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Copper-Catalyzed Synthesis of Difluoromethyl Alkynes from Terminal and Silyl Acetylenes

Xanath Ispizua-Rodriguez, Vinayak Krishnamurti, Vanessa Carpio, Colby Barrett, and G.K. Surya Prakash*

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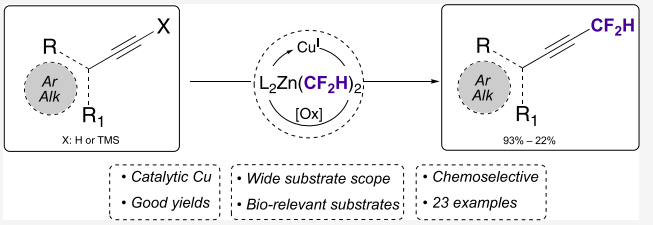
ABSTRACT: An efficient method for the direct C(sp)−H difluoromethylation of terminal alkynes and the desilylation−difluoromethylation of (trimethylsilyl)acetylenes is disclosed. The copper-catalyzed transformation provides access to a wide range of structurally diverse CF_2H alkynes in good yields, utilizing a (difluoromethyl)zinc reagent and an organic oxidant. The difluoromethylation of important synthons and API's is showcased. The synthetic utility of these (difluoromethyl)alkynes is demonstrated by selected cycloaddition reactions. Additionally, a slight modification to the reaction conditions allowed the selective preparation of a 2-difluoromethylindole.



INTRODUCTION

Among the various strategies to introduce fluorine atoms into molecules, the development of difluoromethylation protocols is on the rise and has been of interest for several recent investigations.[1−5] The difluoromethyl group has been described as a lipophilic bioisostere of thiol (−SH) and amino (−NHR) groups due to their similar hydrogen bond acidity and as a less lipophilic bioisostere to the $-CH_3$ group.[6,7] Reportedly, the hydrogen bond donor capabilities of the $-CF_2H$ moiety are heavily influenced by the chemical environment of a given compound. These properties make the difluoromethyl group an attractive moiety to tune the physicochemical properties of bioactive compounds.

In this context, the alkynyl moiety is a widely prevalent functionality in natural products and compounds with biological applications.[8−10] Synthetically, C≡C triple bonds are employed as useful synthons for clickable tags and biomarkers via cycloaddition reactions to form triazoles, pyrazoles, and other heterocycles.[11−14] Additionally, they serve as important synthetic intermediates and are also present in several life-saving medications (Figure 1). Fluoroalkylated alkynes have similarly been described as valuable building blocks, making methods for their efficient preparation highly sought-after. However, there are only a handful of methods available in the literature to prepare difluoromethyl acetylenes directly from their parent terminal alkynes, and most protocols for their synthesis proceed via a difluorocarbene intermediate.

The difluoromethylation of propynyl alcohols with Freon-22 (CHF_2Cl) as a difluorocarbene source was demonstrated in 1996 by Konno and co-workers.[15] More recently, this ozone-depleting gas has been used alongside a palladium catalyst to prepare CF_2H-alkynes.[16] In this same vein, $TMSCF_2Br$,[17] α-difluoromethyl sulfoximine,[18] and fluoroform[19,20] have also been used as alternative difluorocarbene precursors for the preparation of these compounds; however, these display limited substrate scopes or moderate yields (Scheme 1).

Despite the rich chemistry of organocopper compounds[21] and the proven ability of Cu-acetylides to act as alkyne-transfer agents,[22] the reports of the use of copper chemistry for these endeavors are very scarce. Burton's work on the reaction between in situ prepared $CuCF_2H$ and alkynyl halides, along with Qing's oxidative difluoromethylation of terminal alkynes with $TMSCF_2H$ and stoichiometric CuI are the only two reports (Scheme 1).[23,24] Therefore, we envisioned the preparation of CF_2H alkynes employing catalytic loadings of copper and using $(DMPU)_2Zn(CF_2H)_2$ as the difluoromethyl source (which can be prepared by a halon-free approach).[25]

RESULTS AND DISCUSSION

Our previous experience working with this heterobimetallic system[26] led us to hypothesize that under mild oxidative conditions, the in situ-formed (difluoromethyl)copper species could yield the desired compounds from either terminal or silyl alkynes. To test this hypothesis, we selected 4-Cl-phenylacetylene **1a** as the model substrate for the optimization process. The effects of multiple modifications of the reaction conditions are evaluated and summarized in Table 1. The

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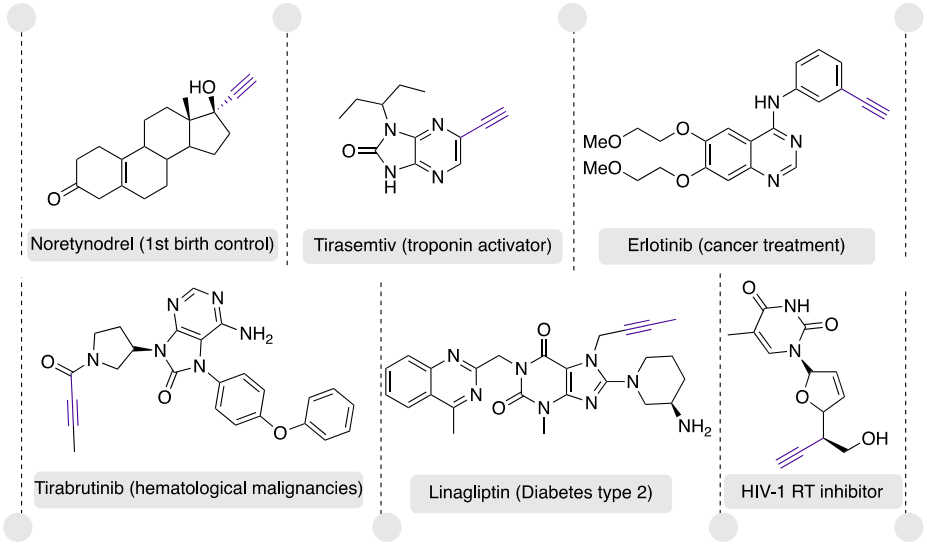


Figure 1. Alkyne-containing pharmaceuticals and API's.

Scheme 1. Prior Art on the Synthesis of Difluoromethyl Alkynes

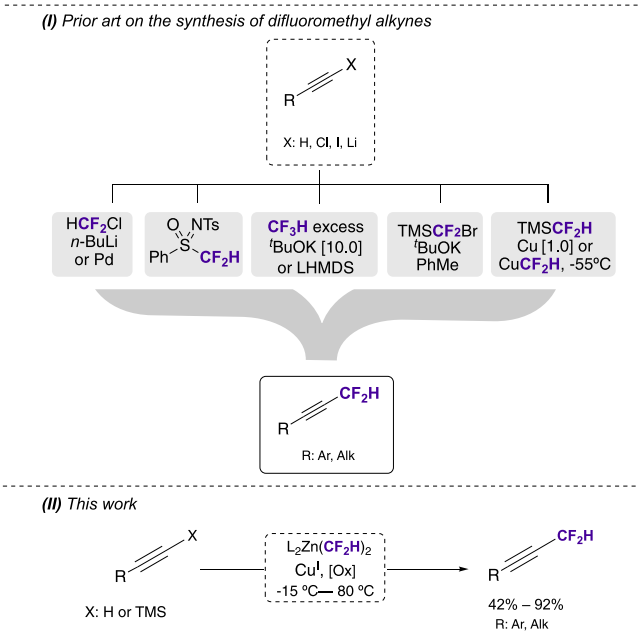
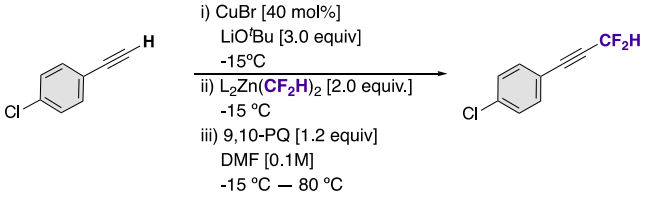


Table 1. Optimization of the Difluoromethylation Reaction[a]



entry	deviations from standard conditions	yield **2a**[b] (%)
1	none	87
2	KO^{t}Bu instead of LiO^{t}Bu	72
3	KO^{t}Bu instead of LiO^{t}Bu at rt	17
4	CuBr or CuCl 65 mol %	78 or 18
5	5, 10, or 15 mol % CuBr	64, 62 or 68
6	−15 °C to rt instead of 80 °C	73
7	6 h at 80 °C instead of 8 h	58
8	18 h at 80 °C instead of 8 h	77
9	No 9,10-PQ or no CuBr	0

[a]9,10-PQ = 9,10-phenanthrenequinone, L = DMPU. To alkyne **1a**, CuBr, and LiO^{t}Bu is added a solution of difluoromethyl zinc reagent in DMF at −15 °C. After 10 min, a DMF solution of 9,10-PQ is added, and the reaction is left at −15 °C for 10 min, then heated at 80 °C for 8 h. See the Supporting Information for full details. [b]Determined by ^{19}F NMR using PhOCF$_2$H as an internal standard.

desired difluoromethylated product **2a** was obtained in 87% yield with 3.0 equivalents of LiO^{t}Bu as the base, 2.0 equivalents of the difluoromethyl zinc reagent, and 40 mol % of CuBr and 1.2 equivalents of 9,10-phenanthrenequinone as the oxidant (Table 1, entry 1). The use of KO^{t}Bu instead of LiO^{t}Bu at −15 °C or at room temperature, afforded lower conversions by ^{19}F NMR (Table 1, entries 2 and 3). Similarly, modifying the copper loadings and identity of the copper salts did not improve the yield of **2a** (Table 1, entry 4). Reducing the copper loadings did not improve the yield; however, it showcased the feasibility of performing the reaction with 5 mol % CuBr if lower loadings are desired (Table 1, entry 5) (see the Supporting Information). Conducting the reaction at room temperature after setting it up at −15 °C resulted in a moderate but lower yield (Table 1, entry 6). The ^{19}F NMR spectrum of this trial shows the presence of unidentified species that are not observed at higher temperatures, which may suggest the reaction does not go to completion at room temperature.

Changing the reaction time to 6 or 18 h did not afford the same results as letting it react for 8 h (Table 1, entries 7 and 8). Finally, the absence of the oxidant (9,10-phenanthrenequinone) or copper did not afford any product (Table 1, entry 9). With the optimized conditions in hand, we explored the scope of the difluoromethylation reaction. Scheme 2 depicts the extent of the method's applicability. (Haloaryl)acetylenes provided the expected compounds in excellent yields, as exemplified by product **2a** from the model substrate, 3,5-difluorophenyl compound **2b** and compound **2c**. Notably no difluoromethylarene byproduct was observed in these cases,[27] and the synthesis of **2a** was successfully performed at ∼10× the

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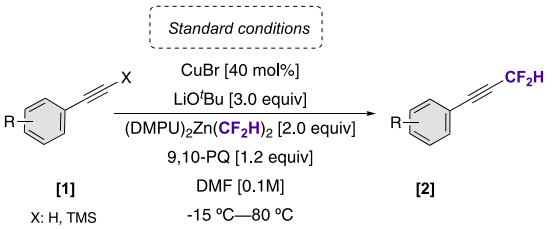
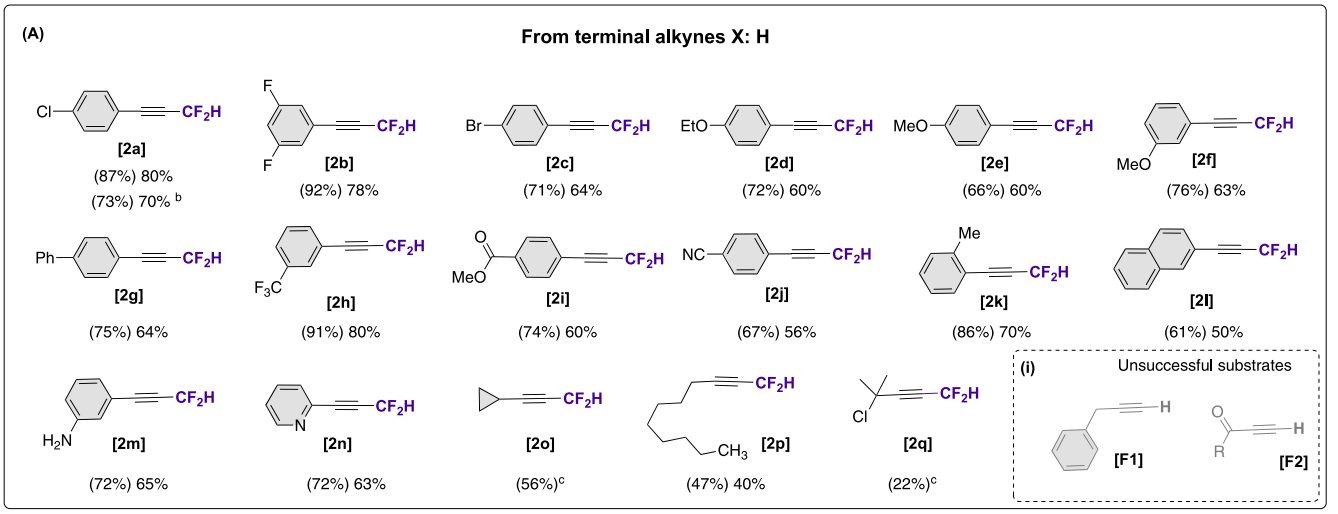
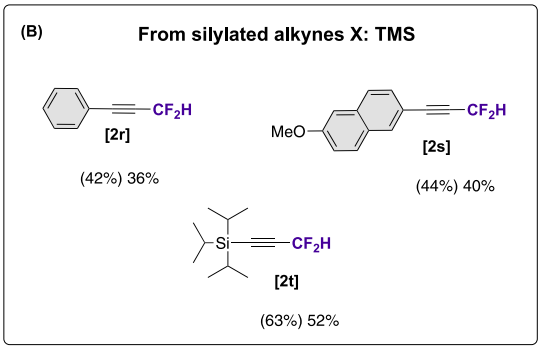
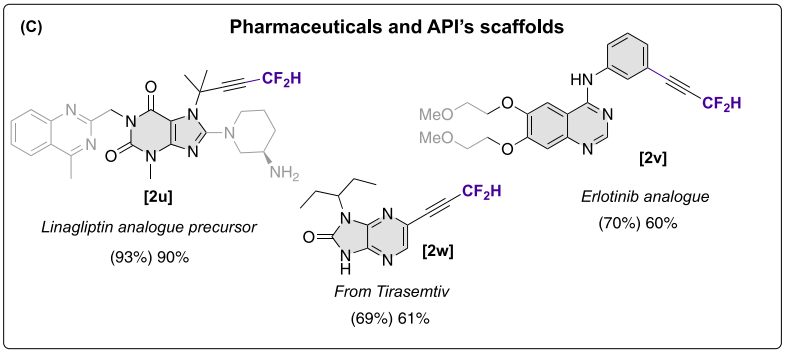
Scheme 2. Substrate Scope of Aryl and Alkyl Difluoromethyl Alkynes[a]









[a][1] (0.15 mmol), LiO^{t}Bu (3.0 equiv), CuBr (40 mol %), (DMPU)$_2$Zn(CF$_2$H)$_2$ (2.0 equiv), 9,10-phenanthrenequinone (1.2 equiv). Set up at −15−80 °C for 8 h. Yields in parentheses determined by ^{19}F NMR spectroscopy, using internal standard (PhOCF$_2$H). [b]Scaled-up reaction: 2 mmol. [c]Not isolated due to volatility, observed by ^{19}F NMR.

scale, giving comparable yield. Ethers were amenable to the reaction conditions, regardless of substitution patterns furnishing compounds **2d** (72%), **2e** (66%), and **2f** (76%) in good yields. Similarly, 4-ethynylbiphenyl **1g** yielded compound **2g** with good conversion (75%). The method similarly tolerates both electron-rich and electron-deficient substrates, affording the target compounds in comparable yields. Substrate **1h** furnished compound **2h** (91%) in excellent yield and compounds containing ester and nitrile substituents afforded compounds **2i** and **2j** in good yields without any side reactions. Ortho-substituted **2k** (86%) was also afforded in excellent conversion by ^{19}F NMR suggesting that sterics may not impede the reaction. 2-Naphthylalkyne **1l** was smoothly converted to the difluoromethyl derivative **2l** in good yield. Furthermore, example **2m** (72%) showcases the method's tolerance to primary amines, and example **2n** (72%) demonstrates the applicability of the method to substrates with pyridyl moieties. Aliphatic alkynes were also found to be successful substrates under these conditions. The difluoromethylation of 1-decyne produced compound **2p** in moderate yield. Cyclopropyl acetylene was also subjected to the reaction conditions, yielding 56% of compound **2o** by ^{19}F NMR. Next, we tested if the method could be extended to silylalted alkynes, instead of terminal alkynes (Scheme 2B). 3-Chloro-3-methyl-1-butyne afforded compound **2q** in moderate yields. This lower yield may be attributed to the formation of an allene via chloride elimination.[28]

(Trimethylsilyl)alkynes have been described in the literature as synthetic alternatives to terminal alkynes, especially in cases where volatility and handling are problematic. We were interested in testing the compatibility of these compounds with our method. We were pleased to find that TMS-phenylacetylene was converted to difluoromethyl derivative **2r** in a yield comparable to that obtained with other Cu-mediated methods with terminal alkynes.[23,24] The desilylation-difluoromethylation of compound **1s** also afforded **2s** in moderate yield. Further synthetic applicability of the method was demonstrated by example **2t** in which the triisopropylsilyl

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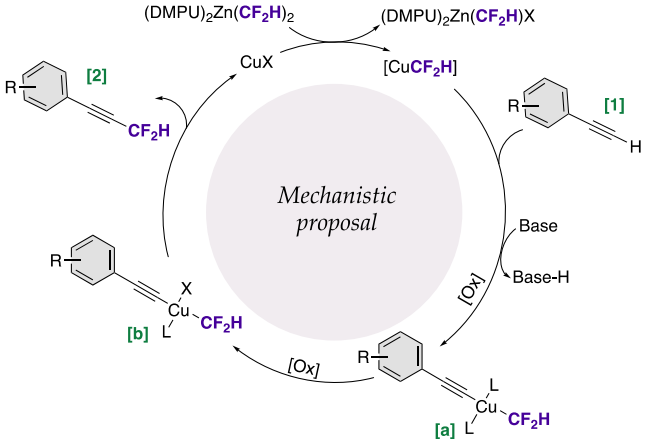
group remained untouched, furnishing TIPS-C≡CCF$_2$H in good yields. The retention of the more sterically encumbered silane may be of significance in further applications of this compound. The method was further applied for the preparation of difluoromethyl analogues of biologically relevant compounds (Scheme 2C). Example **2u** was prepared in 93% yield as a precursor of a CF$_2$H-analogue of Linagliptin, a diabetes medication. This example also showcases the feasibility of difluoromethylation of *N*-propargyl theophylline derivatives with this set of conditions. Example **2v** contains a scaffold based on Erlotinib, a cancer-treating therapeutic. This difluoromethyl analogue was smoothly furnished in 60% yield. Lastly, **2w**, prepared in 69% yield from Tirasemtiv, contains an imidazo[4,5-*b*]pyrazinone scaffold commonly encountered in small molecules that target muscle weakness caused by neurogenic diseases.[29,30] Throughout the exploration of the substrate scope, we encountered two limitations of the method. Compounds with scaffolds like **F1** or **F2** were not able to undergo difluoromethylation under these conditions (Scheme 2i) and instead, 1,1,2,2-tetrafluoroethane {^{19}F NMR ($CDCl_3$) δ −139 (d, 55 Hz)} was formed as the major product (see the Supporting Information).

The proposed reaction pathway for the presented transformation is primarily based on the reported activity of perfluoroalkylcopper species with terminal alkynes,[23] as well as prior art on [Cu−CF$_2$H] species generation from the Vicic-Mikami reagent and copper (I) salts.[31,32] As seen in Scheme 3,

Scheme 3. Mechanistic Proposal

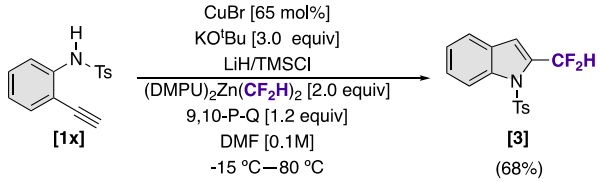


the in situ-formed difluoromethylcopper species can react with alkyne [**1**] to form intermediate difluoromethylcopper acetylide [**a**] in the presence of a base and can then be oxidized to intermediate [**b**]. Upon reductive elimination from this intermediate, the desired compound [**2**] is released along with the regenerated catalyst.

Furthermore, we extended the developed methodology to explore the selective synthesis of 2-difluoromethylindoles through a tandem difluoromethylation−intramolecular cyclization process. Slightly modified conditions were applied to 2-ethynylaniline derivative **1x**, affording 2-difluromethylindole **3** in 68% yield (Scheme 4). The full optimization and scope of this transformation are currently ongoing in our laboratory and will be reported in due course.

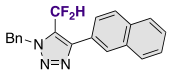
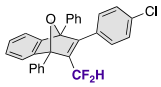
Finally, the utility of the synthesized difluoromethyl alkynes was further exemplified by the preparation of CF$_2$H triazoles **4a** and **4b**, and a (difluoromethyl)dihydro-epoxynaphthalene

Scheme 4. Unoptimized Tandem Difluoromethylation−Cyclization



5a. The [3 + 2] click reaction between difluoromethyl alkyne **2k** and benzyl azide yielded a mixture of the two regioisomers in 50% yield (Table 2). Similarly, compound **5a** was obtained

Table 2. Cycloaddition Reactions

Reagents	Product	Yield
Benzyl azide +**2l**		CF$_2$H triazole **[4b]**[a] from **[2l]**: 1.2:1.0 (50%)
1,3-diphenyl-isobenzofuran +**2a**		CF$_2$H epoxy-dihydronaphthalene **[5a]**[b] from **[2a]**: (quant.) 77%

[a]Regioisomers obtained in a 1.2:1.0 ratio. Isomer **4b** isolated in 50% yield. [b]Obtained by heating a toluene solution of alkyne **2a** and 1,3-diphenylisobenzofuran at 100 °C for 36 h.

as a product from the [4 + 2] Diels−Alder cycloaddition between compound **2a** and 1,3-diphenylisobenzofuran (Table 2). This derivatization reaction was carried out quantitatively, smoothly affording compound **5a** as the first example of this kind of Diels−Alder adducts[33] with difluoromethyl alkynes.

CONCLUSIONS

In conclusion, an efficient protocol for a direct difluoromethylation of silyl and terminal alkynes, using catalytic copper and a difluoromethyl(zinc) reagent, was developed. This protocol enables facile access to a wide assortment of substituted aromatic and aliphatic alkynes, tolerating a broad range of functionalities. The relevance of this method is further accentuated by its applicability to the preparation of a difluoromethyl analogue of Tirasemtiv, among other medicinally relevant scaffolds. Additionally, the developed methodology has been modified to perform a tandem difluoromethylation−cyclization reaction to prepare a 2-difluoromethylindole. Lastly, the prepared CF$_2$H alkynes were utilized in [3 + 2] and [4 + 2] cycloaddition reactions to prepare difluoromethyl triazoles and an ortho-substituted difluoromethylarene.

ASSOCIATED CONTENT

Data Availability Statement

Data Availability: 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.2c02799.

Experimental procedures, NMR spectra, and characterization data (PDF)

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AUTHOR INFORMATION

Corresponding Author

G.K. Surya Prakash − *Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661, United States;* orcid.org/0000-0002-6350-8325; Email: gprakash@usc.edu

Authors

Xanath Ispizua-Rodriguez − *Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661, United States*

Vinayak Krishnamurti − *Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661, United States*

Vanessa Carpio − *Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661, United States*

Colby Barrett − *Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.2c02799

Notes

The authors declare no competing financial interest.

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