available, stable, and less expensive than other DFC precursors, thus removing the necessity for reagent preparation required with PDFA.[36] Deviation from these conditions, using alternative DFC sources, led to reduced yields or a lack of reactivity (see SI). High temperatures (>60 °C) and basic additives are essential for reactivity, as no product was obtained at room temperature, consistent with the thermal activation requirement of DFC precursor (entries 4-8). Differential scanning calorimetry (DSC) analysis revealed that EBDFA is thermally stable up to approximately 120 °C, while in combination with $K_2CO_3$, exothermic events occur above 80 °C, consistent with base-promoted generation of DFC.[36] Notably, only alkali carbonate bases proved to be effective, and alternatives failed to promote the reaction (See SI). Finally, with an excess amount of EBDFA and $K_2CO_3$, full conversion and yields of up to 95% were achieved (entry 9).

**Table 1.** Reaction Optimization for the Synthesis of α-fluoro-γ-lactams.

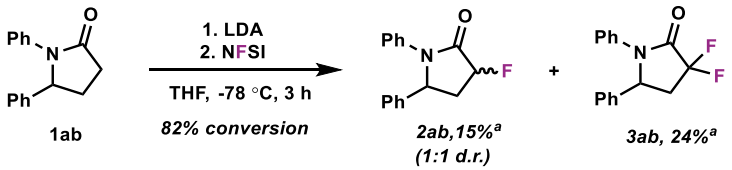



| Entry | Deviation from above conditions | Conversion of **1a** (%)[a] | Yield of **2a** (%)[a] | d.r. |
|---|---|---|---|---|
| 1 | none | 92 | 74 | 89:11 |
| 2 | PDFA | 81 | 51 | 94:6 |

| | | | | |
|---|---|---|---|---|
| 3 | $BrCF_2CO_2K$ | 82 | 49 | 94:6 |
| 4 | r.t. | 64 | 0 | - |
| 5 | 60 °C | 68 | 32 | 91:9 |
| 6 | NaF | 84 | 0 | - |
| 7 | $Cs_2CO_3$ | 65 | 24 | 96:4 |
| 8 | No base[b] | 57 | 0 | - |
| 9 | $BrCF_2CO_2Et$ (3 eq), $K_2CO_3$ (3 eq) | 100 | 95 | 90:10 |

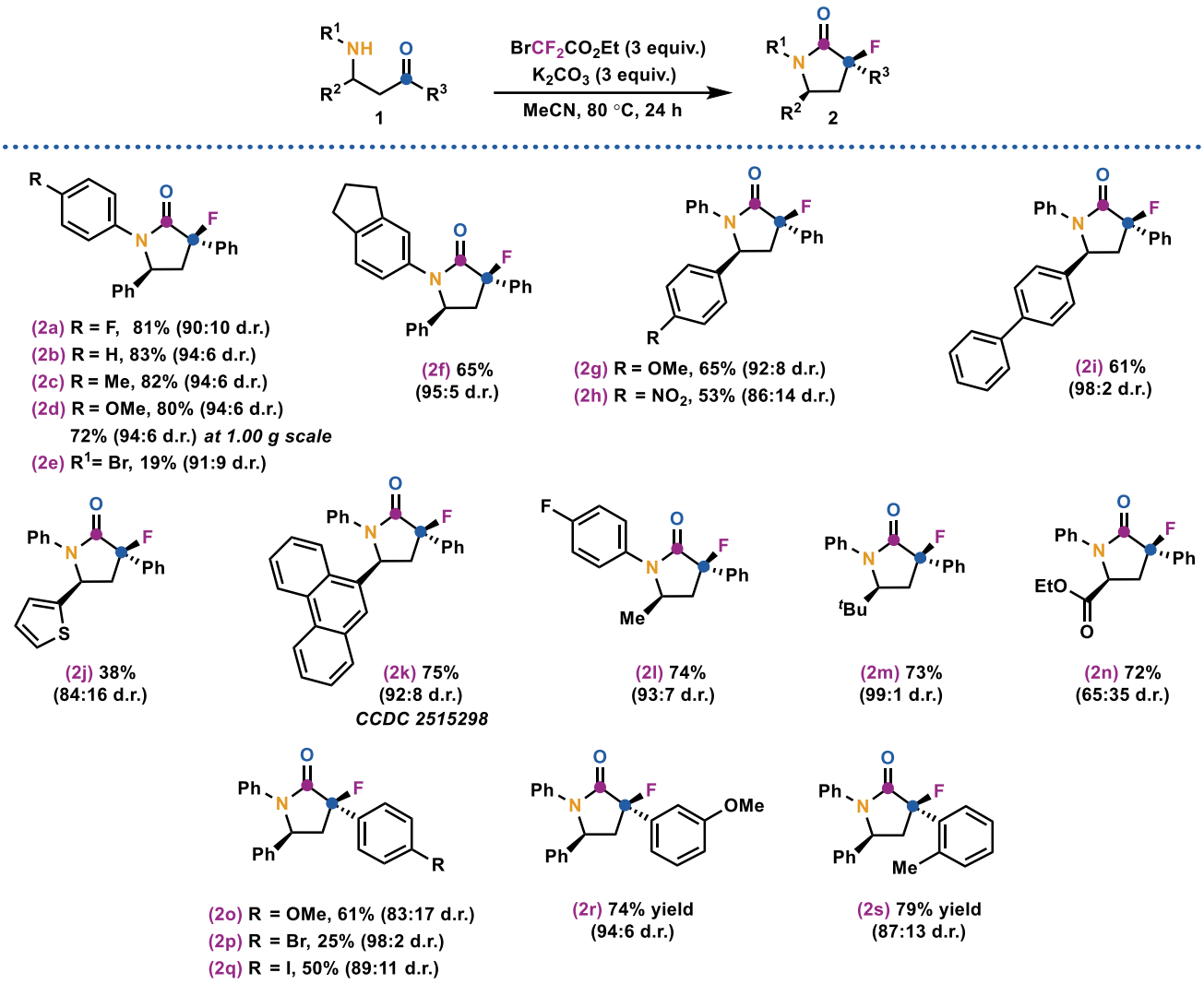
[a]Conversions and yields acquired by $^{19}F$ NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard. [b]$BrCF_2CO_2Et$ (3 equiv). [c]4-methylpyridine *N*-oxide (3 equiv).

As a comparison to our method, the lactam **1ab** was synthesized according to a reported literature procedure[37] and then subjected to standard electrophilic fluorination conditions to access the corresponding *α*-fluoro-*γ*-lactam (Scheme 3). The crude reaction mixture contained both *α*-fluoro-*γ*-lactam **2ab** and *α*,*α*-difluoro-*γ*-lactam **3ab** in low yields and without stereocontrol for the former, underscoring the limitations of the conventional electrophilic fluorination protocols, such as poor efficiency, stereoselectivity, and propensity for over-fluorination.




**Scheme 3.** Comparison with Electrophilic Fluorination Conditions. [a]Conversion and yields acquired by $^1H$ and $^{19}F$ NMR spectroscopy.

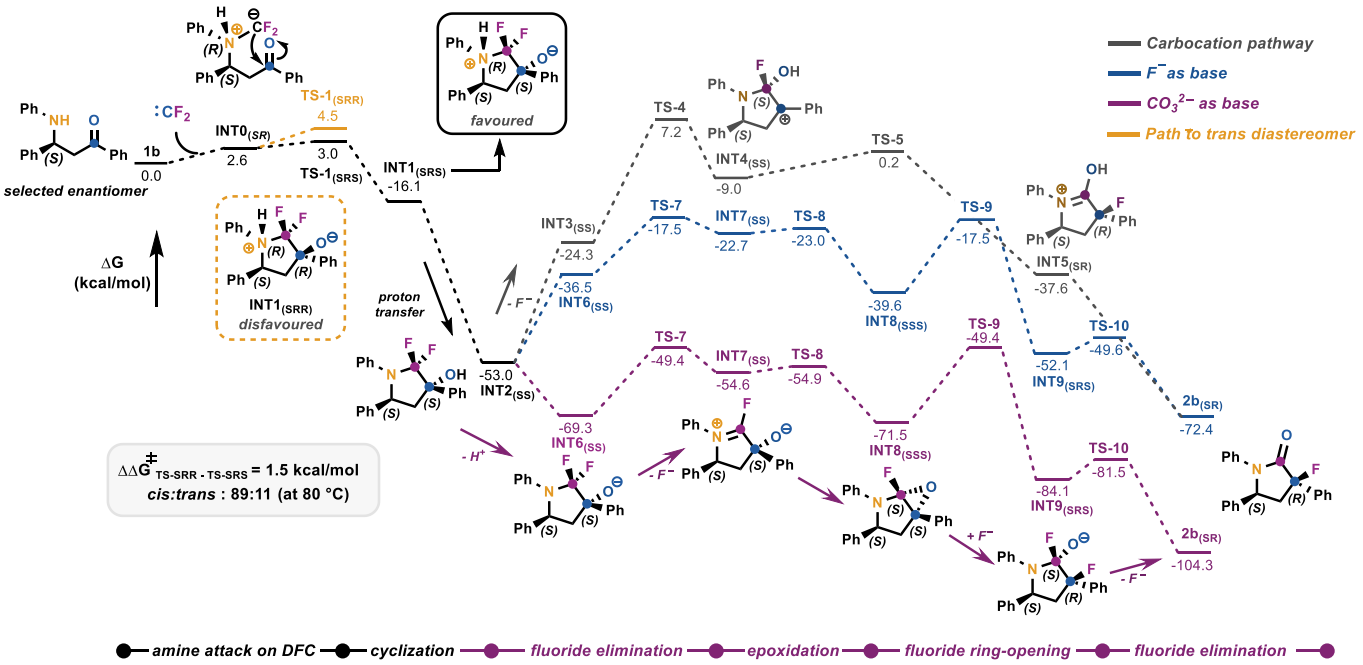
Having established the feasibility of our method, we proceeded to explore the scope of this reaction (Scheme 4). Changes to the substituents on the aryl amine did not drastically impact the yields nor diastereoselectivities (**2b, 2c, 2d, 2f**), with the exception of the low-yielding *p*-Br derivative (**2e**). Slightly improved reactivity was observed for other halogenated compounds (**2p**, **2q**), though the yields remained modest even with more forcing conditions. Notably, the diastereoselectivity remained roughly the same with substrate **2s** bearing a sterically hindered aryl ring (87:13) at the $R^3$ position. Attempts to introduce stronger electron-withdrawing groups (e.g., *p*-CN, *p*-$NO_2$ or *p*-$CF_3$) on either the aniline ring ($R^1$) or aryl ketone ($R^3$) were unsuccessful, as these starting materials underwent facile retro-aza-Michael addition to the corresponding chalcone and aniline (see SI for a full list of incompatible or low-yielding substrates). With such substrates, this decomposition pathway seems to be more accessible, likely due to the increased acidity of *α*-protons, which can initiate a base-mediated elimination reaction (*vide infra*). In contrast, *β*-aminoketone bearing a *p*-$NO_2$ aryl substituent at the $R^2$ position reacted smoothly under the conditions to yield **2h**. In general, aryl methoxy ethers were well tolerated (**2g, 2o, 2r**) at various positions. Whereas incorporation of π-extended rings (**2i, 2k**) did not largely impact the reactivity or stereoselectivity, thiophenyl (**2j**) and ester-containing (**2n**) substrates were formed with lower diastereoselectivities. Nevertheless, the excellent reactivity of **1n** effectively illustrates that the *β*-substituent is not limited to aromatic groups. Remarkably, even simple alkyl groups at this position, such as methyl (**2l**) and *tert*-butyl (**2m**), did not impact the reaction efficiency, and in fact, even higher diastereoselectivities were observed. Notably, γ-lactam **2m** was formed as a single diastereomer (99:1 d.r.), underscoring the importance of steric bulk at the *β*-position in steering the diastereoselectivity of the transformation. Unfortunately, introducing alkyl substituents at the amine $R^1$ site, such as benzyl, or a methyl group at the $R^3$ position, resulted in diminished reactivity (see SI). Finally, the protocol was amenable to the gram-scale synthesis of *γ*-lactam **2d**, providing the product in comparable yield (72% vs 80%) with the same stereoselectivity (94:6 d.r.).




**Scheme 4.** Substrate Scope for the Synthesis of *α*-Fluoro-*γ*-Lactams.

To explore the reaction mechanism and origin of selectivity, we turned to DFT calculations at the M06-2X/aug-cc-pVTZ/SMD(MeCN) level of theory (see SI for full computational details). We used substrate **1b**$_{(S)}$ for our computational model and explored its reactivity with free DFC (Scheme 5). Addition of the amine on DFC to form ylide **INT0**$_{(SR)}$ is barrierless, from which two cyclizations on the ketone carbonyl are possible. Of those, transition structure **TS-1**$_{(SRS)}$ has a minuscule free energy barrier of 3.0 kcal/mol, while diastereomeric **TS-1**$_{(SRR)}$ is 1.5 kcal/mol higher in free energy. The corresponding zwitterions **INT1** are short-lived, as the formation of the neutral amino-alcohols **INT2** is exergonic by 53.0 kcal/mol for **INT2**$_{(SS)}$ and -49.9 kcal/mol for **INT2**$_{(SR)}$ (see SI) compared to the reactants, and as such, irreversible. From the ylide **INT0**, intramolecular deprotonation α to the carbonyl by the difluoromethyl anion is also possible, initiating decomposition to the corresponding chalcone and difluoromethylaniline via concerted elimination process. While this pathway is likely more accessible for substrates bearing electron-withdrawing groups at either $R^1$ and $R^3$, the activation barrier for this proton exchange for electronically neutral **1b** was calculated to be 17.8 kcal/mol—significantly higher than the corresponding cyclization step and thus unfavourable (Figure S3).

From **INT2**$_{(SS)}$, fluoride elimination would lead to iminium ion **INT3**$_{(SS)}$ (Scheme 5, *grey pathway*), which could undergo a sequence of hydroxide and fluoride shifts to form **INT5**$_{(SR)}$ and then the lactam product upon deprotonation. However, this pathway requires crossing a free energy barrier of 60.2 kcal/mol, from **INT2**$_{(SS)}$ to **TS-4**, and is thus impossible even at 80 °C. Instead, a base-mediated pathway appears more likely. Assuming carbonate as base (*purple pathway*), alcohol **INT2**$_{(SS)}$ can form alkoxide **INT6**$_{(SS)}$, from which fluoride elimination leads to zwitterion **INT7**$_{(SS)}$ that can quickly cyclize to fluorinated hemiaminal epoxide **INT8**$_{(SSS)}$. Attempts to locate direct nucleophilic displacement of a fluoride from **INT6**$_{(SS)}$ were unsuccessful but this pathway would lead to the same diastereomer of **INT8**$_{(SSS)}$. Epoxide ring-opening of **INT8**$_{(SSS)}$ by a fluoride ion leads to the rearranged **INT9**$_{(SRS)}$ via stereoinversion, from which a subsequent fluoride elimination leads to the observed **2b**$_{(SR)}$-product. In this base-promoted pathway, the largest barriers are 19.9 kcal/mol (from **INT6**$_{(SS)}$) and 22.1 kcal/mol (from **INT8**$_{(SSS)}$), fully accessible at the reaction temperature.




**Scheme 5.** DFT Calculations: Potential Energy Surface for the Proposed Mechanism.

Of note, our proposed base-promoted pathway would proceed through the same intermediates by using any ejected fluoride anion as base (*blue pathway*). However, its poorer basicity leads to higher barriers relative to **INT2$_{(SS)}$**, making product formation difficult. These computational data offer an explanation as to why carbonate bases are required in this reaction; not only do they enable DFC formation from EBDFA, but they are also needed to promote the rearrangement from amino-alcohol **INT2**$_{(SS)}$ to the lactam product. As the carbonate-promoted pathway is faster than the cationic pathway and proceeds through stereospecific rearrangements, the final stereochemistry of the products is kinetically controlled in the initial cyclization step (see Figure S2 for the other diastereomeric pathways). The transition state **TS-1$_{(SRS)}$**, which eventually leads to the *cis*-**2b$_{(SR)}$**-product, is favored by 1.5 kcal/mol. At 80 °C, this free energy difference is predicted to lead to an 89:11 selectivity in favor of the *cis* product, which is in excellent agreement with the experimental results. Geometric analysis of **TS$_{(SRS)}$** reveals that cyclization occurs through a near-perfect envelope conformation, with all aromatic substituents in pseudo-equatorial positions and low strain around the site of nucleophilic attack (∠NCC = 96.9° and ∠CCO = 101.9°, Figure S4), while the minor **TS-1$_{(SRR)}$** displays an internal N–H···O=C hydrogen bond that distorts the 5-membered ring for attack (∠NCC = 82.4° and ∠CCO = 98.9°).

In conclusion, we have disclosed an efficient diastereoselective route to *α*-fluoro-*γ*-lactams through DFC-mediated cyclization and rearrangement. The method accommodates a wide range of *β*-amino ketones with diverse steric and electronic profiles, and relies on a readily available DFC source, making it particularly amenable to industrial applications. Overall, this work represents the first demonstration that these pharmaceutically relevant *cis*-*α*-fluoro-*γ*-lactam motifs can be accessed without using the harsh and multi-step protocols that have dominated prior syntheses.

## Supporting Information

The authors have cited additional references within the Supporting Information.

## Acknowledgements

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**Keywords:** lactam • fluorine • diastereoselectivity • difluorocarbene

[1] B. M. Johnson, Y.-Z. Shu, X. Zhuo, N. A. Meanwell, "Metabolic and Pharmaceutical Aspects of Fluorinated Compounds" *J. Med. Chem.* **2020**, *63*, 6315–6386.

[2] M. Shimizu, T. Hiyama, "Modern Synthetic Methods for Fluorine-Substituted Target Molecules" *Angew. Chem. Int. Ed.* **2005**, *44*, 214–231.

[3] J. Caruano, G. G. Muccioli, R. Robiette, "Biologically active γ-lactams: synthesis and natural sources" *Org. Biomol. Chem.* **2016**, *14*, 10134–10156.

[4] X. Wang, J. Lei, G. Li, J. Meng, C. Li, J. Li, K. Sun, "Synthetic methods for compounds containing fluoro-lactam units" *Org. Biomol. Chem.* **2020**, *18*, 9762–9774.

[5] Q. Liu, D. G. Batt, C. A. Weigelt, S. Yip, D.-R. Wu, M. Ruzanov, J. S. Sack, J. Wang, M. Yarde, S. Li, D. J. Shuster, J. H. Xie, T. Sherry, M. T. Obermeier, A. Fura, K. Stefanski, G. Cornelius, P. Khandelwal, J. A. Tino, J. E. Macor, L. Salter-Cid, R. Denton, Q. Zhao, T. G. M. Dhar, "Novel Tricyclic Pyroglutamide Derivatives as Potent RORγt Inverse Agonists Identified using a Virtual Screening Approach" *ACS Med. Chem. Lett.* **2020**, *11*, 2510–2518.

[6] K. L. Lee, C. M. Ambler, D. R. Anderson, B. P. Boscoe, A. G. Bree, J. I. Brodfuehrer, J. S. Chang, C. Choi, S. Chung, K. J. Curran, J. E. Day, C. M. Dehnhardt, K. Dower, S. E. Drozda, R. K. Frisbie, L. K. Gavrin, J. A. Goldberg, S. Han, M. Hegen, D. Hepworth, H. R. Hope, S. Kamtekar, I. C. Kilty, A. Lee, L.-L. Lin, F. E. Lovering, M. D. Lowe, J. P. Mathias, H. M. Morgan, E. A. Murphy, N. Papaioannou, A. Patny, B. S. Pierce, V. R. Rao, E. Saiah, I. J. Samardjiev, B. M. Samas, M. W. H. Shen, J. H. Shin, H. H. Soutter, J. W. Strohbach, P. T. Symanowicz, J. R. Thomason, J. D. Trzupek, R. Vargas, F. Vincent, J. Yan, C. W. Zapf, S. W. Wright, "Discovery of Clinical Candidate 1-{[(2*S*,3*S*,4*S*)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide (PF-06650833), a Potent, Selective Inhibitor of Interleukin-1 Receptor Associated Kinase 4 (IRAK4), by Fragment-Based Drug Design" *J. Med. Chem.* **2017**, *60*, 5521–5542.

[7] S. Rakshit, S. Sathasivam, R. Reddy, S. V. Rao, V. Shekarappa, M. Kandasamy, M. Jaleel, S. Murugan, A. Bhat, T. Subramani, T. Lakshminarasimhan, A. Gangu, S. R. Wisniewski, N. Kopp, I. Hale, J. M. Stevens, V. W. Rosso, M. D. Eastgate, R. Vaidyanathan, "Alternative Approach to the Large-Scale Synthesis of the Densely Functionalized Pyrrolidone BMT-415200" *Org. Process Res. Dev.* **2023**, *27*, 707–722.

[8] S. W. Wright, K. A. Farley, S. Han, J. D. Knafels, K. L. Lee, "In Retrospect: Root-Cause Analysis of Structure–Activity Relationships in IRAK4 Inhibitor Zimlovisertib (PF-06650833)" *ACS Med. Chem. Lett.* **2024**, *15*, 540–545.

[9] Z. Chen, H. Yang, Y. Zhang, X. Lyu, Q. Shi, C. Zhang, X. Wang, Z. Wang, Y. Zhang, Y. Deng, Y. Wang, Y. Huang, Y. Xu, X. Huang, Y. Li, "Discovery of CZL-046 with an (*S*)-3-Fluoropyrrolidin-2-one Scaffold as a p300 Bromodomain Inhibitor for the Treatment of Multiple Myeloma" *J. Med. Chem.* **2024**, *67*, 18606–18628.

[10] M. P. Doyle, W. Hu, I. M. Phillips, C. J. Moody, A. G. Pepper, A. M. Z. Slawin, "Reactivity Enhancement for Chiral Dirhodium(II) Tetrakis(carboxamidates)" *Adv. Synth. Catal.* **2001**, *343*, 112–117.

[11] D. A. DiRocco, E. L. Noey, K. N. Houk, T. Rovis, "Catalytic Asymmetric Intermolecular Stetter Reactions of Enolizable Aldehydes with Nitrostyrenes: Computational Study Provides Insight into the Success of the Catalyst" *Angew. Chem. Int. Ed.* **2012**, *51*, 2391–2394.

[12] B. Li, S. M. Guinness, S. Hoagland, M. Fichtner, H. Kim, S. Li, R. J. Maguire, J. C. McWilliams, J. Mustakis, J. Raggon, D. Campos, Chris. R. Voss, E. Sohodski, B. Feyock, H. Murnen, M. Gonzalez, M. Johnson, J. Lu, X. Feng, X. Sun, S. Zheng, B. Wu, "Continuous Production of Anhydrous *tert*-Butyl Hydroperoxide in Nonane Using Membrane Pervaporation and Its Application in Flow Oxidation of a γ-Butyrolactam" *Org. Process Res. Dev.* **2018**, *22*, 707–720.

[13] S. D. Taylor, C. C. Kotoris, G. Hum, "Recent advances in electrophilic fluorination" *Tetrahedron* **1999**, *55*, 12431–12477.

[14] S. W. Wright, B. Li, Z. Peng, L. Wei, E. McInturff, D. Place, D. B. Damon, R. A. Singer, "Improvements to Enable the Large Scale Synthesis of 1-{[(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide (PF-06650833)" *Org. Process Res. Dev.* **2018**, *22*, 1835–1845.

[15] E. J. Itumoh, S. Data, J. L.-Y. Chen, M. Kah, L. P. Padhye, E. M. Leitao, "Addressing the persistence of per- and poly-fluoroalkyl substances (PFAS): current challenges and potential solutions" *RSC Sustainability* **2024**, *2*, 3183–3201.

[16] N. D. Tyrrell, "A Proposal That Would Ban Manufacture, Supply, and Use of All Fluoropolymers and Most Fluorinated Reagents within the Entire EU" *Org. Process Res. Dev.* **2023**, *27*, 1422–1426.

[17] M. K. Nielsen, C. R. Ugaz, W. Li, A. G. Doyle, "PyFluor: A Low-Cost, Stable, and Selective Deoxyfluorination Reagent" *J. Am. Chem. Soc.* **2015**, *137*, 9571–9574.

[18] B. Sun, X. Zhuang, J. Yin, K. Zhang, H. Zhao, C. Jin, "Photoredox-Catalyzed Tandem Radical Cyclization/Hydroxylation for the Synthesis of 4-Hydroxyalkyl-3,3-difluoro-γ-lactams" *J. Org. Chem.* **2022**, *87*, 14177–14185.

[19] M. Zhang, W. Li, Y. Duan, P. Xu, S. Zhang, C. Zhu, "Cascade Photoredox/Iodide Catalysis: Access to Difluoro-γ-lactams via Aminodifluoroalkylation of Alkenes" *Org. Lett.* **2016**, *18*, 3266–3269.

[20] Y. Lv, W. Pu, Q. Wang, Q. Chen, J. Niu, Q. Zhang, “Copper-Catalyzed Aminodifluoroalkylation of Alkenes with α-Bromodifluoroacetamides: Synthesis of 3,3-Difluoropyrrolidin-2-ones” *Adv. Synth. Catal.* **2017**, *359*, 3114–3119.

[21] Y. Yang, J. Shi, C. Liu, Q. Liu, J. Yang, X. Tong, J. Lu, J. Wu, “Engineered Polymeric Carbon Nitride for Photocatalytic Diverse Functionalization of Electronic-Rich Alkenes” *Angew. Chem. Int. Ed.* **2025**, *64*, e202417099.

[22] L.-X. Li, C.-R. Li, X. Guo, Z. Zhang, “Photoredox/Copper-Catalyzed One-Pot Aminoalkylation/Cyclization of Alkenes with Primary Amines to Synthesize Polysubstituted γ-Lactams” *Org. Lett.* **2024**, *26*, 845–849.

[23] R. Giri, I. Mosiagin, I. Franzoni, N. Y. Nötel, S. Patra, D. Katayev, “Photoredox Activation of Anhydrides for the Solvent-Controlled Switchable Synthesis of *gem*-Difluoro Compounds” *Angew. Chem. Int. Ed.* **2022**, *61*, e202209143.

[24] F. Zhu, Z. Li, X.-F. Wu, “Nickel-Catalyzed Aminofluoroalkylative Cyclization of Styrenes with Ethyl Fluoroacetate and Anilines toward Fluoro-γ-Lactams” *Org. Lett.* **2023**, *25*, 8535–8539.

[25] D. Cadwallader, T. R. Tiburcio, G. A. Cieszynski, C. M. Le, “Synthesis of Carbamoyl Fluorides Using a Difluorophosgene Surrogate Derived from Difluorocarbene and Pyridine *N*-Oxides” *J. Org. Chem.* **2022**, *87*, 11457–11468.

[26] C. H. Ni Jinbo, “Recent Advances in the Synthetic Application of Difluorocarbene” *Synthesis* **2014**, *46*, 842–863.

[27] K. Fuchibe, J. Ichikawa, “Generation of difluorocarbenes and introduction of fluorinated one carbon units into carbonyl and related compounds” *Chem. Commun.* **2023**, *59*, 2532–2540.

[28] X. Ma, J. Su, Q. Song, “Unconventional Transformations of Difluorocarbene with Amines and Ethers” *Acc. Chem. Res.* **2023**, *56*, 592–607.

[29] Y. Li, J. Luo, Y. Jiang, “C–F bond functionalizations *via* fluorinated carbenes” *Org. Chem. Front.* **2023**, *10*, 5782–5804.

[30] A. D. Dilman, V. V. Levin, “Difluorocarbene as a Building Block for Consecutive Bond-Forming Reactions” *Acc. Chem. Res.* **2018**, *51*, 1272–1280.

[31] A. Liu, C. Ni, Q. Xie, J. Hu, “$TMSCF_2Br$ - Enabled Fluorination–Aminocarbonylation of Aldehydes: Modular Access to α-Fluoroamides” *Angew. Chem. Int. Ed.* **2022**, *61*, e202115467.

[32] G. Zhang, Q. Shi, M. Hou, K. Yang, S. Wang, S. Wang, W. Li, C. Li, J. Qiu, H. Xu, L. Zhou, C. Wang, S.-J. Li, Y. Lan, Q. Song, “Atom Recombination of Difluorocarbene Enables 3-Fluorinated Oxindoles from 2-Aminoarylketones” *CCS Chem.* **2022**, *4*, 1671–1679.

[33] Y. H. Lin Lei; Junhua, Zou; Xiujuan, Xu, “The Mannich Reaction Between Aromatic Ketones, Aromatic Aldehydes and Aromatic Amines” *Synthesis* **2002**, *1991*, 717–718.

[34] Y. Wu, X. Wang, Y. Luo, J. Wang, Y. Jian, H. Sun, G. Zhang, W. Zhang, Z. Gao, “Solvent strategy for unleashing the Lewis acidity of titanocene dichloride for rapid Mannich reactions” *RSC Adv.* **2016**, *6*, 15298–15303.

[35] H.-M. Yang, L. Li, F. Li, K.-Z. Jiang, J.-Y. Shang, G.-Q. Lai, L.-W. Xu, “Silicon-Based Lewis Acid Assisted Cinchona Alkaloid Catalysis: Highly Enantioselective Aza-Michael Reaction under Solvent-Free Conditions” *Org. Lett.* **2011**, *13*, 6508–6511.

[36] A. E. Goetz, H. Becirovic, F. Blasberg, B. Chen, H. J. Clarke, M. Colombo, P. Daddario, D. B. Damon, C. Depretz, Y. R. Dumond, M. D. Grilli, L. Han, T. L. Houck, A. M. Johnson, K. N. Jones, J. Jung, M. Leeman, F. Liu, C. V. Lu, E. J. Mangual, J. D. Nelson, A. L. A. Puchlopek-Dermenci, S. G. Ruggeri, P. A. Simonds, B. Sitter, D. E. Virtue, S. Wang, L. Yu, T. Yu, “Large-Scale Cyclopropanation of Butyl Acrylate with Difluorocarbene and Classical Resolution of a Key Fluorinated Building Block” *Org. Process Res. Dev.* **2022**, *26*, 683–697.

[37] C. Yeh, R. Prasad Korivi, C. Cheng, “Regioselective Synthesis of γ-Amino Esters, Nitriles, Sulfones, and Pyrrolidinones by Nickel-Catalyzed Reductive Coupling of Aldimines and Activated Alkenes” *Angew. Chem. Int. Ed.* **2008**, *47*, 4892–4895.