OL Organic Letters

pubs.acs.org/OrgLett

Letter

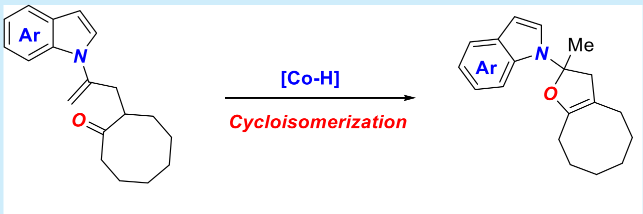
Catalytic Cycloisomerization onto a Carbonyl Oxygen

Shicheng Shi, Jonathan L. Kuo, Tao Chen, and Jack R. Norton*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02272

Read Online

ABSTRACT: We have found that terminal *N*-vinylindoles bearing cycloalkanone substituents are excellent hydrogen atom acceptors, generating α-aminyl radicals with a variety of catalysts (Co(II)/H_2 or Co(III)Cl precatalysts with silane reductants). These radicals can be converted to internal vinylindoles but eventually add to the oxygen of the cycloalkanone substituents. These cyclizations eventually furnish a densely functionalized dihydrofuran (a net cycloisomerization). The internal vinylindoles are slowly converted to the dihydrofurans, but the final cycloisomerization/isomerization ratio is affected by the size of the cycloalkanone ring (seven- and eight-membered rings give the highest ratio). These results demonstrate how HAT can isomerize substrates in nonintuitive ways, here leading to the first HAT-promoted formation of a C−O bond.



■ C-O bond formation ■ Cycloisomerization ■ up to >20:1 selectivity

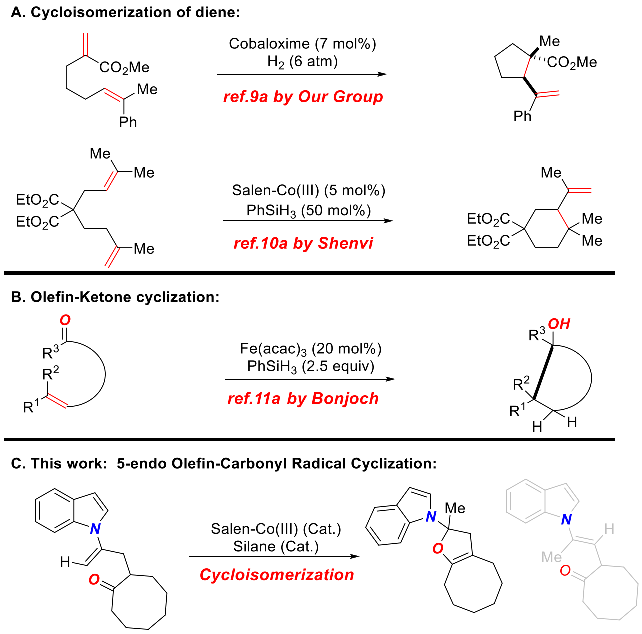
Hydrogen atom transfer (HAT) from metals to olefins, first observed by Sweany and Halpern,[1] has become (since the seminal work of Mukaiyama[2]) a powerful method for hydrofunctionalization of olefins.[3] A wide range of inter- and intramolecular transformations has been documented,[4−7] including cyclizations that are useful in the synthesis of complex natural products.[8]

Our group[9a] and the Shenvi group[10a] independently introduced Co complexes as catalysts for such diene cyclizations (Scheme 1A) and olefin isomerizations; we have employed H_2 as the source of the H•, and they have employed silanes. Since then many Co systems catalyzing isomerization of olefins have been developed by employing different types of ligands.[10b−f] More recently, the Bonjoch group has used Fe catalysts to generate (from olefins and a silane) carbon-centered radicals that add to the carbon of carbonyl groups and eventually give tertiary alcohols (Scheme 1B).[11a−d] We now report a complementary cyclization, that of a carbon-centered radical onto a carbonyl *oxygen* (Scheme 1C). The resulting compounds are highly substituted furans, not easily accessible by other methods,[12] with (1) congested quaternary carbons and (2) a stable hemiaminal attached to a functionalized indole.

The regiochemistry of radical cyclizations onto C═X bonds (X = O,[13] N[14]) is in general less predictable than that of radical cyclizations onto C═C bonds. It is well-known that the 5-exo C═C cyclization of a 5-hexenyl radical is faster than the 6-endo one,[15] but with a shorter chain (e.g., a 4-pentenyl radical) the pattern is inverted because the exo cyclization introduces ring strain.[16] (With substituted 4-pentenyl radicals both 4-exo[17] and 5-endo[18] products have been reported.)

However, both 4-exo (C)[19a] and 5-endo (O)[13,19] products have been reported from cyclizations onto C═O, and the

Scheme 1. Selected Examples of M-HAT-Initiated Intramolecular Radical Cyclization



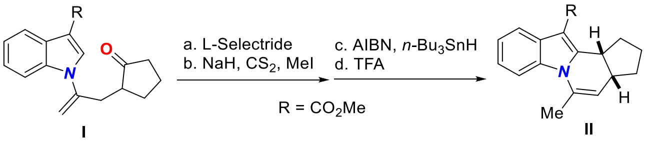
■ C-O bond formation ■ substrated controlled■ cycloisomerization ■ up to >20:1 selectivity

Received: July 8, 2020

outcome of these reactions has not been predictable.[20] Endo additions, onto O, are particularly of interest as they lead to oxygen-containing heterocycles.[21]

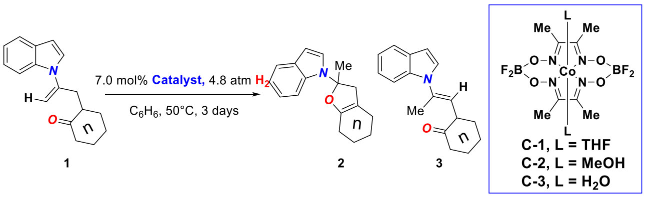
We have generated our carbon-centered radicals by HAT to *N*-vinylindoles **1**. Padwa has shown that such enamines are useful for the synthesis of alkaloids.[12,22] The reduction of the carbonyl of **I** and generation of a xanthate from the resulting alcohol led to a radical that adds to the 2-position of the indole and affords the tetracyclic indole derivatives **II** (Scheme 2).[12]

Scheme 2. *N*-Vinylindole as a Useful Intermediate in Alkaloid Synthesis



We believed that useful radicals might also be generated by H• transfer onto the vinyl groups of **1**. When we tried our cobaloxime/H_2 system[9] on an *N*-vinylindole with a tethered cyclohexanone (**1a**), we obtained the cycloisomerized product **2a** along with the isomerization product **3a** (Scheme 1C and Table 1, entry 2). It seemed likely that both **2a** and **3a** had arisen from the α-aminyl radicals[23],[24] formed by H• transfer (Scheme 3, pathway B), but they could also have come from the acid-promoted olefin/carbonyl cyclization (Scheme 3, pathway A).[25] The latter possibility is, however, unlikely in view of the hydrolytic instability of enamines like **1a** in the presence of acid[12] (attempts to take the NMR of **1a** in $CDCl_3$ just showed indole and the methyl ketone (eq 1), whereas **1a** is stable in acetone-d_6). We believe that both **2a** and **3a** are the result of HAT (Scheme 3, pathway B).[9a,10a]

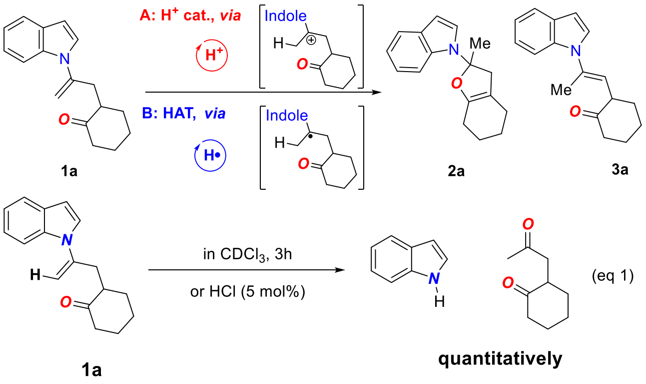
Table 1. Initial Optimization Studies in the Cyclization of *N*-Vinylindoles with Cobaloxime/H_2[a]



entry	substrate	catalyst	conversion[b] (%)	ratio (**2**:**3**)[b]
1	**1d**, *n* = 8	**C-1**	86	55:31
2	**1d**, *n* = 8	**C-2**	45	18:27
3	**1d**, *n* = 8	**C-3**	47	31:16
4	**1b**, *n* = 5	**C-1**	82	14:68
5	**1a**, *n* = 6	**C-1**	88	40:48
6	**1c**, *n* = 7	**C-1**	84	48:36
7	**1e**, *n* = 12	**C-1**	87	49:38
8	**1d**, *n* = 8	$CpCr(CO)_3H$	29	<1:27
9[c]	**1d**, *n* = 8	**C-1**	93	61:32
10[d]	**1d**, *n* = 8	**C-1**	95	69:26
11	**1d**, *n* = 8	no [Co]	<5	[f]
12[e]	**1d**, *n* = 8	**C-1**	<5	[f]

[a] Conditions: **1** (0.2 mmol), 7.0 mol % catalyst, 4.8 atm H_2, benzene (0.05M), 50 °C, 3 days. [b] Determined by ^1H NMR with internal standard. [c] 20 mol % **C-1**. [d] Under 6.1 atm H_2. [e] Under Ar without H_2. [f] Starting material recovered.

Scheme 3. Possible Pathways for Olefin/Carbonyl Cyclization

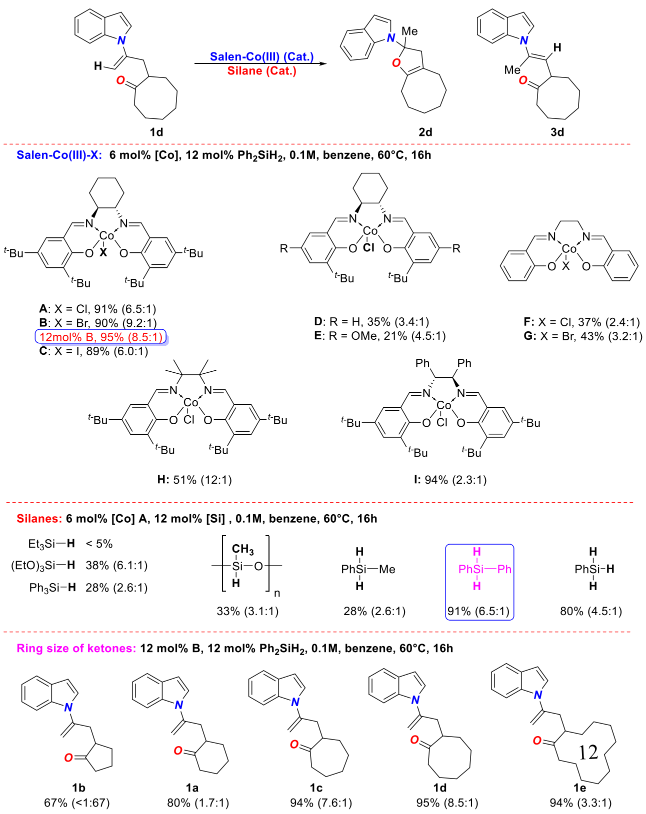


As shown by the first three entries in Table 1, changing the axial ligands in our cobaloxime catalyst,[9b,c] from THF in **C-1** to MeOH in **C-2** and H_2O in **C-3**, decreases the turnover number. (Catalysts **C-2** and **C-3** are known to activate H_2 less effectively than C-1.[9a−c]) **C-1** and **C-3** gave roughly the same product ratios; **C-2** gave a somewhat greater ratio of cycloisomerization to isomerization with low conversion. Changes in the size of the cycloalkanone ring, however, significantly affect the **2**/**3** ratio. A five-membered ring favors isomerization (entry 4), whereas medium-sized rings (seven- or eight-membered, entries 1 and 6) favor cycloisomerization; the larger 12-membered ring (entry 7) shows little selectivity. The use of $CpCr(CO)_3H$[26] as a catalyst (entry 8) induces only isomerization, with low conversion. Increased **C-1** loading (entry 9) or H_2 pressure (entry 10) slightly improves the selectivity. Control experiments (entries 11 and 12) confirm that both cobalt and H_2 are indispensable to the reaction, supporting a HAT mechanism. No hydrogenation of cyclized or uncyclized products has been detected.

We then considered the Co−salen complexes[10a,27] and silane reductants[28,29] that Shenvi had used in the cycloisomerization of dienes.[10] We selected *N*-vinylindole with a tethered cyclooctanone (**1d**) as a model substrate for our cyclizations onto C═O and were encouraged when we obtained 10% **2d** along with a trace of the isomerization product **3d** at room temperature(see the SI).

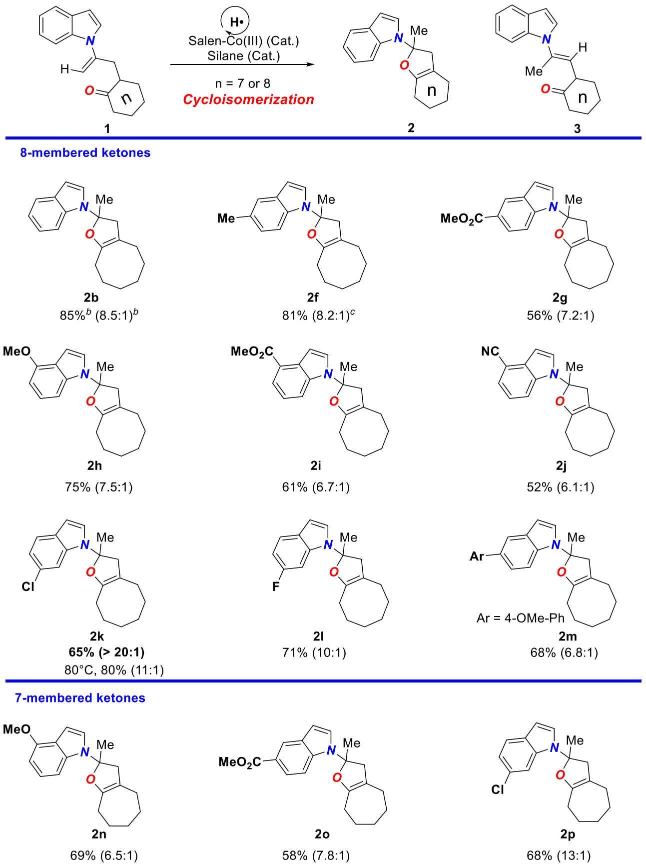
Optimization revealed that the best condition (with 12 mol % catalyst **B** and silane, at 60 °C for 16 h) had the substrate 0.1 M in benzene. The results of catalyst optimizations are summarized in Scheme 4. The nature (steric and electronic) of the salen ligand has a large effect,[27,30] with catalysts **A**, **B**, **C**, and **I** all being effective, whereas catalysts **DG** showed lower reactivity. Catalyst **H** gave the best selectivity for the cycloisomerized product **2d**, but with only moderate conversion (see the SI). The auxiliary ligand (Cl, Br, or I) of the Co(III) salen catalyst affects the selectivity (probably because it affects the rate at which "Co−H" is generated).The nature of the silane reductant is crucial:[29] tertiary silanes are less reactive, presumably for steric reasons, whereas Ph_2SiH_2 shows decent reactivity along with good cycloisomerization selectivity (up to 9.2:1). We saw the same ring size effects as with the cobaloxime/H_2 system, albeit with higher selectivity for **2** and higher conversion; again, the cyclopentanone **1b** gave **3b** as the main product, with only a trace (<1%) of the cycloisomerization product **2b**.

Scheme 4. Optimization Studies in the Cyclization of N-Vinylindoles with Co(III)−Salen/Silane[a]



[a]Isolated yield for the major product; the ratio of **2**/**3** is in parentheses, determined by ^{1}H NMR with internal standard.

Scheme 5. Substrate scope of Cycloisomerization of N-Vinylindoles with Co(III)−Salen/Silane[a]



[a]Conditions: **1** (0.1 mmol), 12.0 mol % B, 12 mol % Ph_2SiH_2, benzene (0.10M), 60 °C, 16 h. [b]Isolated yield, ratio determined by crude ^{1}H NMR with internal standard. [c]1.0 mmol scale.

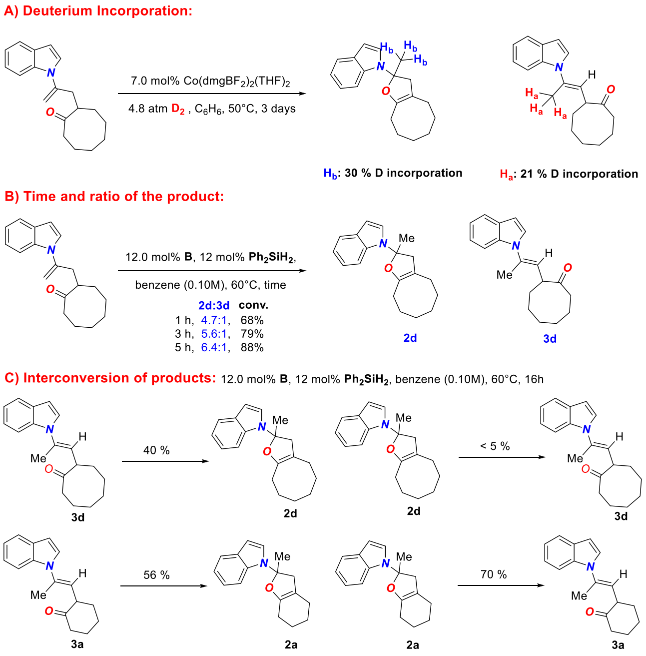


Figure 1. Mechanistic studies.

We have also checked the range of functional groups and substitution patterns that can be tolerated on the indole ring. All of the cyclooctanone substrates in Scheme 5 gave good selectivity for cycloisomerization (from 6.1:1 to >20:1), and no over-reduction was observed. The reaction can be carried out on a 1.0 mmol scale without losing efficiency (**1f**). Esters (**1g**, **1i**), nitriles (**1j**), methoxy (**1h**), and fluoro (**1l**) substituents are well tolerated, as well as conjugated arene (**1m**). The 6-chloro substrate **1k** gave cycloisomerization almost exclusively under standard conditions (with a small amount of isomerization occurred at elevated temperature). Substrates with 7-membered rings (**1n**−**1p**) showed reactivity and selectivity comparable to those of the cyclooctanone substrates.

Mechanism

The deuterium-labeling experiment in Figure 1A supports Scheme 3B. Under D_2, the transfer of deuterium from the catalyst (**C-1**) onto the methylene of **1d** results in the incorporation of deuterium into the methyl groups of **2d** and **3d** (the deuterium content of the **3d** methyl is probably depleted by D/H exchange during the conversion of that compound to **2d**, described below.)

With the salen catalyst **B** and Ph_2SiH_2, the ratio of the cycloisomerized product **2d** to the enamine **3d** increases over time (Figure 1B). This implies that the initial **2d**/**3d** ratio is kinetic, with the thermodynamic ratio being higher and **3d** slowly converted to **2d** under the reaction conditions. This interpretation is confirmed by the experiment in Figure 1C, which shows the interconversion of **2d** and **3d**. Quantitative analysis of the equilibrium is difficult, as a small percentage of **1d** is also formed in these reactions, but the equilibrium constant (from **3d** to **2d**) must be around unity. The equilibrium amount of the cycloisomerized product **2** decreases when the eight-membered ring in **1d** is replaced by the smaller one in **1a**—presumably because the strain in **2a** is increased.

The interconversions of **1**−**3** are summarized in Figure 2. The red arrows indicate the rate constants that probably determine the kinetic ratio of **2**/**3**. The size of the cycloalkanone ring will have little effect on the rate of removal of H● from **4** to form the isomerized vinylindole **3**, but it must affect either **4** (the rate constant k_{cyc} for addition to the O) or **5** (the rate constant k_{re} for removal of H● from the cyclized radical).

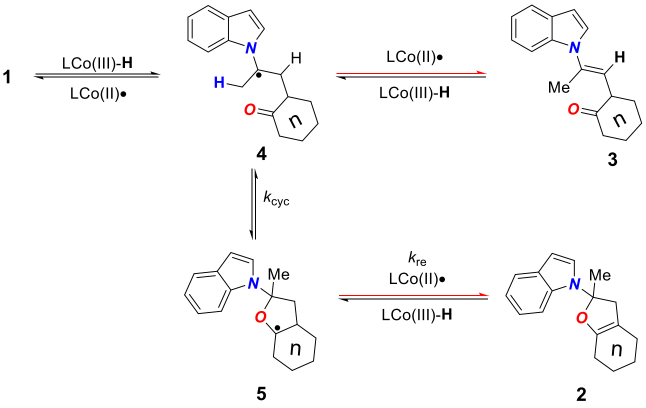


Figure 2. Proposed mechanism for the interconversion of **2** and **3**.

Overall, we have demostrated that *N*-vinylindoles are excellent H● acceptors, and that the resulting α-aminyl radicals can undergo 5-endo addition to the oxygen of a cycloalkanone carbonyl—delivering a densely functionalized dihydrofuran. Deuterium-labeling experiments support this mechanism. The yield of the dihydrofuran is highest with a seven- or eight-membered-ring cycloalkanone.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02272.

Experimental procedures, computational details and compound characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Jack R. Norton − *Department of Chemistry, Columbia University, New York, New York 10027, United States;* orcid.org/0000-0003-1563-9555; Email: Jrn11@columbia.edu

Authors

Shicheng Shi − *Department of Chemistry, Columbia University, New York, New York 10027, United States;* orcid.org/0000-0001-8124-9235

Jonathan L. Kuo − *Department of Chemistry, Columbia University, New York, New York 10027, United States;* orcid.org/0000-0003-1966-9460

Tao Chen − *Department of Chemistry, Columbia University, New York, New York 10027, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02272

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Janine M. Abuyuan (Barnard College) is acknowledged for experimental assistance. Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award No. R01GM124295. J.L.K. was supported by the National Science Foundation Graduate Research Fellowship Program (DGE-11-44155), the Arun Guthikonda Memorial Fellowship, and the National Institutes of Health under the Ruth L. Kirschstein National Research Service Award (FGM126639A).

■ REFERENCES

(1) Sweany, R. L.; Halpern, J. Hydrogenation of α-methylstyrene by hydridopentacarbonylmanganese (I). Evidence for a free-radical mechanism. *J. Am. Chem. Soc.* **1977**, *99*, 8335−8337.

(2) (a) Mukaiyama, T.; Isayama, S.; Inoki, S.; Kato, K.; Yamada, T.; Takai, T. Oxidation-reduction hydration of olefins with molecular oxygen and 2-propanol catalyzed by bis (acetylacetonato) cobalt (II). *Chem. Lett.* **1989**, *18*, 449−452. (b) Isayama, S.; Mukaiyama, T. A new method for preparation of alcohols from olefins with molecular oxygen and phenylsilane by the use of bis (acetylacetonato) cobalt (II). *Chem. Lett.* **1989**, *18*, 1071−1074.

(3) For related reviews, see: (a) Eisenberg, D. C.; Norton, J. R. Hydrogen-Atom Transfer Reactions of Transition-Metal Hydrides. *Isr. J. Chem.* **1991**, *31*, 55−66. (b) Crossley, S. W.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-catalyzed radical hydrofunctionalizations of olefins. *Chem. Rev.* **2016**, *116*, 8912−9000. (c) Green, S. A.; Crossley, S. W. M.; Matos, J. L. M.; Vasquez-Cespedes, S.; Shevick, S. L.; Shenvi, R. A. The High Chemofidelity of Metal-Catalyzed Hydrogen Atom Transfer. *Acc. Chem. Res.* **2018**, *51*, 2628−2640. (d) Shigehisa, H. Studies on Catalytic Activation of Olefins Using Cobalt Complex. *Chem. Pharm. Bull.* **2018**, *66*, 339−346.

(4) Recent examples for hydrogenations: (a) Iwasaki, K.; Wan, K. K.; Oppedisano, A.; Crossley, S. W.; Shenvi, R. A. Simple, chemoselective hydrogenation with thermodynamic stereocontrol. *J. Am. Chem. Soc.* **2014**, *136*, 1300−1303. (b) King, S. M.; Ma, X.; Herzon, S. B. A method for the selective hydrogenation of alkenyl halides to alkyl halides. *J. Am. Chem. Soc.* **2014**, *136*, 6884−6887.

(5) Selected examples for C−C bond formation: (a) Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. Functionalized olefin cross-coupling to construct carbon−carbon bonds. *Nature* **2014**, *516*, 343. (b) Lo, J. C.; Yabe, Y.; Baran, P. S. A practical and catalytic reductive olefin coupling. *J. Am. Chem. Soc.* **2014**, *136*, 1304.

(6) Selected examples for C−O and C−N bond formation: (a) Waser, J.; Carreira, E. M. Catalytic hydrohydrazination of a wide range of alkenes with a simple Mn complex. *Angew. Chem., Int. Ed.* **2004**, *43*, 4099−4102. (b) Waser, J.; Nambu, H.; Carreira, E. M. Cobalt-catalyzed hydroazidation of olefins: convenient access to alkyl azides. *J. Am. Chem. Soc.* **2005**, *127*, 8294−8295. (c) Shigehisa, H.; Aoki, T.; Yamaguchi, S.; Shimizu, N.; Hiroya, K. Hydroalkoxylation of unactivated olefins with carbon radicals and carbocation species as key intermediates. *J. Am. Chem. Soc.* **2013**, *135*, 10306−10309. (d) Shigehisa, H.; Koseki, N.; Shimizu, N.; Fujisawa, M.; Niitsu, M.; Hiroya, K. Catalytic hydroamination of unactivated olefins using a co catalyst for complex molecule synthesis. *J. Am. Chem. Soc.* **2014**, *136*, 13534−13537. (e) Shigehisa, H.; Hayashi, M.; Ohkawa, H.; Suzuki, T.; Okayasu, H.; Mukai, M.; Yamazaki, A.; Kawai, R.; Kikuchi, H.; Satoh, Y. Catalytic Synthesis of Saturated Oxygen Heterocycles by Hydrofunctionalization of Unactivated Olefins:"Unprotected" and "Protected" Strategies. *J. Am. Chem. Soc.* **2016**, *138*, 10597−10604.

(7) Selected examples for C−X (X = Cl, F) bond formation: (a) Gaspar, B.; Carreira, E. M. Catalytic Hydrochlorination of Unactivated Olefins with para-Toluenesulfonyl Chloride. *Angew. Chem., Int. Ed.* **2008**, *47*, 5758−5760. (b) Barker, T. J.; Boger, D. L. Fe (III)/NaBH4-mediated free radical hydrofluorination of unactivated alkenes. *J. Am. Chem. Soc.* **2012**, *134*, 13588−13591. (c) Xie, Y.; Sun, P. W.; Li, Y.; Wang, S.; Ye, M.; Li, Z. Ligand-Promoted Iron (III)-Catalyzed Hydrofluorination of Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 7097−7101.

(8) (a) Romero, K. J.; Galliher, M. S.; Pratt, D. A.; Stephenson, C. R. J. Radicals in natural product synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7851−7866. For recent M-HAT-catalyzed cyclization in total synthesis, see: (b) Thomas, W. P.; Schatz, D. J.; George, D. T.; Pronin, S. V. A Radical-Polar Crossover Annulation To Access Terpenoid Motifs. *J. Am. Chem. Soc.* **2019**, *141*, 12246−12250. (c) Ji, Y.; Xin, Z.; He, H.; Gao, S. Total Synthesis of Viridin and Viridiol. *J. Am. Chem. Soc.* **2019**, *141*, 16208−16212.

(9) (a) Li, G.; Kuo, J. L.; Han, A.; Abuyuan, J. M.; Young, L. C.; Norton, J. R.; Palmer, J. H. Radical isomerization and cycloisomerization initiated by H● transfer. *J. Am. Chem. Soc.* **2016**, *138*, 7698−7704. See other examples from our group using the cobaloxime/H$_2$ system: (b) Li, G.; Han, A.; Pulling, M. E.; Estes, D. P.; Norton, J. R. Evidence for Formation of a Co−H Bond from (H$_2$O)$_2$Co(dmgBF$_2$)$_2$ under H2: Application to Radical Cyclizations. *J. Am. Chem. Soc.* **2012**, *134*, 14662−14665. (c) Estes, D. P.; Grills, D. C.; Norton, J. R. The reaction of cobaloximes with hydrogen: products and thermodynamics. *J. Am. Chem. Soc.* **2014**, *136*, 17362−17365. (d) Li, G.; Estes, D. P.; Norton, J. R.; Ruccolo, S.; Sattler, A.; Sattler, W. Dihydrogen Activation by Cobaloximes with Various Axial Ligands. *Inorg. Chem.* **2014**, *53*, 10743−10747. (e) Lorenc, C.; Vibbert, H. B.; Yao, C.; Norton, J. R.; Rauch, M. H· Transfer-Initiated Synthesis of γ-Lactams: Interpretation of Cycloisomerization and Hydrogenation Ratios. *ACS Catal.* **2019**, *9*, 10294−10298.

(10) (a) Crossley, S. W.; Barabé, F.; Shenvi, R. A. Simple, chemoselective, catalytic olefin isomerization. *J. Am. Chem. Soc.* **2014**, *136*, 16788−16791. For recent examples of Co-catalyzed olefin isomerization, see: (b) Liu, X.; Zhang, W.; Wang, Y.; Zhang, Z.-X.; Jiao, L.; Liu, Q. Cobalt-Catalyzed Regioselective Olefin Isomerization Under Kinetic Control. *J. Am. Chem. Soc.* **2018**, *140*, 6873−6882. (c) Delgado, K. R.; Youmans, D. D.; Diver, S. T. Mild Isomerization of Conjugated Dienes Using Co-Mediated Hydrogen Atom Transfer. *Org. Lett.* **2020**, *22*, 750−754. (d) Zhao, J.; Cheng, B.; Chen, C.; Lu, Z. Cobalt-Catalyzed Migrational Isomerization of Styrenes. *Org. Lett.* **2020**, *22*, 837−841. (e) Liu, H.; Xu, M.; Cai, C.; Chen, J.; Gu, Y.; Xia, Y. Cobalt-Catalyzed Z to E Isomerization of Alkenes: An Approach to (E)-β-Substituted Styrenes. *Org. Lett.* **2020**, *22*, 1193−1198. (f) Zhang, S.; Bedi, D.; Cheng, L.; Unruh, D. K.; Li, G.; Findlater, M. Cobalt(II)-Catalyzed Stereoselective Olefin Isomerization: Facile Access to Acyclic Trisubstituted Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 8910.

(11) (a) Saladrigas, M.; Bosch, C.; Saborit, G. V.; Bonjoch, J.; Bradshaw, B. Radical Cyclization of Alkene-Tethered Ketones Initiated by Hydrogen-Atom Transfer. *Angew. Chem., Int. Ed.* **2018**, *57*, 182−186. (b) Saladrigas, M.; Loren, G.; Bonjoch, J.; Bradshaw, B. Hydrogen Atom Transfer (HAT)-Triggered Iron-Catalyzed Intra- and Intermolecular Coupling of Alkenes with Hydrazones: Access to Complex Amines. *ACS Catal.* **2018**, *8*, 11699−11703. For intramolecular radical addition to aldehydes, see: (c) Matos, J. L. M.; Vásquez-Céspedes, S.; Gu, J.; Oguma, T.; Shenvi, R. A. Branch-Selective Addition of Unactivated Olefins into Imines and Aldehydes. *J. Am. Chem. Soc.* **2018**, *140*, 16976−16981. For a more recently example, see: (d) Wu, B.; Zhu, R. Radical Philicity Inversion in Co- and Fe-Catalyzed Hydrogen-Atom-Transfer-Initiated Cyclizations of Unsaturated Acylsilanes. *ACS Catal.* **2020**, *10*, 510−515.

(12) Li, H.; Boonnak, N.; Padwa, A. N-Alkenyl Indoles as Useful Intermediates for Alkaloid Synthesis. *J. Org. Chem.* **2011**, *76*, 9488−9496.

(13) Menapace, L. W.; Kuivila, H. G. Mechanism of Reduction of Alkyl Halides by Organotin Hydrides. *J. Am. Chem. Soc.* **1964**, *86*, 3047−3051.

(14) Handa, S.; Rose, C. J. Investigations into a free radical-mediated 1,2-imino migration. *Tetrahedron Lett.* **2004**, *45*, 8643−8645.

(15) (a) Walton, J. C. Unusual Radical Cyclisations. In *Radicals in Synthesis II*; Gansäuer, A., Ed.; Springer: Berlin, Heidelberg, 2006; pp 163−200. (b) Beckwith, A. L.; Easton, C. J.; Serelis, A. K. Some guidelines for radical reactions. *J. Chem. Soc., Chem. Commun.* **1980**, 482−483.

(16) Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, T. 5-Endo-trig Radical Cyclizations: Disfavored or Favored Processes? *J. Am. Chem. Soc.* **2002**, *124*, 10765−10772.

(17) Park, S.-U.; Varick, T. R.; Newcomb, M. Acceleration of the 4-exo radical cyclization to a synthetically useful rate. Cyclization of the 2,2-dimethyl-5-cyano-4-pentenyl radical. *Tetrahedron Lett.* **1990**, *31*, 2975−2978.

(18) (a) Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M. Radical cyclizations of N-vinylic α-chloroacetamides. 5-endo-trig and 4-exo-trig cyclizations. *Tetrahedron Lett.* **1991**, *32*, 1725−1728. (b) Bogen, S.; Malacria, M. 5-endo-trig Radical Cyclizations: A New Means to the Stereoselective Synthesis of Cyclopentanes and Diquinanes. *J. Am. Chem. Soc.* **1996**, *118*, 3992−3993.

(19) (a) Beckwith, A. L. J.; Hay, B. P. Kinetics and mechanism of the exo cyclizations of.omega.-formylalkyl radicals. *J. Am. Chem. Soc.* **1989**, *111*, 2674−2681. (b) Mendenhall, G. D.; Protasiewicz, J. D.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. 5-Endo Closure of the 2-Formylbenzoyl Radical. *J. Am. Chem. Soc.* **1994**, *116*, 1718−1724. (c) Rust, F. F.; Seubold, F. H.; Vaughan, W. E. The Reaction of Di-t-butyl Peroxide and Benzaldehyde. *J. Am. Chem. Soc.* **1948**, *70*, 3258−3259. (d) Tsunoi, S.; Ryu, I.; Yamasaki, S.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. Free Radical Mediated Double Carbonylations of Alk-4-enyl Iodides. *J. Am. Chem. Soc.* **1996**, *118*, 10670−10671.

(20) Harrison, D. A.; Schwartz, R. N.; Kagan, J. Radical intermediate in the photolysis of o-phthalaldehyde at 77.deg.K. *J. Am. Chem. Soc.* **1970**, *92*, 5793−5795.

(21) (a) Liu, D.; Liu, C.; Lei, A. Carbon-Centered Radical Addition to C = X Bonds for C−X Bond Formation. *Chem. - Asian J.* **2015**, *10*, 2040−2054 For selected examples of radical addition onto oxygen of carbonyl, see:. (b) Miwa, N.; Yamane, Y.; Nishikata, T. A Ligand Containing Five Nitrogen Atoms Enabled Efficient Homocyclization of α-Bromocarbonyl Amides in the Presence of a Copper Catalyst. *Chem. Lett.* **2017**, *46*, 563−565. (c) Tang, S.; Liu, K.; Long, Y.; Gao, X.; Gao, M.; Lei, A. Iodine-Catalyzed Radical Oxidative Annulation for the Construction of Dihydrofurans and Indolizines. *Org. Lett.* **2015**, *17*, 2404−2407. (d) Lv, L.; Xi, H.; Bai, X.; Li, Z. Iron-Catalyzed Convergent Radical Cyclization of Aldehydes with Two Alkenes to 3,4-Dihydropyrans. *Org. Lett.* **2015**, *17*, 4324−4327. (e) Lv, L.; Lu, S.; Guo, Q.; Shen, B.; Li, Z. Iron-Catalyzed Acylation-Oxygenation of Terminal Alkenes for the Synthesis of Dihydrofurans Bearing a Quaternary Carbon. *J. Org. Chem.* **2015**, *80*, 698−704. (f) Guo, L.-N.; Wang, S.; Duan, X.-H.; Zhou, S.-L. Iron-catalyzed tandem cyclization of olefinic dicarbonyl compounds with benzylic Csp3−H bonds for the synthesis of dihydrofurans. *Chem. Commun.* **2015**, *51*, 4803−4806.

(22) (a) Li, H.; Boonnak, N.; Padwa, A. Synthesis of N-vinyl substituted indoles and their acid-catalyzed behavior. *Tetrahedron Lett.* **2011**, *52*, 2062−2064. (b) Ghosh, A.; Stanley, L. M. Enantioselective hydroacylation of N-vinylindole-2-carboxaldehydes. *Chem. Commun.* **2014**, *50*, 2765−2768.

(23) (a) Nakajima, K.; Miyake, Y.; Nishibayashi, Y. Synthetic utilizationof α-aminoalkyl radicals and related species in visible ligt photoredox catalysis. *Acc. Chem. Res.* **2016**, *49*, 1946−1956. (b) Henry, D. J.; Parkinson, C. J.; Mayer, P. M.; Radom, L. Bond Dissociation Energies and Radical Stabilization Energies Associated with Substituted Methyl Radicals. *J. Phys. Chem. A* **2001**, *105*, 6750−6756.

(24) Roberts, B. P. Polarity-reversal catalysis of hydrogen-atom abstraction reactions: concepts and applications in organic chemistry. *Chem. Soc. Rev.* **1999**, *28*, 25−35.

(25) For strong acid-catalyzed olefin/ketone cyclization under harsh condition, see: (a) Ebel, K.; Brunner, B.; Stock, C.; Pelzer, R. Process for the preparation of cyclic enol ethers. US2013/005994A1, 2013-01-03. For related Lewis acid catalyzed olefin cyclization with 1,3-dicarbonyl compounds, see this and references cited therein: (b) Cao, Z.; Zhang, R.; Meng, X.; Li, H.; Li, J.; Zhu, H.; Chen, G.; Sun, X.; You, J. Sc (OTf) 3-catalyzed cyclization of α-allylated 1, 3-dicarbonyls: an efficient access to 2, 2-disubstituted 2, 3-dihydrofuran derivatives. *RSC Adv.* **2016**, *6*, 74582−74585.

(26) (a) Smith, D. M.; Pulling, M. E.; Norton, J. R. Tin-free and catalytic radical cyclizations. *J. Am. Chem. Soc.* **2007**, *129*, 770−771. (b) Hartung, J.; Norton, J. R.: *Catalysis Involving the H● Transfer Reactions of First-Row Transition Metals*; Wiley-VCH Verlag: Weinheim, 2010; pp 1−24.

(27) Chiang, L.; Allan, L. E.; Alcantara, J.; Wang, M. C.; Storr, T.; Shaver, M. P. Tuning ligand electronics and peripheral substitution on cobalt salen complexes: structure and polymerisation activity. *Dalton Trans.* **2014**, *43*, 4295−4304.

(28) Ye, K.-Y.; McCallum, T.; Lin, S. Bimetallic Radical Redox-Relay Catalysis for the Isomerization of Epoxides to Allylic Alcohols. *J. Am. Chem. Soc.* **2019**, *141*, 9548−9554.

(29) Obradors, C.; Martinez, R. M.; Shenvi, R. A. Ph(i-PrO)SiH_2: an exceptional reductant for metal-catalyzed hydrogen atom transfers. *J. Am. Chem. Soc.* **2016**, *138*, 4962−4971.

(30) Studer, A.; Curran, D. P. Catalysis of radical reactions: A radical chemistry perspective. *Angew. Chem., Int. Ed.* **2016**, *55*, 58−102.