JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Organoiodine-Catalyzed Enantioselective Intermolecular Oxyamination of Alkenes

Chisato Wata and Takuya Hashimoto*

Cite This: J. Am. Chem. Soc. 2021, 143, 1745−1751
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Metal-free, catalytic enantioselective intermolecular oxyamination of alkenes is realized by use of organoiodine(I/III) chemistry. The protocol is applicable toward aryl- and alkyl-substituted alkenes with high enantioselectivity and electronically controlled regioselectivity. The oxyaminated products can be easily deprotected in one step to reveal free amino alcohols in high yields without loss of enantioselectivity. A key to our success is the discovery of a virtually unexplored chemical entity, *N*-(fluorosulfonyl)carbamate, as a bifunctional N,O-nucleophile.

β-Amino alcohol is a common structural motif in natural products and pharmaceuticals,[1] and also in asymmetric synthesis as chiral auxiliaries, ligands, and catalysts.[2] One ideal way to access enantioenriched *β*-amino alcohols is catalytic enantioselective intermolecular oxyamination of alkenes given its ease of synthesis planning and the availability of a vast number of alkenes.[3] The standard procedure for this purpose has long been the osmium-catalyzed Sharpless asymmetric aminohydroxylation (AA),[4] while it is plagued with poor regioselectivity,[5] and the toxicity and cost of osmium,[6] hampering its more comprehensive application.

A handful of reports have emerged to address this challenge by using transition metal catalysis,[7] although few offer ways to transform alkenes to unprotected *β*-amino alcohols. Yoon and co-workers have described the iron-catalyzed enantioselective oxyamination of vinylarenes and terminal dienes with an *N*-nosyl oxaziridine which reveals free *β*-amino alcohols after two-step deprotection.[7b] The Arnold group has disclosed the engineered hemeprotein-catalyzed enantioselective aminohydroxylation of vinylarenes which directly affords unprotected *β*-amino alcohols.[7f] It is of note that these two studies are not a direct replacement of the Sharpless AA, as these methodologies exhibit complementary regioselectivity. Outside transition metal catalysis, Denmark and co-workers have reported the selenium-catalyzed syn-oxyamination of a single 1,2-diarylethylene without referring to deprotection.[8] Even with these advances, aliphatic alkenes remain a very challenging substrate class in catalytic enantioselective intermolecular oxyamination.[9]

Chiral organoiodine(I/III) catalysis has become a reliable tool to difunctionalize alkenes in a stereocontrolled manner without the need for transition metals,[10] owing to the rapid development of this field in the past 15 years.[11] However, two identical functionalities are inevitably incorporated into an alkene (Figure 1a),[12] unless at least one of the nucleophiles is preinstalled in the substrate.[13] An unmet challenge in this field is, therefore, intermolecular heterodifunctionalization of alkenes with high regio- and stereocontrol,[14] which will enable valuable synthetic transformations like oxyamination. With

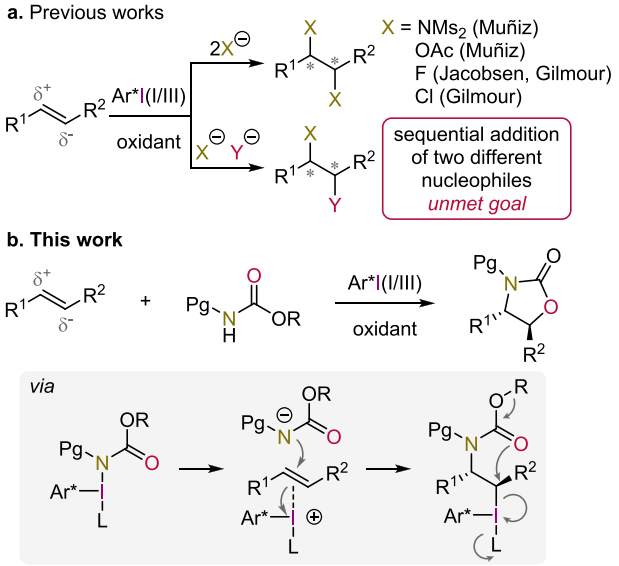


Figure 1. Organoiodine(I/III)-catalyzed enantioselective intermolecular difunctionalization of alkenes.

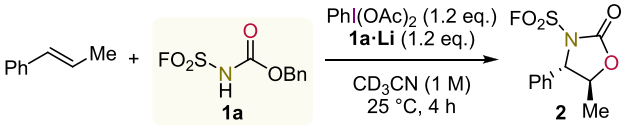
regard to the use of organoiodine chemistry for the oxyamination of alkenes,[15] the fully intramolecular, stoichiometric oxyamination using a chiral organoiodine(III) reagent remains the state-of-the-art as reported by the Wirth group.[16,29]

Herein, we report the realization of an organoiodine(I/III)-catalyzed enantioselective intermolecular oxyamination of alkenes, capitalizing on the discovery of a novel carbamate as

Received: November 3, 2020
Published: January 22, 2021

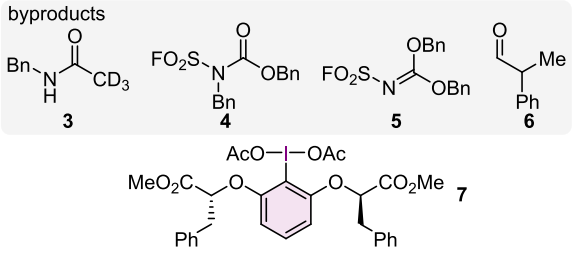
https://dx.doi.org/10.1021/jacs.0c11440
J. Am. Chem. Soc. 2021, 143, 1745−1751

Table 1. Optimization of Stoichiometric Oxyamination

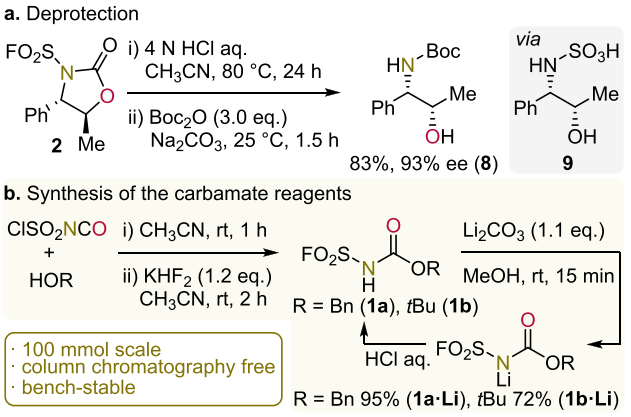


entry	change from the standard conditions	yield (%)[a,b]
1	none	73 (72)[c]
2	without **1a·Li**	45
3	without **1a**	5
4	$CDCl_3$ as solvent	55
5	$TsNHCO_2Bn$ and $TsN(Li)CO_2Bn$ instead of **1a** and **1a·Li**	0
6[d]	**1b** and **1b·Li** instead of **1a** and **1a·Li**	76
7[e]	**7** instead of $PhI(OAc)_2$	(72%, 93% ee)

[a]0.10 mmol scale. [b]NMR yield (isolated yield). [c]0.3 mmol scale. [d]$PhI(OAc)_2$ (0.20 mmol), **1b** (0.20 mmol), **1b·Li** (0.12 mmol). [e]**7** (0.12 mmol), CH_3CN (0.5 M), −20 °C, 48 h.



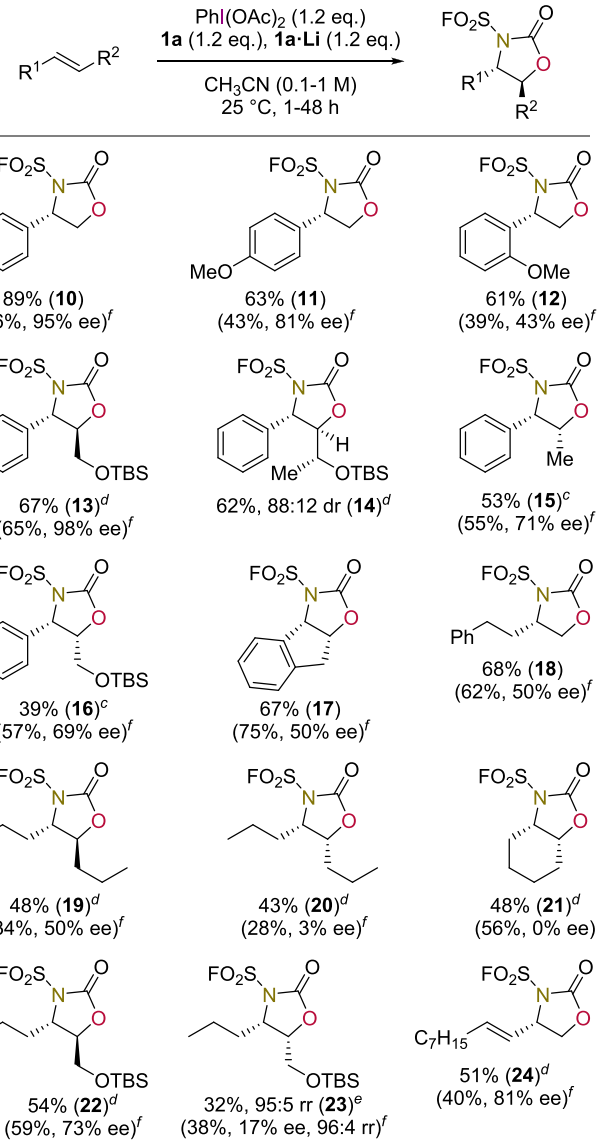
Scheme 1. Deprotection and Reagent Synthesis



a bifunctional N,O-nucleophile. The oxyamination and successive deprotection are conducted without needs for transition metals, harsh conditions, or inert atmosphere. Compared with the Sharpless AA, the equal level of enantioselectivities and higher regioselectivities are achieved over a broad range of vinylarenes.[17] Furthermore, the first highly regio- and enantioselective intermolecular oxyamination of aliphatic alkenes is accomplished.

Our conceptual blueprint is the use of a carbamate reagent,[8,18] which acts as a bifunctional nitrogen and oxygen nucleophile sequentially toward an alkene (Figure 1b). A suitable carbamate reagent needs to have two seemingly opposite properties: one is high acidity to facilitate the generation of a reactive alkene-coordinated iodonium intermediate; the other is high nucleophilicity toward the activated alkene. For the successful implementation of this protocol, the amide nitrogen, not the carbonyl oxygen, of the carbamate must attack at the alkene carbon with more positive charge. At the same time, facile deprotection of the oxyaminated products must be taken into consideration to reveal free *β*-amino alcohols without loss of stereochemical integrity and overall yield.

Table 2. Scope of Stoichiometric Oxyamination[a,b]

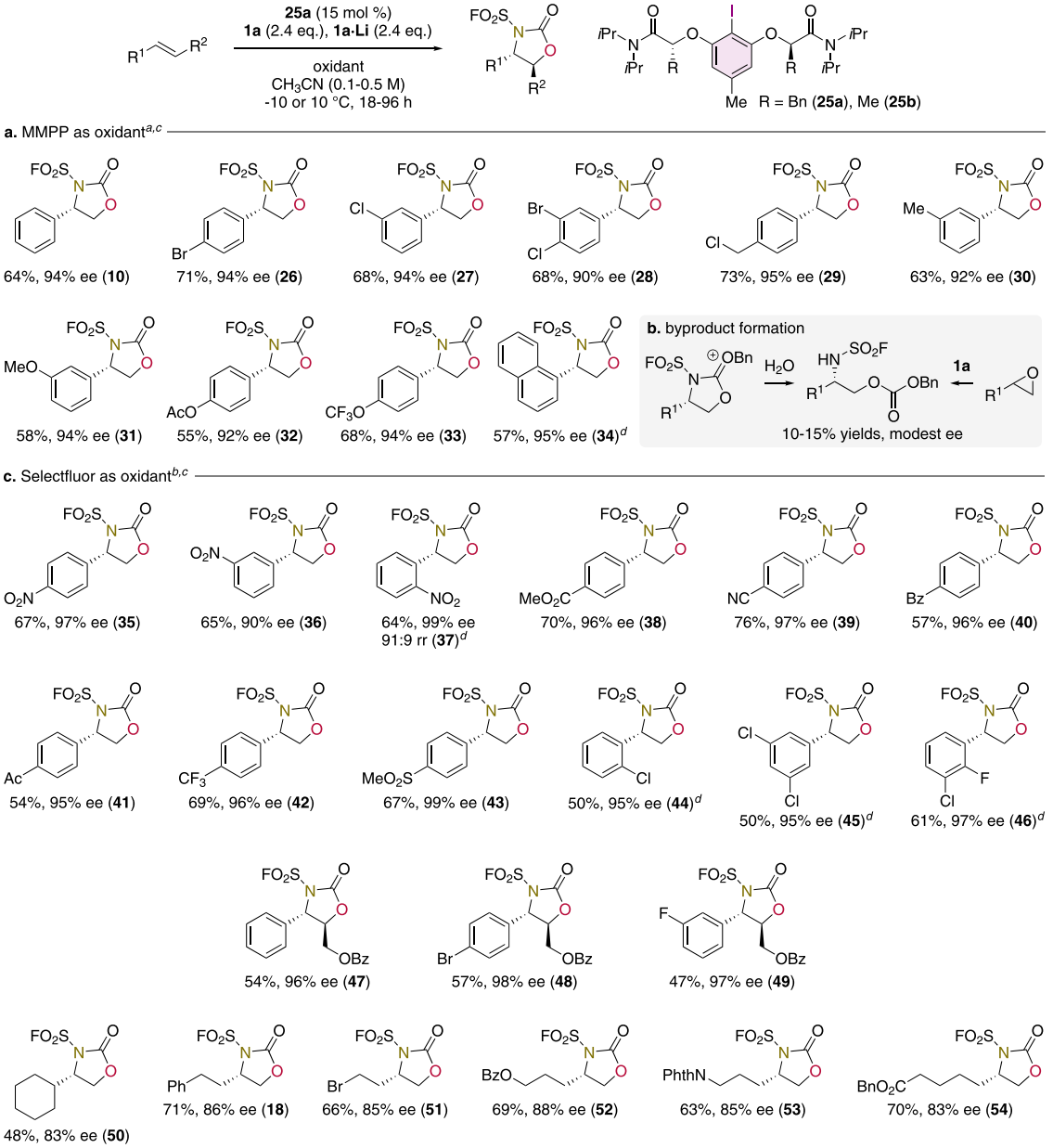


[a]0.30 mmol scale. [b]Isolated yield of single regioisomer, see the SI for regioselectivity of each reaction. [c]**1a** (0.72 mmol), **1a·Li** (0.72 mmol). [d]$PhI(OAc)_2$ (0.60 mmol), **1b** (0.60 mmol), **1b·Li** (0.36 mmol). [e]$PhI(OAc)_2$ (0.90 mmol), **1b** (0.90 mmol), **1b·Li** (0.36 mmol). [f]0.10 mmol scale with **7** (0.12 mmol), **1a** (0.12−0.24 mmol), **1a·Li** (0.12−0.24 mmol), see the SI for details.

We first sought to identify a carbamate reagent which fulfills all these criteria, in a stoichiometric oxyamination of *trans*-*β*-methylstyrene using $PhI(OAc)_2$. A crucial breakthrough in this attempt was the discovery of benzyl *N*-(fluorosulfonyl)-carbamate **1a**, a chemical entity that has never been used before in organic synthesis,[19] as a bifunctional N,O-nucleophile (Table 1). Under the optimized conditions, *trans*-*β*-methylstyrene reacted with **1a** and its lithium salt **1a·Li** under air at 25 °C to give *trans*-oxazolidinone **2** in 73% yield. The observed syn-stereospecificity and high regioselectivity (>95:5) are consistent with our proposed mechanism

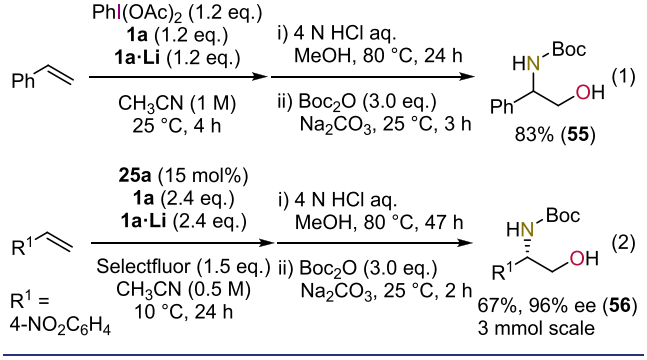
https://dx.doi.org/10.1021/jacs.0c11440
J. Am. Chem. Soc. 2021, 143, 1745−1751

Table 3. Scope of Catalytic Enantioselective Intermolecular Oxyamination of Alkenes



[a]0.10 mmol scale with MMPP (0.10 mmol) at −10 °C. [b]0.10 mmol scale with Selectfluor (0.15 mmol) at 10 °C. [c]Isolated yield of single regioisomer; see the SI for regioselectivity of each reaction. [d]Performed with **25b**.

Scheme 2. One-pot Oxyamination−Deprotection



(see Figure 1b). We assume that the strong electron-withdrawing nature and small size of the fluorosulfonyl group are crucial for the generation of the iodonium intermediate and the successive attack of the nitrogen atom, respectively. In this reaction, the benzyl moiety of **1a** was trapped by acetonitrile and the carbamate reagent, generating byproducts **3**−**5**. Without lithium salt **1a·Li**, the yield was reduced, and aldehyde **6**, which stemmed from competitive addition of water, became the major byproduct (entry 2).[20] Essentially no reaction took place when lithium salt **1a·Li** alone was used in the absence of **1a** (entry 3). Acetonitrile is the solvent of choice, considering its ability to scavenge the benzyl group of the carbamate and dissolve **1a·Li** (entry 4). The exquisite reactivity of *N*-(fluorosulfonyl)carbamate was underlined by the reaction using $TsNHCO_2Bn$ and its lithium salt instead of **1a** and **1a·Li**,[8,18a] which gave no desired product (entry 5). In the evaluation of substrate scope (*vide infra*), we noticed that byproducts **4** and **5** occasionally became an

https://dx.doi.org/10.1021/jacs.0c11440
J. Am. Chem. Soc. 2021, 143, 1745−1751

obstacle for the isolation of the products. Accordingly, *tert*-butyl carbamate **1b** (see Scheme 1b) was introduced as an alternative, which forms volatile isobutene as the byproduct. This traceless strategy worked equally well to give **2** in 76% yield by modifying the stoichiometry of the reagents (entry 6). At this stage, we also optimized an enantioselective oxyamination using a stoichiometric amount of a chiral organoiodine(III) reagent. By examining several lactate-based reagents developed by Fujita and Ishihara,[21] we found out that the oxyamination with chiral reagent **7** furnished (4*S*,5*S*)-**2** in 72% yield and 93% ee (entry 7).[22]

The *N*-fluorosulfonyl group of the carbamate reagent also plays a vital role in deprotection of the oxyaminated product (Scheme 1a), building on the labile sulfur−fluorine bond in protic media.[23] Acid hydrolysis of (4*S*,5*S*)-**2** furnished the corresponding free amino alcohol in one step, which was isolated as N-Boc protected form **8** in 83% yield without erosion of its stereochemical integrity. Examination of the reaction solution revealed formation of sulfamic acid **9** as the intermediate. The carbamate reagent synthesis was also optimized to secure its availability on a large scale (Scheme 1b). The procedure is column chromatography free and routinely carried out on a 100 mmol scale in the lab, and carbamates **1** and lithium salts **1**·**Li** are obtained in good yields as bench-stable, crystalline solids.

Transforming unactivated *trans*- and *cis*-alkenes to the corresponding β-amino alcohols with reliable regio- and diastereoselectivities is still a daunting challenge even in racemic fashion, although considerable progress has been achieved in both stoichiometric and catalytic racemic oxyaminations.[18,24] Accordingly, we initially evaluated the scope of stoichiometric oxyamination (Table 2), with a focus on difficult substrates for our catalytic oxyamination (*vide infra*).

Styrene, *o*- and *p*-methoxystyrenes reacted to afford **10**−**12** in good yields and >95:5 regioselectivities. TBS-protected cinnamyl alcohol reacted to give amino diol **13** with perfect syn-stereospecificity. The oxyamination of a cinnamyl alcohol derivative with an α-chiral center took place from the congested side of the alkene to give all syn amino diol **14** with good diastereoselectivity. Acyclic aryl-substituted *cis*-alkenes, which are prone to give a mixture of diastereomers in other oxyaminations,[7d,18a,24a,d,k,n,v] were converted to **15** and **16** in moderate yields without compromising syn-stereospecificity (>95:5 dr). Indene was also a viable substrate to give **17** in good yield.

The oxyamination of a terminal aliphatic alkene provided **18** with electronically controlled regioselectivity, as in the case of vinylarenes, forging the C−N bond at the internal carbon. It is of note that, in preceding oxyaminations, deterioration or reversal of the regioselectivity is frequently observed by switching from aryl- to alkyl-substituted alkenes.[18b,24b,h,v] Symmetrical, *trans*- and *cis*-aliphatic alkenes were also tolerated to give **19**−**21** in moderate yields. While unsymmetrical internal aliphatic alkenes present a challenge due to lack of a strong electronic and steric bias required for regioselective oxyamination,[25] *trans*- and *cis*-allylic silyl ethers underwent oxyamination to generate **22** and **23** with high regioselectivity and syn-stereospecificity. The oxyamination of a terminal diene also gave product **24** in moderate yield.[26]

These substrates were then subjected to chiral organoiodine(III)-mediated oxyamination (see Table 1, entry 7). Styrene, *p*-methoxystyrene, TBS-protected cinnamyl alcohol, and 1,3-nonadiene reacted to afford **10**, **11**, **13**, and **24** with high enantioselectivities. The reactions with *cis*-aryl alkenes and aliphatic alkenes, except for *cis*-aliphatic alkenes, led to moderate enantioselectivities.

We next shifted focus on our final goal of achieving an organoiodine(I/III)-catalyzed enantioselective intermolecular oxyamination of alkenes (Table 3). By investigating catalyst structures, reaction conditions, and external oxidants (see the SI), we reached to a couple of principles to implement catalytic highly enantioselective oxyamination. Chiral organoiodine catalysts based on a 5-methylresorcinol core with *N*,*N*-diisopropylamide side arms **25**, introduced by Muñiz,[12f] are indispensable to attain good turnover and high enantioselectivity. Catalyst **25a** with pendant benzyl groups worked well for a broad range of alkenes, while methyl-substiuted catalyst **25b** performed better for ortho-substituted vinylarenes in terms of both the yield and ee.

The judicious choice of an oxidant depending on the electronic properties of vinylarenes is also an important factor. For electronically neutral and slightly electron-poor vinylarenes, magnesium monoperoxyphthalate hexahydrate (MMPP) was found to be optimal (Table 3a).[27] The conditions were applicable to halogenated (**26**−**28**), alkylated (**29** and **30**), oxygenated (**31**−**33**), and fused (**34**) vinylarenes with excellent enantioselectivities. Concomitantly, ring-opened byproducts were obtained in 10−15% yields with moderate ee (Table 3b). We have confirmed the byproducts could stem from vinylarenes via epoxidation and ring opening with **1a** in the absence an organoiodine catalyst.[12f] The observed moderate enantioselectivity implies hydrolysis of the reaction intermediate as the second pathway.[10c]

As for electron-deficient or ortho-halogenated vinylarenes, the use of Selectfluor as an oxidant constantly gave the products in good yields and high enantioselectivities (Table 3c). Typical electron-withdrawing functionalities such as nitro, alkoxycarbonyl, cyano, acyl, trifluoromethyl, and sulfonyl groups were all tolerated as showcased in products **35**, **38**-**43**. The substitution pattern of the aromatic ring was examined with nitrostyrenes, generating **35**−**37** with excellent enantioselectivities. In the oxyamination of *o*-nitrostyrene, catalyst **25b** was selected to give product **37** which contained a small amount of the regioisomer. The catalytic oxyamination with *trans*- and *cis*-β-methylstyrenes led to poor yields irrespective of the reaction conditions. Meanwhile, cinnamyl benzoates reacted to give **47**−**49** as a single diastereomer with high enantioselectivities using Selectfluor.[12d] Catalytic enantioselective intermolecular oxyamination of aliphatic alkenes is an unsolved challenge in synthetic organic chemistry.[28] Accordingly, we were delighted that the catalytic oxyamination using Selectfluor tolerated terminal aliphatic alkenes, giving **18**, **50**−**54** having different functionalities in good yields and enantioselectivities over 80%.

Finally, we developed one-pot reactions that give unprotected amino alcohols straightforwardly (Scheme 2). By use of the stoichiometric oxyamination with $PhI(OAc)_2$, styrene was converted to (*rac*)-N-Boc-phenylglycinol **55** in 83% overall yield (eq 1). The catalytic enantioselective oxyamination/deprotection sequence was implemented on 3 mmol scale using *p*-nitrostyrene to give **56** in 67% overall yield and 96% ee (eq 2).

In conclusion, we have realized the organoiodine(I/III)-catalyzed, highly enantioselective intermolecular oxyamination of alkenes which generates enanitoenriched β-amino alcohols from aryl- and alkyl-substituted alkenes. A critical element in

https://dx.doi.org/10.1021/jacs.0c11440
J. Am. Chem. Soc. 2021, 143, 1745−1751

the successful achievement is the discovery of *N*-(fluorosulfonyl)carbamates as a new reagent in synthetic organic chemistry.[29]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11440.

Detailed experimental procedures, characterization data, copies of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra, and HPLC data (PDF)

Accession Codes

CCDC 1963253, 1963807−1963808, and 2036171−2036172 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Takuya Hashimoto − *Chiba Iodine Resource Innovation Center and Department of Chemistry, Graduate School of Science, Chiba University, Chiba 263-8522, Japan;* orcid.org/0000-0002-6963-4322; Email: takuya.hash@chiba-u.jp

Author

Chisato Wata − *Chiba Iodine Resource Innovation Center and Department of Chemistry, Graduate School of Science, Chiba University, Chiba 263-8522, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c11440

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

In memory of Prof. Kilian Muñiz. We thank Yamato Omatsu, Prof. Yoshiyuki Mizuhata, and Prof. Norihito Tokitoh for X-ray crystallography of **14** and TBDPS analog of **22**, and Prof. Keiji Maruoka for the access to ESI-MS. This work was supported by JSPS KAKENHI Grant Number JP18H04256 in Precisely Designed Catalysts with Customized Scaffolding, Grant-in-Aid for Scientific Research (B) JP19H02710, the Society of Iodine Science, Ube Industries Foundation and Toyo Gosei Memorial Foundation.

■ REFERENCES

(1) Bergmeier, S. C. The synthesis of vicinal amino alcohols. *Tetrahedron* **2000**, *56*, 2561−2576.

(2) (a) Ager, D. J.; Prakash, I.; Schaad, D. R. 1,2-Amino alcohols and their heterocyclic derivatives as chiral auxiliaries in asymmetric synthesis. *Chem. Rev.* **1996**, *96*, 835−876. (b) Desimoni, G.; Faita, G.; Jørgensen, K. A. Update 1 of: C2-Symmetric chiral bis(oxazoline) ligands in asymmetric catalysis. *Chem. Rev.* **2011**, *111*, PR284−PR437. (c) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic reactions enabled by N-heterocyclic carbenes. *Chem. Rev.* **2015**, *115*, 9307−9387. (d) Ni, H.; Chan, W.-L.; Lu, Y. Phosphine-catalyzed asymmetric organic reactions. *Chem. Rev.* **2018**, *118*, 9344−9411.

(3) (a) Karjalainen, O. K.; Koskinen, A. M. P. Diastereoselective synthesis of vicinal amino alcohols. *Org. Biomol. Chem.* **2012**, *10*, 4311−4326. (b) Donohoe, T. J.; Callens, C. K. A.; Flores, A.; Lacy, A. R.; Rathi, A. H. Recent developments in methodology for the direct oxyamination of olefins. *Chem. - Eur. J.* **2011**, *17*, 58−76.

(4) Li, G.; Chang, H.-T.; Sharpless, K. B. Catalytic asymmetric aminohydroxylation (AA) of olefins. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451−454.

(5) (a) O'Brien, P. Sharpless asymmetric aminohydroxylation: Scope, limitations, and use in synthesis. *Angew. Chem., Int. Ed.* **1999**, *38*, 326−329. (b) Bodkin, J. A.; McLeod, M. D. The Sharpless asymmetric aminohydroxylation. *J. C. S., Perkin Trans.* **2002**, *1*, 2733−2746. (c) Muñiz, K. Imido-osmium(VIII) compounds in organic synthesis: aminohydroxylation and diamination reactions. *Chem. Soc. Rev.* **2004**, *33*, 166−174.

(6) Luttrell, W. E.; Giles, C. B. Toxic tips: Osmium tetroxide. *J. Chem. Health Saf.* **2007**, *14*, 40−41.

(7) (a) Michaelis, D. J.; Williamson, K. S.; Yoon, T. P. Oxaziridine-mediated enantioselective aminohydroxylation of styrenes catalyzed by copper(II) bis(oxazoline) complexes. *Tetrahedron* **2009**, *65*, 5118−5124. (b) Williamson, K. S.; Yoon, T. P. Iron catalyzed asymmetric oxyamination of olefins. *J. Am. Chem. Soc.* **2012**, *134*, 12370−12373. (c) Lu, D.-F.; Zhu, C.-L.; Jia, Z.-X.; Xu, H. Iron(II)-catalyzed intermolecular amino-oxygenation of olefins through the N−O bond cleavage of functionalized hydroxylamines. *J. Am. Chem. Soc.* **2014**, *136*, 13186−13189. (d) Zhu, C.-L.; Lu, D.-F.; Sears, J. D.; Jia, Z.-X.; Xu, H. Practical synthetic procedures for the iron-catalyzed intermolecular olefin aminohydroxylation using functionalized hydroxylamines. *Synthesis* **2016**, *48*, 3031−3041. (e) Shen, H. C.; Wu, Y. F.; Zhang, Y.; Fan, L. F.; Han, Z. Y.; Gong, L. Z. Palladium-catalyzed asymmetric aminohydroxylation of 1,3-dienes. *Angew. Chem., Int. Ed.* **2018**, *57*, 2372−2376. (f) Cho, I.; Prier, C. K.; Jia, Z.-J.; Zhang, R. K.; Görbe, T.; Arnold, F. H. Enantioselective aminohydroxylation of styrenyl olefins catalyzed by an engineered hemoprotein. *Angew. Chem., Int. Ed.* **2019**, *58*, 3138−3142.

(8) Tao, Z.; Gilbert, B. B.; Denmark, S. E. Catalytic, enantioselective syn-diamination of alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 19161−19170.

(9) Coombs, J. R.; Morken, J. P. Catalytic enantioselective functionalization of unactivated terminal alkenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 2636−2649.

(10) (a) 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. (b) Molnár, I. G.; Thiehoff, C.; Holland, M. C.; Gilmour, R. Catalytic, vicinal difluorination of olefins: Creating a hybrid, chiral bioisostere of the trifluoromethyl and ethyl groups. *ACS Catal.* **2016**, *6*, 7167−7173. (c) Fujita, M. Mechanistic aspects of alkene oxidation using chiral hypervalent iodine reagents. *Tetrahedron Lett.* **2017**, *58*, 4409−4419. (d) Li, X.; Chen, P.; Liu, G. Recent advances in hypervalent iodine(III)-catalyzed functionalization of alkenes. *Beilstein J. Org. Chem.* **2018**, *14*, 1813−1825.

(11) (a) Dohi, T.; Kita, Y. Hypervalent iodine reagents as a new entrance to organocatalysts. *Chem. Commun.* **2009**, 2073−2085. (b) Uyanik, M.; Ishihara, K. Conformationally-flexible chiral hypervalent organoiodine catalysts for enantioselective oxidative transformations. *Yuki Gosei Kagaku Kyokaishi* **2012**, *70*, 1116−1122. (c) Singh, F. V.; Wirth, T. Hypervalent iodine-catalyzed oxidative functionalizations including stereoselective reactions. *Chem. - Asian J.* **2014**, *9*, 950−971. (d) Claraz, A.; Masson, G. Asymmetric iodine catalysis-mediated enantioselective oxidative transformations. *Org. Biomol. Chem.* **2018**, *16*, 5386−5402. (e) Flores, A.; Cots, E.; Berges, J.; Muñiz, K. Enantioselective iodine(I/III) catalysis in organic synthesis. *Adv. Synth. Catal.* **2019**, *361*, 2−25.

(12) (a) Romero, R. M.; Souto, J. A.; Muñiz, K. Substitution effects of hypervalent iodine(III) reagents in the diamination of styrene. *J. Org. Chem.* **2016**, *81*, 6118−6122. (b) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. Catalytic, diastereoselective 1,2-difluorination of alkenes. *J. Am. Chem. Soc.* **2016**, *138*, 5000−5003. (c) Molnar, I. G.; Gilmour, R. Catalytic difluorination of olefins. *J. Am. Chem. Soc.* **2016**,

138, 5004−5007. (d) Wöste, T. H.; Muñiz, K. Enantioselective vicinal diacetoxylation of alkenes under chiral iodine(III) catalysis. *Synthesis* **2016**, *48*, 816−827. (e) Haubenreisser, S.; Woste, T. H.; Martinez, C.; Ishihara, K.; Muñiz, K. Structurally defined molecular hypervalent iodine catalysts for intermolecular enantioselective reactions. *Angew. Chem., Int. Ed.* **2016**, *55*, 413−417. (f) Muñiz, K.; Barreiro, L.; Romero, R. M.; Martínez, C. Catalytic asymmetric diamination of styrenes. *J. Am. Chem. Soc.* **2017**, *139*, 4354−4357. (g) Scheidt, F.; Schafer, M.; Sarie, J. C.; Daniliuc, C. G.; Molloy, J. J.; Gilmour, R. Enantioselective, catalytic vicinal difluorination of alkenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 16431−16435. (h) Haj, M. K.; Banik, S. M.; Jacobsen, E. N. Catalytic, enantioselective 1,2-difluorination of cinnamamides. *Org. Lett.* **2019**, *21*, 4919−4923. (i) Sarie, J. C.; Neufeld, J.; Daniliuc, C. G.; Gilmour, R. Catalytic vicinal dichlorination of unactivated alkenes. *ACS Catal.* **2019**, *9*, 7232−7237.

(13) (a) Shimogaki, M.; Fujita, M.; Sugimura, T. Enantioselective oxidation of alkenylbenzoates catalyzed by chiral hypervalent iodine(III) to yield 4-hydroxyisochroman-1-ones. *Eur. J. Org. Chem.* **2013**, *2013*, 7128−7138. (b) Suzuki, S.; Kamo, T.; Fukushi, K.; Hiramatsu, T.; Tokunaga, E.; Dohi, T.; Kita, Y.; Shibata, N. Iodoarene-catalyzed fluorination and aminofluorination by an Ar-I/HF·pyridine/mCPBA system. *Chem. Sci.* **2014**, *5*, 2754−2760. (c) Alhalib, A.; Kamouka, S.; Moran, W. J. Iodoarene-catalyzed cyclizations of unsaturated amides. *Org. Lett.* **2015**, *17*, 1453−1456. (d) Woerly, E. M.; Banik, S. M.; Jacobsen, E. N. Enantioselective, catalytic fluorolactonization reactions with a nucleophilic fluoride source. *J. Am. Chem. Soc.* **2016**, *138*, 13858−13861. (e) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. Catalytic, asymmetric difluorination of alkenes to generate difluoromethylated stereocenters. *Science* **2016**, *353*, 51−54. (f) Gelis, C.; Dumoulin, A.; Bekkaye, M.; Neuville, L.; Masson, G. Chiral hypervalent iodine(III) catalyst promotes highly enantioselective sulfonyl- and phosphoryl-oxylactonizations. *Org. Lett.* **2017**, *19*, 278−281. (g) Mennie, K. M.; Banik, S. M.; Reichert, E. C.; Jacobsen, E. N. Catalytic diastereo- and enantioselective fluoroamination of alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 4797−4802. (h) Scheidt, F.; Thiehoff, C.; Yilmaz, G.; Meyer, S.; Daniliuc, C. G.; Kehr, G.; Gilmour, R. Fluorocyclisation via I(I)/I(III) catalysis: a concise route to fluorinated oxazolines. *Beilstein J. Org. Chem.* **2018**, *14*, 1021−1027. (i) Sarie, J. C.; Thiehoff, C.; Neufeld, J.; Daniliuc, C. G.; Gilmour, R. Enantioselective synthesis of 3-fluorochromanes via iodine(I)/iodine(III) catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 15069−15075. (j) Sharma, H. A.; Mennie, K. M.; Kwan, E. E.; Jacobsen, E. N. Enantioselective aryl-iodide-catalyzed Wagner−Meerwein rearrangements. *J. Am. Chem. Soc.* **2020**, *142*, 16090−16096. (k) Levin, M. D.; Ovian, J. M.; Read, J. A.; Sigman, M. S.; Jacobsen, E. N. Catalytic enantioselective synthesis of difluorinated alkyl bromides. *J. Am. Chem. Soc.* **2020**, *142*, 14831−14837. (l) Wang, Q.; Lübcke, M.; Biosca, M.; Hedberg, M.; Eriksson, L.; Himo, F.; Szabó, K. J. Enantioselective Construction of Tertiary Fluoride Stereocenters by Organocatalytic Fluorocyclization. *J. Am. Chem. Soc.* **2020**, *142*, 20048−20057.

(14) Kong, W.; Feige, P.; de Haro, T.; Nevado, C. Regio- and enantioselective aminofluorination of alkenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 2469−2473.

(15) (a) Lovick, H. M.; Michael, F. E. Metal-free highly regioselective aminotrifluoroacetoxylation of alkenes. *J. Am. Chem. Soc.* **2010**, *132*, 1249−1251. (b) Cochran, B. M.; Michael, F. E. Metal-free oxidative cyclization of urea-tethered alkenes with hypervalent iodine. *Org. Lett.* **2008**, *10*, 5039−5042. (c) Jeon, H.; Kim, D.; Lee, J. H.; Song, J.; Lee, W. S.; Kang, D. W.; Kang, S.; Lee, S. B.; Choi, S.; Hong, K. B. Hypervalent iodine-mediated alkene functionalization: Oxazoline and thiazoline synthesis via inter-/intramolecular amino-hydroxylation and thioamination. *Adv. Synth. Catal.* **2018**, *360*, 779−783. (d) Yang, S.; Chen, Y.; Yuan, Z.; Bu, F.; Jiang, C.; Ding, Z. Divergent synthesis of oxazolidines and morpholines via $PhI(OAc)_2$-mediated difunctionalization of alkenes. *Org. Biomol. Chem.* **2020**, *18*, 9873−9882.

(16) Farid, U.; Wirth, T. Highly stereoselective metal-free oxyaminations using chiral hypervalent iodine reagents. *Angew. Chem., Int. Ed.* **2012**, *51*, 3462−3465.

(17) Reddy, K. L.; Sharpless, K. B. From styrenes to enantiopure α-arylglycines in two steps. *J. Am. Chem. Soc.* **1998**, *120*, 1207−1217.

(18) (a) Curle, J. M.; Perieteanu, M. C.; Humphreys, P. G.; Kennedy, A. R.; Tomkinson, N. C. O. Alkene syn- and anti-oxyamination with malonoyl peroxides. *Org. Lett.* **2020**, *22*, 1659−1664. (b) Kuszpit, M. R.; Giletto, M. B.; Jones, C. L.; Bethel, T. K.; Tepe, J. J. Hydroxyamination of olefins using Br-N-$(CO_2Me)_2$. *J. Org. Chem.* **2015**, *80*, 1440−1445. (c) Reed, N. L.; Herman, M. I.; Miltchev, V. P.; Yoon, T. P. Photocatalytic oxyamination of alkenes: Copper(II) salts as terminal oxidants in photoredox catalysis. *Org. Lett.* **2018**, *20*, 7345−7350.

(19) (a) Roesky, H. W.; Hoff, A. Sulfur-nitrogen compounds. II. Preparation and investigation of fluorosulfuryl compounds. *Chem. Ber.* **1968**, *101*, 162−173. (b) Roesky, H. W.; Babb, D. P. Bis-(dimethylamido)bis(N-fluorosulfonylimido)-sulfur, a covalent compound containing the SN_4 Group. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 674−675.

(20) Kikuchi, H.; Kogure, K.; Toyoda, M. A facile preparation of 2-arylpropionaldehyde from 1-aryl-1-propene. *Chem. Lett.* **1984**, *13*, 341−344.

(21) (a) Fujita, M.; Okuno, S.; Lee, H. J.; Sugimura, T.; Okuyama, T. Enantiodifferentiating tetrahydrofuranylation of but-3-enyl carboxylates using optically active hypervalent iodine(III) reagents via a 1,3-dioxan-2-yl cation intermediate. *Tetrahedron Lett.* **2007**, *48*, 8691−8694. (b) Uyanik, M.; Yasui, T.; Ishihara, K. Enantioselective Kita oxidative spirolactonization catalyzed by in situ generated chiral hypervalent iodine(III) species. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175−2177. (c) Fujita, M.; Yoshida, Y.; Miyata, K.; Wakisaka, A.; Sugimura, T. Enantiodifferentiating endo-selective oxylactonization of ortho-alk-1-enylbenzoate with a lactate-derived aryl-λ^3-iodane. *Angew. Chem., Int. Ed.* **2010**, *49*, 7068−7071.

(22) Zhou, B.; Haj, M. K.; Jacobsen, E. N.; Houk, K. N.; Xue, X.-S. Mechanism and origins of chemo- and stereoselectivities of aryl iodide-catalyzed asymmetric difluorinations of β-substituted styrenes. *J. Am. Chem. Soc.* **2018**, *140*, 15206−15218.

(23) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. Sulfur(VI) fluoride exchange (SuFEx): Another good reaction for click chemistry. *Angew. Chem., Int. Ed.* **2014**, *53*, 9430−9448.

(24) (a) Minakata, S.; Nishimura, M.; Takahashi, T.; Oderaotoshi, Y.; Komatsu, M. Direct asymmetric synthesis of oxazolines from olefins using a chiral nitridomanganese complex: a novel three-component coupling leading to chiral oxazolines. *Tetrahedron Lett.* **2001**, *42*, 9019−9022. (b) Liu, G.; Stahl, S. S. Highly regioselective Pd-catalyzed intermolecular aminoacetoxylation of alkenes and evidence for cis-aminopalladation and S_N2 C−O bond formation. *J. Am. Chem. Soc.* **2006**, *128*, 7179−7181. (c) Minakata, S.; Morino, Y.; Ide, T.; Oderaotoshi, Y.; Komatsu, M. Direct synthesis of oxazolines from olefins and amides using t-BuOI. *Chem. Commun.* **2007**, 3279−3281. (d) Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. Copper(II)-catalyzed aminohydroxylation of olefins. *J. Am. Chem. Soc.* **2007**, *129*, 1866−1867. (e) Benkovics, T.; Du, J.; Guzei, I. A.; Yoon, T. P. Anionic halocuprate(II) complexes as catalysts for the oxaziridine-mediated aminohydroxylation of olefins. *J. Org. Chem.* **2009**, *74*, 5545−5552. (f) DePorter, S. M.; Jacobsen, A. C.; Partridge, K. M.; Williamson, K. S.; Yoon, T. P. N-Nosyl oxaziridines as terminal oxidants in copper(II)-catalyzed olefin oxyaminations. *Tetrahedron Lett.* **2010**, *51*, 5223−5225. (g) Williamson, K. S.; Yoon, T. P. Iron-catalyzed aminohydroxylation of olefins. *J. Am. Chem. Soc.* **2010**, *132*, 4570−4571. (h) Martinez, C.; Wu, Y.; Weinstein, A. B.; Stahl, S. S.; Liu, G.; Muñiz, K. Palladium-catalyzed intermolecular amino-acetoxylation of alkenes and the influence of $PhI(OAc)_2$ on aminopalladation stereoselectivity. *J. Org. Chem.* **2013**, *78*, 6309−6315. (i) Zhang, B.; Studer, A. Stereoselective radical azidooxygenation of alkenes. *Org. Lett.* **2013**, *15*, 4548−4551. (j) Miyazawa, K.; Koike, T.; Akita, M. Regiospecific intermolecular aminohydroxylation of olefins by photoredox catalysis. *Chem. - Eur. J.* **2015**, *21*, 11677−

https://dx.doi.org/10.1021/jacs.0c11440
J. Am. Chem. Soc. 2021, 143, 1745−1751

11680. (k) Li, Y.; Hartmann, M.; Daniliuc, C. G.; Studer, A. Radical aminooxygenation of alkenes with N-fluoro-benzenesulfonimide (NFSI) and TEMPONa. *Chem. Commun.* **2015**, *51*, 5706−5709. (l) Sun, X.; Li, X.; Song, S.; Zhu, Y.; Liang, Y.-F.; Jiao, N. Mn-Catalyzed highly efficient aerobic oxidative hydroxyazidation of olefins: A direct approach to β-azido alcohols. *J. Am. Chem. Soc.* **2015**, *137*, 6059−6066. (m) Martínez, C.; Pérez, E. G.; Iglesias, Á.; Escudero-Adán, E. C.; Muñiz, K. Regioselective intermolecular diamination and aminooxygenation of alkenes with saccharin. *Org. Lett.* **2016**, *18*, 2998−3001. (n) Legnani, L.; Morandi, B. Direct catalytic synthesis of unprotected 2-amino-1-phenylethanols from alkenes by using iron(II) phthalocyanine. *Angew. Chem., Int. Ed.* **2016**, *55*, 2248−2251. (o) Hemric, B. N.; Shen, K.; Wang, Q. Copper-catalyzed amino lactonization and amino oxygenation of alkenes using O-benzoylhydroxylamines. *J. Am. Chem. Soc.* **2016**, *138*, 5813−5816. (p) Hemric, B. N.; Wang, Q. Copper-catalyzed intermolecular oxyamination of olefins using carboxylic acids and O-benzoylhydroxylamines. *Beilstein J. Org. Chem.* **2016**, *12*, 22−28. (q) Herrera-Leyton, C.; Madrid-Rojas, M.; López, J. J.; Cañete, Á.; Hermosilla-Ibáñez, P.; Pérez, E. G. Copper-catalyzed intermolecular aminooxygenation of styrenes using n-fluorobenzenesulfonimide and simple alcohols. *ChemCatChem* **2016**, *8*, 2015−2018. (r) Weng, S.-S.; Zhang, J.-W. N-Oxyl-radical-catalyzed intermolecular aminooxygenation of styrenes and inter/intramolecular aminoalkoxylation of homoallylic alcohols. *ChemCatChem* **2016**, *8*, 3720−3724. (s) Zeng, T.; Liu, Z.; Schmidt, M. A.; Eastgate, M. D.; Engle, K. M. Directed, palladium-(II)-catalyzed intermolecular aminohydroxylation of alkenes using a mild oxidation system. *Org. Lett.* **2018**, *20*, 3853−3857. (t) Siu, J. C.; Sauer, G. S.; Saha, A.; Macey, R. L.; Fu, N.; Chauviré, T.; Lancaster, K. M.; Lin, S. Electrochemical azidooxygenation of alkenes mediated by a TEMPO−N_3 charge-transfer complex. *J. Am. Chem. Soc.* **2018**, *140*, 12511−12520. (u) Hemric, B. N.; Chen, A. W.; Wang, Q. Copper-catalyzed 1,2-amino oxygenation of 1,3-dienes: A chemo-, regio-, and site-selective three-component reaction with O-acylhydroxylamines and carboxylic acids. *ACS Catal.* **2019**, *9*, 10070−10076. (v) Wu, F.; Alom, N. E.; Ariyarathna, J. P.; Nass, J.; Li, W. Regioselective formal [3 + 2] cycloadditions of urea substrates with activated and unactivated olefins for intermolecular olefin amino-oxygenation. *Angew. Chem., Int. Ed.* **2019**, *58*, 11676−11680.

(25) Ma, Z.; Naylor, B. C.; Loertscher, B. M.; Hafen, D. D.; Li, J. M.; Castle, S. L. Regioselective base-free intermolecular aminohydroxylations of hindered and functionalized alkenes. *J. Org. Chem.* **2012**, *77*, 1208−1214.

(26) The general reactivity trend is electron-rich vinylarenes > styrene > aliphatic alkenes > electron-poor vinylarenes.

(27) Shimogaki, M.; Fujita, M.; Sugimura, T. Metal-free enantioselective oxidative arylation of alkenes: Hypervalent-iodine-promoted oxidative C−C bond formation. *Angew. Chem., Int. Ed.* **2016**, *55*, 15797−15801.

(28) (a) Feldman, K. S.; Saunders, J. C.; Wrobleski, M. L. Alkynyliodonium salts in organic synthesis. Development of a unified strategy for the syntheses of (−)-agelastatin A and (−)-agelastatin B. *J. Org. Chem.* **2002**, *67*, 7096−7109. (b) Harding, M.; Bodkin, J. A.; Issa, F.; Hutton, C. A.; Willis, A. C.; McLeod, M. D. The asymmetric aminohydroxylation route to GABOB and homoserine derivatives. *Tetrahedron* **2009**, *65*, 831−843. (c) Harris, L.; Mee, S. P. H.; Furneaux, R. H.; Gainsford, G. J.; Luxenburger, A. Alkyl 4-chlorobenzoyloxycarbamates as highly effective nitrogen source reagents for the base-free, intermolecular aminohydroxylation reaction. *J. Org. Chem.* **2011**, *76*, 358−372. (d) Borah, A. J.; Phukan, P. Bromamine-T as an efficient amine source for Sharpless asymmetric aminohydroxylation of olefins. *Tetrahedron Lett.* **2014**, *55*, 713−715.

(29) During the revision of this manuscript, a paper on organoiodine-catalyzed intramolecular oxyamination appeared: Deng, X.-J.; Liu, H.-X.; Zhang, L.-W.; Zhang, G.-Y.; Yu, Z.-X.; He, W. Iodoarene-catalyzed oxyamination of unactivated alkenes to synthesize 5-imino-2-tetrahydrofuranyl methanamine derivatives. *J. Org. Chem.* **2021**, *86*, 235−253.

https://dx.doi.org/10.1021/jacs.0c11440
J. Am. Chem. Soc. 2021, 143, 1745−1751