

Tethered Silanoxyiodination of Alkenes

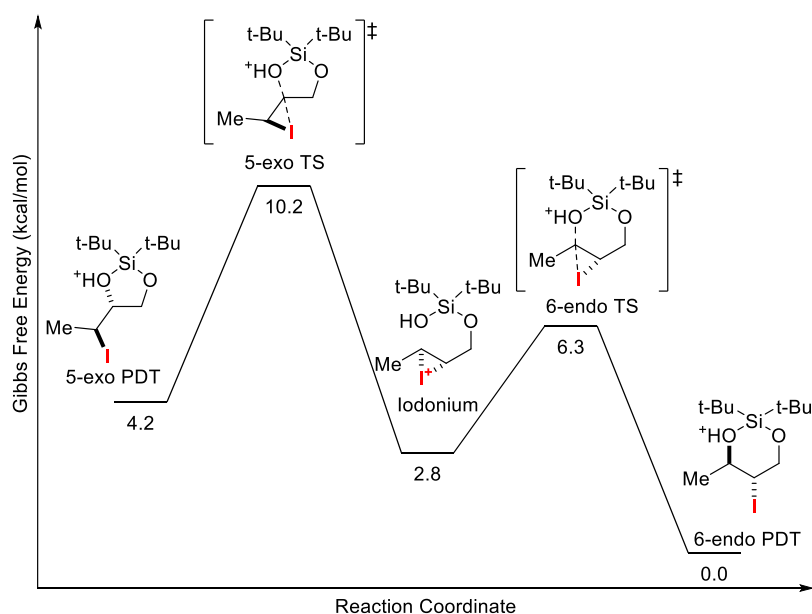
Ranjeet A. Dhokale,^[a] Frederick J. Seidl,^[b] Anand H. Shinde,^[a] Joel T. Mague,^[c] and Shyam Sathyamoorthi*^[a]

^aDepartment of Medicinal Chemistry, University of Kansas, Lawrence, Kansas, United States

^bIndependent Researcher, San Bruno, CA, United States

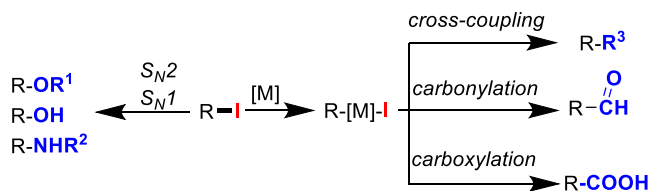
^cDepartment of Chemistry, Tulane University, New Orleans, Louisiana, United States

Supporting Information Placeholder



ABSTRACT: We present the first examples of tethered silanoxyiodination reactions of allylic alcohols. The products are useful silanediol organoiodide synthons and are formed with high regioselectivity and diastereocontrol. The reaction is scalable greater than 10-fold without loss of yield or selectivity. Furthermore, the products are starting materials for further transformations, including de-iodination, C–N bond installation, epoxide synthesis, and de-silylation. DFT calculations provide a basis for understanding the exquisite 6-*endo* selectivity of this silanoxyiodination reaction and show that the observed products are both kinetically and thermodynamically preferred.

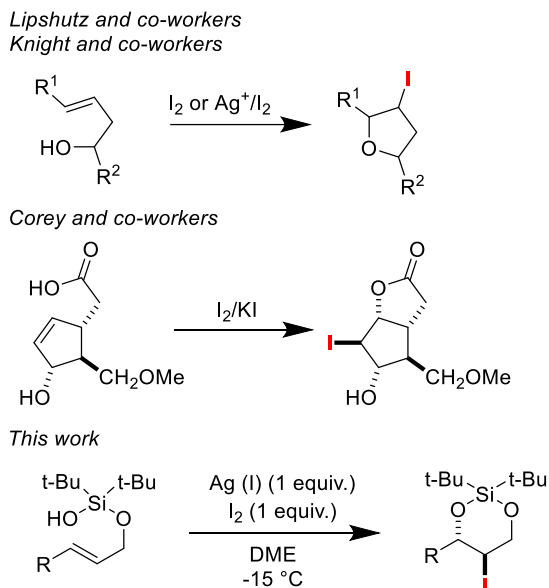
Tethered alkene functionalization reactions allow the synthetic chemist to transform olefins with unusual precision.^{1–7} Because of the predisposition for six- and seven-membered cyclic transition states, one can simply count the number of atoms from the nucleophilic auxiliary (“the tether”) where the functionalization event is likely to take place; due to geometric constraints, these reactions generally proceed with high regio- and diastereoselectivity. Our laboratory is deeply invested in developing tethered olefin functionalization reactions, and we have disclosed such reactions using sulfamate,^{8,9} phosphoramidate,¹⁰ and di-*tert*-butyl-silanoxy tethers.^{11,12}



Scheme 1. Organoiodides have proven versatility.

Iodofunctionalization of olefins is a particularly powerful method for the synthesis of organoiodides, which are versatile precursors for C–O,¹³ C–N,¹⁴ and C–C bonds¹⁵ (**Scheme 1**). Two particularly well-known classes within this large area are iodolactonization^{16–20} and

iodoetherification²¹⁻²⁴ of olefins (**Scheme 2**), and examples of both are found in complex molecule syntheses. Building on this precedent, we imagined a silanoxiyodination reaction, which would yield protected diol iodides in a single step and with high regio- and diastereoselectivity. We reasoned that the di-*tert*-butyl silyl group could be readily removed to reveal useful iodo-diol synthons. Here, we describe our efforts to reduce this idea to practice.



Optimization of this tethered silanoxiyodination reaction began with (E)-di-*tert*-butyl(hex-2-en-1-yloxy)silanol, conveniently prepared in one step from commercially available di-*tert*-butylsilyl bis(trifluoromethanesulfonate) and trans-2-hexen-1-ol.¹¹ With I₂ (3 equivalents) and NaHCO₃ (6 equivalents) in acetonitrile at 0 °C, we were pleased to observe 65% of desired product (**Table 1, Entry 1**). However, we soon discovered that these conditions were much too corrosive with other allylic silanols and led to markedly reduced product yields. The use of Ag (I) in conjunction with I₂ is well known for the mild generation of I⁺.^{21, 23, 25} With AgNO₃/I₂ (**Table 1, Entry 2**) and with Ag(TFA)/I₂ (**Table 1, Entry 3**), we did not observe any cyclized product formation. In both cases, we isolated linear alkyl iodide products, which we presume result from intermolecular opening of the transient iodonium intermediate by NO₃⁻ and CF₃CO₂⁻. We hypothesized that switching to a silver salt with a *non-nucleophilic* counterion would eliminate intermolecular ring-opening. With AgBF₄ in acetonitrile, tetrahydrofuran, or ethyl acetate (**Table 1, Entries 4-6**) at 0 °C, we observed ~60% cyclized product formation. Using CH₂Cl₂ as a solvent was markedly deleterious (**Table 1, Entry 7**). In THF, when the temperature was reduced from 0 °C to -15 °C, the yield of cyclized product increased slightly (**Table 1, Entry 8**); however, dropping the temperature further to -45 °C led to a dramatic decrease in product formation (**Table 1, Entry 9**). We found that Ag(OTf)/I₂ in THF, Ag(OTf)/I₂ in DME, and AgBF₄/I₂ in DME at -15 °C (**Table 1, Entries 10-12**) all gave comparable, good yields of cyclized product. Overall, we chose three protocols (A: AgBF₄/I₂/THF, B:

AgBF₄/I₂/DME, C: AgOTf/I₂/DME) for further exploration of scope.

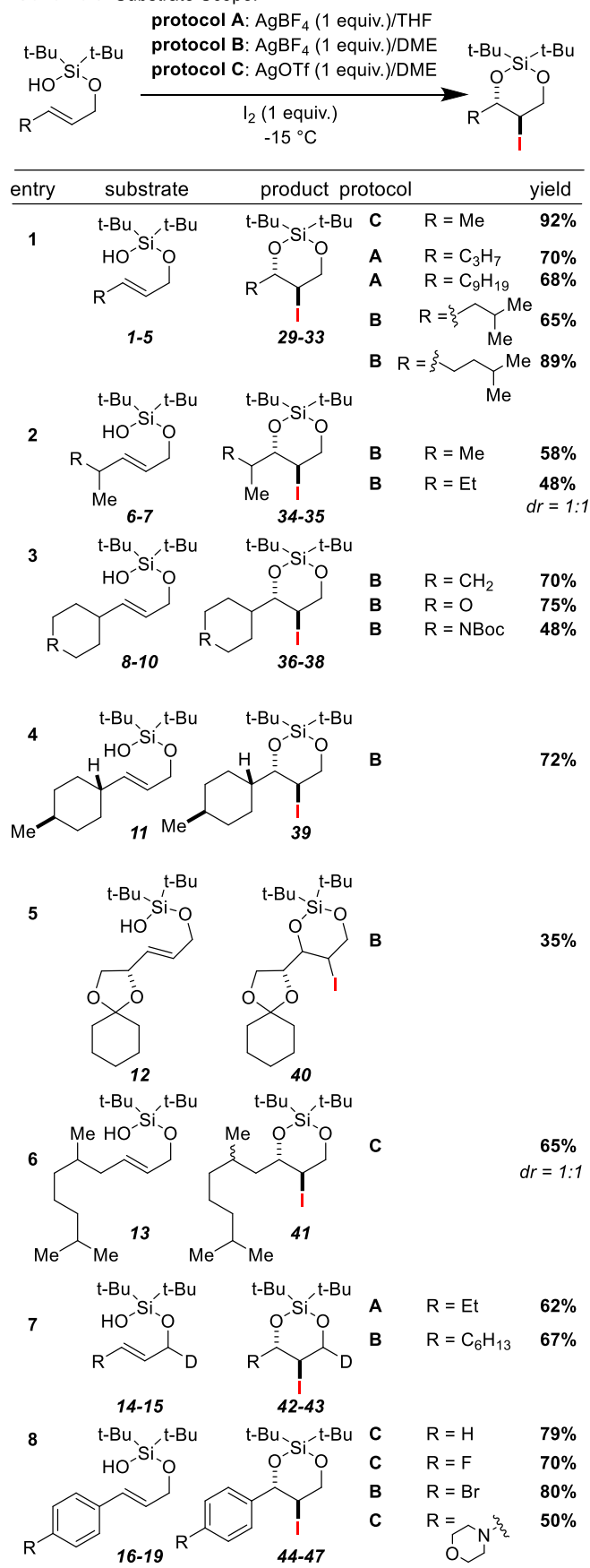
Table 1. Optimization of a tethered silanoxiyodination reaction.

	Ag (I) (equiv.)	I ₂ equiv.	Solvent	Temp. ^a	B/A ^b
1	None	3 ^c	MeCN	0 °C	65/0
2	AgNO ₃ (1)	1	MeCN	0 °C	0/0 ^d
3	Ag(TFA) (1)	1	MeCN	0 °C	0/0 ^e
4	AgBF ₄ (1)	1	MeCN	0 °C	58/0
5	AgBF ₄ (1)	1	THF	0 °C	60/0
6	AgBF ₄ (1)	1	EtOAc	0 °C	62/11
7	AgBF ₄ (1)	1	CH ₂ Cl ₂	0 °C	22/0
8	AgBF ₄ (1)	1	THF	-15 °C	65/0
9	AgBF ₄ (1)	1	THF	-45 °C	45/0
10	AgOTf (1)	1	THF	-15 °C	70/0
11	AgBF ₄ (1)	1	DME	-15 °C	75/0
12	AgOTf (1)	1	DME	-15 °C	80/0

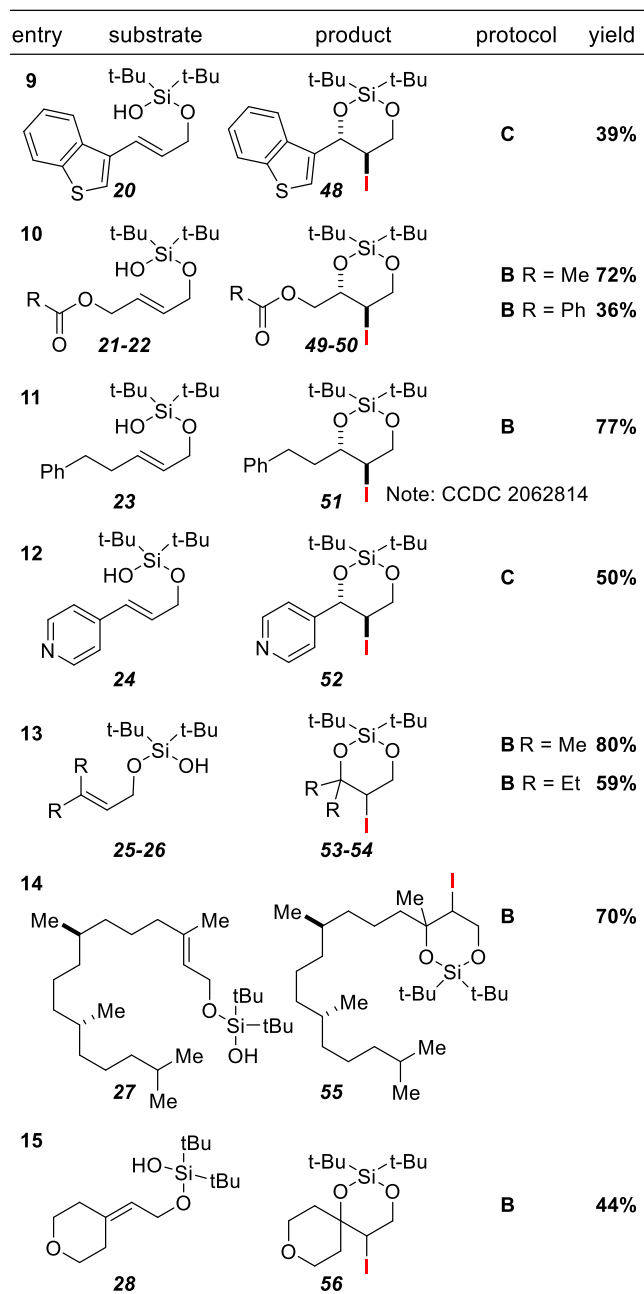
^areaction times were between 1 and 2 hours in all cases. ^bYield estimated from ¹H NMR integration with methyl phenyl sulfone as an internal standard. ^cWith 6 equivalents of NaHCO₃. ^dTwo non-cyclized products, which we presume result from NO₃⁻ opening of the iodonium intermediate. ^eTwo non-cyclized products, which we presume result from CF₃CO₂⁻ opening of the iodonium intermediate.

Examination of a variety of allylic silanol substrates (**Scheme 3**) with these protocols revealed that this transformation is quite general, tolerant of diverse functional groups, and in most cases, proceeds with high regio- and diastereoselectivity. We have determined the relative configuration of one of these products through x-ray diffraction analysis, which establishes that the iodine and the pendant alkyl chain are *trans* to each other (**Scheme 3, Entry 11**, CCDC: 2062814). While protocol A (AgBF₄/I₂/THF) gave good product yields with several substrates (**Scheme 3, Entries 1 and 7**), a curious side product complicated crude NMR analysis and purification. Amazingly, this side product has been previously characterized and arises from a ring-opening polymerization of THF by I₂.²⁶ We thus abandoned THF in favor of DME, and we recommend that for substrates not shown here, both protocol B (AgBF₄/I₂/DME) and protocol C (AgOTf/I₂/DME) should be empirically tested for best results. We were pleased to find that a variety of alkyl chains (**Scheme 3, Entries 1, 2, & 6**), rings (**Scheme 3, Entries 3-4**), alkyl ethers (**Scheme 3, Entry 3**), ketals (**Scheme 3, Entry 5**), esters (**Scheme 3, Entry 10**), aromatic rings (**Scheme 3, Entries 8 & 11**), and heteroaromatic rings (**Scheme 3, Entries 9 & 12**) were all tolerated by our optimized protocols. Furthermore, we were not limited to disubstituted olefins. A variety of tri-substituted olefins (**Scheme 3, Entries 13-15**) reacted smoothly as well.

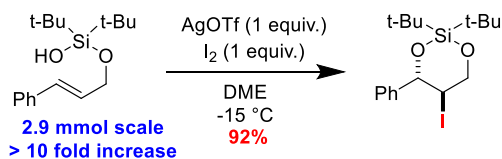
Scheme 3. Substrate Scope.



Scheme 3. Substrate Scope continued.

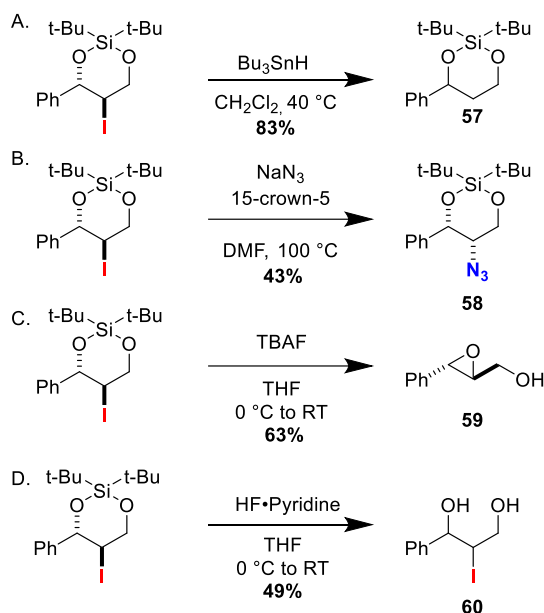


We were pleased to see that the reaction scaled greater than ten-fold without loss of yield or selectivity (**Scheme 4**).



Scheme 4. Silanoxiodination scales greater than ten fold without loss of yield or selectivity.

Furthermore, the cyclic silanediol organoiodide products were amenable to a variety of further transformations, including, de-iodination, nucleophilic azide displacement, epoxide formation, and silicon removal (**Scheme 5**).

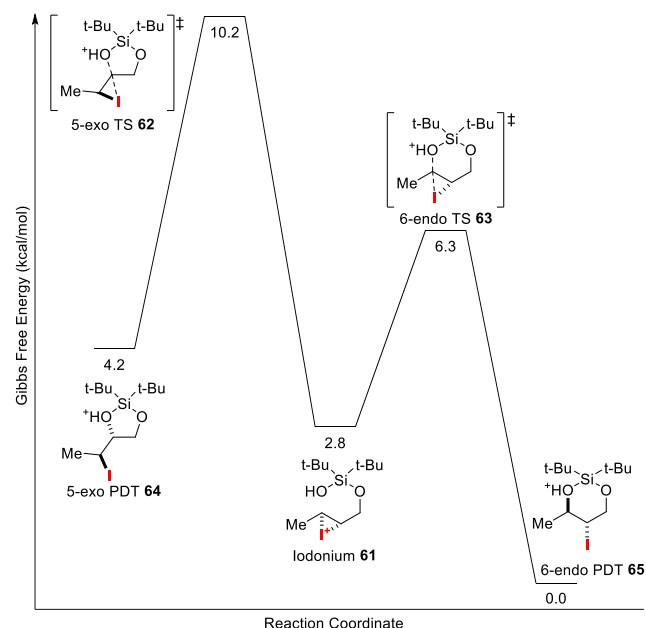


Scheme 5. Products are versatile synthons for: (A) de-iodination (B) C-N bond formation (C) epoxide formation and (D) silicon removal.

In all cases, we exclusively observed products of 6-*endo-trig* cyclization reactions. In order to rationalize such exquisite selectivity for the 6-*endo* product over the 5-*exo* isomer, we turned to DFT calculations using the ORCA software package.^{27,28} All calculations were performed using the B3LYP functional^{29,30} with D3BJ dispersion correction^{31,32} using the RIJCOSX approximation.³³ The def2-TZVP basis set³⁴ was used, and implicit THF solvation was applied using the SMD model.³⁵ When iodine was present, the def2-ECP³⁶ was applied automatically. Counterions were not modelled for ionic species. Further details and atomic coordinates are reported in the Supporting Information.

Upon exposing substrate alkene **1** to molecular iodine, the immediate product is an intermediate iodonium **61**. Intramolecular ring closure can proceed either *via* a 5-*exo* (**62**) or a 6-*endo* (**63**) transition state, leading to isomeric protonated products **64** and **65**. For the 5-*exo* pathway, both the transition state and the cationic product are more than 4 kcal/mol higher in energy than their 6-*endo* counterparts (**Figure 1**). This overwhelming preference for the 6-*endo* pathway agrees with the experimental absence of any 5-*exo* product, even in trace amounts. The origin of the 6-*endo* selectivity is most likely due to ring strain. For acyclic iodonium **61**, the O-Si-O angle is 102.6°, which is 6.9° lower than the ideal tetrahedral angle of 109.5°. This initial acyclic perturbation is likely due to the presence of the *tert*-butyl groups on the silicon, a manifestation of the Thorpe-Ingold effect.³⁷ The 6-*endo* transition state **63** has an O-Si-O angle of 101.3°, and the 6-*endo* product **65** has an O-Si-O angle of 97.6°, the latter of which is only 5° smaller than the acyclic angle on iodonium **61**. By contrast, the 5-*exo* transition state **62** has an O-Si-O angle of 96.7°, and the 5-*exo* product **64** has an O-Si-O angle of 89.8°, the latter of which is now geometrically acute and 12.8° smaller than the acyclic angle on iodonium **61**. Thus, the *tert*-butyl groups on silicon promote a Si-O-Si angle close to that required for 6-*endo* ring closure, while 5-*exo* ring closure requires a much more strained and energetically unfavorable Si-O-Si angle.

Figure 1. DFT energies for cationic iodonium rearrangements of substrate **1**.



In summary, we present the first examples of tethered silanoxiyodination reactions of allylic alcohols. The products are useful silanediol organoiodide synthons and are formed with high regioselectivity and diastereocontrol. The reaction is scalable greater than 10-fold without loss of yield or selectivity. Furthermore, the products are starting materials for further transformations, including de-iodination, C-N bond installation, epoxide synthesis, and de-silylation. DFT calculations provide a basis for understanding the exquisite 6-*endo* selectivity of this silanoxiyodination reaction. We expect this reaction to find much use in the construction of complex molecules containing functional group stereochemical arrays.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, crystal structure data, NMR spectra and computational details

The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

*ssathyam@ku.edu

ACKNOWLEDGMENT

This work was supported by start-up funding provided jointly by the University of Kansas Office of the Provost and the Department of Medicinal Chemistry, an NIH COBRE Chemical Biology of Infectious Diseases Research Project Grant (P20GM113117), and a New Faculty General Research Fund Grant.

REFERENCES

1. Degennaro, L.; Trinchera, P.; Luisi, R., Recent Advances in the Stereoselective Synthesis of Aziridines. *Chemical Reviews* **2014**, *114*, 7881-7929.
2. Overman, L. E.; Campbell, C. B., Hemiacetal mediated reactions. Directed synthesis of diols and acetals. *The Journal of Organic Chemistry* **1974**, *39*, 1474-1481.
3. Sarraf, S. T.; Leighton, J. L., Oxymercuration of Homoallylic Alcohol Derived Hemiacetals: Diastereoselective Synthesis of Protected 1,3-Diols. *Organic Letters* **2000**, *2*, 403-405.
4. Oswald, J. P.; Woerpel, K. A., Cobalt-Catalyzed Intramolecular Silylperoxidation of Unsaturated Diisopropylsilyl Ethers. *The Journal of Organic Chemistry* **2019**, *84*, 7564-7574.
5. Kotov, V.; Scarborough, C. C.; Stahl, S. S., Palladium-Catalyzed Aerobic Oxidative Amination of Alkenes: Development of Intra- and Intermolecular Aza-Wacker Reactions. *Inorganic Chemistry* **2007**, *46*, 1910-1923.
6. Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S., Ligand-Promoted Palladium-Catalyzed Aerobic Oxidation Reactions. *Chemical Reviews* **2018**, *118*, 2636-2679.
7. Thomas, A. A.; Nagamalla, S.; Sathyamoorthi, S., Salient features of the aza-Wacker cyclization reaction. *Chemical Science* **2020**, *11*, 8073-8088.
8. Shinde, A. H.; Sathyamoorthi, S., Oxidative Cyclization of Sulfamates onto Pendant Alkenes. *Organic Letters* **2020**, *22*, 896-901.
9. Shinde, A. H.; Nagamalla, S.; Sathyamoorthi, S., N-arylated oxathiazinane heterocycles are convenient synthons for 1,3-amino ethers and 1,3-amino thioethers. *Medicinal Chemistry Research* **2020**, *29*, 1223-1229.
10. Shinde, A. H.; Thomas, A. A.; Mague, J. T.; Sathyamoorthi, S., Highly Regio- and Diastereoselective Tethered Aza-Wacker Cyclizations of Alkenyl Phosphoramidates. *Chemrxiv* **2021**.
11. Shinde, A. H.; Sathyamoorthi, S., Tethered Silanoxymercuration of Allylic Alcohols. *Organic Letters* **2020**, *22*, 8665-8669.
12. Dhokale, R. A.; Seidl, F. J.; Sathyamoorthi, S., A Rearrangement of Allylic Silanols. *Chemrxiv* **2021**.
13. Nakamura, E.; Inubushi, T.; Aoki, S.; Machii, D., Aerobic conversion of organic halides to alcohols. An oxygenative radical cyclization. *Journal of the American Chemical Society* **1991**, *113*, 8980-8982.
14. Matier, C. D.; Schwaben, J.; Peters, J. C.; Fu, G. C., Copper-Catalyzed Alkylation of Aliphatic Amines Induced by Visible Light. *Journal of the American Chemical Society* **2017**, *139*, 17707-17710.
15. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D., Substitution reactions of secondary halides and epoxides with higher order, mixed organocuprates, R₂Cu(CN)Li₂: synthetic, stereochemical, and mechanistic aspects. *The Journal of Organic Chemistry* **1984**, *49*, 3928-3938.
16. Denmark, S. E.; Burk, M. T., Lewis base catalysis of bromo- and iodolactonization, and cycloetherification. *Proceedings of the National Academy of Sciences* **2010**, *107*, 20655.
17. Manuel, S. L.; Ajoy, K. B.; Elvia, V. C., Iodolactonization: Past and Present Examples. *Current Organic Chemistry* **2009**, *13*, 720-730.
18. Nolsøe, J. M. J.; Hansen, T. V., Asymmetric Iodolactonization: An Evolutionary Account. *European Journal of Organic Chemistry* **2014**, *2014*, 3051-3065.
19. Oderinde, M. S.; Hunter, H. N.; Bremner, S. W.; Organ, M. G., Iodolactonization: Synthesis, Stereocontrol, and Compatibility Studies. *European Journal of Organic Chemistry* **2012**, *2012*, 175-182.
20. Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W., Stereo-controlled synthesis of dl-prostaglandins F₂.α. and E₂. *Journal of the American Chemical Society* **1969**, *91*, 5675-5677.
21. Bedford, S. B.; Bell, K. E.; Fenton, G.; Hayes, C. J.; Knight, D. W.; Shaw, D., Iodoetherification of homoallylic alcohols : A stereoselective approach to tetrahydrofurans. *Tetrahedron Letters* **1992**, *33*, 6511-6514.
22. Brimble, M. A.; Edmonds, M. K., Synthesis of bis-2,5-linked tetrahydrofurans via iodoetherification. *Tetrahedron* **1995**, *51*, 9995-10012.
23. Lipshutz, B. H.; Barton, J. C., Reagent-based stereocontrol in formation of substituted tetrahydrofurans. *Journal of the American Chemical Society* **1992**, *114*, 1084-1086.
24. Campbell, M. J.; Johnson, J. S., Asymmetric Synthesis of (+)-Polyanthellin A. *Journal of the American Chemical Society* **2009**, *131*, 10370-10371.
25. Guindon, Y.; Slassi, A.; Ghiro, É.; Bantle, G.; Jung, G., Stereoselective silver triflate-mediated iodocyclization of carbamates. *Tetrahedron Letters* **1992**, *33*, 4257-4260.
26. Cataldo, F., Iodine: A ring opening polymerization catalyst for tetrahydrofuran. *European Polymer Journal* **1996**, *32*, 1297-1302.
27. Neese, F., The ORCA program system. *WIREs Computational Molecular Science* **2012**, *2*, 73-78.
28. Neese, F., Software update: the ORCA program system, version 4.0. *WIREs Computational Molecular Science* **2018**, *8*, e1327.
29. Becke, A. D., A new mixing of Hartree-Fock and local density-functional theories. *The Journal of Chemical Physics* **1993**, *98*, 1372-1377.
30. Lee, C.; Yang, W.; Parr, R. G., Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Physical Review B* **1988**, *37*, 785-789.
31. Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H., A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *The Journal of Chemical Physics* **2010**, *132*, 154104.
32. Grimme, S.; Ehrlich, S.; Goerigk, L., Effect of the damping function in dispersion corrected density functional theory. *Journal of Computational Chemistry* **2011**, *32*, 1456-1465.
33. Weigend, F., Accurate Coulomb-fitting basis sets for H to Rn. *Physical Chemistry Chemical Physics* **2006**, *8*, 1057-1065.
34. Weigend, F.; Ahlrichs, R., Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence

quality for H to Rn: Design and assessment of accuracy. *Physical Chemistry Chemical Physics* **2005**, *7*, 3297-3305.

35. Marenich, A. V.; Cramer, C. J.; Truhlar, D. G., Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *The Journal of Physical Chemistry B* **2009**, *113*, 6378-6396.

36. Peterson, K. A.; Figgen, D.; Goll, E.; Stoll, H.; Dolg, M., Systematically convergent basis sets with relativistic pseudopotentials. II. Small-core pseudopotentials and correlation consistent basis sets for the post-d group 16–18 elements. *The Journal of Chemical Physics* **2003**, *119*, 11113-11123.

37. Luh, T.-Y.; Hu, Z., Thorpe–Ingold effect in organosilicon chemistry. *Dalton Transactions* **2010**, *39*, 9185-9192.