

Diethylzinc-Mediated Radical 1,2-Addition of Alkenes and Alkynes

Xin Li, Songtao He, and Qiuling Song*



purifications. The mild conditions enable this protocol to exhibit excellent functional group compatibility.

T he 1,2-difunctionalization of alkenes and alkynes is an ideal reaction because two new functional groups are equipped in a single reaction. As a consequence, numerous elegant methods have been developed to install various kinds of groups onto the C–C multiple bonds.¹⁻⁶ Ordinarily, there are two common strategies for the 1,2-difunctionalization of alkenes and alkynes. One is the extensively studied three-component difunctionalization, which employs two different reagents to install the two target functional groups one by one or simultaneously (Figure 1A, route a). The other one, which



Figure 1. Integration of 1,2-difunctionalization and zinc chemistry.

uses a single reagent to provide both of the two target functional groups, is more challenging (route b). Among the successful examples, perfluoroalkyl halides are regarded as favorable difunctionalization reagents because fluorine atoms widely exist in pharmaceutical molecules and halides are readily transformed into many other groups based on the reliable $S_N 2$ reactions and the abundance of cross-coupling reactions (route c).^{7–9} However, most catalytic systems heavily rely on precious and toxic photocatalysts (PCs)⁷ or transitionmetal (TM) catalysts.⁸ Some reaction conditions are too harsh to maintain good functional group tolerance. Hence there is still a demand for a practical protocol that employs simple and inexpensive catalysts, gives excellent yields, and exhibits broad functional group compatibility.

Zinc is an essential element for plants, animals, and human beings.¹⁰ Organozinc compounds have become famous for Negishi coupling, the Reformatsky reaction, the Fukuyama reaction, and Baran's reagent (Figure 1B).¹¹ In most cases, the reaction conditions are mild, and thus good functional groups compatibilities are achieved. Zinc salts are also widely used as versatile catalysts to catalyze a series of reactions. In addition, zinc compounds are found in radical chemistry.^{12,13} For example, diethylzinc acts as a source that provides alkyl radicals under the influence of oxygen.^{12c-k} Thus we envision that the integration of difunctionalization reactions and zinc chemistry will become a promising research field (Figure 1C).

In this work, we demonstrate a unique reaction mode of diethylzinc and ethyl iododifluoroacetate in the radical 1,2-addition of C–C multiple bonds. In addition to achieving high efficiency, excellent functional group compatibility, and good stereoselectivity, our protocol realized an ideal "clean reaction"; that is to say, the starting materials were fully transformed into the target products and negligible byproducts were generated, and thus no column chromatography purifications were demanded after the reaction (Figure 1C).

After a preliminary screening of works,¹⁴ 50 mol % of Et_2Zn efficiently induced a radical 1,2-addition of ethyl iododifluoroacetate 1a to allylbenzene 2a, affording the desired product 3a in excellent yield at -20 °C (eq 1). After the completion of the reaction, simple extraction, drying, filtration, and

Received: February 25, 2021 Published: April 5, 2021





Letter



concentration procedures afforded the target product **3a** with perfect purity. Conventional purification via column chromatography gave a comparable isolated yield.

Because of the lack of a proximal group with a π -electron system (e.g., aryl, carbonyl, and heteroatom) to stabilize the nascent alkyl radical intermediates, unactivated alkenes are much more difficult to difunctionalize than activated alkenes such as styrene derivatives via radical pathways. Accordingly, a series of unactivated alkenes bearing various kinds of functional groups was submitted to the standard reaction conditions to test the generalizability of our method. For aliphatic terminal alkenes, the reaction proceeded well and gave excellent yields despite the structures of the carbon backbones (Scheme 1,



^{*a*}Reaction conditions: ICF₂CO₂Et **1a** (0.2 mmol), alkenes **2** (0.2 mmol), Et₂Zn (50 mol %), acetonitrile (2.0 mL), -20 °C, 16 h. ^{*b*}Without column chromatography. ^{*c*}20 mol % of Me₂Zn instead of Et₂Zn. ^{*d*}Ethyl iododifluoroacetate **1a** (0.4 mmol) and Et₂Zn (100 mol %) were used. ^{*c*}Isolated yield.

3b-3d). Diene gave the double-functionalized product when 2 equiv of reagents was employed (3e). The chemistry exhibited good functional group compatibility. A broad spectrum of functional groups was tolerated without any problems during the reaction, affording the corresponding products in perfect yields. For example, bromide, acetate, benzoate, and sulfonate, which are good leaving groups under nucleophilic conditions, all survived during the reaction (3f-i). Substrates bearing protected alcohols and ether groups efficiently afforded the target products (3k-m). After the reaction, azide and protected amines were intact, whereas the difunctionalized products were obtained in high yields (3n and 3o). Carboxylic acid derivatives such as nitrile, ester, and amide were also compatible with the reaction (3p-r). For internal cyclic alkenes, the desired products were also obtained in good yields and with high levels of stereocontrol; that is, only trans isomers

were obtained (3s and 3t).¹⁵ When two equivalent or nonequivalent C–C double bonds existed in the same molecule, this chemistry exhibited good chemoselectivity. For example, employing 1 equiv of iodide gave a monofunctionalized product, whereas the other C–C double bond was left intact (3t). The exocyclic terminal double bond is more reactive than its cyclic counterpart; only the former was functionalized when 1 equiv of iodide was employed (3u).

Our attention was then turned to alkyne substrates. Fortunately, this reaction also worked well for alkynes and once again showed very good generalizability. For phenyl-acetylene derivatives, a wide range of substituents on the aromatic rings were well tolerated (Scheme 2, 5a-p). The data





^{*a*}Reaction conditions: ICF₂CO₂Et **1a** (0.2 mmol), alkynes **4** (0.2 mmol), Et₂Zn (50 mol %), acetonitrile (2.0 mL), -20 °C, 8 h. ^{*b*}Without column chromatography. ^cE/Z ratios were determined from the relative intensities of ¹⁹F NMR signals. ^{*d*}25 mol % of Me₂Zn instead of Et₂Zn. ^{*c*}Isolated yield.

revealed that the electronic factor had little influence on the outcome of the reaction. From electron-donating alkoxys, alkyls, and halogens to electron-withdrawing formyl and trifluoromethyl, the high efficiency of the reaction and the good functional group tolerance were well maintained. In addition, steric factors did not affect the reaction. For example, more sterically hindered o- and m-substituted phenylacetylenes (51-p) gave almost the same yields as their p-substituted counterparts (5b-k). The stereoselectivity was good; in most cases only E isomers were observed.¹⁶ Addtionally, heterocyclic arene was compatible with the reaction (5q). Aliphatic terminal alkynes readily reacted with the iodides, affording the target products in high yields. However, the E/Z ratios were not as good as those of the phenylacetylene derivatives (5r-u), indicating that the conjugated aromatic rings play a crucial role in the stereoselectivity of the reaction. A saturated heterocyclic substrate suffered moderate conversion and required column chromatography purification to obtain a pure product (5v). Internal carbon-carbon triple bonds had lower reactivities

Organic Letters

under the standard reaction conditions, affording tetrasubstituted olefins in moderate yields (5w,x). Again, alkyne with a conjugated aromatic ring (5x, E only) gave a better stereoselectivity than its alkyl counterpart (5w, E/Z = 7:1). Good functional group compatibility was also achieved at this time, although moderate conversions and E/Z ratios were obtained for those differentially functionalized alkynes (5y-af).

To further explore the generalizability of this chemistry, we explored other fluoro-containing iodides. Gratifyingly, both primary and secondary perfluoroalkyls were successfully incorporated into the C–C double bonds. Desired products were obtained without any difficulties only at the expense of lower conversions and the requirements of column chromatography purification (Scheme 3).



^{*a*}IC_{*m*} F_n 1 (0.2 mmol), allylbenzene 2a (0.2 mmol), Et₂Zn (50 mol %), acetonitrile (2.0 mL), -20 °C, 16 h. ^{*b*}Isolated yield.

More importantly, the reaction showed good potential for the late-stage structural modifications of natural products and pharmaceutical molecules (Scheme 4). A series of derivatives of those compounds, such as camphorsulfonic acid, estrone, (+)-fenchol, ibuprofen, dihydrocholesterol, and (+)-dehydroabietylamine, all reacted well to give the desired products in





^{*a*}ICF₂CO₂Et **1a** (0.2 mmol), alkenes **2** (0.2 mmol), Et₂Zn (50 mol %), acetonitrile (2.0 mL), -20 °C, 16 h. ^{*b*}Without column chromatography. ^{*c*}Isolated yield. ^{*d*}ICF₂CO₂Et **1a** (0.2 mmol), alkenes **2** (0.1 mmol), Et₂Zn (100 mol %), acetonitrile (2.0 mL), rt, 16 h. ^{*c*}Yield of recovered starting material.

satisfying to excellent yields. The other functional groups on the parent compounds were all well tolerated throughout the reactions. It should be noted that for those examples with moderate yields, the reactions were also clean. Starting materials were recovered, and a good mass balance was obtained (7e).

To shed light on the mechanism, a series of studies was performed. First, under similar conditions, other organometallic reagents such as n-butyllithium and methyl magnesium iodide both failed to promote the reaction, although the latter is well known in radical processes (Scheme 5A). That

Scheme 5. Mechanism Studies



result also excluded a base-catalyzed mechanism, which is one probable mechanism in Hu's work.^{8a} To determine whether metal zinc is the real catalytic species, we examined zinc powder, as well as other reductive metals (Cu, Mn, Mg, Fe), to promote the reaction. However, even at elevated temperatures, those metals all failed to give the desired products (Scheme 5A). Hence the data excluded a metal-promoted mechanism, which is proposed by several groups.¹⁷ The reaction performed well in the dark, thus excluding a light-induced mechanism (Scheme 5B). The addition of TEMPO totally shut down the reaction, whether or not alkene 2a was added, and the TEMPO-captured ethyl difluoroacetate radical 8 was detected by gas chromatography-mass spectrometry (GC-MS), which strongly indicated that radical species were involved in the reaction (Scheme 5C). Moreover, a couple of radical ringopening and ring-closure reactions further consolidated a radical mechanism. For example, α -pinene gave a ring-opening product 9 (Scheme 5D), whereas allyl ether and allyl amine substrates both gave ring-closure products 10 (Scheme 5E). In combination with the result that no protonated products were isolated after the reaction, these data also excluded a carbozincation mechanism.¹⁸ Further studies showed that after reacting with 1.0 equiv of diethylzinc in the absence of alkenes or alkynes, ICF2CO2Et fully transformed into enolate I because its protonated product HCF₂CO₂Et 11 was detected as the only fluorine-containing species by crude ¹⁹F NMR (Scheme 5F).¹⁹ Trace amounts of oxygen were proven to be

necessary to initiate the reaction, as only <5% product was obtained when the reaction was performed in freshly distilled MeCN with freeze-pump-thaw cycling.

On the basis of those results, a probable mechanism is proposed. First, diethylzinc undergoes metal/iodine exchange upon reaction with ethyl iododifluoroacetate 1a to afford intermediate I (Scheme 6, step 1).²⁰ In the meantime,





diethylzinc reacts with a trace amount of oxygen to release ethyl radical II (step 2).¹² The latter then attacks I to produce ethyl difluoroacetate radical III and regenerate the diethylzinc (step 3). Radical III then undergoes an atom transfer radical addition (ATRA) reaction;^{2b} that is, radical III first adds to a C-C multiple bond to form an adduct radical IV (step 4), which captures an iodide radical from the starting material 1a to furnish the target addition product (step 5). Meanwhile, this process regenerates the difluoroacetate radical III, which could react with another molecule of substrates.

The synthesized products are versatile building blocks and exhibit broad synthetic utility. Both the iodide and the difluoroester are readily transformed into other groups. For example, iodide in compound **3b** was smoothly substituted by sodium azide via a $S_N 2$ reaction (Scheme 7A). The





difluoroester in compound **3a** was readily reduced to alcohol and subsequently underwent an intramolecular $S_N 2$ reaction to form a novel fluoro-containing tetrahydrofuran motif (Scheme 7B). Importantly, on the basis of multifarious cross-coupling reactions, a series of groups could be installed on the fluorocontaining backbones. This utility was exemplified by a palladium-catalyzed Sonogashira coupling and a cobaltcatalyzed Kumada coupling. Both the vinyl iodide and the alkyl iodide successfully reacted with the corresponding coupling partners to afford the desired products **14** and **15** in good yields (Scheme 7C,D).

In conclusion, we have developed a simple but efficient protocol to install two functional groups of synthetic values onto C-C multiple bonds. This work demonstrates a novel way to generate an ethyl difluoroacetate radical. The mild conditions, high yields, excellent functional group compatibility, and good stereoselectivity make our protocol of great synthetic importance and a good complement to the existing catalytic systems. The application of zinc-mediated radical chemistry to other reactions is under investigation in our lab.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00669.

Detailed experimental procedures, characterization data, and copies of 1 H and 13 C NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

Qiuling Song – Institute of Next Generation Matter	
	Transformation, College of Materials Science & Engineering,
	Huaqiao University, Xiamen 361021, Fujian, China; State
	Key Laboratory of Organometallic Chemistry and Key
	Laboratory of Organofluorine Chemistry, Shanghai Institute
	of Organic Chemistry, Chinese Academy of Sciences,
	Shanghai 200032, China; @ orcid.org/0000-0002-9836-
	8860; Email: gsong@hgu.edu.cn

Authors

- Xin Li Institute of Next Generation Matter Transformation, College of Materials Science & Engineering, Huaqiao University, Xiamen 361021, Fujian, China
- Songtao He Institute of Next Generation Matter Transformation, College of Materials Science & Engineering, Huaqiao University, Xiamen 361021, Fujian, China

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00669

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge the financial support from the National Natural Science Foundation of China (21772046 and 2193103). We also thank the Instrumental Analysis Center of Huaqiao University.

REFERENCES

(1) For selected reviews on transition-metal-catalyzed 1,2difunctionalization, see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483–2547. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications. *Chem. Rev.* **2011**, *111*, 2981–3019. (c) Yin, G.; Mu, X.; Liu, G. Palladium(II)-Catalyzed Oxidative Difunctionalization of Alkenes: Bond Forming at a High-Valent Palladium Center. *Acc.* (2) For selected reviews on photocatalyzed 1,2-difunctionalization, see: (a) Koike, T.; Akita, M. New Horizons of Photocatalytic Fluoromethylative Difunctionalization of Alkenes. *Chem.* **2018**, *4*, 409–437. (b) Courant, T.; Masson, G. Recent Progress in Visible-Light Photoredox-Catalyzed Intermolecular 1,2-Difunctionalization of Double Bonds via an ATRA-Type Mechanism. J. Org. Chem. **2016**, *81*, 6945–6952. (c) Cao, M.-Y.; Ren, X.; Lu, Z. Olefin Difunctionalizations via Visible Light Photocatalysis. *Tetrahedron Lett.* **2015**, *56*, 3732–3742.

(3) For selected reviews on 1,2-difunctionalization through radical pathways, see: (a) Li, Z.-L.; Fang, G.-C.; Gu, Q.-S.; Liu, X.-Y. Recent Advances in Copper-Catalysed Radical-Involved Asymmetric 1,2-Difunctionalization of Alkenes. *Chem. Soc. Rev.* **2020**, *49*, 32–48. (b) Gu, Q.-S.; Li, Z.-L.; Liu, X.-Y. Copper(I)-Catalyzed Asymmetric Reactions Involving Radicals. *Acc. Chem. Res.* **2020**, *53*, 170–181. (c) Wu, Y.-C.; Xiao, Y.-T.; Yang, Y.-Z.; Song, R.-J.; Li, J.-H. Recent Advance in Silver-Mediated Radical Difunctionalization of Alkenes. *ChemCatChem* **2020**, *12*, 5312–5329. (d) Lan, X.-W.; Wang, N.-X.; Xing, Y. Recent Advances in Radical Difunctionalization of Simple Alkenes. *Eur. J. Org. Chem.* **2017**, *2017*, 5821–5851. (e) Zeng, Y.; Liu, X.-D.; Guo, X.-Q.; Gu, Q.-S.; Li, Z.-L.; Chang, X.-Y.; Liu, X.-Y. Cu/ Chiral Phosphoric Acid-Catalyzed Radical-Initiated Asymmetric Aminosilylation of Alkene with Hydrosilane. *Sci. China: Chem.* **2019**, *62*, 1529–1536.

(4) For selected reviews on 1,2-difunctionalization through electrosynthesis, see: (a) Siu, J. C.; Fu, N.; Lin, S. Catalyzing Electrosynthesis: A Homogeneous Electrocatalytic Approach to Reaction Discovery. *Acc. Chem. Res.* **2020**, *53*, 547–560. (b) Sauer, G. S.; Lin, S. An Electrocatalytic Approach to the Radical Difunctionalization of Alkenes. *ACS Catal.* **2018**, *8*, 5175–5187.

(5) For selected reviews on 1,2-difunctionalization through other pathways, see: (a) Matviitsuk, A.; Panger, J. L.; Denmark, S. E. Catalytic, Enantioselective Sulfenofunctionalization of Alkenes: Development and Recent Advances. *Angew. Chem., Int. Ed.* 2020, 59, 19796–19819. (b) Romero, R. M.; Wöste, T. H.; Muñiz, K. Vicinal Difunctionalization of Alkenes with Iodine(III) Reagents and Catalysts. *Chem. - Asian J.* 2014, 9, 972–983.

(6) For selected reviews on introducing fluoro-containing groups into C–C multiple bonds, see: (a) Merino, E.; Nevado, C. Addition of CF3 Across Unsaturated Moieties: a Powerful Functionalization Tool. *Chem. Soc. Rev.* **2014**, *43*, 6598–6608. (b) Besset, T.; Poisson, T.; Pannecoucke, X. Direct Vicinal Difunctionalization of Alkynes: An Efficient Approach Towards the Synthesis of Highly Functionalized Fluorinated Alkenes. *Eur. J. Org. Chem.* **2015**, *2015*, 2765–2789.

(7) (a) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. Intermolecular Atom Transfer Radical Addition to Olefins Mediated by Oxidative Quenching of Photoredox Catalysts. J. Am. Chem. Soc. 2011, 133, 4160-4163. (b) Iqbal, N.; Jung, J.; Park, S.; Cho, E. J. Controlled Trifluoromethylation Reactions of Alkynes through Visible-Light Photoredox Catalysis. Angew. Chem., Int. Ed. 2014, 53, 539-542. (c) Arceo, E.; Montroni, E.; Melchiorre, P. Photo-Organocatalysis of Atom-Transfer Radical Additions to Alkenes. Angew. Chem., Int. Ed. 2014, 53, 12064-12068. (d) Tang, X.-J.; Dolbier, W. R., Jr. Efficient Cu-Catalyzed Atom Transfer Radical Addition Reactions of Fluoroalkylsulfonyl Chlorides with Electron-Deficient Alkenes Induced by Visible Light. Angew. Chem., Int. Ed. 2015, 54, 4246-4249. (e) Rawner, T.; Lutsker, E.; Kaiser, C. A.; Reiser, O. The Different Faces of Photoredox Catalysts: Visible-Light-Mediated Atom Transfer Radical Addition (ATRA) Reactions of Perfluoroalkyl Iodides with Styrenes and Phenylacetylenes. ACS Catal. 2018, 8, 3950-3956. (f) Han, H. S.; Lee, Y. J.; Jung, Y. S.; Han, S. B.

Stereoselective Photoredox-Catalyzed Chlorotrifluoromethylation of Alkynes: Synthesis of Tetrasubstituted Alkenes. Org. Lett. 2017, 19, 1962–1965. (g) Wang, K.; Meng, L. G.; Wang, L. Visible-Light-Initiated Na2-Eosin Y Catalyzed Highly Regio- and Stereoselective Difunctionalization of Alkynes with Alkyl Bromides. J. Org. Chem. 2016, 81, 7080–7087. (h) Mao, T.; Ma, M.-J.; Zhao, L.; Xue, D.-P.; Yu, Y.; Gu, J.; He, C.-Y. A General and Green Fluoroalkylation Reaction Promoted via Noncovalent Interactions Between Acetone and Fluoroalkyl Iodides. Chem. Commun. 2020, 56, 1815–1818. (i) Lin, Q.-Y.; Ran, Y.; Xu, X.-H.; Qing, F.-L. Photoredox-Catalyzed Bromodifluoromethylation of Alkenes with (Difluoromethyl)triphenylphosphonium Bromide. Org. Lett. 2016, 18, 2419–2422. (j) Li, K.; Zhang, X.; Chen, J.; Gao, Y.; Yang, C.; Zhang, K.; Zhou, Y.; Fan, B. Blue Light Induced Difluoroalkylation of Alkynes and Alkenes. Org. Lett. 2019, 21, 9914–9918.

(8) (a) Xu, T.; Cheung, C. W.; Hu, X. Iron-Catalyzed 1,2-Addition of Perfluoroalkyl Iodides to Alkynes and Alkenes. Angew. Chem., Int. Ed. 2014, 53, 4910–4914. (b) Wu, G.; Jacobi von Wangelin, A. Stereoselective Cobalt-Catalyzed Halofluoroalkylation of Alkynes. Chem. Sci. 2018, 9, 1795–1802. (c) Belhomme, M. C.; Dru, D.; Xiong, H.-Y.; Cahard, D.; Besset, T.; Poisson, P.; Pannecoucke, X. Copper-Mediated Direct Functionalization of Unsaturated C–C Bonds with Ethyl Bromo(difluoro)acetate: A Straightforward Access to Highly Valuable Difluoromethylated Alkenes. Synthesis 2014, 46, 1859–1870. (d) Deng, W.; Li, Y.; Li, Y.-G.; Bao, H. Iron-Catalyzed Carboiodination of Alkynes. Synthesis 2018, 50, 2974–2980. (e) Li, D.; Mao, T.; Huang, J.; Zhu, Q. Copper-Catalyzed Bromodifluoroacetate. J. Org. Chem. 2018, 83, 10445–10452.

(9) Zhao, L.; Huang, Y.; Wang, Z.; Zhu, E.; Mao, T.; Jia, J.; Gu, J.; Li, X.-F.; He, C.-Y. Organophosphine-Catalyzed Difluoroalkylation of Alkenes. *Org. Lett.* **2019**, *21*, 6705–6709.

(10) (a) Rink, L. Zinc in Human Health; IOS Press BV: Amsterdam, The Netherlands, 2011. (b) Mills, C. F. Zinc in Human Biology; Springer-Verlag, 1989. (c) Supuran, C. T.; Winum, J.-Y. Drug Design of Zinc-Enzyme Inhibitors: Functional, Structural, and Disease Applications; John Wiley & Sons, Inc.: Hoboken, NJ, 2009.

(11) (a) Knochel, P.; Jones, P. Organozinc Reagents A Practical Approach; Oxford University Press: New York, 1999. (b) Rappoport, Z.; Marek, I. The Chemistry of Organozinc Compounds; John Wiley & Sons, Inc.: West Sussex, England, 2006. (c) Enthaler, S.; Wu, X.-F. Zinc Catalysis Applications in Organic Synthesis; Wiley-VCH: Weinheim, Germany, 2015.

(12) (a) Bazin, S.; Feray, L.; Bertrand, M. P. Diethylzinc in Radical Reactions. Chimia 2006, 60, 260-265. (b) van der Deen, H.; Kellogg, R. M.; Feringa, B. L. Remarkable O2-Effect in 1,4-Additions of Diethylzinc to 6-Acyloxy-2H-pyran-3(6H)-ones and 6-Alkoxy-2Hpyran-3(6H)-ones. Org. Lett. 2000, 2, 1593-1595. (c) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. Diethylzinc: A Chain-Transfer Agent in Intermolecular Radical Additions. A Parallel with Triethylborane. J. Org. Chem. 1999, 64, 9189-9193. (d) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Akindele, T.; Umeki, H.; Tomioka, K. Tin-Free Intermolecular Addition of Primary Alkyls to Imines via the Dimethylzinc-Air Radical Process. Org. Lett. 2006, 8, 87-89. (e) Bazin, S.; Feray, L.; Vanthuyne, N.; Bertrand, M. P. Dialkylzinc mediated radical additions to chiral N-enoyloxazolidinones in the presence of benzaldehyde. Mechanistic investigation, structural characterization of the resulting γ -lactones. Tetrahedron 2005, 61, 4261-4274. (f) Cohen, T.; Gibney, H.; Ivanov, R.; Yeh, E. A.-H.; Marek, I.; Curran, D. P. Intramolecular Carbozincation of Unactivated Alkenes Occurs through a Zinc Radical Transfer Mechanism. J. Am. Chem. Soc. 2007, 129 (49), 15405-15409. (g) Stadtmüller, H.; Vaupel, A.; Tucker, C. E.; Stüdemann, T.; Knochel, P. Stereoselective Preparation of Polyfunctional Cyclopentane Derivatives by Radical Nickel- or Palladium-Catalyzed Carbozincations. Chem. - Eur. J. 1996, 2, 1204-1220. (h) Yamada, K.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. Radical Addition of Ethers to Imines Initiated by Dimethylzinc. Org. Lett. 2002, 4, 3509-3511. (i) Yamada, K.; Yamamoto, Y.; Tomioka,

K. Initiator-Dependent Chemoselective Addition of THF Radical to Aldehyde and Aldimine and Its Application to a Three-Component Reaction. Org. Lett. **2003**, *5*, 1797–1799. (j) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Tomioka, K. Introduction of Functionalized C1, C2, and C3 Units to Imines through the Dimethylzinc–Air-Initiated Radical Addition. J. Org. Chem. **2004**, *69*, 1531–1534. (k) Chen, Z.; Zhang, Y.-X.; An, Y.; Song, X.-L.; Wang, Y.-H.; Zhu, L.-L.; Guo, L. Radical Addition of Ethers to Terminal Alkynes with High E-Selectivity. Eur. J. Org. Chem. **2009**, 2009, 5146–5152. (l) Beniazza, B.; Romain, E.; Chemla, F.; Ferreira, F.; Jackowski, O.; Perez-Luna, A. Zinc Radical Transfer Based Modular Approach to Enantiopure Alkylidene- β -prolines from N-(tert-Butylsulfinyl)- α -(aminomethyl)acrylates. Eur. J. Org. Chem. **2015**, 2015, 7661–7665.

(13) (a) Cozzi, P. G. A Catalytic, Me2Zn-Mediated, Enantioselective Reformatsky Reaction with Ketones. Angew. Chem., Int. Ed. 2006, 45, 2951-2954. (b) Mileo, E.; Benfatti, F.; Cozzi, P. G.; Lucarini, M. Me2Zn as a radical source in Reformatsky-type reactions. Chem. Commun. 2009, 469-470. (c) Maury, J.; Feray, L.; Perfetti, P.; Bertrand, M. P. A Flexible, Stereoselective Dimethylzinc-Mediated Radical-Anionic Cascade: Dramatic Influence of Additional Lewis Acids. Org. Lett. 2010, 12, 3590-3593. (d) Maury, J.; Feray, L.; Bertrand, M. P. Unprecedented Noncatalyzed anti-Carbozincation of Diethyl Acetylenedicarboxylate through Alkylzinc Group Radical Transfer. Org. Lett. 2011, 13, 1884-1887. (e) Maury, J.; Mouysset, D.; Feray, L.; Marque, S. R. A.; Siri, D.; Bertrand, M. P. Aminomethylation of Michael Acceptors: Complementary Radical and Polar Approaches Mediated by Dialkylzincs. Chem. - Eur. J. 2012, 18, 3241-3247. (f) Jammi, S.; Maury, J.; Suppo, J.-S.; Bertrand, M. P.; Feray, L. Intramolecular Trapping of Allenylzincs by Carbonyl Groups. J. Org. Chem. 2013, 78, 12566-12576. (g) Pérez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. Radical-Polar Crossover Domino Reaction Involving Alkynes: A Stereoselective Zinc Atom Radical Transfer. Chem. - Eur. J. 2008, 14, 8784-8788. (h) Chemla, F.; Dulong, F.; Ferreira, F.; Nüllen, M. P.; Pérez-Luna, A. Radical Zinc-Atom Transfer Based Multicomponent Approaches to 3-Alkylidene-Substituted Tetrahydrofurans. Synthesis 2011, 2011, 1347-1360. (i) Romain, E.; Fopp, F.; Chemla, F.; Ferreira, F.; Jackowski, O.; Oestreich, M.; Pérez-Luna, A. Trans-Selective Radical Silylzincation of Ynamides. Angew. Chem., Int. Ed. 2014, 53, 11333-11337. (j) Fopp, F.; Romain, E.; Isaac, K.; Chemla, F.; Ferreira, F.; Jackowski, O.; Oestreich, M.; Pérez-Luna, A. Stereodivergent Silylzincation of a-Heteroatom-Substituted Alkynes. Org. Lett. 2016, 18, 2054-2057. (k) Fopp, F.; Isaac, K.; Romain, E.; Chemla, F.; Ferreira, F.; Jackowski, O.; Oestreich, M.; Pérez-Luna, A. Stereodivergent Synthesis of β -Heteroatom-Substituted Vinylsilanes by Sequential Silylzincation-Copper(I)-Mediated ElectrophilicSubstitution. Synthesis 2017, 49, 724-735. (l) de la Vega-Hernández, K.; Romain, E.; Coffinet, A.; Bijouard, K.; Gontard, G.; Chemla, F.; Ferreira, F.; Jackowski, O.; Pérez-Luna, A. Radical Germylzincation of α -Heteroatom-Substituted Alkynes. J. Am. Chem. Soc. 2018, 140, 17632-17642.

(14) See the Supporting Information for more details.

(15) The relative configuration of product **3s** was determined by NOESY and compared with the literature-reported spectra: (a) Xiao, F.; Wu, F.; Shen, Y.; Zhou, L. Synthesis of α,α -Difluoro- γ -Butyrolactones via Ethyl Iododifluoroacetate. *J. Fluorine Chem.* **2005**, *126*, 63–67. For using the NOE experiment to determine the relative configuration of the vicinal substituted cycloalkane products, see: (b) Wang, F.; Qi, X.; Liang, Z.; Chen, P.; Liu, G. Copper-Catalyzed Intermolecular Trifluoromethylazidation of Alkenes: Convenient Access to CF3-Containing Alkyl Azides. *Angew. Chem., Int. Ed.* **2014**, *53*, 1881–1886.

(16) The configuration of product **5a** was determined by comparing with the literature-reported spectra: Li, G.; Cao, Y.-X.; Luo, C.-G.; Su, Y.-M.; Li, Y.; Lan, Q.; Wang, X.-S. Copper-Catalyzed Decarboxylative Atom Transfer Radical Addition of Iododifluoroacetate to Alkynyl Carboxylic Acids. *Org. Lett.* **2016**, *18*, 4806–4809.

(17) (a) Yang, Z.-Y.; Burton, D. G. A New Approach to α,α -Difluoro-Functionalized Esters. J. Org. Chem. **1991**, 56, 5125–5132.

(b) Chen, Q.-Y.; Yang, Z.-Y. Studies on Fluoroalkylation and Fluoroalkoxylation. Part 3. Perfluoroalkylation of Olefins with Perfluoroalkyl-Iodides and Copper in Various Solvenets. *J. Fluorine Chem.* **1985**, *28*, 399–411. (c) Liu, X.; Zhu, S.; Wang, S. Zinc-Mediated Radical Reactions of Per- (or Poly)fluorophenyl Aromatic Aldimines in Aqueous Media. *Synthesis* **2004**, *2004*, 683–691.

(18) For a review on the carbozincation of alkenes and alkynes, see ref 11b, chapter 19.

(19) See the Supporting Information for more details.

(20) (a) Charette, A. B.; Beauchemin, B.; Marcoux, J. F. Photoinduced Synthesis of Diorganozinc and Organozinc Iodide Reagents. J. Am. Chem. Soc. 1998, 120, 5114–5115. (b) Ito, S.; Shinokubo, H.; Oshima, K. Synthesis of Cyclopropanols via Cyclopropanation of Zinc Enolates. Tetrahedron Lett. 1998, 39, 5253–5256. (c) Aikawa, K.; Nakamura, Y.; Yokota, Y.; Toya, W.; Mikami, K. Stable but Reactive Perfluoroalkylzinc Reagents: Application in Ligand-Free Copper-Catalyzed Perfluoroalkylation of Aryl Iodides. Chem. - Eur. J. 2015, 21, 96–100. (d) Kato, K.; Hirano, K.; Kurauchi, D.; Toriumi, N.; Uchiyama, M. Dialkylzinc-Mediated Cross-Coupling Reactions of Perfluoroalkyl and Perfluoroaryl Halides with Aryl Halides. Chem. - Eur. J. 2015, 21, 3895–3900.