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Reactions of In Situ-Generated Difluorocarbene (:CF_2) with Aromatic/Heteroaromatic Alcohols, Thiols, Olefins, and Alkynes under Environmentally Responsible Conditions

Erfan Oftadeh, Madison J. Wong, Julie Yu, Xiaohan Li, Yilin Cao, Fabrice Gallou, Luisa Heinz, and Bruce H. Lipshutz*

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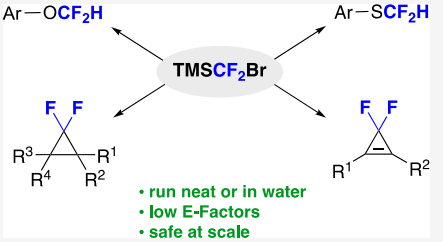
ABSTRACT: Environmentally respectful methods for generating and utilizing difluorocarbene (:CF_2) in the synthesis of a wide array of valuable difluoromethylated compounds are disclosed. In particular, the insertion of the CF_2 moiety into aromatic/heteroaromatic alcohols, thiols, olefins, and alkynes under neat or aqueous micellar catalysis conditions is demonstrated. These methods yield both satisfactory results and significantly lower E-Factors compared to traditional synthetic approaches. Key applications of these methodologies include optimization en route to a pantoprazole intermediate and development of a representative one-pot chemoenzymatic sequence. Additionally, analysis via calorimetry indicates no significant safety risk in the context of the developed solvent-free conditions.



INTRODUCTION

Insertion of the difluoromethylene moiety (CF_2) into numerous target molecules has been recognized for decades as an attractive means of altering the properties of the resulting species.[1] Several areas of research have pursued the inclusion of this functional group: agrochemicals,[2] polymers,[3] liquid crystals,[4] and in particular, pharmaceuticals[5−7] are common recipients, such as ether derivatives Flomoxef,[5] Pantoprazole,[6] and Roflumilast,[7] as well as the recently reported PI3Kγ inhibitor developed by Arcus[8] (Figure 1). Moreover, as discussed in a review by Ni and Hu, the CF_2 residue can also be found in many other types of functionalities, including thioethers, cyclopropanes, and cyclopropenes.[9] Access to this mildly electrophilic carbene leading to the resulting derivatives follows from a variety of sources, although some approaches involve reagents that are dangerous and/or environmentally questionable, e.g., those having ozone-depleting properties.[10] Recent advances, however, have led to several species that are considered not only far more attractive but, indeed, are also oftentimes more efficient.[11]

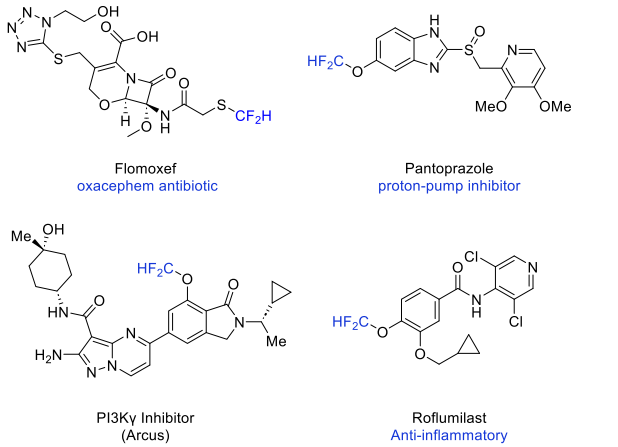


Figure 1. Representative bioactive difluoromethylated (thio)ethers.

Notwithstanding the extensive development of fluorinated carbene chemistry and its increasing importance in these areas of interest, what is characteristic today of every known method for introducing the CF_2 residue is its negative impact from an environmental perspective. Thus, there does not appear to be any technology for inserting this valued CF_2 group that even mentions, let alone considers, the environmental aspects associated with the chemistry being used. In this report, therefore, we disclose new technologies leading to products that contain the CF_2 residue, including aromatic/heteroaromatic ethers and thioethers of the types Ar-OCF_2H and Ar-SCF_2H. In addition, inroads to both difluorocyclopropanes and -cyclopropenes are described utilizing environ-

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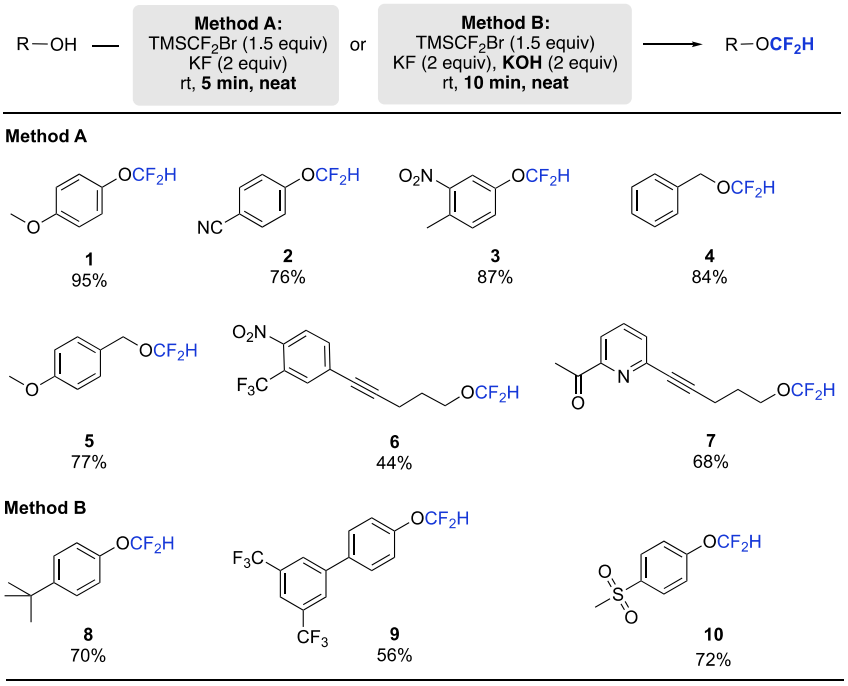
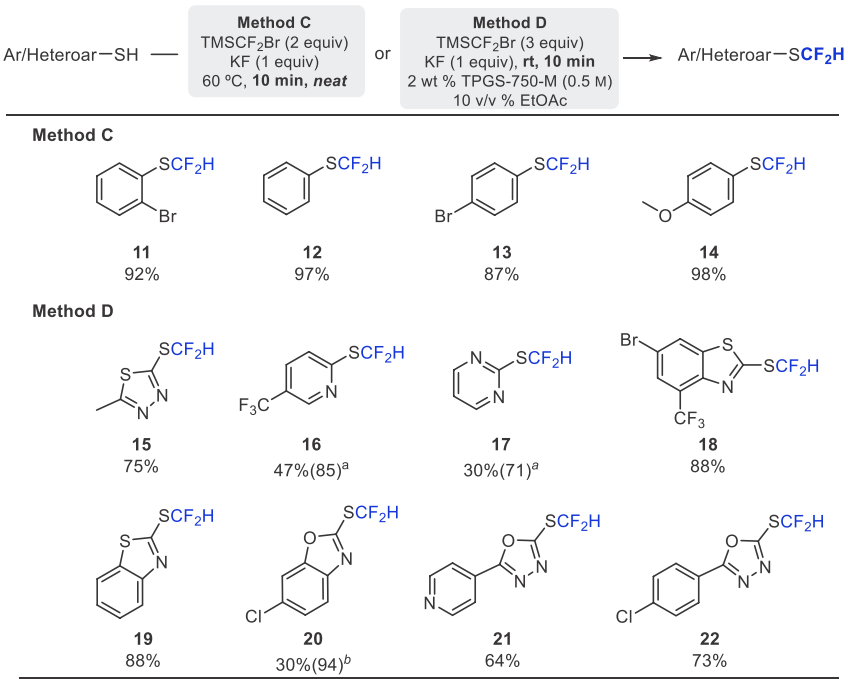
Table 1. Conversion of Alcohols to Their Difluoromethyl Ethers under Neat Conditions[a]



[a]Isolated yields.

Table 2. Conversion of Thiols to Their Difluoromethyl Thioethers under Neat Conditions[a]



[a]Isolated yields. [b]NaOH solution (4 equiv) in place of KF and 20% toluene as the cosolvent were used. [c]NaOH solution (2 equiv) in place of KF was used in the absence of the cosolvent.

mentally responsible conditions that take place in a synthetically competitive fashion.

According to the ACS Green Chemistry Institute, organic solvents constitute a substantial percentage of the organic waste generated by the chemical enterprise, especially in the pharmaceutical industry.[12,13] In recognition of the ongoing depletion of the world's petroleum reserves, which provide several commonly used organic solvents, as well as the unavoidable burning of large portions of organic waste derived from these solvents leading to emission of CO_2 and hence contributing to climate change,[14] we continue to develop new technologies that minimize their usage. Their replacement with recyclable water containing a designer surfactant enables them to function as nanoreactors for a

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J. Org. Chem. XXXX, XXX, XXX−XXX

variety of important reactions.[15,16] While chemistry in water accomplishes most of the intended goals, it remains prudent to appreciate the words of Sheldon, who stated in very clear and uncompromising terms that "The best solvent is no solvent,..."[17] The unavoidable interpretation is that in circumstances where the intended reaction can be done safely and under neat conditions, this is the preferred approach, i.e., in the complete absence of any reaction medium.

The notion of doing reactions under neat conditions is certainly not new; indeed, there are reviews on this subject.[18] However, what is also apparent is that most of the chemistry amenable to such an approach does not include the types of reactions of greatest interest to the fine chemical industry.[19] We have started, therefore, to examine the possibilities for either running reactions neat (e.g., as described for ketone allylations),[20] or alternatively, using very high concentrations of "green" organic solvents, such as EtOAc or 2-MeTHF, as we recently applied to an environmentally respectful and economical route to nirmatrelvir (the key ingredient in Paxlovid).[21] The resulting E-Factors, as expected, were very low, especially when compared with those from prior art that utilized organic solvents (vide infra).

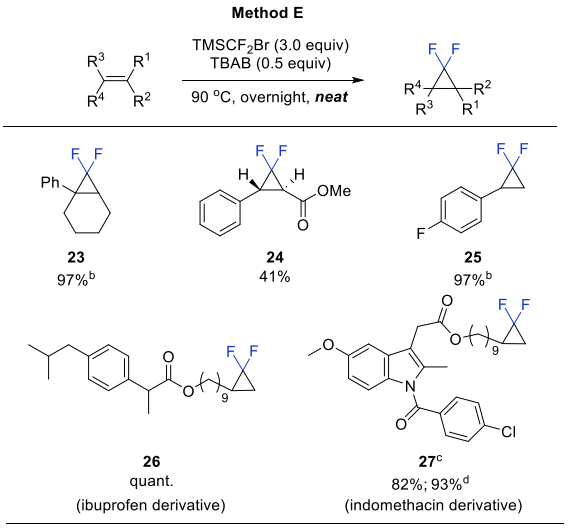
RESULTS AND DISCUSSION

Initially, both aromatic and heteroaromatic alcohols and thiols were derivatized to arrive at the corresponding $-OCF_2H$ and $-SCF_2H$ ethers. Several sources of CF_2 carbene were screened (e.g., $TMSCF_3$), and ultimately, the reagent first described by Hu and co-workers,[22] $TMSCF_2Br$, was identified as the most effective when used in the presence of an initiator (e.g., KF). Alternatively, initiators such as tetrabutylammonium bromide (TBAB) were found to be the most effective for cyclopropanations/cyclopropenations (vide infra).[22] Other fluoride sources such as TBAF, KHF_2, NaF, and CsF were far less effective. Various alkanols could be converted to the corresponding difluoromethyl ethers at room temperature in minutes (Table 1, Method A; all reactions were run on a 0.25 mmol scale). In some cases, the presence of KOH was found to enhance the extent of conversion (Table 1, Method B). The order of addition follows the sequence: substrate, initiator, and then $TMSCF_2Br$. Yields tended to be variable, ranging from a modest 44% to a high of 95%. Product isolation involves either direct loading of the reaction mixture onto a silica gel column or a simple aqueous wash; either is sufficient to ultimately obtain pure material. Traditionally, these ethers are made in aqueous CH_3CN at −78 to rt over a 30 min period in highly variable yields.[23]

Likewise, the treatment of various aromatic thiols neat at 60 °C for only 10 min afforded the desired thioethers typically in high isolated yields (Table 2, Method C). Since educts bearing more acidic thiols were often found to form side products under neat conditions, several nitrogen-rich heteroaromatic mercaptans were best converted to their difluorinated ethers under aqueous micellar catalysis conditions (0.5 M), in these cases with reactions occurring at ambient temperature also in only 10 min (Table 2, Method D). The presence of EtOAc as the cosolvent (10%, v/v) was needed to assist with the initial dissolution of the otherwise highly crystalline educts.

Due to the weak nucleophilicity of some electron-deficient thiols, the addition of a stronger base than in situ-generated bromide from $TMSCF_2Br$, or fluoride from KF, was needed to assist trapping the proton of the thiols (see compounds **16**−**17** and **20**)[24−28] The addition of CF_2 carbene to both alkenes and alkynes could also be effected, neat, to afford the corresponding difluorocyclopropanes and difluorocyclopropenes, respectively, although more vigorous conditions were required. That is, reactions were heated neat at 90 °C for ca. a 12 h period (Tables 3 and 4). This was expected given the

Table 3. Formation of Difluorocyclopropanes under Neat Conditions[a]



[a]Isolated yields. [b]1.5 equiv of $TMSCF_2Br$ used. [c]Demethylated side product was observed when using TBAB. [d]TBAI was used instead of TBAB.

weakly electrophilic nature of the carbene generated and the weakly nucleophilic character of each unsaturated system. When run traditionally in toluene, refluxing conditions are normally required (110 °C) over a 2−4 h period. Nonetheless, considerable functionality was tolerated in both types of starting materials. In the former case, difluorocyclopropane products were formed, one featured example being product **26** derived from the olefin-containing ester of ibuprofen. A second example leading to product **27** originates with the same type of ester but, in this case, derived from indomethacin. Various terminal and disubstituted acetylenes smoothly participated to give the desired cyclopropenes **28**−**36**, with most additions of CF_2 carbene proceeding in good-to-excellent yields.

Comparisons of E-Factors associated with both literature conditions vs those being used in these studies for insertions of CF_2 carbene can be found in Table 5.[23,28−34] The values associated with these neat reactions do not exceed 2.8, while those associated with known procedures performed in organic solvents are typically far higher.

With an extensive toolbox of technologies available based on chemistry in water, options for creating sequences (i.e., telescoping) are now readily carried out. As an example involving the application of this difluorocarbene chemistry, the synthesis of a critical intermediate for pantoprazole, a proton pump inhibitor frequently prescribed for gastroesophageal reflux disease, is illustrated in Scheme 1. The conventional route toward this intermediate that uses the same starting material is also shown. The former

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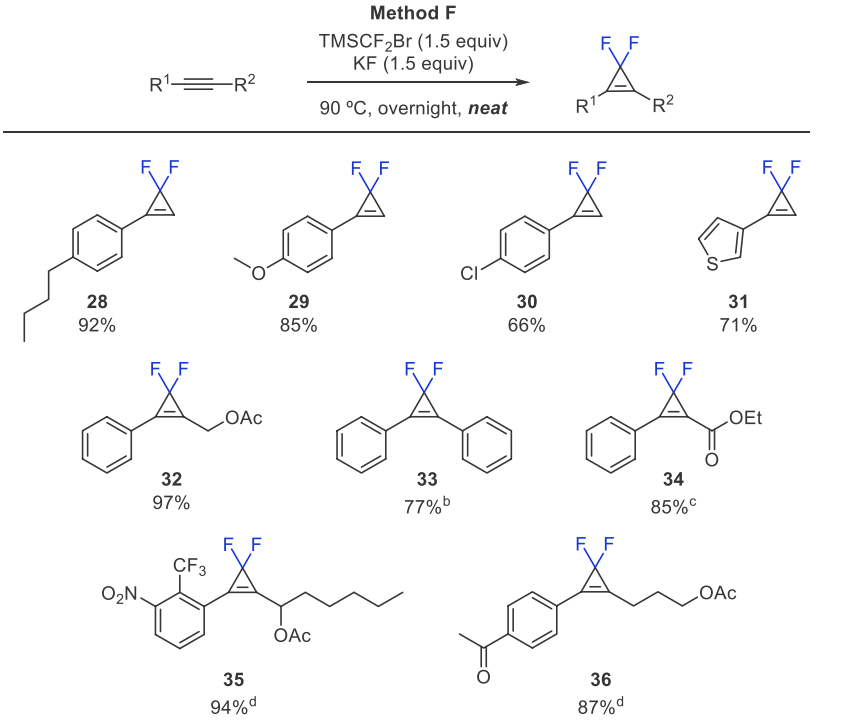
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 4. Formation of Difluorocyclopropenes under Neat Conditions[a]



[a]Isolated yields. [b]60 °C instead of 90 °C. [c]0.5 equiv of TBAI instead of KF. [d]Additional 1.5 equiv of $TMSCF_2Br$ was added after 12 h; total reaction time: 2 days.

encompasses a two-step, two-pot process, where $BrCF_2CO_2Et$ serves as the difluorocarbene source, requires a 12 h reaction period, and utilizes DMF, a solvent known for its significant reproductive toxicity.[35] In this sequence, the resultant difluoromethyl ether is isolated and then subjected to reduction of both nitro groups (utilizing up to 10 mol % Pd as the catalyst); cyclization afforded the final product in 49% overall yield. By contrast, this new, greener technology achieves difluoromethylation in a solvent-free environment, the reaction being completed within five minutes. Nitro group reduction is subsequently carried out using carbonyl iron powder (CIP) in an aqueous micellar environment. The resultant reaction mixture is then filtered through a Celite plug, and the entire filtrate containing the diamine is subjected to cyclization, arriving at the same product (**37**) in an overall yield of 84%. Notably, this sequence eliminates the use of organic solvents, as well as precious metal catalysts. Moreover, in addition to dramatically improving the overall efficiency, it features a considerable improvement in time economy.[36]

A second sequence, shown in Scheme 2, demonstrates the feasibility of incorporating difluoromethylation as part of a chemoenzymatic process[37] run under aqueous micellar conditions. Treatment of *p*-bromophenol under solvent-free difluoromethylation conditions at only 40 °C was followed by Suzuki−Miyaura coupling to yield the corresponding biaryl ketone **38**. Reduction of the carbonyl group upon addition of ADH101 (and necessary cofactors) into a buffered aqueous solution containing TPGS-750-M led to nonracemic alcohol **39** in an overall yield of 60% and in high ee.

A practical consideration associated with any solvent-free reaction run at scale raises the issue of safety, an inherent concern regarding a reaction's exothermicity. Thus, calorimetry analysis was performed on heteroaromatic product **19**, selected as a representative thioether resulting from this procedure. The data obtained indicate that the reaction is moderately exothermic, with a value of −53 kJ/kg at 30 °C. This corresponds to an adiabatic temperature rise of approximately 36 °C. Meanwhile, the dynamic part of the SETARAM thermostability test, spanning a temperature range of 30−60 °C for this reaction mixture, displayed only a very minor exothermic signal above roughly 30 °C (approximately −2 kJ/kg). In addition, a further differential scanning calorimetry (DSC) analysis of the product mixture conducted up to 400 °C revealed that the first exotherm of safety significance emerges above approximately 205 °C (approximately 347 kJ/kg). Overall, the conclusion is that no significant heat release compromises safety at the prescribed reaction temperature of 60 °C (see the Supporting Information for details).

In summary, environmentally responsible routes to various difluoromethylated derivatives, including difluoromethyl ethers, thioethers, cyclopropanes, and cyclopropenes, are reported. The potential for applying these technologies is demonstrated by the synthesis of a pantoprazole intermediate, achieving notable yield improvements along with a significant reduction in the sequence's original environmental footprint. Additionally, this approach has been successfully integrated into a one-pot sequence, featuring a representative chemoenzymatic route to a nonracemic product. The implied safety aspect associated with green chemistry is established for these neat reactions via a calorimetric analysis, further emphasizing the viability of solvent-free conditions. Overall, these advances pave the way for more sustainable and safer chemical practices, with potential applications extending across various sectors of the chemical enterprise.

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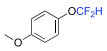
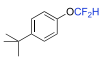
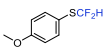
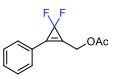
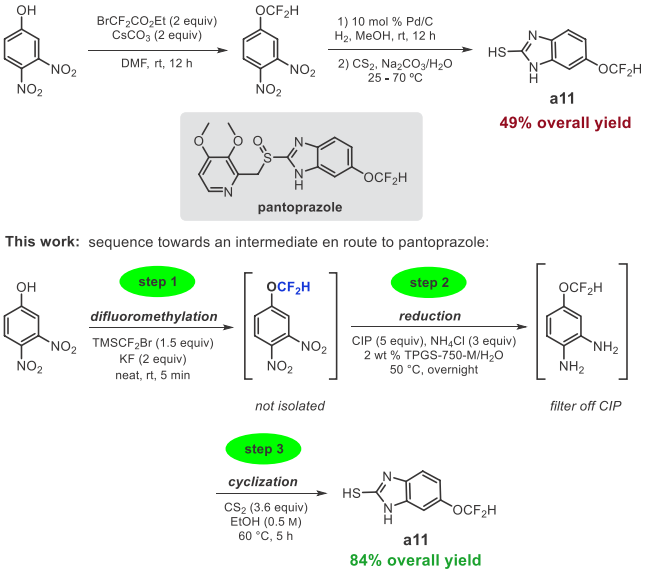
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 5. Comparisons with Existing Literature Procedures

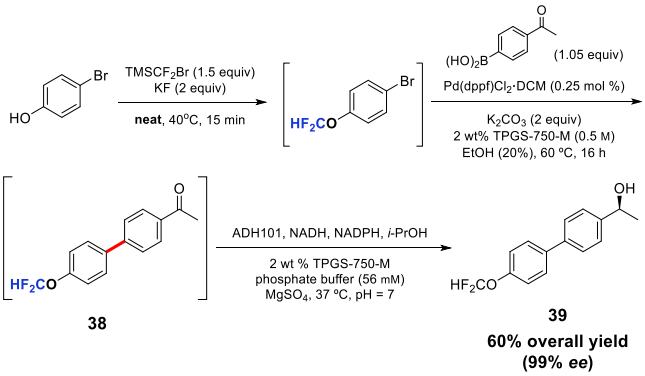
compound	literature conditions	this work
	$BrCF_2P(O)(OC_2H_5)_2$ (2 equiv) KOH (20 equiv) MeCN (5 mL) H_2O (5 mL)	KF (2.0 equiv) $TMSCF_2Br$ 1.5 equiv) 5 min
1[23]	E-Factor = 93.9	E-Factor = 1.4
	*p*-nitrophenyl-chlorodifluoromethyl-sulfone (1.5 equiv) KOH (16 equiv) MeCN (3 mL) H_2O (3 mL)	KF (2.0 equiv) $TMSCF_2Br$ (1.5 equiv) KOH (2 equiv)
8[28]	E-Factor = 41.4	E-Factor = 2.4
	K_2CO_3 (1.5 equiv) SCDA (2 equiv)[b] DMF (5 mL)	KF (1.0 equiv) $TMSCF_2Br$ (2 equiv) 10 min
14[29]	E-Factor = 28.7	E-Factor = 1.4
	LiOH (1.2 equiv) *S*-(difluoromethyl) sulfonium salt (1.2 equiv) fluorobenzene (2 mL)	KF (1.0 equiv) $TMSCF_2Br$ (2 equiv) EtOAc (0.05 mL) 2 wt % TPGS-750-M (0.45 mL)
19[30]	E-Factor = 52.2	E-Factor = 3.4
	KI (2.25 equiv) MDFA (1.5 equiv)[c] TMS-Cl (2 equiv) dioxane/diglyme mixture 2 d	TBAB (0.5 equiv) $TMSCF_2Br$ (3.0 equiv) 16 h
23[31]	E-Factor = 5.6	E-Factor = 2.8
	NaI (0.2 equiv) $TMSCF_3$ (1.5 equiv) THF, 2 h	TBAB (0.5 equiv) $TMSCF_2Br$ (3.0 equiv) 16 h
25[32]	E-Factor = 118.9	E-Factor = 3.4
	NaI (0.35 equiv) $TMSCF_3$ (1.5 equiv) THF, 4 h	KF (2.0 equiv) $TMSCF_2Br$ (1.5 equiv) 16 h
29[33]	E-Factor = 9.8	E-Factor = 1.4
	TBAC (2.0 equiv) $TMSCF_2Br$ (1.5 equiv) toluene, 4 h	KF (2.0 equiv) $TMSCF_2Br$ (1.5 equiv) 16 h
32[34]	E-Factor = 13.9	E-Factor = 1.0

[a]Calculations: see the Supporting Information. [b]Sodium chlorodifluoroacetate. [c]MDFA, methyl 2,2-difluoro-2-(fluorosulfonyl)acetate.

Scheme 1. Comparison of Routes toward an Intermediate Leading to Pantoprazole



Scheme 2. Three-Step Chemoenzymatic Sequence



■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01955.

Experimental procedures, characterization data, and NMR spectra for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Bruce H. Lipshutz − *Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States;* orcid.org/0000-0001-9116-7049; Email: bhlipshutz@ucsb.edu

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Authors

Erfan Oftadeh − *Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States*

Madison J. Wong − *Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States;* orcid.org/0000-0001-8094-9678

Julie Yu − *Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States*

Xiaohan Li − *Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States*

Yilin Cao − *Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States*

Fabrice Gallou − *Chemical & Analytical Development, Novartis Pharma AG, 4056 Basel, Switzerland;* orcid.org/0000-0001-8996-6079

Luisa Heinz − *Chemical & Analytical Development, Novartis Pharma AG, 4056 Basel, Switzerland*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.4c01955

Author Contributions

This manuscript was written with contributions from all authors.

Notes

The authors declare no competing financial interest.

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