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Stereoselective Synthesis of Terminal Monofluoroalkenes from Trifluoromethylated Alkenes

Pauline Poutrel, Xavier Pannecoucke, Philippe Jubault,* and Thomas Poisson*

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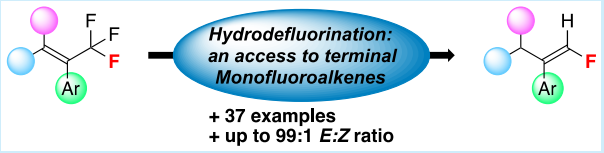
ABSTRACT: Herein we report the hydrodefluorination reaction of trifluoromethylated alkenes to access terminal monofluoroalkenes. The use of $LiAlH_4$ allowed the stereoselective synthesis of the terminal monofluoroalkenes in good to excellent yields with good to excellent diastereoselectivities. Mechanistic studies suggested a hydroalumination reaction followed by a stereoselective fluoride elimination.



Fluorine is one of the most intriguing atoms in the periodic table. The intrinsic properties of the fluorine atom such as its electronegativity and small radius, for instance, provide specific physicochemical properties to organofluorine compounds.[1] Its introduction on a molecule can drastically change the metabolic profile, the lipophilicity, the conformation, or the hydrogen-bonding ability of a neighboring functional group, for instance. These features readily explain its ubiquity in pharmaceuticals and agrochemicals as well as the broad portfolio of available fluorinated groups for the design of bioactive molecules in discovery programs.[2] As important fluorinated motifs, it is worth mentioning the CF_3, CF_2H, OCF_3, or the SCF_3 groups,[3] for example. Among these fluorinated groups, monofluoroalkenes are of high interest.[4] The α-substituted monofluoroalkene motif is well recognized as a bioisostere of the amide bond, whereas the terminal monofluoroalkene motif is considered as a mimic of an enol.[2e,5]

It is noteworthy that these terminal monofluoroalkenes are found in a significant number of bioactive compounds, and the stereoisomers often have different bioactivities (Figure 1).[6]

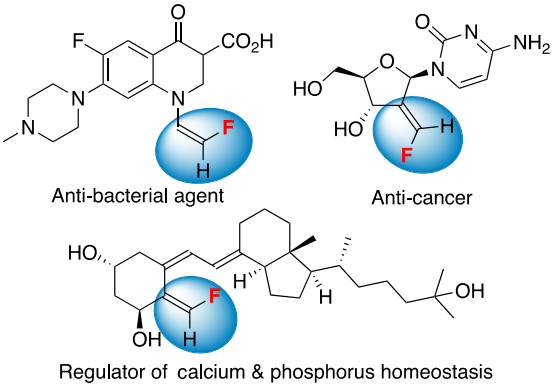


Figure 1. Bioactive molecules with terminal fluoroalkenes.

Therefore, the development of straightforward methods to access terminal monofluoroalkenes in a stereoselective manner has attracted much interest (Figure 2).[4] Among the reported

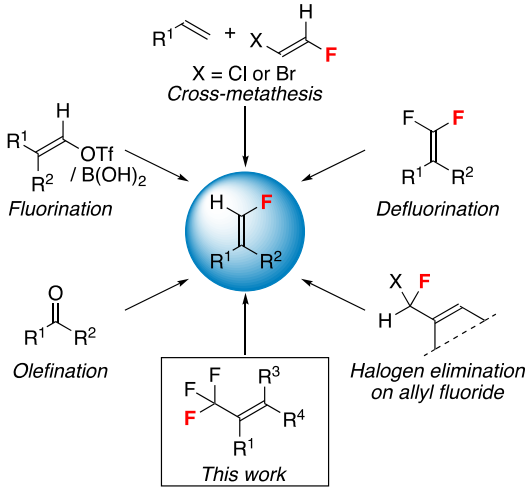


Figure 2. State of the art and present strategy.

methods to access this important motif, the olefination of carbonyl derivatives is probably the most popular one, even though it often suffers from a lack of stereoselectivity.[7] Note that Hu recently reported a stereoselective olefination protocol affording the synthesis of terminal monofluoroalkenes with high stereoselectivity.[8] As alternative pathways, the nucleophilic fluorination of vinyl triflates or boronic acids using

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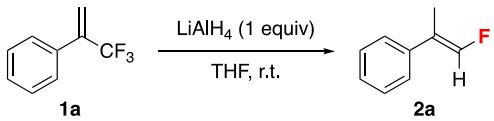
AgOTf[9a] or a Pd catalyst, respectively,[9b] as well as the cross-metathesis reaction,[10] although restricted to disubstituted monofluoroalkenes, were reported.

The hydrodefluorination of *gem*-difluoroalkenes has also been described using copper catalysts, for instance.[11] Finally, the halogen elimination on allyl fluorides has been widely explored by the group of Paquin to build up monofluoroalkenes in the course of an allylic substitution reaction (Figure 2).[12] Surprisingly, no report has described the synthesis of monofluoroalkenes from the corresponding trifluoromethylated alkenes according to a controlled hydrodefluorination strategy. As part of our research program dedicated to the use of tri-, di-, and monofluorinated alkenes as key building blocks to build up complex fluorinated molecules,[13] we sought to develop such an original approach as a complementary strategy to the existing ones. Hence, we report herein the stereoselective hydrodefluorination strategy of trifluoromethylated alkenes to build up monofluoroalkenes.

After a careful examination of the reaction parameters using the α,α,α-trifluoromethylstyrene **1a**, we found that the use of 1 equiv of $LiAlH_4$ in THF at room temperature allowed the formation of the monofluoroalkene **2a** in a very good 78% NMR yield with a 95:5 diastereoisomeric ratio, and it was isolated in a moderate 56% yield due to its high volatility (Table 1, entry 1). The use of DIBAL did not afford the desired product but led to the *gem*-difluoromethylalkene **I** in 74% NMR yield (entry 2).[14] The use of 2 equiv of RedAl as a reductant allowed the formation of the desired terminal monofluoroalkene **2a** in 62% yield but with a lower 85:15 diastereoisomeric ratio (entry 3). Finally, the use of lithium or sodium borohydride did not afford the expected product (entries 4 and 5). Then, with these optimized conditions in hand, we explored the scope of this transformation to showcase the panel of accessible terminal monofluoroalkenes (Scheme 1).

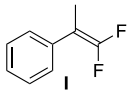
Table 1. Synthesis of Monofluoroalkene 2a from 1a[a]



1a 2a

entry	change from the standard conditions	yield (%)[b,c]	dr[d]
1	*none*	78 (56)	95:5
2	DIBAL (4 equiv)	0	
3	RedAl (2 equiv)	62	85:15
4	$NaBH_4$	NR	
5	$LiBH_4$	NR	

[a]Reaction conditions: **1a** (0.23 mmol), $LiAlH_4$ (0.23 mmol), THF (0.15 M), 21 h, rt. [b]Yield determined by ^{19}F NMR using 4-nitrofluorobenzene as an internal standard. [c]Isolated yield is reported. [d]Diastereoisomeric ratio (dr) was determined by ^{19}F NMR on the crude reaction mixture. NR = no reaction.



I

Scheme 1).

First, the reaction was tested on α-trifluoromethylstyrene derivatives. The reaction proceeded well with alkyl-substituted aromatic rings whatever the position of the substituent at the cost of an increase in the reaction temperature from room temperature to 70 °C (**2b–e**). Isolated yields were somehow lower than the NMR yields due to the high volatility of the products, and the diastereosiomeric ratios were excellent, except for the *ortho*-methyl-substituted styrene **2d** (82:18). A styrene derivative with a phenyl substituent at the para position **2f** as well as the naphthyl derivative **2g** were isolated in good yields with good dr. The presence of strong electron-donating groups at the para or meta position required an increase in the reaction temperature from rt to 70 °C to obtain excellent yields and a 95:5 dr (**2h–j**). Halogens and CF_3 groups were also tolerated, and the terminal monofluoroalkenes were obtained in good yields with good dr (**2k–n**). In addition heterocyclic derivatives were compatible under our standard conditions. The thiophene derivative **1o** was tested, and the corresponding terminal monofluoroalkene **2o** was isolated in moderate yield with a moderate dr. The indole derivative **2p** was obtained in 78% yield with an excellent dr, whereas the N-Ts-pyrrole-substituted monofluoroalkene was isolated in 83% yield with a 88:12 dr. Then, β-substituted α-trifluoromethylstyrenes were used in this hydrodefluorination reaction. A slight increase in the $LiAlH_4$ stoichiometry from 1 to 2 equiv was required to ensure a complete conversion of the products into the monofluoroalkenes. The presence of an alkyl chain did not affect the reaction efficiency, and products **2r–t** were isolated in good to excellent yields. In all cases, the diastereoisomeric ratio were excellent (>96:4). Unprotected alcohol **1t** was tested, and the product **2t** was isolated in a decent 72% yield with an 81:19 dr. Then, various protected alcohols were tested to demonstrate the synthetic utility of our methodology. Benzyl, MOM, and TBDMS protecting groups were well tolerated, and the terminal monofluoroalkenes **2v–x** were isolated in good yields with excellent dr (up to 99:1). As part of our interest in the use of β-trifluoromethyl acrylates as versatile fluorinated building blocks,[15] we sought to use them to access the corresponding terminal monofluoroalkenes. A slight increase in the $LiAlH_4$ stoichiometry from 1 to 2.5 equiv allowed the concomitant reduction of the ester group and the hydrodefluorination process. A large panel of β-trifluoromethyl acrylates was reduced into the terminal monofluoroalkenes in good to excellent yields, whatever the substitution pattern. In all cases, the diasteroisomeric ratio remained lower than those obtained from the hydrodefluorination of α-trifluoromethylstyrenes (66:34 to 82:18 dr), and both diastereoisomers were easily separable using silica gel flash chromatography. Finally, the potential of this hydrodefluorination process was demonstrated using the tetra-substituted trifluoromethylated olefin **1ak**. Using an extended reaction time, **1ak** was readily converted into the monofluoroalkene **2ak** in a good 72% yield, albeit with no diastereoselectivity. Unfortunately, some substrates remained reluctant in our hand, highlighting the limitation of the process. The β-alkyl-substituted β-trifluoromethylated acrylate and the β-trifluoromethylstyrene were not reactive and showcased the need to have an aromatic substituent on the trifluoromethylated alkenes. The β-trifluoromethylated nitrostyrene and acrylonitrile were not suitable substrates, and the hydrodefluorination product was not observed.[14] In the case of the phosphonate and sulfone derivatives, the reaction proceeded, but the hydrodefluorinated products were obtained in low yields (<30%).

Then, control experiments were carried out to get insight into the mechanism of this hydrodefluorinative process (Scheme 2). First, the influence of the olefin geometry was evaluated with the *E* and *Z* isomers of β-trifluoromethyl acrylate **1af**. Regardless of the stereoisomer used, the diastereoisomeric ratio and the yield remained unchanged,

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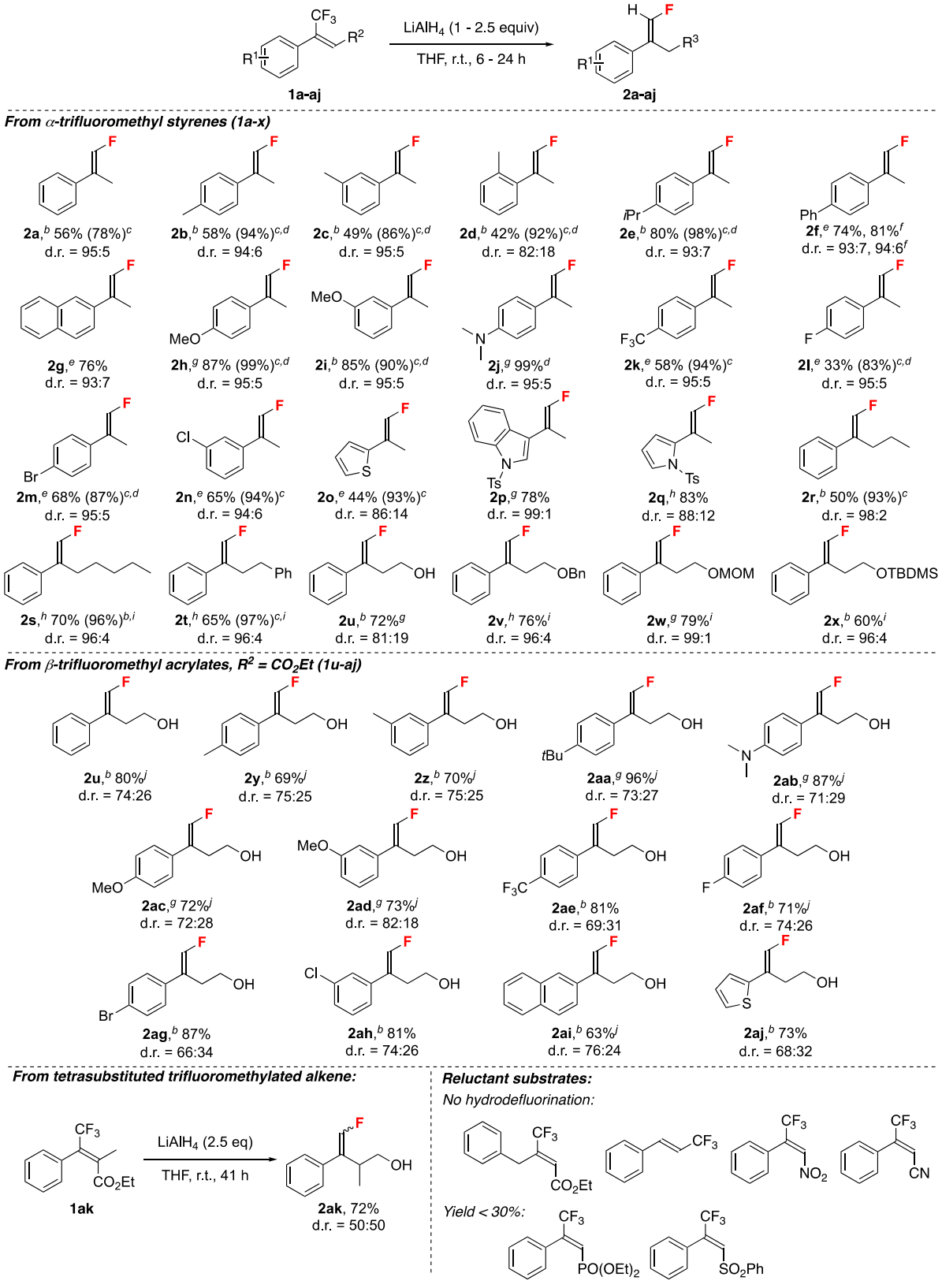
Scheme 1. Scope of the Reaction[a]



[a]**1** (0.3 mmol), $LiAlH_4$ (0.3 mmol), THF (0.1 M), rt, 6–24 h. The major diastereoisomer is shown. [b]24 h reaction time. [c]Yield determined by ^{19}F NMR using 4-nitrofluorobenzene as an internal standard. [d]Reaction was carried out at 70 °C for 24 h. [e]6 h reaction time. [f]Reaction was performed on a gram scale (4.1 mmol). [g]20 h reaction time. [h]17 h reaction time. [i]2 equiv of $LiAlH_4$ was used. [j]2.5 equiv of $LiAlH_4$ was used.

demonstrating that the olefin geometry has no influence on the stereochemical outcome of the reaction. To understand the reaction mechanism, the reaction was performed with the α-difluoromethylstyrene derivative **3** to ascertain if this species

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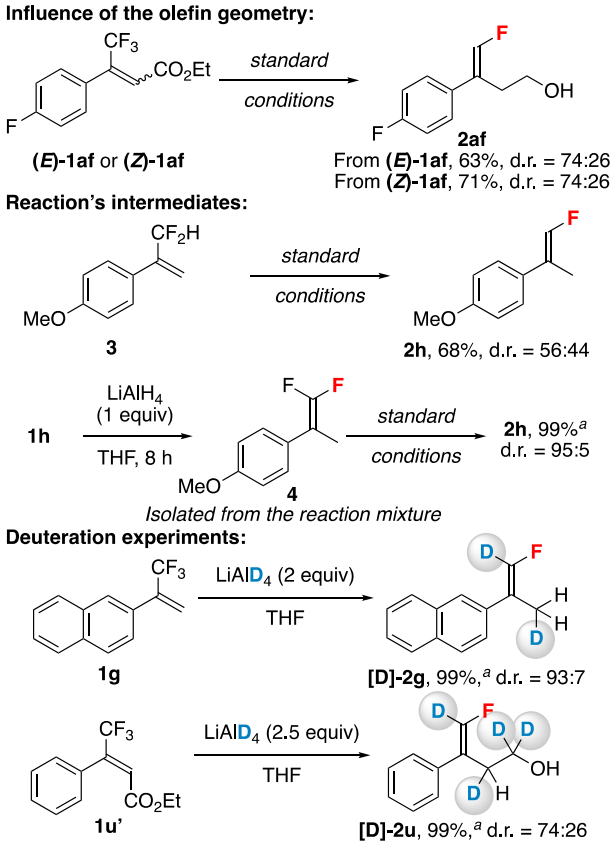
Scheme 2. Mechanistic Studies

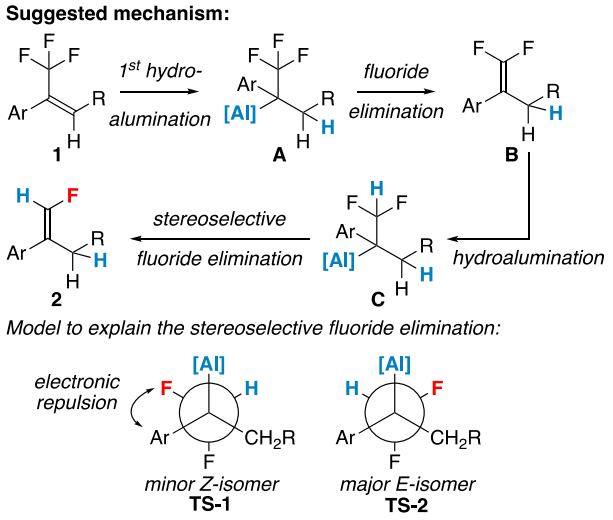


[a]Yield determined by ^{19}F NMR using 4-nitrofluorobenzene as an internal standard.

might be a reaction intermediate. The hydrodefluorination proceeded well, giving the target terminal monofluoroalkene in an excellent NMR yield but with a poor dr of 56:44. This result precluded the involvement of this species as a reaction intermediate. To get further insights, the reaction from **1h** was interrupted after 8 h, and we have been able to isolate the *gem*-difluoroalkene **4**. The latter was then submitted to the standard reaction conditions, giving **2h** in a similar yield with a similar dr compared to the those observed starting from **1h**, demonstrating its possible role as a reaction intermediate. Finally, experiments with $LiAlD_4$ were performed with **1g** and **1u′** to understand the mechanism of the hydrodefluorination reaction. The reaction of **1g** with $LiAlD_4$ clearly demonstrated the incorporation of a deuterium atom on the terminal position of the alkene and a single D atom at the allylic position of **2g**. Similarly, the reaction with **1u′** led to a similar incorporation of deuterium on the monofluoroalkene and at the allylic position. These results pointed out the two different sites of hydride incorporation. Hence, with all of these data in hand, we suggested the following mechanism (Scheme 3).

First, the hydroalumination of the α-trifluoromethylstyrene **1** led to the hydro-aluminated derivative **A**. A first fluoride elimination afforded the *gem*-difluoromethylalkene **B**, which has been isolated from the reaction mixture (*vide supra*). The regioselectivity of the hydride incorporation was supported by the deuteration experiment carried out with **1g** (Scheme 2). Then, a second hydroalumination occurred, providing a transient Al-species **C**, which was then involved in a stereoselective fluoride elimination to provide the (*E*)-

Scheme 3. Suggested Mechanism



monofluoroalkene **2** as a major product. The stereochemical outcome of this fluoride elimination could be explained using a Newman projection of the different conformers potentially involved in the antiperiplanar elimination of the fluoride ion. Indeed, the predictive model (**TS-1**) that leads to the minor *Z* isomer clearly highlights an electronic repulsion between the fluorine atom and the aromatic ring,[16] in contrast with **TS-2**, which predicts the formation of the *E* isomer.

In conclusion, we reported a simple and practical method for the synthesis of terminal monofluoroalkenes from trifluoromethylated alkenes. The reaction proceeded well with α-trifluoromethylstyrenes derivatives, β-trifluoromethyl acrylates, and tetrasubstituted trifluoromethylated olefins. The terminal monofluoroalkenes were obtained in good to excellent yields. The reaction proved to be diastereoselective in favor of the *E* isomer. Mechanistic studies supported the succession of two hydroalumination reactions followed by a final stereoselective fluoride elimination to explain the reaction outcome and the diastereoselectivity of the process. We hope that this simple and practical method will be useful to build up stereoselectively more complex terminal monofluoroalkenes to access fluorinated molecules of interest.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01701.

Experimental procedures, compound characterization data, and ^1H and ^{13}C spectra of the products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Philippe Jubault − *Normandie Université, INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), 76000 Rouen, France;* orcid.org/0000-0002-3295-9326; Email: philippe.jubault@insa-rouen.fr

Thomas Poisson − *Normandie Université, INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), 76000 Rouen, France; Institut Universitaire de France, 75231 Paris, France;* orcid.org/0000-0002-0503-9620; Email: thomas.poisson@insa-rouen.fr

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Authors

Pauline Poutrel − *Normandie Université, INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), 76000 Rouen, France*

Xavier Pannecoucke − *Normandie Université, INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), 76000 Rouen, France*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01701

Notes

The authors declare no competing financial interest.

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