Anomeric Nitroamide Enabled, Cobalt Catalyzed Alkene Hydronitration

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Abstract:

Tertiary nitroalkanes, as well as its reduced products, α-tertiary amines, play an essential role in drug discovery either as key synthetic precursors or final incorporation in targeted molecules. Existing methods to prepare tertiary nitro compounds generally rely on polar-bond disconnections, in which strong bases or highly active electrophiles are needed. Here, we report the development of an anomeric nitroamide-based reagent that enables exquisitely selective MHAT-based Co-catalyzed alkene hydronitration for the preparation of valuable tertiary nitro compounds. This mild, scalable reaction shows broad functional group tolerance, is applied to a variety of structures. Late-stage nitration of complex contexts (9 examples) derived from drugs and natural products is also pursued. Its high prowess is further highlighted in simplifying the synthesis of a rare naturally occurring nitro sugar. Simple access to isotopically labeled ^{15}N-containing nitro compounds is also disclosed. The anomeric nitroamide reagent was deemed safe by energetic

measurements and its unique reactivity rationalized based on X-ray crystallographic analysis.

Main text:

Aliphatic nitro-containing structures are found in a variety of materials such as medicines, agrochemicals, energetics, natural products, and key building blocks.[1] Tertiary nitroalkanes, in particular, are useful functional groups as outlined in Figure 1A. For instance, pyrrolidine **3** exhibits a dramatic difference in biological activity relative to **2**,[2] compound **4** has been used as a key intermediate towards rolapitant,[3] and molecules **5**[4]–**6**[5] have been derived or found from natural sources. Conventional routes to tertiary nitro compounds generally rely on polar-bond disconnections as outlined in Figure 1B.[6] Thus, anionic reactions of secondary nitro compounds (**7**) using strong base or potent electrophiles under transition metal[7-9] or enzymatic catalysis[10] are commonly employed. Another popular strategy has been to oxidize α-tertiary amines (**8**) which suffers from chemoselectivity issues and incomplete oxidation.[11] Meanwhile, as illustrated in Figure 1C, numerous methods are available for both one and two-electron Markovnikov olefin hydrofunctionalization yet none are applicable to hydronitration despite the obvious simplifying nature of such a disconnection. Classic two-electron methods for olefin functionalization generally rely on acidic conditions and traverse through carbocation intermediates.[12] One-electron based methods, relying on a MHAT-mechanism feature enhanced chemoselectivity and have been used to achieve diverse functionalizations such as hydration,[13] halogenation,[14-17] azidation,[18] and cyanation.[19] Given the large body of literature on metal-hydride hydrogen atom transfer catalysis (MHAT),[20] a more direct radical-based method to access tertiary nitro compounds from simple olefins (**9**) was pursued. This disclosure (Figure 1D) reports the invention of anomeric nitroamides such as **16** and ^{15}N-**16** that singularly address this problem to provide tertiary nitro compounds or their isotopically labeled ^{15}N-analogs in a mild (neutral conditions) and chemoselective way. As outlined herein, these reagents are stable, easily prepared on decagram-scale, and can be utilized in concert with Co-MHAT conditions on a range of olefins to provide simple access to tertiary nitro compounds in a scalable fashion.

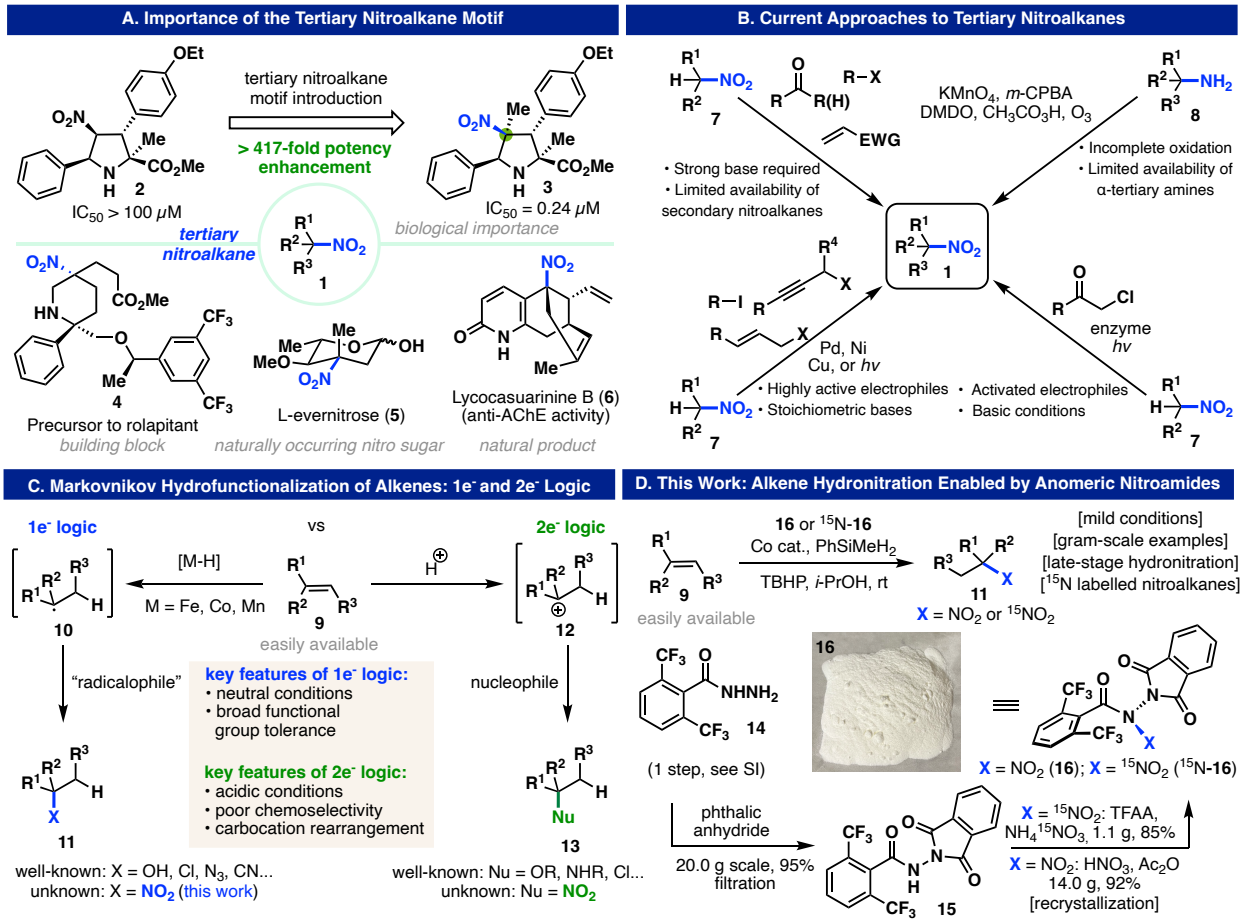
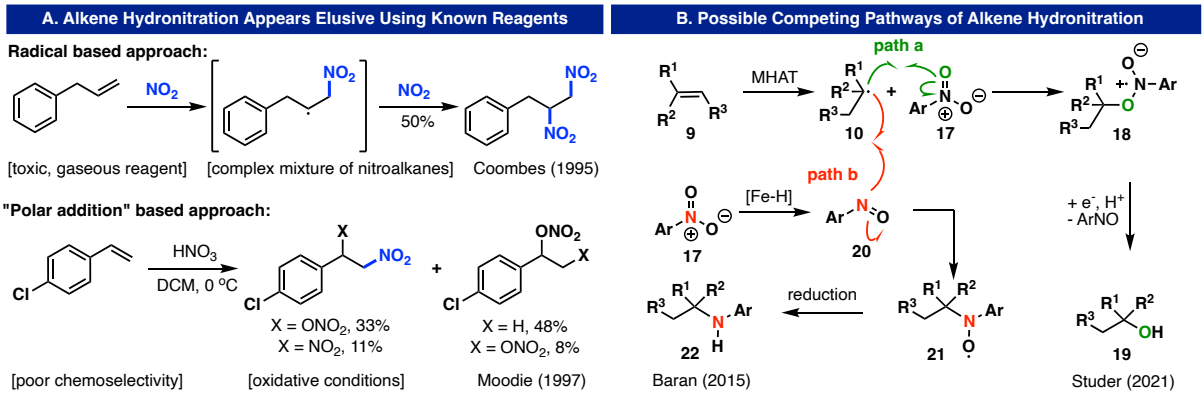
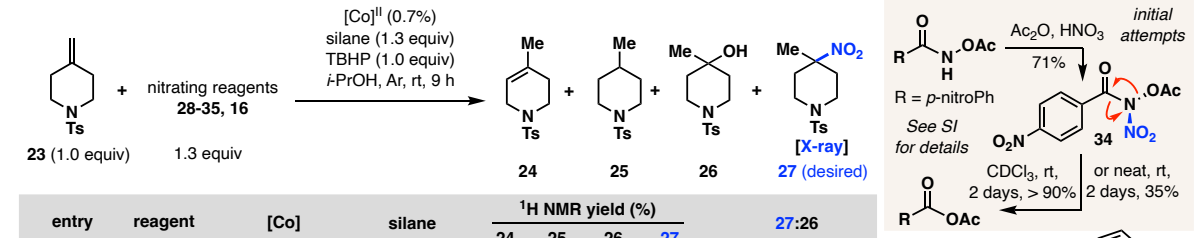


Figure 1. Strategies to access tertiary nitroalkanes. a, Tertiary nitroalkanes play an essential role in drug discovery, and are found in nitro sugars and natural products; **b**, Existing approaches to tertiary nitroalkanes; **c**, Compared to numerous one and two-electron Markovnikov alkene hydrofunctionalization methods, alkene hydronitration is unknown; **d**, This work: invention of anomeric nitroamides and their application in Cobalt catalyzed alkene hydronitration to access tertiary nitroalkanes or their isotopically labeled analogs. *m*-CPBA, *meta*-chloroperoxybenzoic acid; DMDO, dimethyldioxirane; TBHP, *tert*-butyl hydroperoxide; TFAA, trifluoroacetic anhydride.

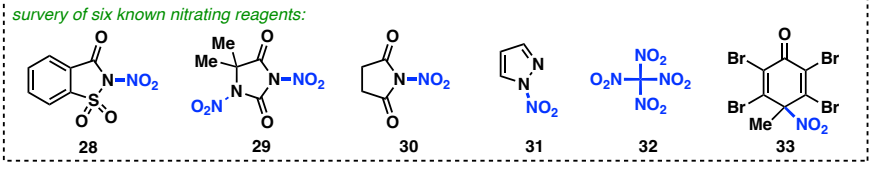
It is apparent that taming the nitryl radical (•NO_2) to controllably react with olefins at the more substituted positions is difficult as illustrated in Table 1A. For instance, rare examples of trapping this species using toxic NO_2 gas with a radical include the thermolysis of AIBN to deliver an adduct in 31% yield[21] (not shown) or of light hydrocarbons at elevated temperature (not shown).[22] Reacting this gas with simple olefins such as allyl benzene is rare and delivers doubly nitrated species.[23] Switching to polar methods, the reaction of fuming nitric acid with olefins is not chemoselective and generally

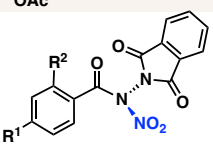
delivers mixtures of nitrate esters.[24] The main challenge for the present study, as outlined in Table 1B, was to identify an •NO_2 donor reagent that is capable of reacting at N rather than O *without altering the oxidation state at N*. Existing precedent using MHAT chemistry in concert with arylnitro compounds (**17**) illustrates this challenge with Fe-H based methods from this lab[25] and Studer.[26] In the former case, the reductive conditions proceed via Path B (presumably through intermediates **20** and **21**) but exhaustive reduction delivers amine product **22** whereas the latter case reacts exclusively via Path A (via **18**) to deliver tertiary alcohol **19**.

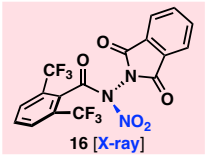




entry	reagent	[Co]	silane	^{1}H NMR yield (%)				27:26
				24	25	26	27	
1	**28**	Co^{II}(Salen)-**I**	$PhSiMeH_2$	32	18	14	17	1.2:1
2	**29**	Co^{II}(Salen)-**I**	$PhSiMeH_2$	5	4	50	4	0.08:1
3	**30**	Co^{II}(Salen)-**I**	$PhSiMeH_2$	12	15	56	3	0.05:1
4[b]	**31**	Co^{II}(Salen)-**I**	$PhSiMeH_2$	0	0	20	4	0.2:1
5[c]	**32**	Co^{II}(Salen)-**I**	$PhSiMeH_2$	39	0	0	0	0
6[d]	**33**	Co^{II}(Salen)-**I**	$PhSiMeH_2$	17	2	3	0	0
7	**35A**	Co^{II}(Salen)-**I**	$PhSiMeH_2$	4	15	29	30	1:1
8	**35B**	Co^{II}(Salen)-**I**	$PhSiMeH_2$	2	11	28	33	1.2:1
9	**16**	Co^{II}(Salen)-**I**	$PhSiMeH_2$	14	14	5	53	10.6:1
10	**16**	Co^{II}(Salen)-**I** (5%)	$PhSiMeH_2$	36	12	6	28	4.7:1
11	**16**	Co^{II}(Salen)-**II**	$PhSiMeH_2$	5	19	9	33	3.7:1
12	**16**	Co^{II}(Salen)-**III**	$PhSiMeH_2$	36	7	8	21	2.6:1
13	**16**	Co^{II}(Salen)-**I**	$PhSiH_3$ (1.0)	16	21	5	43	8.6:1
14	**16**	Co^{II}(Salen)-**I**	Ph_2SiH_2 (1.5)	7	24	6	39	6.5:1
15	**16**	Co^{II}(Salen)-**I**	TMDSO (1.5)	ND	ND	ND	trace	0







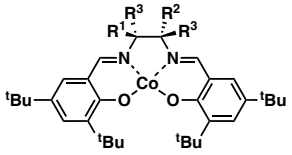


Table 1. **Reaction optimization and comparison of 16 with precedented nitrating agents.** **a**, To the best of our knowledge, alkene hydronitration appears elusive using known reagents. The reaction of NO_2 gas or fuming nitric acid with alkenes delivers doubly nitrated product or mixture of nitrate esters. **b**, Possible competing pathways of alkene radical hydronitration. **c**. Optimization of reaction conditions: a survey of anomeric nitroamide **35A** with precedented nitrating reagents reveals its superior reactivity, further structural optimization leads to **16** as the optimal reagent. [a]All reactions were performed on a 0.1 mmol scale. ^{1}H NMR yields were calculated using CH_2Br_2 as the internal standard. [b]40% **23** was recovered. [c]47% **23** was recovered. [d]32% **23** was recovered. TMDSO, tetramethyldisiloxane; Ac_2O, acetic anhydride; ND, not determined; rt, room temperature.

Although the precedent described above suggested a very low likelihood of success, an extensive exploration under a variety of MHAT conditions for the hydronitration of alkene **23** with numerous potential •NO_2 donors (**28**–**33**, **35A**/**B**, **16**, entries 1-9, and others as listed in the SI) was pursued, as partly summarized in Table 1C. Mn-, Fe-, and Co-based catalysts were all evaluated at the outset with Co-salen complexes being identified as the most promising starting point. Nitrating agent candidates were chosen from the literature based on their bench-stability and precedent for use in aromatic nitration and alkene difunctionalization.[27] For instance, saccharin-based reagent **28**[28] (entry 1) along with inexpensive Co^{II}(salen**)-I** delivered 17% of the desired nitrated product **27**. Unfortunately, this was one of the minor adducts, accompanied with significant quantities of isomerized olefin **24**, alkane **25**, and tertiary alcohol **26** (anaerobic Mukaiyama hydration[26]). It was reasoned that the reagent structure would have the most profound impact on the ratio between **26** (arising from a Path A mechanism, *vide supra*) and the desired nitro compound **27**. Several additional known reagents were thus screened such as hydantoin **29**[29] (entry 2), succinimide **30**[30] (entry 3), pyrazole **31** (entry 4), tetranitromethane **32** (TNM, entry 5), and cyclohexadienone **33**[31] (entry 6) furnished either no desired product or **26** as the major adduct. Given the high reactivity observed with anomeric amide-based halogenating reagents we reasoned that a similar boost in reactivity might translate to the corresponding anomeric nitroamides.[32] Unfortunately, all attempts to prepare an analogous anomeric nitroamide (such as **34**) failed due to the instability of the resulting products via rearrangement pathways (Table 1C, top right, see SI for details).[33] Eventually it was discovered that exchanging the N-O for an N-N bond in such structures led to

enhanced stability (**35A/B**, **16**, see SI for additional analogs). To our knowledge, no such structures have ever been prepared despite their simple synthesis via the corresponding hydrazides in two simple steps without any chromatography.[34] Anomeric nitroamide **35A** (entry 7) showed promise delivering **27** in 30% yield albeit as a 1:1 mixture with **26**. Moving the trifluoromethyl group to the *ortho* position (reagent **35B**, entry 8) led to a slight improvement. The addition of another CF_3 group (reagent **16**, entry 9) had a profound effect delivering **27** as the major product (53% yield) with only a small amount of **26** (5%) being observed. Increasing the Co-loading (entry 10) led to increased olefin isomerization (**24**) while altering the Co-source dramatically reduced the yield (entries 11-12). An exploration of silanes (entries 13-15) confirmed that $PhSiMeH_2$ was ideally suited for the reaction. The final optimized conditions are simple to perform: A flask containing olefin (1.0 equiv.), Co^{II}(salen)-**I** (0.7 mol%), and nitroamide **16** (1.3 equiv.) is purged with Ar followed by addition of *i*-PrOH (0.13 M), silane (1.3 equiv.), and TBHP (1.0 equiv.). After stirring at room temperature for 9 hours the reaction is quenched (sat. aq. NH_4Cl), extracted (DCM), and purified. Although dry *i*-PrOH is employed, strictly anhydrous conditions are not required (the deliberate addition of 55 equiv. of water leads to ca. 8% lower yield, see SI).

The optimal conditions developed above proved to be general across a wide range of unactivated alkenes featuring cyclic, acyclic and those originating from natural products and drugs, as shown in Table 2. High chemoselectivity is observed as a variety of functional groups, such as free alcohol (**36**), bromide (**37**), azide (**38**), ester (**39**), acetal (**40**), ether (**41**), phthalimides (**44**, **54**), arenes (**42**, **55**) and triazole (**57**) were all tolerated. External double bonds of five-, six-, seven-membered rings as well as simple acyclic trisubstituted alkenes were all nitrated to give rise to tertiary nitroalkanes. Cyclic internal alkenes (**42**–**44**, **53**–**54**) can also be enlisted. Compounds such as the tertiary nitroalkane **39** bearing a four-carbon ester subunit are generally prepared through laborious and somewhat dangerous protocols originating from secondary nitroalkanes. For instance, after preparing the requisite nitroalkane, base-promoted Michael addition followed by Arndt-Eistert homologation (requiring diazomethane, See SI) is required.[35] In contrast, **39**

is easily accessed in two steps from the commercial ketone (Wittig followed by alkene hydronitration).

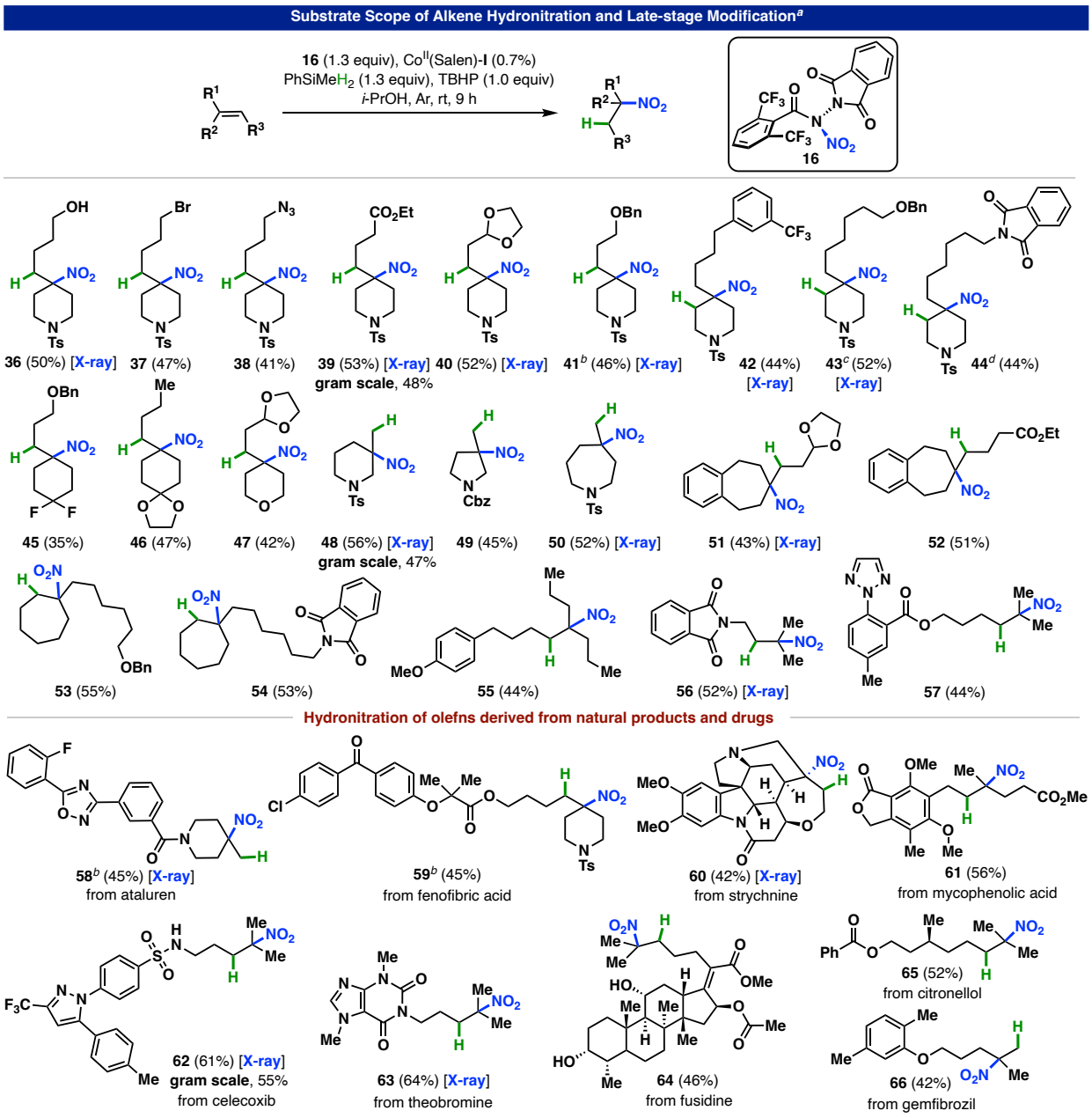


Table 2. Substrate scope of alkene hydronitration and late-stage modification of alkenes derived from natural products and drugs. [a]All reactions were performed on a 0.1 mmol scale. Isolated yields are shown. [b]Co^{II}(Salen)-**I** (1.5%), $PhSiMeH_2$ (2.0 equiv), TBHP (2.0 equiv) were used. [c]Co^{II}(Salen)-**I** (5%), $PhSiMeH_2$ (3.0 equiv), TBHP (2.0 equiv) were used. [d]Co^{II}(Salen)-**I** (1.5%), $PhSiMeH_2$ (2.0 equiv), TBHP (2.0 equiv) were used at 50 °C.

The utility of this transformation in a more complex settings was also pursued. Thus, alkenes derived from drugs and natural products were subjected to the conditions, leading to the formation of desired tertiary nitroalkanes (**58**–**66**) in good to excellent yields. In particular, diverse multi-substituted (hetro)arenes, esters, tertiary amines, electron rich arenes, and sulfonamides were found to be compatible with the reaction conditions, indicating the potential application of this reaction in late-stage nitration of complex contexts. It is worth noting that none of the compounds depicted in Table 2 have been prepared before and 14 of them were unambiguously confirmed by X-ray crystallographic analysis. In terms of limitations, this method is best suited towards the preparation of tertiary nitro compounds. Using simple terminal olefins results in ca. 20% yield of secondary alkyl nitro compounds (see SI for details) with the mass balance being reduced olefin.

Isotopic labeling with ^{15}N has a myriad of useful applications in a variety of different contexts due to its low abundance in nature thereby aiding analytical detection (NMR, MS, and MRI).[36-38] To be sure, the incorporation of ^{15}N labels can aid in food safety analysis and nutrient metabolism research,[39] the study of organic and organometallic mechanisms,[40] structural biology,[41] biogeochemistry,[42] and in chemical biology pursuits.[43] There is a documented need for new approaches to molecules incorporating ^{15}N without the need for expensive reagents or a complete redesign of synthetic pathways for their preparation.[44-46] Given the ease with which nitroamide **16** can be prepared, the corresponding ^{15}N-labeled reagent was prepared from inexpensive $NH_4{}^{15}NO_3$ (ca. $170/gram compared to ca. $150,000/gram for $Na^{15}N_3$, Figure 1D) and evaluated under the same reaction conditions (Figure 2A). Substrates ^{15}N-**27**, ^{15}N-**39**, ^{15}N-**50**, ^{15}N-**54**, ^{15}N-**56** and ^{15}N-**62** could be prepared following the same general procedure using ^{15}N-**16** in comparable yields to their non-labeled analogs. Given the versatility of the nitro group to downstream functionalization, it is anticipated that this simple method for ^{15}N-incorporation will find widespread use. As an example of this, compound **39** in either isotopic form could be converted to the spirocyclic lactam **67**, piperidine **68**, and amino alcohol **69** under well-precedented conditions (Figure 2B). In particular, the core scaffold

of **67** (1,9-diazaspiro[5.5]undecan-2-one, marked in red), is a biologically important dipiperidine spirocycle used in drug discovery (commercially available for ca. $1100/gram, Sigma-Aldrich). For example, compound **70** bearing this subunit shows good inhibitory activity (IC_{50} = 14 nM) toward leucine-rich repeat kinase 2 (LRRK2).[47]

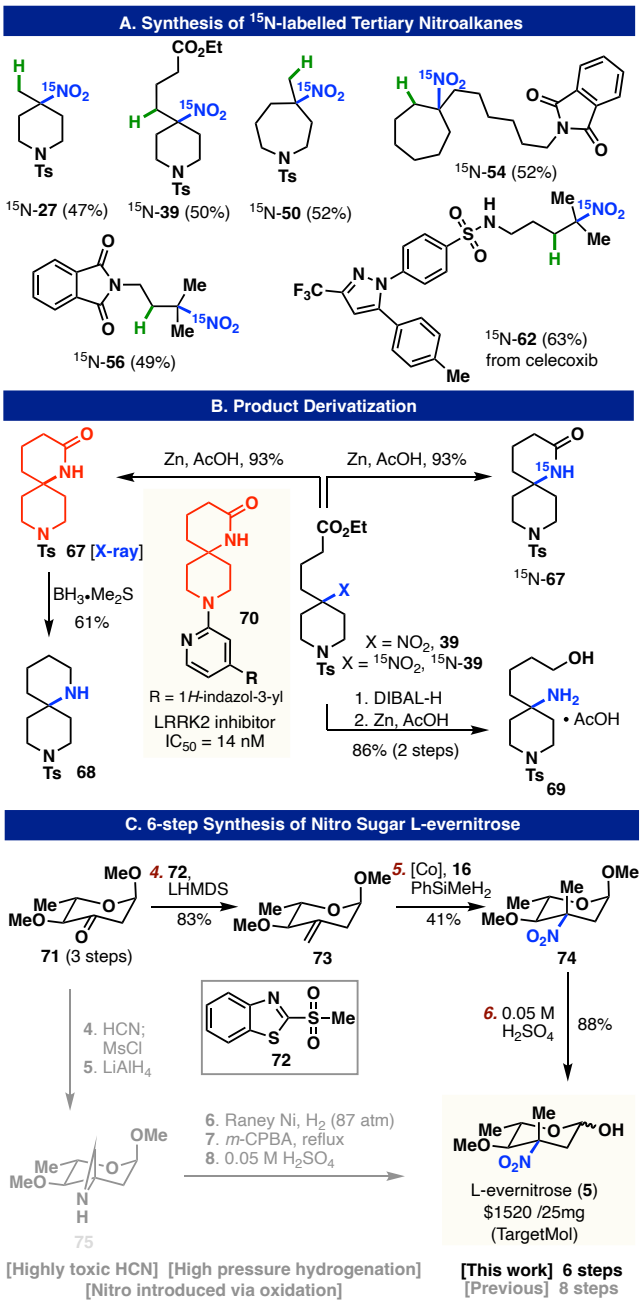


Figure 2. Synthetic applications. **a**, Synthesis of ^{15}N-labeled tertiary nitroalkanes. **b**, Synthetic application of the tertiary nitroalkane products. **c**. 6-step synthesis of nitro sugar L-evernitrose. DIBAL-H, diisobutylaluminum hydride; LHMDS, lithium bis(trimethylsilyl)amide; MsCl, methanesulfonyl chloride.

The simplifying power of alkene hydronitration was further demonstrated on the synthesis of L-evernitrose (**5**, $1520 /25mg, TargetMol), a naturally occurring nitro sugar found in the antibiotics everninomicins B-D.[4,48] This unique sugar has stimulated significant interest from the synthetic chemistry community, with five synthetic routes being reported to date, generally requiring 8-15 steps (see SI for a full summary). The shortest of those reported sequences commences with ketosugar **71**[49] (derived in 3 steps from an inexpensive rhamnopyranoside) and requires toxic HCN, LAH, high-pressure Raney-Ni reductive aziridine opening (on **75**), and the oxidation of a primary amine to the nitro group.[50] In contrast, the same starting material can be olefinated to **73** using reagent **72**, hydronitrated under standard conditions to deliver **74** as a single diastereomer, and hydrolyzed to deliver **5**.

The unique alkene hydronitration reaction raises two important mechanistic questions (Figure 3): (1) Is this conventional MHAT reactivity[20] (Path A, Figure 3A) or does the reagent act as an oxidant in a radical polar crossover pathway[51-53] (Path B, Figure 3A)? and (2) what is special about reagent **16** that favors N vs. O addition (Figure 3B)? To address the first question, during the course of this study etherification byproducts from interception of a putative carbocation with *i*-PrOH were never detected.[54-55] Even when intramolecular ether formation was possible in the reaction of olefin **76**, ether product **77** was not observed.[56] Although this is not definitive proof of the mechanism, taken together with the vast body of MHAT literatures,[14,19,57-58] a standard radical pathway is presumably operative. With regards to the second question, a series of computational experiments on all of the tested nitrating agents (Table 1C) were conducted. No correlation could be identified with regards to N-NO_2 bond length or O-N-O bond angles to explain the disparate results (see SI for details). At the moment our best hypothesis is that the presence of two *ortho*-CF_3 groups somehow shield the oxygen atoms of the pendant nitro

group thereby favoring radical attack at nitrogen (Figure 3B, compare X-ray crystallographic structures of **16** to **35B**). Indeed, X-ray crystallographic analysis revealed that reagent **16** adopts a more cup-like shape shielding the oxygen atoms (an electrostatic interaction of the oxygen atoms to the CF_3 groups is possible) on the nitro group relative to mono-CF_3-containing reagent **35B** (compare 121.5° to 116.9° angles of the C-C-N bonds in **16** and **35B**, respectively).

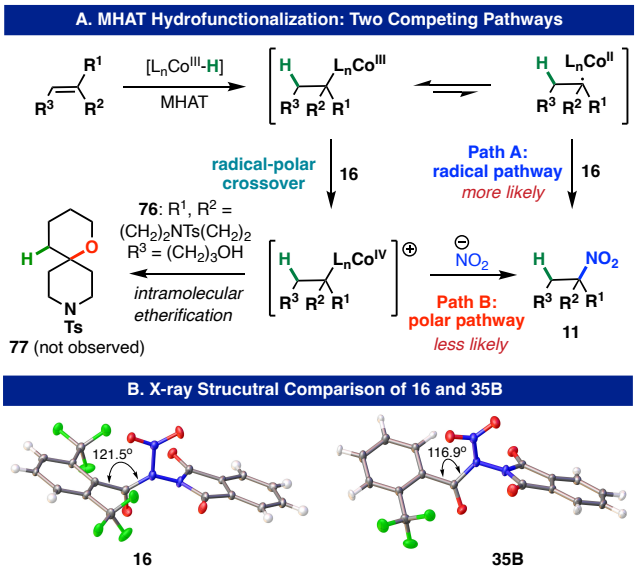


Figure 3. Mechanistic discussion. **a**, Alkene hydronitration via radical pathway (Path A) is more likely. **b**, X-ray structural analysis of nitrating reagents **16** and **35B**.

Finally, nitroamide **16** is an air- and bench-stable powder and its thermal stability was studied using differential scanning calorimetry (DSC) analysis, revealing an onset temperature around 180 °C (see SI for DSC spectra). Based on the Yoshida correlation (see SI),[59] reagent **16** is therefore not predicted to be either explosive or shock sensitive.

Conclusion

The study outlined herein describes the synthesis of challenging tertiary nitro-containing compounds under mild conditions from easily available olefins. The success of this Co-catalyzed transformation hinges on the use of a new nitro-transfer reagent (**16**) containing

an anomeric amide. As expected from radical based MHAT olefin functionalization methods it is chemoselective and scalable. Its use can simplify the synthesis of medicinally relevant molecules and the analogously prepared ^{15}N-**16** can be used to easily access isotopically labeled molecules. This work adds another facet to the unique reactivity of anomeric amide-based reagents for heteroatom transfer[32,60] and oxidation.[61]

Acknowledgements

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References

(1) Ballini, R.; Palmieri, A. Nitroalkanes: Synthesis, Reactivity, and Applications. Wiley-VCH: New York, **2021**.

(2) Qiu, H.; Du, Z.; Zhao, Y.; Yuan, S.; Xi, S.; Zhou, T.; Yang, J.; Zhang, C.; Xiong, Y.; Xia, Y.; Zhang, S.; Fu, L.; He, L.; Zhang, M. Enantioselective Synthesis and Biological Evaluation of Pyrrolidines Bearing Quaternary Stereogenic Centers. *J. Med. Chem.* **2023**, *66*, 9866-9880.

(3) Mergelsberg, I.; Scherer, D. H.; Huttenloch, M. E.; Tsui, H.-C.; Paliwal, S.; Shih, N.-Y. Process and Intermediates for the Synthesis of 8-[{1-(3,5-bis(thrifluoromethyl)phenyl)ethoxy}methyl]-8-phenyl-1,7-diazadpiro[4,5]decan-2-one Compounds. WO2008118328A2 (**2008**)

(4) Ganguly, A. K.; Sarre, O. Z.; Reimann, H. Chemistry of everninomicin antibiotics. III. Evernitrose, a naturally occurring nitro sugar from everninomicins. *J. Am. Chem. Soc.* **1968**, *90*, 7129-7130.

(5) Liu, Y.; Xu, P.-S.; Ren, Q.; Chen, X.; Zhou, G.; Li, D.; Li, X.-M.; Xu, K.-P.; Yu, X.; Tan, G.-S. Lycodine-type alkaloids from *Lycopodiastrum casuarinoides* and their cholinesterase inhibitory activities. *Fitoterapia* **2018**, *130*, 203-209.

(6) Ballini, R.; Palmieri, A. Synthetic Procedures for the Preparation of Nitroalkanes. *Adv. Synth. Catal.* **2018**, *360*, 2240-2266.

(7) Trost, B. M.; Surivet, J.-P. Asymmetric Alkylation of Nitroalkanes. *Angew. Chem., Int. Ed.* **2000**, *39*, 3122-3124.

(8) Kim, R. S.; Dinh-Nguyen, L. V.; Shimkin, K. W.; Watson, D. A. Copper-Catalyzed Propargylation of Nitroalkanes. *Org. Lett.* **2020**, *22*, 8106-8110.

(9) Rezazadeh, S.; Martin, M. I.; Kim, R. S.; Yap, G. P. A.; Rosenthal, J.; Watson, D. A. Photoredox-Nickel Dual-Catalyzed C-Alkylation of Secondary Nitroalkanes: Access to Sterically Hindered α-Tertiary Amines. *J. Am. Chem. Soc.* **2023**, *145*, 4707-4715.

(10) Fu, H.; Qiao, T.; Carceller, J. M.; MacMillan, S. N.; Hyster, T. K. Asymmetric C-Alkylation of Nitroalkanes via Enzymatic Photoredox Catalysis. *J. Am. Chem. Soc.* **2023**, *145*, 787-793.

(11) Gilbert, K. E.; Borden, W. T. Peracid oxidation of aliphatic amines: general synthesis of nitroalkanes. *J. Org. Chem.* **1979**, *44*, 659-661.

(12) Lajunen, M.; Hiukka, R. Acid-catalyzed hydrolysis of bridged bi- and tricyclic compounds. 25. Comparison of the hydrations of 2-methyl-2-norbornene and 2-methylenenorbornane with those of 1-methylcyclohexene and methylenecyclohexane. *J. Org. Chem.* **1986**, *51*, 1522-1525.

(13) 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*, 1071-1074.

(14) Gaspar, B.; Carreira, E. M. Catalytic Hydrochlorination of Unactivated Olefins with *para*-Toluenesulfonyl Chloride. *Angew. Chem., Int. Ed.* **2008**, *47*, 5758-5760.

(15) Barker, T. J.; Boger, D. L. Fe(III)/$NaBH_4$-Mediated Free Radical Hydrofluorination of Unactivated Alkenes. *J. Am. Chem. Soc.* **2012**, *134*, 13588-13591.

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

(17) Elfert, J.; Frye, N. L.; Rempel, I.; Daniliuc, C. G.; Studer, A. Iron-catalyzed radical Markovnikov hydrohalogenation and hydroazidation of alkenes. *Nat. Commun.* **2024**, *15*, 7230.

(18) 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.

(19) Gaspar, B.; Carreira, E. M. Mild Cobalt-Catalyzed Hydrocyanation of Olefins with Tosyl Cyanide. *Angew. Chem., Int. Ed.* **2007**, *46*, 4519-4522.

(20) 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*, 8912-9000.

(21) Tilney-Bassett, J. F.; Waters, W. A. 610. Properties and reactions of free alkyl radicals in solution. Part IX. Synthesis and reactions of some tertiary nitroalkanes. *J. Chem. Soc.* **1957**, 3129-3134.

(22) Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. An Efficient Nitration of Light Alkanes and the Alkyl Side-Chain of Aromatic Compounds with Nitrogen Dioxide and Nitric Acid Catalyzed by *N*-Hydroxyphthalimide. *J. Org. Chem.* **2002**, *67*, 5663-5668.

(23) Chatterjee, J.; Coombes, R. G.; Barnes, J. R.; Fildes, M. J. Mechanism of reaction of nitrogen dioxide with alkenes in solution. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1031-1032.

(24) Lewis, R. J.; B. Moodie, R. B. The nitration of styrenes by nitric acid in dichloromethane. *J. Chem. Soc., Perkin Trans. 2* **1997**, 563-568.

(25) Gui, J.; Pan, C.-M.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; La Cruz, T. E.; Schmidt, M. A.; Darvatkar, N.; Natarajan, S. R.; Baran, P. S. Practical olefin hydroamination with nitroarenes. *Science* **2015**, *348*, 886-891.

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

(27) Patra, S.; Mosiagin, I.; Giri, R.; Katayev, D. Organic Nitrating Reagents. *Synthesis* **2022**, *54*, 3432-3472.

(28) Calvo, R.; Zhang, K.; Passera, A.; Katayev, D. Facile access to nitroarenes and nitroheteroarenes using N-nitrosaccharin. *Nat. Commun.* **2019**, *10*, 3410.

(29) Jia, F.; Li, A.; Hu, X. Dinitro-5,5-Dimethylhydantoin: An Arene Nitration Reagent. *Org. Lett.* **2023**, *25*, 4605-4609.

(30) Zhang, K.; Jelier, B.; Passera, A.; Jeschke, G.; Katayev, D. Synthetic Diversity from a Versatile and Radical Nitrating Reagent. *Chem. Eur. J.* **2019**, *25*, 12929-12939.

(31) Arnatt, C. K.; Zhang, Y. Facile synthesis of 2,3,5,6-tetrabromo-4-methyl-nitrocyclohexa-2,5-dien-1-one, a mild nitration reagent. *Tetrahedron Lett.* **2012**, *53*, 1592-1594.

(32) Wang, Y.; Bi, C.; Kawamata, Y.; Grant, L. N.; Samp, L.; Richardson, P. F.; Zhang, S.; Harper, K. C.; Palkowitz, M. D.; Vasilopoulos, A.; Collins, M. R.; Oderinde, M. S.; Tyrol, C. C.; Chen, D.; LaChapelle, E. A.; Bailey, J. B.; Qiao, J. X.; Baran, P. S. Discovery of N–X

anomeric amides as electrophilic halogenation reagents. *Nat. Chem.* **2024**, *16*, 1539-1545.

(33) Glover, S. A. Anomeric amides — Structure, properties and reactivity. *Tetrahedron* **1998**, *54*, 7229-7271.

(34) Xu, X.; Wang, M.; Peng, L.; Guo, C. Nickel-Catalyzed Asymmetric Propargylation for the Synthesis of Axially Chiral 1,3-Disubstituted Allenes. *J. Am. Chem. Soc.* **2022**, *144*, 21022-21029.

(35) Mimura, M.; Hayashida, M.; Nomiyama, K.; Ikegami, S.; Iida, Y.; Tamura, M.; Hiyama, Y.; Ohishi, Y. Synthesis and Evaluation of (Piperidinomethylene)bis(phosphonic acid) Derivatives as Anti-osteoporosis Agents. *Chem. Pharm. Bull* **1993**, *41*, 1971-1986.

(36) von Philipsborn, W.; Müller, D.-C. R. ^{15}N-NMR Spectroscopy—New Methods and Applications. *Angew. Chem., Int. Ed.* **1986**, *25*, 383-413.

(37) Benson, L. M.; Naylor, S.; Tomlinson, A. J. Investigation of Maillard reaction products using ^{15}N isotope studies and analysis by electrospray ionization-mass spectrometry. *Food Chem.* **1998**, *62*, 179-183.

(38) von Morze, C.; Engelbach, J. A.; Reed, G. D.; Chen, A. P.; Quirk, J. D.; Blazey, T.; Mahar, R.; Malloy, C. R.; Garbow, J. R.; Merritt, M. E. ^{15}N-carnitine, a novel endogenous hyperpolarized MRI probe with long signal lifetime. *Magn. Reson. Med.* **2021**, *85*, 1814-1820.

(39) Xia, W.; Fang, X.; Gao, Y.; Wu, W.; Han, Y.; Liu, R.; Yang, H.; Chen, H.; Gao, H. Advances of stable isotope technology in food safety analysis and nutrient metabolism research. *Food Chem.* **2023**, *408*, 135191.

(40) Lloyd-Jones, G. C.; Muñoz, M. P. Isotopic labelling in the study of organic and organometallic mechanism and structure: an account. *J. Label. Compd. Radiopharm.* **2007**, *50*, 1072-1087.

(41) Dayie, K. T. Key Labeling Technologies to Tackle Sizeable Problems in RNA Structural Biology. *Int. J. Mol. Sci.* **2008**, *9*, 1214-1240.

(42) Mariotti, A.; Landreau, A.; Simon, B. ^{15}N isotope biogeochemistry and natural denitrification process in groundwater: Application to the chalk aquifer of northern France. *Geochim. Cosmochim. Acta* **1988**, *52*, 1869-1878.

(43) May, D. S.; Crnkovic, C. M.; Krunic, A.; Wilson, T. A.; Fuchs, J. R.; Orjala, J. E. ^{15}N Stable Isotope Labeling and Comparative Metabolomics Facilitates Genome Mining in Cultured Cyanobacteria. *ACS Chem. Biol.* **2020**, *15*, 758-765.

(44) Finkelstein, P.; Reisenbauer, J. C.; Botlik, B. B.; Green, O.; Florin, A.; Morandi, B. Nitrogen atom insertion into indenes to access isoquinolines. *Chem. Sci.* **2023**, *14*, 2954-2959.

(45) Bartholomew, G. L.; Kraus, S. L.; Karas, L. J.; Carpaneto, F.; Bennett, R.; Sigman, M. S.; Yeung, C. S.; Sarpong, R. ^{14}N to ^{15}N Isotopic Exchange of Nitrogen Heteroaromatics through Skeletal Editing. *J. Am. Chem. Soc.* **2024**, *146*, 2950-2958.

(46) Xing, Q.; Chandrachud, P. P.; Tillett, K.; Lopchuk, J. M. Regioselective hydroamination of unactivated olefins with diazirines as a diversifiable nitrogen source. *Nat. Commun.* **2024**, *15*, 6049.

(47) Miller, M.; Basu, K.; Demong, D.; Scott, J.; Liu, H.; Dai, X.; Harris, J. M.; Neustadt, B.; Stamford, A. W.; Poirier, M.; McCauley, J. A.; Greshok, T.; Stevenson, H.; Sanders, J.; Kern, J. 3-Pyridinylindazole compounds as inhibitors of leucine-rich repeat kinase enzyme activity and their preparation. WO2014137728 (**2014**)

(48) Ganguly, A. K.; Szmulewicz, S. Structure of everninomicin C. *J. Antibiot.* **1975**, *28*, 710-712.

(49) Clode, D. M.; Horton, D.; Weckerle, W. Reaction of derivatives of methyl 2,3-*O*-benzylidene-6-deoxy-α-L-mannopyranoside with butyllithium: Synthesis of methyl 2, 6-dideoxy-4-*O*-methyl-α-L-erytho-hexopyranosid-3-ulose. *Carbohydr. Res.* **1976**, *49*, 305-314.

(50) Yoshimura, J.; Matsuzawa, M.; Sato, K.-i.; Nagasawa, Y. The synthesis of evernitrose and 3-*epi*-evernitrose. *Carbohydr. Res.* **1979**, *76*, 67-78.

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

(52) Zhou, X.-L.; Yang, F.; Sun, H.-L.; Yin, Y.-N.; Ye, W.-T.; Zhu, R. Cobalt-Catalyzed Intermolecular Hydrofunctionalization of Alkenes: Evidence for a Bimetallic Pathway. *J. Am. Chem. Soc.* **2019**, *141*, 7250-7255.

(53) Wilson, C. V.; Holland, P. L. Mechanism of Alkene Hydrofunctionalization by Oxidative Cobalt(salen) Catalyzed Hydrogen Atom Transfer. *J. Am. Chem. Soc.* **2024**, *146*, 2685-2700.

(54) 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.

(55) Nakagawa, M.; Matsuki, Y.; Nagao, K.; Ohmiya, H. A Triple Photoredox/Cobalt/Brønsted Acid Catalysis Enabling Markovnikov Hydroalkoxylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2022**, *144*, 7953-7959.

(56) 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*, 10597-10604.

(57) Zhang, B.; He, J.; Li, Y.; Song, T.; Fang, Y.; Li, C. Cobalt-Catalyzed Markovnikov-Selective Radical Hydroacylation of Unactivated Alkenes with Acylphosphonates. *J. Am. Chem. Soc.* **2021**, *143*, 4955-4961.

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

(59) Sperry, J. B.; Minteer, C. J.; Tao, J.; Johnson, R.; Duzguner, R.; Hawksworth, M.; Oke, S.; Richardson, P. F.; Barnhart, R.; Bill, D. R.; Giusto, R. A.; Weaver III, J. D. Thermal Stability Assessment of Peptide Coupling Reagents Commonly Used in Pharmaceutical Manufacturing. *Org. Process Res. Dev.* **2018**, *22*, 1262-1275.

(60) Kwon Y-D, Joaquin D, Carpio M, Yousufuddin M, Kurti L. Catalyst-Free Direct Olefin Halo-Hydroxylamination: Rapid Synthesis of Multifunctional Hydroxylamines (MFHAs) for

Structurally Complex Amines and N-Heterocycles. ChemRxiv. **2024**; doi:10.26434/chemrxiv-2024-l1k7m.

(61) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. Skeletal editing through direct nitrogen deletion of secondary amines. *Nature* **2021**, *593*, 223-227.

Data Availability

The data supporting the findings of this study are available within the article and its Supplementary Information. Crystallographic data for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre, under the deposition numbers CCDC 2385494 (**16**), 2329539 (**27**), 2329540 (**35A**), 2383725 (**35B**), 2380454 (**36**), 2373356 (**39**), 2376555 (**40**), 2376557 (**41**), 2377801 (**42**), 2377800 (**43**), 2375144 (**48**), 2376556 (**50**), 2373359 (**51**), 2383726 (**56**), 2377632 (**58**), 2375142 (**60**), 2382868 (**62**), 2380180 (**63**), 2382867 (**67**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

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