Formation of TEMPO Adducts with Hydrogen Atom Transfer: A New Pathway to Versatile Hydrofunctionalizations of Olefins

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Abstract:

Since the seminal work by Mukaiyama, many research groups reported hydrofunctionalization of olefin with different metal hydrides in situ. Despite the rapid development of MHAT (metal-catalyzed hydrogen atom transfer)-derived reactions, the need for using different catalyst systems to accommodate different reactivities makes it not appealing. Here, we describe a two-step process to access a broad range of hydrofunctionalization of olefins. The first step involves a cobalt-catalyzed formation of TEMPO adduct from olefins. The reaction demonstrates a broad substrate scope and functional group tolerance. The second step involves a photocatalytic nucleophilic addition to generate a new C-C, C-N, C-O, C-F, and C-Cl bond. Interestingly with our methodology, nucleophilic fluorination could be achieved with a short reaction time, showing its potential in PET applications. Combining the two steps, a net hydrofunctionalization of olefins with a broad range can be achieved by simply changing the nucleophiles in the second step. A two-step diastereoselective hydration of olefins was also demonstrated by employing the bulkiness of TEMPO.

Introduction

Olefins are popular starting material in organic synthesis, and metalhydride-catalyzed hydrogen atom transfer (MHAT) has been demonstrated to be a robust and powerful strategy for forming carbon-carbon and carbon-heteroatom bonds from olefins (through a radical intermediate). Metal hydrides based on abundant first-row transition metals have relatively weak M-H bonds, and thus demonstrate high reactivity towards even unactivated olefins.¹⁻⁵ Typical MHAT reactions proceed under mild conditions, give good chemo- and regio-selectivity, and tolerate a broad range of functional groups. The synthetic utility of MHATinitiated reactions is demonstrated by the rapidly growing applications of MHAT in total synthesis.⁶⁻⁷ In a typical MHAT-initiated hydrofunctionalization, a transition metal hydride transfers a hydrogen atom to the less substituted carbon of an olefin and thus generates a more substituted and more stable carboncentered radical (Scheme 1a)⁸⁻¹⁴. The radical can then react with a range of radicalophiles, via addition to unsaturated bonds, atom transfer reactions, and so on, to give the hydrofunctionalization products. This strategy has been employed by many research groups with earth-abundant metals, such as Co,¹⁵⁻³³ Mn,³⁴⁻³⁵, and Fe.36-43

Scheme 1: Hydrofunctionalization of olefins via MHAT: prior work and this work



Despite the rapid development of MHAT-derived reactions, different catalyst systems have been required for different reactivities. For example, the Carreira group developed different metal catalysts to achieve hydrohydrazination, hydroazidination, and hydrocyanation of olefins (Scheme 1b)^{15-16, 35}. In this regard, the Boger group has reported an iron(III)/NaBH₄ system which can facilitate a broad range of C-N, C-O, C-S, and C-C bond-forming reactions (however, the iron complex is used in stoichiometric amount, and the borohydride and radical traps are used in superstoichiometric amounts) (Scheme 1c)³⁸. The Herzon group⁴⁴ reported a cobalt system for the same purpose, but it suffered from the same issues: not catalytic and a large excess of the other reagents needed.

In view of the work of Knowles⁴⁵⁻⁴⁶ and others⁴⁷⁻⁴⁸ on the generation of carbocations from oxidizing TEMPO (2,2,6,6-tetramethylpiperidinyloxy) adducts, we felt that a two-step catalytic sequence using TEMPO adducts could access a broad range of hydrofunctionalizations of olefins (Scheme 1d). The first step involves H• transfer from an *in situ* generated metal hydride followed by TEMPO trapping, to give TEMPO adducts. With the TEMPO adducts, the photocatalytic system developed by the Knowles group⁴⁵ can then be employed to form various C-X bonds. Taken together, the two steps will give a net hydrofunctionalization of olefins. By changing the nucleophiles, various hydrofunctionalization products can be accessed, thus obviating the need to develop different MHAT systems.

Synthesis of TEMPO Adducts

Existing methods for the generation of TEMPO adducts from olefins are not very general. Hawker and his co-workers⁴⁹ have used a manganese catalyst to prepare TEMPO adducts from styrenes — but only those with substituents on the phenyl ring. We had no success when we tried to extend this reaction to internal alkenes such as β -methyl styrene and 1,2-dihydronapthalene and aliphatic alkenes such as 2-methyl-4-phenyl-1-butene. Boger and his coworkers³⁸ have used an Fe(III)/NaBH₄ system to make TEMPO adducts from internal aliphatic alkenes, but they have had to use a large excess of the iron complex, and have obtained only moderate yields.

We believed that it might be possible to make TEMPO adducts by H• transfer to olefins from metal hydrides, although we expected competition from the exothermic transfer of H• to the oxygen of TEMPO. The O-H bond of TEMPO-H is 69.6 kcal/mol while the bond dissociation energy (BDE) of M-H within a typical isolable HAT catalyst HCpCr(CO)₃ is 62 kcal/mol.⁵⁰ Moreover, metal hydrides generated in situ are even weaker, with BDE of Co(salen)-H estimated to be around 42 kcal/mol and BDE of Fe(acac)₂–H to be only 17-20 kcal/mol.⁵¹⁻⁵² We tried a number of Fe and Mn complexes that proved ineffective (even with high catalyst loading), but obtained moderate yields with simple cobalt salts (Co(acac)₂ and Co(acac)₃), and better results with cobalt salen complexes.

Extensive optimization on both the ethylene amine backbone and the salicylaldehyde moiety revealed Co(^{4Me}salen^{*t*Bu,*t*Bu</sub>) as the optimal catalyst with a loading of 2.5 mol% (See ESI for details). With sodium borohydride as the hydride donor, and tert-butyl hydroperoxide as the oxidant, the reaction was conducted at room temperature with a mixture of ethanol and water as solvents. The major byproduct in this reaction is a Markovnikov hydration product, presumably derived from oxygen reacting with the radical generated by MHAT, a mechanism similar to the Mukaiyama hydration. The catalyst loading can be reduced to 0.5 mol% and still gives a 72% yield.}

With the optimal conditions in hand, the substrate scope of this transformation was evaluated (Scheme 2). The reaction works well with styrenes substituted with either electron donating or electron withdrawing groups (2a-2f). An ortho substituent on the phenyl ring (2g) does not reduce the yield significantly, and an internal alkene (2i) is also well tolerated. Aliphatic alkenes also prove to be good substrates for this reaction. Monosubstituted (2n), 1,1-disubstituted (2j-2m), 1,2-disubstituted (2o, 2p), and trisubstituted olefins (2j) all give good yields.

Scheme 2: Substrate scope of Co-catalyzed TEMPO adduct formation from olefins



Photocatalytic Nucleophilic Substitution on TEMPO Adducts

With the synthesis of TEMPO adducts solved, we moved on to explore the substitution of TEMPO adducts with various nucleophiles. Upon irradiation, the excited Ir photocatalyst oxidizes TEMPO adducts which undergoes mesolytic cleavage to give carbocations. The carbocations then get trapped with a broad range of nucleophiles to access net nucleophilic substitution products. They demonstrated that this reaction could be applied to a broad range of C-, N-, and O-centered nucleophiles (Scheme 3). Starting from the TEMPO adduct made

from our aforementioned cobalt catalysis, the photocatalytic substitution worked well to offer some new products, with C-C, C-N, or C-O bond formation.

Scheme 3: Photocatalytic substitution of TEMPO adducts by the Knowles group



We decided to explore the possibility of applying other nucleophiles with respect to hydrofunctionalization of olefins (Scheme 4a). Various fluoride sources were tested for a net hydrofluorination of olefins. Triethylamine trihydrofluoride gave the best yield of 81%, while other fluoride sources including KHF₂, NH₄F and Olah reagent (pyridine•xHF) all gave a yield of less than 20%. Other nucleophiles were also explored. Chlorination and bromination products were obtained with collidinium chloride and bromotrimethylsilane, respectively, offering a complementary approach to Ohmiya's work.⁵³. Electronrich arene, such as 1,3-dimethoxybenzene also works well as a nucleophile. When acetonitrile was used as the reaction solvent, a Ritter-type⁵⁴ product was generated, albeit in a relatively low yield. With TMSCN, a cyanation product was obtained with a 29% yield. Given the growing presence of fluorine in pharmaceuticals and agrochemicals, as well as the wide use of ¹⁸F in positron emission tomography

Scheme 4. Exploration of other nucleophiles in photocatalytic substitution



c) Nucleophilic fluorination at a shorter time



2i-F 82% (NMR yield)

Me

(PET) imaging,⁵⁵ we decided to explore the hydrofluorination of our substrates (Scheme 4b). Various substituents on the aromatic ring of styrenes can be tolerated, including an ortho methyl (**2g-F**). The TEMPO adducts derived from para-CF₃ styrene gave only 22% yield (**2f-F**), probably due to the destabilization of the benzylic carbocation by the electron-withdrawing group. The relatively low yield of para-F styrene is probably due to the low boiling point nature of the fluorination product (**2d-F**). A TEMPO adduct derived from an internal alkene also afforded the corresponding fluorination product in high yield (**2i-F**). The aromatic ring is not necessary for the reaction: a TEMPO adduct derived from an aliphatic alkene gave a 62% yield (**2m-F**). The Doyle group noted in their paper:⁵⁶ "The Knowles group introduced a methodology ... the method was not shown to work with fluoride and the substrates can be challenging to access". We demonstrated that fluoride can indeed be employed as the nucleophile in the photocatalytic substitution of TEMPO adducts. Moreover, a facile synthesis of TEMPO adducts was developed.

When we shortened the reaction time for the synthesis of **2i-F** to 30 minutes, an NMR yield of 82% was obtained (Scheme 4c). Given that ¹⁸F has a half-life of 110 minutes, this result shows the potential of applying this methodology to the synthesis of ¹⁸F-labelled pharmaceuticals. Moreover, the use of fluoride as F source also makes it suitable for PET applications, since 18F is typically obtained in the form of fluoride ions. In contrast, most previous reports on MHATcatalyzed hydrofluorination of olefins all used expensive electrophilic sources of fluorine, such as selectfluor, NFSI, and N-fluoropyridinium salt, which require multi-step synthesis from ¹⁸F₂.^{21, 37, 44, 57} During the preparation of this manuscript, the Song Lin group⁵⁸ combined Co-catalyzed MHAT and photoredox catalysis to achieve hydrofluorination of olefins also with triethylamine trihydrofluoride as the fluorine source, and demonstrates its application in the synthesis of ¹⁸Fanalogs.

Diastereoselective Hydration of Olefins

Given the prevalence of the alcohol functionality in pharmaceutical compounds and natural products, the hydration of olefins to alcohols is an important process in synthesis. The Mukaiyama hydration is one of the most commonly used methods for the Markovnikov hydration of olefins on a laboratory scale.⁵⁹ The widely accepted mechanism involves MHAT from *in situ* generated metal hydride to an olefin. The resulting alkyl radical reacts with oxygen to install the oxygen functionality. Given the high reactivity and low steric bulk of O_2 , the Mukaiyama hydration typically gives negligible diastereoselectivity. The Studer group recently reported a possible solution with iron catalysis by employing substituted nitrobenzene as the oxygen donor in place of O_2 .⁶⁰ Given the steric bulk of the substituted nitrobenzene, the reaction gives high diastereoselectivity.

Reductive cleavage of the N-O bonds in TEMPO-derived alkoxyamines is well-established. Combined with the MHAT catalyzed TEMPO adduct formation, this two step-process can provide an alternative to formal hydration of olefins. Moreover, the bulky TEMPO may trap the carbon-centered radicals with high diastereoselectivity, which will be preserved in the following reductive cleavage step. Thus, the TEMPO adduct may serve as an intermediate for the diastereoselective hydration of olefins. During the evaluation of substrate scope for TEMPO adduct formation, we found only one diastereomer in the crude ¹H-NMR when using α -, or β -pinene as the starting material. Reduction of the TEMPO adduct with Zn under acidic conditions gave the alcohol product as a single diastereomer in 81% yield (scheme 5).

Scheme 5: Diastereoselective hydration of olefins



Conclusion

In summary, we have described a new two-step protocol for accessing a broad range of hydrofunctionalizations of olefin: TEMPO adduct formation from olefins and photocatalytic nucleophilic substitution of the TEMPO adducts. Upon extensive screening of the reaction conditions, a Co(salen) catalyst and NaBH₄ was found to be the optimal combination for TEMPO adduct formation from olefins. A broad range of substrates with distinct substitution patterns prove to be good substrates for this transformation. Combined with photocatalytic nucleophilic substitution previously reported by the Knowles group, various hydrofunctionalizations of olefins were accessed, including hydrofluorination, hydroazidation, hydroamination, hydroalkoxylation, hydroalkylation, and so on. Moreover, reductive cleavage of N-O bond following TEMPO adduct formation gave access to diastereoselective olefin hydration, benefiting from the bulky nature of TEMPO.

References

1. Ricca, M.; Yao, S. L.; Le, T. M. Y.; White, J. M.; Donnelly, P. S.; Rizzacasa, M. A., A -β-iron(iii) SALPN catalyst for hydrogen atom transfer reductions and olefin cross couplings. *Org Biomol Chem* **2023**.

2. Mandal, D.; Roychowdhury, S.; Biswas, J. P.; Maiti, S.; Maiti, D., Transition-metalcatalyzed C-H bond alkylation using olefins: recent advances and mechanistic aspects. *Chem. Soc. Rev.* **2022**, *51* (17), 7358-7426.

3. Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A., Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016**, *116* (15), 8912-9000.

4. Shevick, S. L.; Wilson, C. V.; Kotesova, S.; Kim, D.; Holland, P. L.; Shenvi, R. A., Catalytic hydrogen atom transfer to alkenes: a roadmap for metal hydrides and radicals. *Chem Sci* **2020**, *11* (46), 12401-12422.

5. Yan, H. P.; Shan, J. R.; Zhang, F. Z.; Chen, Y. Q.; Zhang, X. Y.; Liao, Q.; Hao, E. R.; Shi, L., Radical Crotylation of Aldehydes with 1,3-Butadiene by Photoredox Cobalt and Titanium Dual Catalysis. *Org. Lett.* **2023**.

6. Green, S. A.; Crossley, S. W. M.; Matos, J. L. M.; Vásquez-Céspedes, S.; Shevick, S. L.; Shenvi, R. A., The High Chemofidelity of Metal-Catalyzed Hydrogen Atom Transfer. *Acc. Chem. Res.* **2018**, *51* (11), 2628-2640.

7. Wu, J. H.; Ma, Z. Q., Metal-hydride hydrogen atom transfer (MHAT) reactions in natural product synthesis. *Org. Chem. Front.* **2021**, *8* (24), 7050-7076.

8. Sweany, R. L.; Halpern, J., Hydrogenation of Alpha-Methylstyrene by Hydridopentacarbonylmanganese(I) - Evidence for a Free-Radical Mechanism. *J. Am. Chem. Soc.* **1977**, *99* (25), 8335-8337.

9. Feder, H. M.; Halpern, J., Mechanism of the cobalt carbonyl-catalyzed homogeneous hydrogenation of aromatic hydrocarbons. *J. Am. Chem. Soc.* **1975**, *97* (24), 7186-7188.

10. Gu, Y. T.; Norton, J. R.; Salahi, F.; Lisnyak, V. G.; Zhou, Z. Y.; Snyder, S. A., Highly Selective Hydrogenation of C=C Bonds Catalyzed by a Rhodium Hydride. *J. Am. Chem. Soc.* **2021**, *143* (25), 9657-9663.

11. Shi, S. C.; Salahi, F.; Vibbert, H. B.; Rahman, M.; Snyder, S. A.; Norton, J. R., Generation of α -Boryl Radicals by H

Transfer and their Use in Cycloisomerizations. *Angew Chem Int Edit* **2021**, *60* (42), 22678-22682.

12. 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* (24), 7698-7704.

13. Choi, J.; Tang, L.; Norton, J. R., Kinetics of Hydrogen Atom Transfer from (η5-C5H5)Cr(CO)3H to Various Olefins: Influence of Olefin Structure. *J. Am. Chem. Soc.* **2007**, *129* (1), 234-240.

14. Eisenberg, D. C.; Lawrie, C. J. C.; Moody, A. E.; Norton, J. R., Relative rates of hydrogen atom (H.cntdot.) transfer from transition-metal hydrides to trityl radicals. *J. Am. Chem. Soc.* **1991**, *113* (13), 4888-4895.

15. Waser, J.; Nambu, H.; Carreira, E. M., Cobalt-catalyzed hydroazidation of olefins: Convenient access to alkyl azides. *J. Am. Chem. Soc.* **2005**, *127* (23), 8294-8295.

16. Gaspar, B.; Carreira, E. M., Mild cobalt-catalyzed hydrocyanation of olefins with tosyl cyanide. *Angew Chem Int Edit* **2007**, *46* (24), 4519-4522.

Gaspar, B.; Carreira, E. M., Cobalt Catalyzed Functionalization of Unactivated
Alkenes: Regioselective Reductive C–C Bond Forming Reactions. *J. Am. Chem. Soc.* 2009, 131 (37), 13214-13215.

18. Gaspar, B.; Carreira, E. M., Catalytic hydrochlorination of unactivated olefins with -toluenesulfonyl chloride. *Angew Chem Int Edit* **2008**, *47* (31), 5758-5760.

19. Girijavallabhan, V.; Alvarez, C.; Njoroge, F. G., Regioselective Cobalt-Catalyzed Addition of Sulfides to Unactivated Alkenes. *J. Org. Chem.* **2011**, *76* (15), 6442-6446.

20. 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* (28), 10306-10309.

21. Shigehisa, H.; Nishi, E.; Fujisawa, M.; Hiroya, K., Cobalt-Catalyzed Hydrofluorination of Unactivated Olefins: A Radical Approach of Fluorine Transfer. *Org. Lett.* **2013**, *15* (20), 5158-5161.

22. 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* (39), 13534-13537.

23. Shigehisa, H.; Ano, T.; Honma, H.; Ebisawa, K.; Hiroya, K., Co-Catalyzed Hydroarylation of Unactivated Olefins. *Org. Lett.* **2016**, *18* (15), 3622-3625.

24. Shigehisa, H.; Hayashi, M.; Ohkawa, H.; Suzuki, T.; Okayasu, H.; Mukai, M.; Yamazaki, A.; Kawai, R.; Kikuchi, H.; Satoh, Y.; Fukuyama, A.; Hiroya, K., Catalytic Synthesis of Saturated Oxygen Heterocycles by Hydrofunctionalization of Unactivated Olefins: Unprotected and Protected Strategies. *J. Am. Chem. Soc.* **2016**, *138* (33), 10597-10604.

25. Touney, E. E.; Foy, N. J.; Pronin, S. V., Catalytic Radical-Polar Crossover Reactions of Allylic Alcohols. *J. Am. Chem. Soc.* **2018**, *140* (49), 16982-16987.

26. Discolo, C. A.; Touney, E. E.; Pronin, S. V., Catalytic Asymmetric Radical-Polar Crossover Hydroalkoxylation. *J. Am. Chem. Soc.* **2019**, *141* (44), 17527-17532.

27. 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* (19), 6884-6887.

28. Ma, X.; Herzon, S. B., Non-classical selectivities in the reduction of alkenes by cobaltmediated hydrogen atom transfer. *Chem Sci* **2015**, *6* (11), 6250-6255.

29. Ma, X.; Herzon, S. B., Intermolecular Hydropyridylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2016**, *138* (28), 8718-8721.

30. Ma, X.; Dang, H.; Rose, J. A.; Rablen, P.; Herzon, S. B., Hydroheteroarylation of Unactivated Alkenes Using N-Methoxyheteroarenium Salts. *J. Am. Chem. Soc.* **2017**, *139* (16), 5998-6007.

31. Green, S. A.; Matos, J. L. M.; Yagi, A.; Shenvi, R. A., Branch-Selective Hydroarylation: Iodoarene–Olefin Cross-Coupling. *J. Am. Chem. Soc.* **2016**, *138* (39), 12779-12782.

32. Shevick, S. L.; Obradors, C.; Shenvi, R. A., Mechanistic Interrogation of Co/Ni-Dual Catalyzed Hydroarylation. *J. Am. Chem. Soc.* **2018**, *140* (38), 12056-12068.

33. 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* (49), 16976-16981.

34. 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* (4), 1300-3.

35. Waser, J.; Carreira, E. M., Catalytic Hydrohydrazination of a Wide Range of Alkenes with a Simple Mn Complex. *Angewandte Chemie International Edition* **2004**, *43* (31), 4099-4102.

36. Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L., Total Synthesis of Vinblastine, Vincristine, Related Natural Products, and Key Structural Analogues. *J. Am. Chem. Soc.* **2009**, *131* (13), 4904-4916.

37. Barker, T. J.; Boger, D. L., Fe(III)/NaBH4-mediated free radical hydrofluorination of unactivated alkenes. *J. Am. Chem. Soc.* **2012**, *134* (33), 13588-91.

38. Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L., Iron(III)/NaBH4-mediated additions to unactivated alkenes: synthesis of novel 20'-vinblastine analogues. *Org. Lett.* **2012**, *14* (6), 1428-31.

39. 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* (7531), 343-8.

40. Zheng, J.; Wang, D.; Cui, S., Fe-Catalyzed Reductive Coupling of Unactivated Alkenes with β-Nitroalkenes. *Org. Lett.* **2015**, *17* (18), 4572-4575.

41. 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 Catalysis* **2018**, *8* (12), 11699-11703.

42. Saladrigas, M.; Bosch, C.; Saborit, G. V.; Bonjoch, J.; Bradshaw, B., Radical Cyclization of Alkene-Tethered Ketones Initiated by Hydrogen-Atom Transfer. *Angewandte Chemie International Edition* **2018**, *57* (1), 182-186.

43. Green, S. A.; Vásquez-Céspedes, S.; Shenvi, R. A., Iron–Nickel Dual-Catalysis: A New Engine for Olefin Functionalization and the Formation of Quaternary Centers. *J. Am. Chem. Soc.* **2018**, *140* (36), 11317-11324.

44. Ma, X.; Herzon, S. B., Cobalt bis(acetylacetonate)-tert-butyl hydroperoxidetriethylsilane: a general reagent combination for the Markovnikov-selective hydrofunctionalization of alkenes by hydrogen atom transfer. *Beilstein J Org Chem* **2018**, *14*, 2259-2265.

45. Zhu, Q.; Gentry, E. C.; Knowles, R. R., Catalytic Carbocation Generation Enabled by the Mesolytic Cleavage of Alkoxyamine Radical Cations. *Angewandte Chemie International Edition* **2016**, *55* (34), 9969-9973.

46. Gentry, E. C.; Rono, L. J.; Hale, M. E.; Matsuura, R.; Knowles, R. R., Enantioselective Synthesis of Pyrroloindolines via Noncovalent Stabilization of Indole Radical Cations and Applications to the Synthesis of Alkaloid Natural Products. *J. Am. Chem. Soc.* **2018**, *140* (9), 3394-3402.

47. Zhang, L.; Laborda, E.; Darwish, N.; Noble, B. B.; Tyrell, J. H.; Pluczyk, S.; Le Brun, A. P.; Wallace, G. G.; Gonzalez, J.; Coote, M. L.; Ciampi, S., Electrochemical and Electrostatic Cleavage of Alkoxyamines. *J. Am. Chem. Soc.* **2018**, *140* (2), 766-774.

48. Norcott, P. L.; Hammill, C. L.; Noble, B. B.; Robertson, J. C.; Olding, A.; Bissember, A. C.; Coote, M. L., TEMPO–Me: An Electrochemically Activated Methylating Agent. *J. Am. Chem. Soc.* **2019**, *141* (38), 15450-15455.

49. Dao, J.; Benoit, D.; Hawker, C. J., A versatile and efficient synthesis of alkoxyamine LFR initiators via manganese based asymmetric epoxidation catalysts. *Journal of Polymer Science Part A: Polymer Chemistry* **1998**, *36* (12), 2161-2167.

50. Mahoney, L. R.; Mendenhall, G. D.; Ingold, K. U., Calorimetric and equilibrium studies on some stable nitroxide and iminoxy radicals. Approximate oxygen-hydrogen bond

dissociation energies in hydroxylamines and oximes. J. Am. Chem. Soc. **1973**, 95 (26), 8610-8614.

51. Kim, D.; Rahaman, S. M. W.; Mercado, B. Q.; Poli, R.; Holland, P. L., Roles of Iron Complexes in Catalytic Radical Alkene Cross-Coupling: A Computational and Mechanistic Study. *J. Am. Chem. Soc.* **2019**, *141* (18), 7473-7485.

52. Jiang, H.; Lai, W. Z.; Chen, H., Generation of Carbon Radical from Iron-Hydride/Alkene: Exchange-Enhanced Reactivity Selects the Reactive Spin State. *Acs Catalysis* **2019**, *9* (7), 6080-6086.

53. Shibutani, S.; Nagao, K.; Ohmiya, H., A Dual Cobalt and Photoredox Catalysis for Hydrohalogenation of Alkenes. *J. Am. Chem. Soc.* **2024**.

54. Yin, Y. N.; Ding, R. Q.; Ouyang, D. C.; Zhang, Q.; Zhu, R., Highly chemoselective synthesis of hindered amides via cobalt-catalyzed intermolecular oxidative hydroamidation. *Nat Commun* **2021**, *12* (1), 2552.

55. Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H., Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). *Chem. Rev.* **2014**, *114* (4), 2432-2506.

56. Webb, E. W.; Park, J. B.; Cole, E. L.; Donnelly, D. J.; Bonacorsi, S. J.; Ewing, W. R.; Doyle, A. G., Nucleophilic (Radio)Fluorination of Redox-Active Esters via Radical-Polar Crossover Enabled by Photoredox Catalysis. *J. Am. Chem. Soc.* **2020**, *142* (20), 9493-9500.

57. Lemaire, C.; Damhaut, P.; Lauricella, B.; Mosdzianowski, C.; Morelle, J.-L.; Monclus, M.; Van Naemen, J.; Mulleneers, E.; Aerts, J.; Plenevaux, A.; Brihaye, C.; Luxen, A., Fast [18F]FDG synthesis by alkaline hydrolysis on a low polarity solid phase support. *J. Labelled Compd. Radiopharmaceut.* **2002**, *45* (5), 435-447.

58. Liu, J.; Rong, J.; Wood, D. P.; Wang, Y.; Liang, S. H.; Lin, S., Co-Catalyzed Hydrofluorination of Alkenes: Photocatalytic Method Development and Electroanalytical Mechanistic Investigation. *J. Am. Chem. Soc.* **2024**.

59. 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.* **2006**, *18* (6), 1071-1074.

60. Bhunia, A.; Bergander, K.; Daniliuc, C. G.; Studer, A., Fe-Catalyzed Anaerobic Mukaiyama-Type Hydration of Alkenes using Nitroarenes. *Angew Chem Int Ed Engl* **2021**, *60* (15), 8313-8320.