



HAL
open science

Electrophilic Fluorination of Silyl Dienol Ethers: a General and Selective Access to γ -Fluoro Enals

Yang Li, Marina Briand, Karinne Miqueu, Elsa Anselmi, Emmanuel Magnier, Guillaume Dagousset

► **To cite this version:**

Yang Li, Marina Briand, Karinne Miqueu, Elsa Anselmi, Emmanuel Magnier, et al.. Electrophilic Fluorination of Silyl Dienol Ethers: a General and Selective Access to γ -Fluoro Enals. Chemistry - A European Journal, 2024, 30 (10), pp.e202303545. 10.1002/chem.202303545 . hal-04404468

HAL Id: hal-04404468

<https://hal.science/hal-04404468v1>

Submitted on 11 Mar 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Electrophilic Fluorination of Silyl Dienol Ethers: a General and Selective Access to γ -Fluoro Enals

Yang Li,^[a] Marina Briand,^[a] Karinne Miqueu,^[b] Elsa Anselmi,^[a, c] Emmanuel Magnier,^{*[a]} and Guillaume Dagousset^{*[a]}

We describe the direct synthesis of γ -fluoro enals from the corresponding silyl dienol ethers. This simple process operates under mild conditions and is compatible with a wide range of

functionalities. The high γ regioselectivity of this protocol was rationalized by means of theoretical calculations.

Introduction

α,β -Unsaturated aldehydes play a central role in organic synthesis due to their peculiar structure, one C=O double bond conjugated with one C=C double bond, which offers many possible reactivities such as 1,2-addition to C=O bond, 1,4-Michael addition, hetero-Diels–Alder reaction, and Morita–Baylis–Hillman reaction, among others.^[1] Consequently, they constitute key building blocks in organic chemistry, and have been extensively employed in many synthetic methodologies, ranging from the synthesis of heterocycles to the total synthesis of alkaloids.^[1] In addition, in the case of γ -enolizable enals, another interesting possibility lies in their remote γ functionalization, which generally proceeds *via* the formation of a nucleophilic dienolate equivalent (metal dienolate, silyl dienol ether, dienamine). An early example of such reactivity is the well-known vinylogous Mukaiyama aldol reaction, in which a preformed silyl dienol ether adds onto an aldehyde or one of its surrogate (imine, acetal).^[2] More recently, the emergence of dienamine catalysis has had a strong impact in this area.^[3] However, dienamine-catalyzed protocols for the γ functionalization of enals still suffer from two main drawbacks: i) The first issue is the α/γ regioselectivity. Indeed, the dienamine has two

nucleophilic carbon centers in α and γ positions which can both react with the electrophilic partner. While α -hindered enals generally give the desired γ -functionalized product,^[4] α -unbranched enals may lead to unwanted α -selective functionalization.^[5] ii) Second, in spite of some recent progress,^[6] the reaction scope is still limited to specific electrophilic partners.

Such statement can be applied to the field of fluorine chemistry: *to the best of our knowledge, the remote γ fluorination of enals is completely unknown to date.* So far, the reactivity of dienolate equivalents towards electrophilic fluorinating reagents has been described in only two reports, with full α -selectivity: i) In 2012, Lin and Sun showed that γ -prefunctionalized enals led to α -fluorinated compounds under NHC catalysis (Scheme 1a),^[7] ii) In 2016, Arimitsu studied the fluorination of enals under dienamine catalysis, which gave access to α,α -difluorinated β,γ -unsaturated aldehydes (Scheme 1b).^[8] However, no γ -fluorination was mentioned in these works.

Given the importance of organofluorine chemistry and the increasing number of fluorine-containing products both in the pharmaceutical and agrochemical industries,^[9] an efficient access to γ -fluorinated enals would be a key asset for future developments in these areas. We wish to report herein the synthesis of a wide variety of γ -fluoro enals, which operates with full regioselectivity in favor of the γ position (Scheme 1c).

[a] Y. Li, Dr. M. Briand, Dr. E. Anselmi, Dr. E. Magnier, Dr. G. Dagousset
Université Paris-Saclay, UVSQ, CNRS, UMR 8180
Institut Lavoisier de Versailles, 45 avenue des Etats-Unis, 78000 Versailles,
France
E-mail: emmanuel.magnier@uvsq.fr
guillaume.dagousset@uvsq.fr

[b] Dr. K. Miqueu
CNRS/Université de Pau et des Pays de l'Adour, E2S-UPPA
Institut des Sciences Analytiques et de Physico-Chimie pour l'Environnement
et les Matériaux (IPREM UMR 5254)
Hélioparc, 2 Avenue du Président Angot, 64053 Pau Cedex 09, France

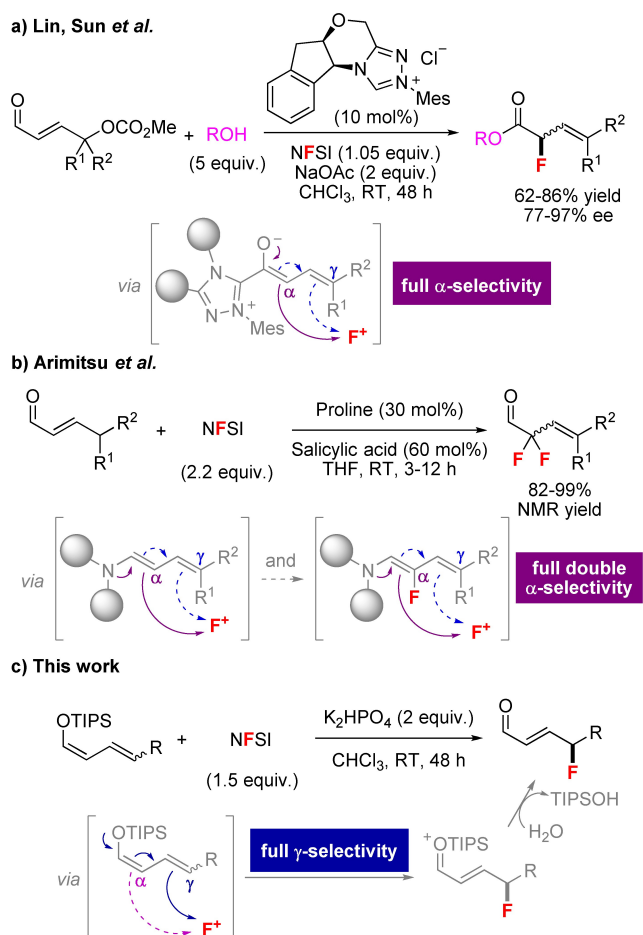
[c] Dr. E. Anselmi
Université de Tours, Faculté des Sciences et Techniques, 37200 Tours, France

Supporting information for this article is available on the WWW under
<https://doi.org/10.1002/chem.202303545>

© 2023 The Authors. Chemistry - A European Journal published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Results and Discussion

Based on the general γ -selectivity observed in vinylogous Mukaiyama aldol reactions for carbon-carbon bond formation, we thought that the same regioselectivity would be obtained for carbon-fluorine bond formation. Therefore, we started our investigations by studying the reactivity of silyl dienol ethers **1** towards electrophilic sources of fluorine. Substrate **1a** derived from (*E*)-dodecenal was chosen as model substrate. As shown in Table 1, we were pleased to see that **1a** reacted smoothly in the presence of NFSI **2a** (N-fluorobenzenesulfonimide) and K_2CO_3 in acetonitrile, giving the desired γ -fluorinated enal **3a** in 48% NMR yield (entry 1). Importantly, only one signal could be detected in ^{19}F NMR of the crude mixture, which demonstrated the full selectivity of the process in favor of the γ -regioisomer,

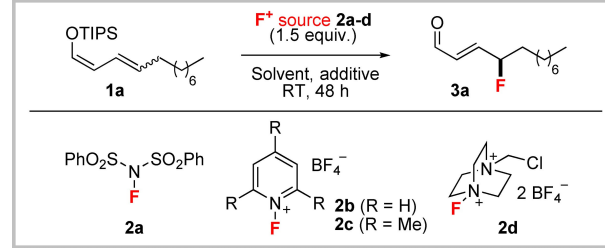


Scheme 1. Fluorination of dienolate equivalents. NFSI = *N*-fluorobenzenesulfonamide.

without any trace of formation of the α -adduct. Testing other solvents revealed that the reaction proceeded best in chloroform (entries 2–6). The base was also found to have a strong influence in the reaction efficiency (entries 7–11), probably by preventing hydrolysis of **1a** into (*E*)-dodecenal. In its absence, the yield dropped to 30%. While organic bases showed low efficiency, inorganic salts were highly beneficial to the reaction, K_2HPO_4 being the optimal base (57%, entry 8). Other electrophilic sources of fluorine, such as *N*-fluoropyridinium salts **2b–c** and Selectfluor™ **2d** were tested but were either inefficient (**2b–c**, entry 12) or provided only poor yield of product **3a** (30%, entry 13). Finally, the best reaction conditions were found by carrying out the reaction at a 0.1 M concentration, affording **3a** in 65% yield (entry 14). Trying to decrease the reaction time under either traditional heating or microwave irradiation was possible, but did not result in an increase in overall efficiency (entries 15–16).

Having established the optimized conditions, we then decided to examine the scope and limitations of this protocol. As illustrated in Scheme 2, a wide range of γ -fluoro enals **3a–3q** could be efficiently prepared in good yields (44–79% ^{19}F NMR yield). The main issue encountered during this study was the volatility of some fluorinated enals. Notably, products

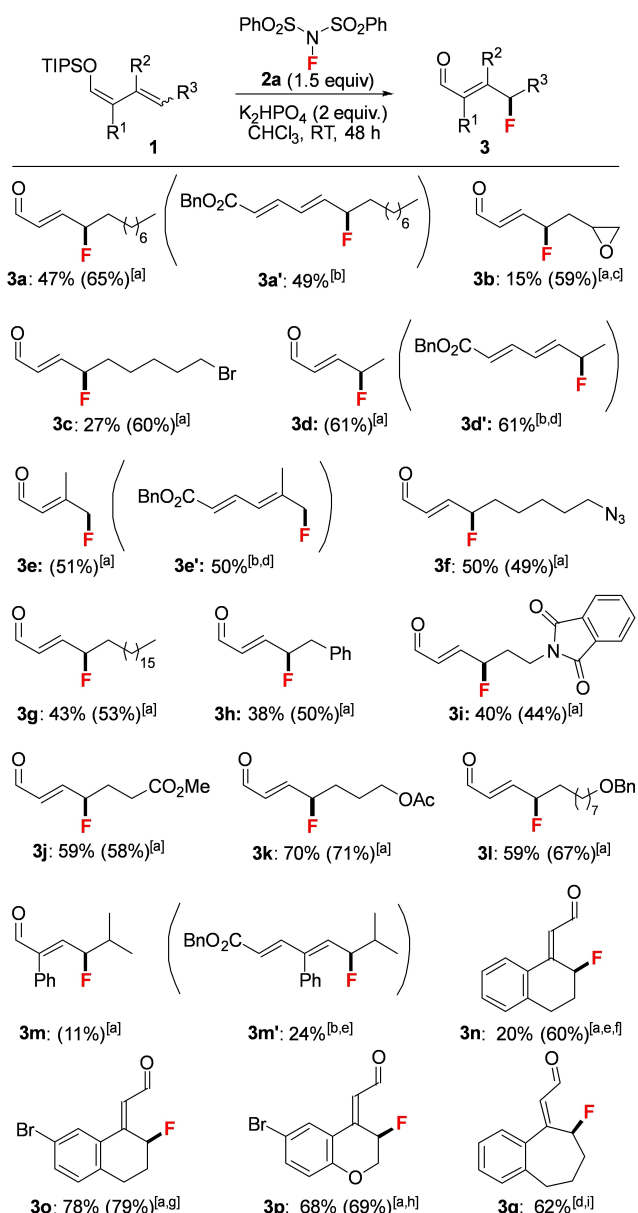
Table 1. Optimization studies for the γ -fluorination of dienol silyl ether **1a**.



Entry	F ⁺ source	Solvent	Additive	Yield (%) ^[a,b]
1	2a	MeCN	K_2CO_3	48
2	2a	Acetone	K_2CO_3	35
3	2a	DMF	K_2CO_3	0
4	2a	Toluene	K_2CO_3	13
5	2a	CH_2Cl_2	K_2CO_3	53
6	2a	$CHCl_3$	K_2CO_3	57
7	2a	$CHCl_3$	$NaHCO_3$	52
8	2a	$CHCl_3$	K_2HPO_4	58
9	2a	$CHCl_3$	Pyridine	38
10	2a	$CHCl_3$	Et_3N	21
11	2a	$CHCl_3$	none	30
12	2b–c	$CHCl_3$	K_2HPO_4	< 5
13	2d	MeCN	K_2HPO_4	30
14 ^[c]	2a	$CHCl_3$	K_2HPO_4	65
15 ^[c,d]	2a	$CHCl_3$	K_2HPO_4	50
16 ^[c,e]	2a	$CHCl_3$	K_2HPO_4	57

[a] General conditions: **1a** (0.15 mmol), **2** (0.225 mmol), additive (0.3 mmol) in 3 mL of solvent at RT for 48 h. [b] Yields determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [c] Reaction performed in 1.5 mL of solvent. [d] Reaction performed at 50 °C. [e] Reaction performed at 80 °C for 30 min under microwave irradiation.

3a–3c could be synthesized and fully characterized, but were isolated in lower yields compared to the corresponding NMR yields due to their volatility. To circumvent this issue, compound **3a** was for example *in situ* post-functionalized via a Wittig reaction, affording the corresponding $\alpha,\beta,\gamma,\delta$ -unsaturated ester **3a'** with a higher efficiency. The same transformation was performed for fluorinated enals **3d–3e** which exhibit even higher volatility: in these cases, the related unsaturated esters **3d'–3e'** were isolated with good isolated yields over two steps, very close to those obtained in ^{19}F NMR for the first step.^[10] Remarkably, a wide range of functionalities (such as epoxyde, bromide, azide, phthalimide, ester, ether) were compatible with the mild reaction conditions, leading to the corresponding fluorinated enals in up to 67% yield, always with perfect γ regioselectivity. In previous reports on α -fluorination, α -substituted enals showed very poor reactivity (5% yield^[7]): in our case, we were therefore pleased to see that sterically hindered α -aryl enal **1m** was converted into product **3m'** in higher efficiency (24% yield over two steps). Similarly, β -functionalized substrates (**1e**, **1n–1q**) were also readily fluorinated in their γ position. Notably, 1-tetralone, 4-chromanone and 1-benzosu-



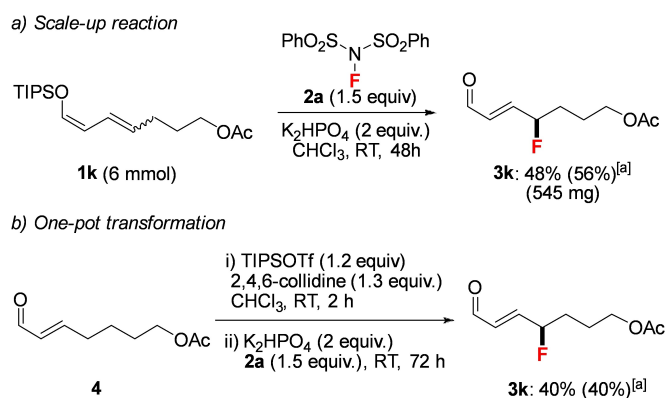
Scheme 2. Reaction scope for the γ -fluorination of enals. General conditions: **1** (0.15 mmol), **2** (0.225 mmol), K_2HPO_4 (0.3 mmol) in 1.5 mL of $CHCl_3$ at RT for 48 h. Unless otherwise noted, given yields refer to chromatography pure products. Unless otherwise noted, compounds **3** were isolated as a single *E* isomer. [a] Yields into brackets refer to ^{19}F NMR yield using $PhOCF_3$ as internal standard. [b] Overall isolated yield of the corresponding $\alpha,\beta,\gamma,\delta$ -unsaturated ester **3'** after Wittig reaction in the case of volatile compounds. See ESI for more details. [c] dr = 1.2:1. [d] TIPSOH was present in the isolated compound. See ESI for more details. [e] The product contains 15–20% of an inseparable impurity. [f] Z/E = 2:1. [g] Z/E = 4:1. [h] Z/E = 85:15. [i] Z/E = 9:1. dr = diastereomeric ratio.

berone derivatives are important bicyclic compounds which can show important biological and pharmaceutical activities and can act as interesting building blocks in medicinal chemistry, especially when combined with fluorine.^[11] We were therefore delighted to see that the corresponding γ -fluoro bicyclic products **3n–3q** were efficiently prepared in up to 79% yield.

In order to illustrate the applicability of the method, a scale-up experiment was performed using substrate **1k** under the

same reaction conditions, which delivered 545 mg of the corresponding fluorinated product **3k** (Scheme 3a). In addition, to demonstrate the synthetic utility of this new protocol and to avoid the purification of the silyl dienol ether intermediate **1**, a two-step, one-pot procedure was developed for the direct γ -fluorination of enals. Hence, (*E*)-7-oxohept-5-en-1-yl acetate **4** was directly transformed into γ -fluoro enal **3k** in a satisfactory yield of 40% over 2 steps (Scheme 3b). Even though the γ selectivity is generally accepted for silyl dienol ethers, no clear rationalization has been proposed so far, especially in the case of enal derivatives. As a matter of fact, the coefficients at the α - and γ -carbons of the HOMO (Highest Occupied Molecular Orbital) have been calculated, but only for ketone- or ester-derived silyl dienol ethers.^[2c] Concerning dienamines, Jørgensen *et al.* stated in their seminal work that their α - and γ -coefficients did not differ significantly, but no data have been provided.^[12]

In order to gain more insight into this difference in regioselectivity, we computed the HOMO of the dienamine **I** (from Hayashi-Jørgensen catalyst) and the silyl dienol ether **II** derived from the same enal substrate, (*E*)-pentenal, by using Density Functional Theory (DFT) at the B3LYP/6-31G** level.^[13] We analyzed the relative contributions of the main atoms in the HOMO, especially those of the α - and γ -carbons. As illustrated in Figure 1a, the difference in the HOMO coefficients for dienamine **I**-(*Z*) (kinetically preferred)^[14] or **I**-(*E*) (thermodynamically more stable) is small (in slight favor of C_α), and can only partly explain the preference for α -functionalization.^[15] By contrast, the contribution of the γ -carbon (~22.5%) is significantly higher than that at the α -carbon (~18.4%) for the silyl dienol ether **II**-(*Z*) or **II**-(*E*) (Figure 1b). This clear-cut difference (up to 4.5% in the case of *E* isomer) is in accordance with the γ functionalization observed for silyl dienol ethers of the present study. These results were confirmed by using local chemical reactivity descriptors (condensed f_k^- Fukui function, see ESI).^[13] For compound **II**, the most reactive nucleophilic site was found to be the γ carbon (f_k^- : 0.22 for C_γ vs. 0.12 for C_α), in agreement with experimental reactivity. For compound **I**, the γ and α carbons (f_k^- : 0.18 for C_γ vs. 0.16 for C_α) appeared both to be suitable nucleophilic reactive centers.



Scheme 3. Scale-up reaction and one-pot procedure directly from the enal substrate. [a] Yield refers to ^{19}F NMR yield using $PhOCF_3$ as internal standard.

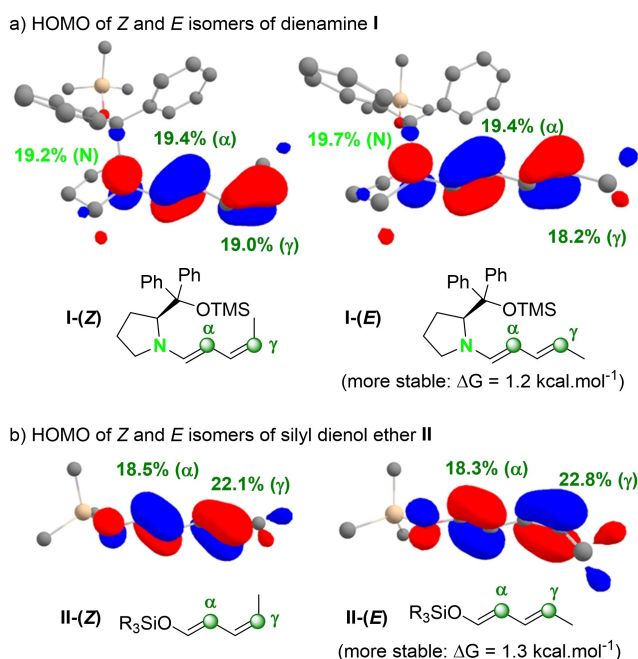


Figure 1. Plot of the HOMO (cutoff: 0.05) of the pentenal-derived dienamine I and the silyl dienol ether II. Contributions (in %) of the main atoms in the HOMO. Relative stability (ΔG in kcal.mol⁻¹) between Z and E isomers.

To support these theoretical results, we computed the energy profiles of the α - and γ -fluorinations of II-(E) and II-(Z) using NFSI as reagent (level of theory: SMD(CHCl₃)-B3LYP/6-31G**//B3LYP/6-31G**, see Figure 2). Consistent with the experimental data, the formation of the γ -fluorinated compounds were found kinetically favored (ΔG^\ddagger : 23.4 and 24.6 kcal.mol⁻¹ for E and Z-isomers respectively versus 26.1 and 27.1 kcal.mol⁻¹ for α -fluorination). The energy difference between the activation barriers of α - and γ -fluorinations ($\Delta\Delta G^\ddagger$: 2.5 to 2.7 kcal/mol) are perfectly consistent with full γ -regioselectivity. Moreover, the γ isomers are thermodynamically more stable than the α -

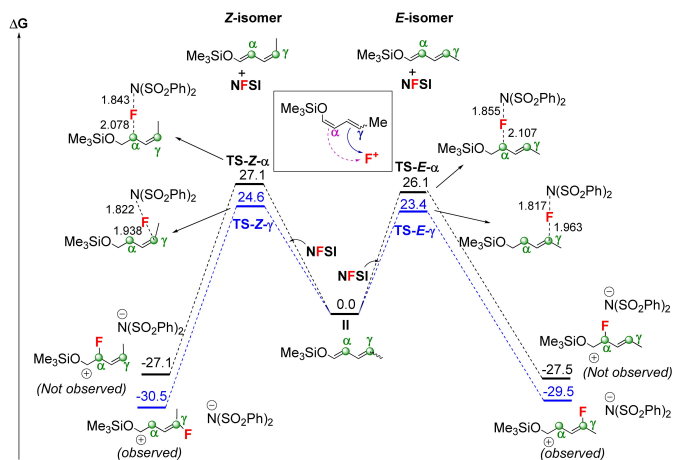


Figure 2. Reaction profiles of the fluorination using compound II and NFSI as model reaction. Attacks of F⁺ on C α (black line) at C γ (blue line) of II-(Z) and II-(E) computed at SMD(CHCl₃)-B3LYP/6-31G**//B3LYP/6-31G**. Free energy values (ΔG) are given in kcal.mol⁻¹. Main distances in Å.

isomers by 2 to 3.4 kcal.mol⁻¹. Analysis of the main geometrical features of the transition states indicates that TSs of the γ -fluorination (C...F~1.95 Å, N...F~1.82 Å) are later than those of α -fluorination (C...F~2.10 Å, N...F~1.85 Å), in line with the highest contribution of C γ in the HOMO of II.

Conclusions

In conclusion, a general and fully selective synthesis of γ -fluoro enals was successfully developed for the first time. The regioselectivity for the remote γ position was rationalized by computing condensed Fukui index f_k^- , by analyzing the contribution of C α /C γ atoms in the HOMO of the substrate and by computing the energy profiles of fluorination with NFSI. This new protocol operates under mild reactions conditions and is compatible with a variety of functional groups. Further developments in the introduction of other unknown moieties in the γ position of enals are currently underway and will be reported in due course.

Supporting information

The authors have cited additional references within the Supporting Information.^[16–24]

Experimental Section

Details about the characterization methods and computational details can be found in the Supporting Information.

Typical procedure for the synthesis of γ -fluoro enals: Silyl dienol ether 1 (0.15 mmol, 1 equiv.), K₂HPO₄ (0.3 mmol, 2 equiv.), NFSI 2a (0.225 mmol, 1.5 equiv.) and chloroform (1.5 mL, 0.1 M) were added in the described order in a haemolysis tube. The reaction mixture was agitated at RT for 48–72 hours. After TLC indicating a total conversion, the mixture was diluted in saturated NH₄Cl solution (10 mL) and extracted with DCM (10 mL*3). The combined organic layers were dried over anhydrous MgSO₄, concentrated under reduced pressure, then purified by flash chromatography or preparative TLC affording the desired product 3.

Acknowledgements

Y. L. thanks the LabEx Charmmmat for a Master grant and the CNRS for a PhD grant. M. B. thanks UVSQ and the French ministry of research for a PhD grant. The “Direction du Numérique” of the Université de Pau et des Pays de l’Adour and Mésocentre de Calcul Intensif Aquitain (MCIA) are acknowledged for the support of computational facilities. GIS Fluor is warmly acknowledged.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Fluorination · Enals · Regioselective · Remote functionalization · DFT calculations

- [1] Selected reviews: a) L. V. Reddy, V. Kumar, R. Sagar, A. K. Shaw, *Chem. Rev.* **2013**, *113*, 3605–3631; b) N. A. Keiko, N. V. Vchislo, *Asian J. Org. Chem.* **2016**, *5*, 439–461; c) N. A. Keiko, N. V. Vchislo, *Asian J. Org. Chem.* **2016**, *5*, 1169–1197; d) E. A. Verochkina, N. V. Vchislo, *ChemistrySelect* **2020**, *5*, 9579–9589; e) E. A. Verochkina, N. V. Vchislo, I. B. Rozentsveig, *Molecules* **2021**, *26*, 4297.
- [2] a) T. Mukaiyama, A. Ishida, *Chem. Lett.* **1975**, *4*, 319–322; Selected reviews: b) G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu, *Chem. Rev.* **2000**, *100*, 1929–1972; c) S. E. Denmark, J. R. Heemstra, Jr., G. L. Beutner, *Angew. Chem. Int. Ed.* **2005**, *44*, 4682–4698; d) M. Kalesse, M. Cordes, G. Symkenberg, H.-H. Lu, *Nat. Prod. Rep.* **2014**, *31*, 563–594; e) S. Hosokawa, *Tetrahedron Lett.* **2018**, *59*, 77–88.
- [3] Selected reviews: a) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, *2012*, 865–887; b) I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre, *Chem. Commun.* **2013**, *49*, 4869–4883; c) H. Jiang, L. Albrecht, K. A. Jørgensen, *Chem. Sci.* **2013**, *4*, 2287–2300; d) I. Kumar, P. Ramaraju, N. A. Mir, *Org. Biomol. Chem.* **2013**, *11*, 709–716; e) H. B. Hepburn, L. Dell'Amico, P. Melchiorre, *Chem. Rec.* **2016**, *16*, 1787–1806; f) V. Marcos, J. Alemán, *Chem. Soc. Rev.* **2016**, *45*, 6812–6832.
- [4] Selected examples: a) N. Bergonzini, S. Vera, P. Melchiorre, *Angew. Chem. Int. Ed.* **2010**, *49*, 9685–9688; b) C. Cassani, P. Melchiorre, *Org. Lett.* **2012**, *14*, 5590–5593; c) M. Silvi, C. Cassani, A. Moran, P. Melchiorre, *Helv. Chim. Acta* **2012**, *95*, 1985–2006.
- [5] Selected examples: a) N. Utsumi, H. Zhang, F. Tanaka, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2007**, *46*, 1878–1880; b) B. Han, Y.-C. Xiao, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2009**, *11*, 4660–4663; c) J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmman, M. Christmann, *Org. Lett.* **2011**, *13*, 70–73.
- [6] For recent progress involving the addition of electrophilic radicals, see: a) E. Arceo, I. D. Jurberg, A. A. Ivarez-Fernández, P. Melchiorre, *Nat. Chem.* **2013**, *5*, 750–756; b) M. Silvi, E. Arceo, I. D. Jurberg, C. Cassani, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 6120–6123; c) M. Balletti, E. Marcantonio, P. Melchiorre, *Chem. Commun.* **2022**, *58*, 6072–6075; d) K. F. Szabó, K. Goliszewska, J. Szurmak, K. Rybicka-Jasińska, D. Gryko, *Org. Lett.* **2022**, *24*, 8120–8124; e) M. Briand, L. D. Thai, F. Bourdreux, N. Vanthuyne, X. Moreau, E. Magnier, E. Anselmi, G. Dagousset, *Org. Lett.* **2022**, *24*, 9375–9380; f) C. Banoun, F. Bourdreux, G. Dagousset, *Chem. Commun.* **2023**, *59*, 760–763; g) M. Balletti, T. Wachsmuth, A. Di Sabato, W. C. Hartley, P. Melchiorre, *Chem. Sci.* **2023**, *14*, 4923–4927.
- [7] Y.-M. Zhao, M. S. Cheung, Z. Lin, J. Sun, *Angew. Chem. Int. Ed.* **2012**, *51*, 10359–10363.
- [8] S. Arimitsu, M. Nakasone, *J. Org. Chem.* **2016**, *81*, 6707–6713.
- [9] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; c) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518; d) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640; e) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467.
- [10] For a complementary deoxyfluorination approach for the synthesis of fluorinated $\alpha,\beta,\gamma,\delta$ -unsaturated ester, see a) D. M. Grée, C. J. M. Kermark, J. T. Martelli, R. L. Grée, J.-P. Lellouche, L. J. Toupet, *J. Org. Chem.* **1996**, *61*, 1918–1919; b) A. Boukerb, D. Grée, M. Laabassi, R. Grée, *J. Fluorine Chem.* **1998**, *88*, 23–27.
- [11] Selected examples: a) W. M. Welch, C. A. Harbert, R. Sarges, W. P. Stratten, A. Weissman, *J. Med. Chem.* **1977**, *20*, 699–705; b) T. A. Nakib, V. Bezjakl, M. J. Meeganz, R. Chandy, *Eur. J. Med. Chem.* **1990**, *25*, 455–462; c) J. R. Dimmock, M. P. Padmanilyam, G. A. Zello, J. W. Quail, E. O. Oloo, J. S. Prisciak, H. B. Kraatz, A. Cherkasov, J. S. Lee, T. M. Allen, C. L. Santos, E. K. Manavathu, E. De Clercq, J. Balzarini, J. P. Stables, *Eur. J. Med. Chem.* **2002**, *37*, 813–824; d) T. A. Farghaly, N. A. Abdel Hafez, E. A. Ragab, H. M. Awad, M. M. Abdalla, *Eur. J. Med. Chem.* **2010**, *45*, 492–500; e) A. S. Aboaraia, B. Makowski, A. Bahja, D. Prosser, A. Brancale, G. Jones, C. Simons, *Eur. J. Med. Chem.* **2010**, *45*, 4427–4434; f) S. Emami, Z. Ghanbarimasir, *Eur. J. Med. Chem.* **2015**, *93*, 539–563.
- [12] S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980.
- [13] See ESI for computational details.
- [14] A. Seegerer, J. Hioe, M. M. Hammer, F. Morana, P. J. W. Fuchs, R. M. Gschwind, *J. Am. Chem. Soc.* **2016**, *138*, 9864–9873.
- [15] A reappraisal of Arimitsu's work on dienamine-catalyzed fluorination of enals confirmed the observed α selectivity without any γ product. See ESI for more details.
- [16] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, *Gaussian 16, Revision C.01*, Gaussian, Inc., Wallingford CT, **2016**.
- [17] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.
- [18] Chemcraft – graphical software for visualization of quantum chemistry computations. <https://www.chemcraftprog.com>.
- [19] T. Lu, F. Chen, *J. Comput. Chem.* **2012**, *33*, 580–592.
- [20] a) K. Fukui, T. Yonezawa, H. Shingu, *J. Chem. Phys.* **1952**, *20*, 722–725; b) R. G. Parr, W. Yang, *J. Am. Chem. Soc.* **1984**, *106*, 4049–4050.
- [21] a) A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899–926; b) J. P. Foster, F. Weinhold, *J. Am. Chem. Soc.* **1980**, *102*, 7211–7218; c) A. E. Reed, F. Weinhold, *J. Chem. Phys.* **1985**, *83*, 1736–1740.
- [22] NBO 5.0 program: E. D. Glendening, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, J. A. Bohmann, C. M. Morales, F. Weinhold, Theoretical Chemistry Institute, University of Wisconsin, Madison, **2001**. Website: <https://nbo6.chem.wisc.edu/>
- [23] a) K. Fukui, *Acc. Chem. Res.* **1981**, *14*, 363–368; b) H. P. Hratchian, H. B. Schlegel, in *Theory and Applications of Computational Chemistry: The First 40 Years*, Ed. C. E. Dykstra, G. Frenking, K. S. Kim, G. Scuseria, Elsevier, Amsterdam, **2005**, 195.
- [24] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

Manuscript received: October 26, 2023

Accepted manuscript online: December 6, 2023

Version of record online: December 28, 2023