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Nickel-catalyzed remote and proximal Wacker-type oxidation

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Wacker oxidation chemistry is widely applied to oxidation of olefins to carbonyls in the synthesis of pharmaceuticals, natural products, and commodity chemicals. However, in this chemistry efficient oxidation of internal olefins and highly selective oxidation of unbiased internal olefins without reliance upon suitable coordinating groups have remained significant challenges. Here we report a nickel-catalyzed remote Wacker-type oxidation where reactions occur at remote and less-reactive sp^3 C-H sites in the presence of a priori more reactive ones through a chain-walking mechanism with excellent regio- and chemo- selectivity. This transformation has attractive features including the use of ambient air as the sole oxidant, naturally-abundant nickel as the catalyst, and polymethylhydrosiloxane as the hydride source at room temperature, allowing for effective oxidation of challenging olefins. Notably, this approach enables direct access to a broad array of complex, medically relevant molecules from structurally complex substrates and chemical feedstocks.

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Wacker oxidation, that is, the reaction of Pd-catalyzed oxidation of alkenes into high value-added and synthetically versatile carbonyls, is a central transformation in chemistry^{1–4} (Fig. 1a). This classical transformation is well established for oxidation of terminal olefins. However, in this reaction internal olefins are relatively unactivated without reliance upon suitable coordinating groups^{5–9}. Moreover, the internal olefins, particularly unbiased internal olefins, commonly provide inseparable regioisomers with comparable yields^{5–9}. Actually, the regioselectivity issue of oxidation of internal olefins represents another longstanding challenge in Wacker chemistry^{1–9}. Consequently, these challenges inherently undermine the utility of Wacker chemistry because the vast majority of alkenes are unbiased internal olefins readily accessible from petroleum and renewable resources such as seed oils¹⁰ and through well-established synthetic routes such as carbonyl olefination¹¹ and olefin metathesis¹².

Remote functionalization that allows direct bond formation at a distal and specific position other than the initial reactive site is a significant challenge^{13–21}, particularly in remote Wacker-type oxidation. This is because the remote Wacker-type oxidation would involve transition-metal hydride addition of an alkene into the organometallic intermediate transition-metal alkyl, followed by a sequential β -hydride elimination/migratory-insertion iteration process reaching a specific remote sp^3 C–H position where oxidation occurs to liberate the desired single carbonyl product^{13,14}; unfortunately, both the reductive transition-metal

hydride and the unstable organometallic intermediate are commonly sensitive to oxidative conditions. Moreover, alkenes are more reactive than alkanes owing to the exposed π -bonding electrons, leading to oxidation of carbon–carbon double bonds in preference to the remote sp^3 C–H. Indeed, there were few clues in the literature implying the exceptional difficulty for the development of this protocol^{22–33}. For example, isomerization of olefinic alcohols enabled by transition-metal hydride species leads to the ketone products, which requires migration of the olefinic unsaturations toward the tethered alcohols^{22–29}. Alternatively, internal olefins isomerization/hydroborations or isomerization/hydrosilylations followed by oxidations can realize remote oxidations^{30–34}. While these methods are efficient, they all require prefunctionalized starting materials. Apparently, straightforward oxidation of olefins' remote sp^3 C–H to valuable ketones serves as a more practical approach (For an example of Pd-catalyzed tandem isomerization–Wacker oxidation of allyl arenes, see ref. 35).

We previously identified an iron catalysis system enabling highly efficient Wacker-type oxidation³⁶. This oxidation transformation involves iron hydride in situ generated from iron(II) and hydrosilane to react with an alkene producing the adduct alkyl iron intermediate that gives carbon-centered radical via single-electron transfer^{37,38}, followed by generation of the iron peroxide complex in the presence of oxygen, ultimately to release the desired carbonyl product³⁶. This work led us to attempt remote Wacker-type oxidation with an analogous process. Apparently, this new strategy would require the discovery of a

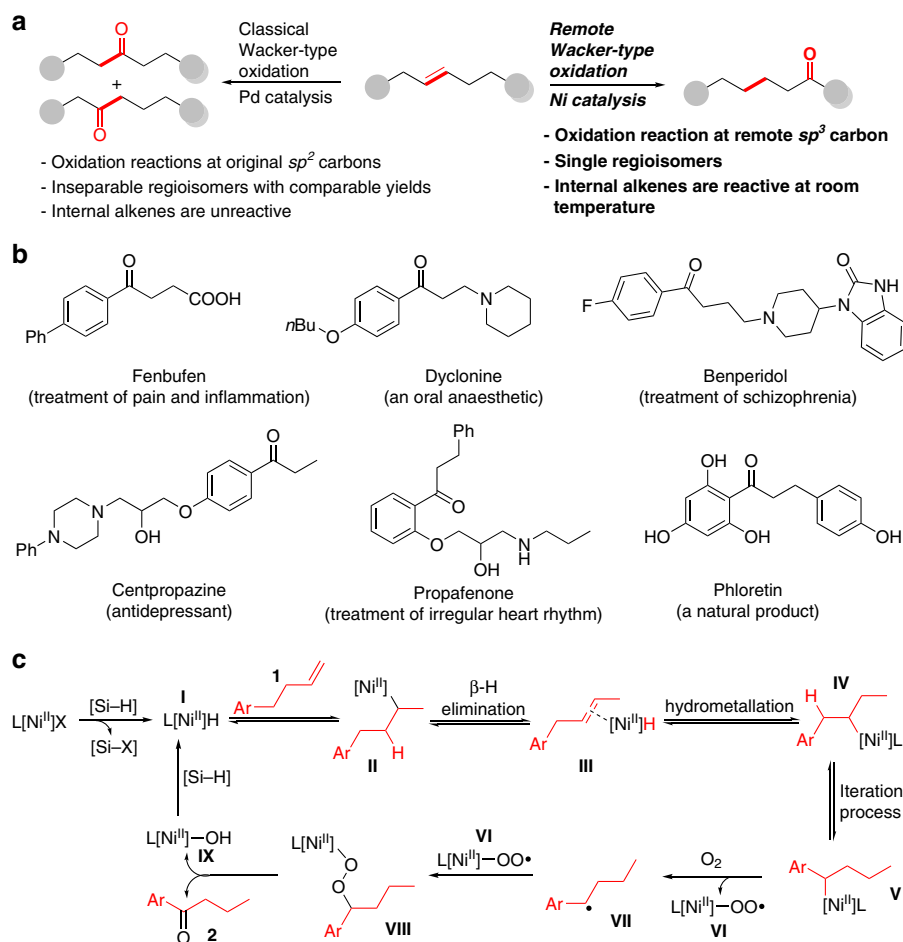


Fig. 1 Nickel-catalyzed Wacker-type oxidation at remote sp^3 C–H sites. **a** Classical Wacker oxidation vs. remote Wacker-type oxidation. **b** Examples of biologically active organic molecules that contain an aromatic ketone motif. **c** Mechanistic rationale for the nickel-catalyzed Wacker-type oxidation at remote sp^3 C–H sites

catalyst enabling migration of an olefinic unsaturation toward a specific position where oxidation occurs. Encouragement in this regard was found in the work of inexpensive nickel-catalyzed remote sp^3 C–H functionalizations through a chain-walking mechanism via iterative β -hydride elimination/nickel-hydride species migratory insertion yielding a nickel alkyl sequences^{31,32,39–44}. Inspired by these investigations, we questioned whether we could utilize a nickel catalyst for the challenging remote oxidation of unactivated sp^3 C–H sites in the presence of a priori more reactive carbon–carbon double bonds.

On the basis of the above-mentioned results, we hypothesize that the remote Wacker-type oxidation proceeds through a single electron transfer (SET) process. To achieve requisite selectivity and avoid the formation of regioisomeric oxidation products, this remote Wacker-type oxidation process should preferably have sufficient kinetic and thermodynamic favorability. In this context, aryl-substituted olefins selected as substrates would be the optimal choice because they can generate stable benzyl radical intermediates and give the corresponding conjugated aryl ketone products. Notably, aryl-substituted olefins that are widely present in readily available and renewable plants of the family Anacardiaceae and Ginkgo biloba fruits^{10,45} undergo such a transformation to deliver aryl ketones, a privileged scaffold in medicinal chemistry and pharmaceutical agents (Fig. 1b).

Here we develop an alternative disconnection, in which internal olefins, including unbiased internal olefins, can be easily converted to single regioisomeric ketones with high activity in the absence of coordinating groups through remote Wacker-type oxidation. This method is highlighted by the successful employment of ideal ambient air as the sole oxidant, natural abundance of nickel as the catalyst, and a byproduct of the silicone industry, polymethylhydrosiloxane (PMHS) as the hydride source under room temperature allowing for effective oxidation of challenging alkenes with excellent selectivity.

Results

Design principle. Details of our design principle are outlined in Fig. 1c. Nickel hydride **I**, formed in situ from the reaction of L [Ni^{II}]X with hydrosilane, undergoes hydrometalation of olefin to

provide alkyl nickel intermediate **II**^{40–43}, followed by β -hydride elimination to give a new metal-bonded hydride with a concomitant migration of the double bond **III**. Subsequently, re-addition of the metal hydride generates a new alkyl–Ni species **IV**. Iterative the β -hydride elimination/migratory insertion sequences achieve a chain-walking process, delivering a critical benzyl nickel intermediate **V**^{39–43}. Then the reaction of **V** with oxygen would form a thermodynamically favored benzyl radical **VII**, followed by generation of a nickel peroxide complex **VIII**^{46–50}. Finally, **VIII** would undergo homolytic cleavage of O–O and C–H bond breaking to liberate the thermodynamically more stable product aryl ketone **2**, while providing the LNi^{II}–OH species, which could regenerate the nickel hydride **I** catalyst by hydride transfer in the presence of a hydrosilane^{50,51}.

To probe this potential, our initial studies tested the isomerization–Wacker-type oxidation of 4-allylanisole (**1a**) with NiCl₂/L1 (neocuproine) catalyst system using PhSiD₃ as hydrosilane and EtOH as solvent and was found to allow the formation of desired aryl ketone **2a–d** bearing similar degrees of D-incorporation at all positions of its hydrocarbon chain (Fig. 2a), suggesting that the process proceeds via Ni–D hydrometalation and subsequent β -hydride elimination/migratory insertion sequences and is bidirectional^{39–43}. Furthermore, when olefin **1p** was subjected to the reaction conditions under N₂, a mixture of olefins originating from olefin isomerization was observed by gas chromatographic–mass spectrometric (MS) analysis and subjected to the oxidation reaction conditions to produce only one regioconvergent aryl ketone **2p** (Fig. 2b), indicating that olefin isomerization is independent of an oxidant and chain walking precedes oxidation event. In the following oxidation section, a benzyl nickel intermediate undergoing SET oxidation to form a benzyl radical is supported by a radical capture experiment where addition of a radical inhibitor Galvinoxyl to the reaction mixture of **1a** resulted in total inhibition of the oxidation transformation and intercepted the corresponding benzyl radical to provide **2a'** based on high-resolution MS (electrospray ionization) analysis (Fig. 2c). Collectively, these results demonstrate the feasibility of the elementary steps in our design principle.

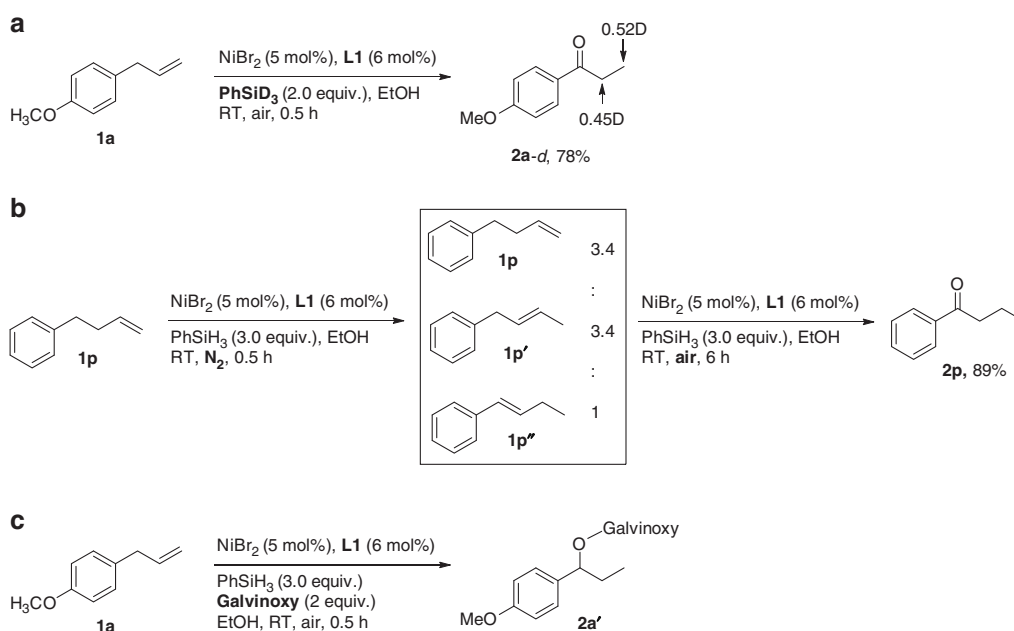


Fig. 2 Mechanistic studies. **a** Isotopic labeling experiment. **b** Intermediates analysis and oxidation of olefin isomers. The ratio of the mixture of alkenes was determined by GC/MS. **c** Radical-trapping experiment

Encouraged by the above results, we systematically evaluated various parameters with exposure of **1a** to a nickel species in the presence of hydrosilane as a hydride source under aerobic conditions at room temperature and found that optimal conditions were achieved by using a combination of NiBr₂ (5.0 mol%) and bench-stable **L1** (6.0 mol%) as the catalyst and PMHS (3.0 equiv) as the hydride source in EtOH under ambient air to yield the desired aryl ketone **2a** in 80% yield as a single regioisomer (see Supplementary Table 1). Notably, compared with **L1**, in 1,10-phenanthroline **L2** lack of encumbered two methyl groups at C2 and C9 led to no desired oxidation product. Additionally, in line with our design principle, nickel catalyst, PMHS, and air are all essential for oxidation. Without any one of the three elements, no oxidation was possible.

Substrate scope. With the optimized conditions established, the scope of the nickel-catalyzed remote and proximal Wacker-Type oxidation was investigated (Fig. 3). Allyl benzenes bearing electron-donating or/and electron-withdrawing groups could be oxidized efficiently to afford the corresponding aryl ketones

2a–2m in good-to-excellent yields. The reaction of **1a** could be run on a 5 mmol scale to give a similar yield (78%). Although steric hindrance on the aryl ring had a deleterious effect on the yield, a synthetic useful yield could also be obtained (**2c**). Particularly noteworthy is the tolerance of bromo, chloro, fluoro, and iodo groups (**2e–2h** and **2m**), which can be used as pre-functionalities for further transformations. Additionally, methoxy, trifluoromethyl, cyano, and trimethylsilyl substitutes and esters were unaffected under the normal reaction conditions. Gratifyingly, the transformation can move beyond the simple aryl group. For instance, allyl-substituted naphthalene and indole were viable reagents in this reaction to build-up aryl ketones (**2n–2o**). Compared with allylbenzene (**1d**), homoallylbenzene (**1p**) could achieve an identical result in a longer reaction time (6 h). Even further increasingly distal functionality, such as a thiophene ring three methylene and a phenyl ring four methylene units away (**1r–1s**), provided the desired products in 82% and 88% yields, respectively. Notably, internal olefins such as **1t–1v**, **1s'**, **1s''**, and **1r'** are not successfully oxidized through conventional Wacker-type reaction but are suitable substrates for oxidation via the present nickel catalysis. A variety of styrenes could also

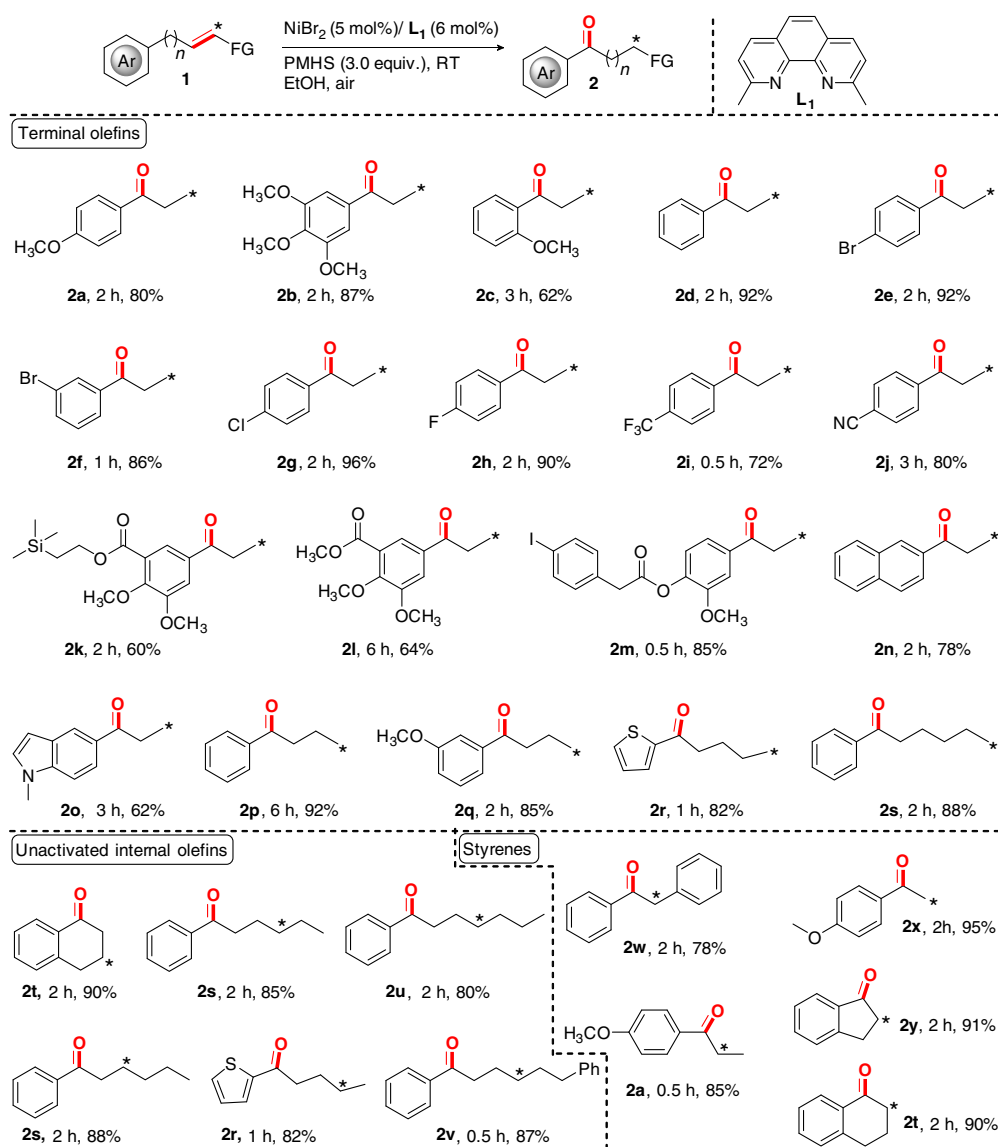


Fig. 3 Substrate scope for the nickel-catalyzed Wacker-type oxidation. Reported yields are for the isolated products; asterisk "*" denotes the initial position (right side) of the unsaturated carbon atom of a red double bond

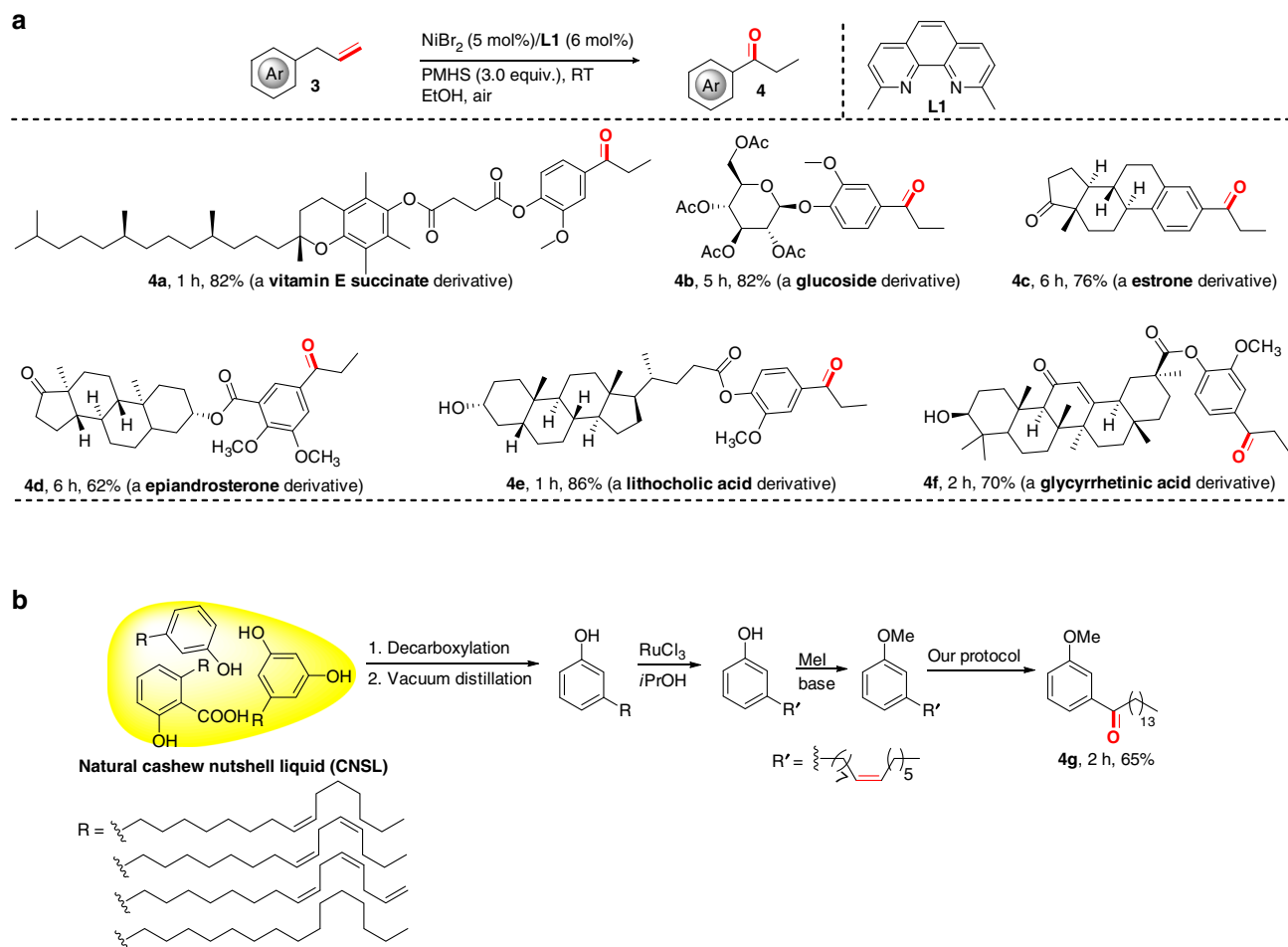


Fig. 4 Late-stage oxidation of complex molecules. Reported yields are for the isolated products. **a** Complex medicinally relevant molecules as the substrates. **b** Cashew nutshell liquid (CNSL) as the substrate; the yellow shape is analogous to a drop of cashew nutshell liquid

undergo direct oxidation under the reaction conditions to provide the corresponding products **2w–2y**, **2a**, and **2t** in good-to-excellent yields.

A particularly noteworthy aspect of this protocol is its amenability to late-stage synthetic applications (Fig. 4). For instance, remote Wacker-Type oxidation of a Vitamin E succinate derivative proceeded smoothly to give the desired product **4a** in 82% yield. Eugenol peracetyl-glucoside **3b** having activity against the fungi⁵² was also oxidized in 82% yield (**4b**). In addition, the steroidal substrates **3b–3f** synthesized from estrone, epiandrosterone, lithocholic acid, and glycyrrhetic acid, respectively, were subjected to the oxidation procedure, affording the desired products in 62–86% yields (**4b–4f**). Notably, oxidatively labile functional groups such as a hydroxy group and a carbon–carbon double bond conjugated with a highly electron-withdrawing substitute remained intact (**4e–4f**). Furthermore, cashew nutshell liquid, a raw material, is directly obtained from the shell of the cashew nut and contains cardol, cardanol, and anacardic acid. It undergoes decarboxylation, vacuum distillation, hydrogenation, and methylation to deliver **3g**⁵³. With our protocol, **3g** could be transformed to **4g** in 65% yield with ideal selectivity (Fig. 4b).

Ultimately, a major benefit of this mild, nickel-catalyzed aerobic oxidation is its viability to demonstrate regioconvergent oxidation of mixtures of alkenes to produce single-regioisomer aryl ketones. To demonstrate this potential, an equimolar mixture of three olefin regioisomers was subjected to the standard reaction conditions to selectively generate a single product **2s** in 88% yield (Fig. 5a). This finding showcased the potential of the

catalytic platform for conversion of cheap and abundant petroleum-derived alkenes that are often mixtures of regioisomers to value-added products containing single regioisomers. In addition, elimination reactions frequently result in a mixture of at least two olefin regioisomers that are difficult to separate. For example, aliphatic tosylate **5a** underwent elimination in alcoholic MeONa solution⁵⁴ to give a mixture of two regioisomers **1p'** and **1p''** (molar ratio, 4.1:1) that could be directly transformed to a single-regioisomer aryl ketone **2p** in 78% yield by using our protocol (Fig. 5b). Similarly, alcohol **5b** dehydration⁵⁵ generated a mixture of olefins **1s'** and **1s''** with a 1.5:1 molar ratio, which was subjected to the reaction conditions and produced only one regioconvergent oxidation product **2s** in 62% yield (Fig. 5c). Neither purification nor isolation of the intermediate olefinic isomers was necessary, showing the robustness of our method.

Discussion

In summary, we have developed a conceptually new approach to selective oxidation of remote sp^3 C–H bonds to produce ketones. The transformation proceeds through the nickel-catalyzed alkene isomerization to transfer the unit of unsaturation to the most thermodynamically favored position in the molecule and subsequent oxidation using ambient air as the sole oxidant at room temperature. The mild, expeditious, and operationally simple protocol allows efficient remote oxidation of terminal olefins and unactivated internal olefins with excellent functional-group tolerance and regio- and chemo-selectivity. Even unrefined mixtures of olefins can undergo regioconvergent oxidation to selectively

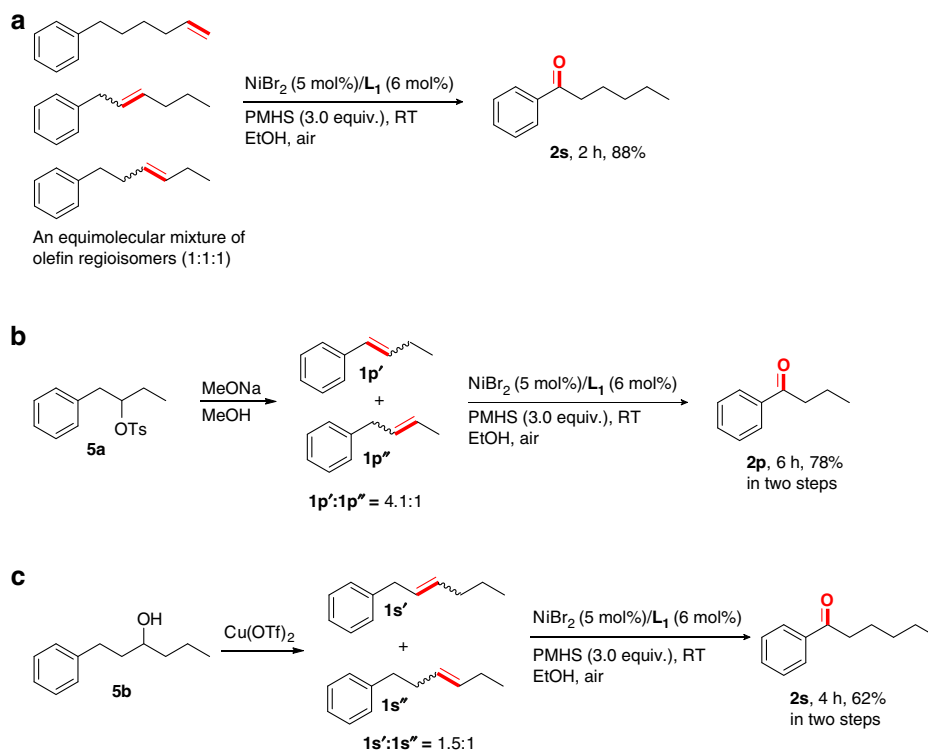


Fig. 5 Regioconvergent Ni-catalyzed remote Wacker-type oxidation of mixtures of alkenes. **a** Regioconvergent oxidation of mixtures of alkenes to produce a single-regioisomer aryl ketone. **b** Regioconvergent oxidation of a mixture of alkenes from an elimination reaction of an alkyl tosylate. **c** Regioconvergent oxidation of a mixture of alkenes from dehydration of an alcohol. Reported yields are for the isolated products. The ratios of mixtures of alkenes were determined by GC/MS

produce a single product, which is not currently accessible. Notably, the protocol is particularly useful for late-stage oxidation of structurally complex substrates, which offers a unique approach to conceptualize the remote oxidation disconnections in organic synthesis.

Methods

General procedure. A 25 mL flask was charged with NiBr_2 (2.8 mg, 0.0125 mmol), neocuproine (3.2 mg, 0.0150 mmol), olefin (0.25 mmol), EtOH (2 mL), and PMHS (170 μL , 0.75 mmol). The reaction mixture was stirred in an open air atmosphere at room temperature until the reaction was complete (observed by thin layer chromatography). The resulting reaction solution was directly purified by column chromatography (petroleum ether/ethyl acetate) on silica gel to afford the corresponding product.

Synthesis and characterization. See Supplementary Methods for general information about chemicals and analytical methods, synthetic procedures, 5 mmol-scale synthesis, regioconvergent oxidation of mixtures of olefins (see Supplementary Figures 6–8), and characterization of products. For ^1H and ^{13}C nuclear magnetic resonance data, see Supplementary Figures 9–40.

Optimization. See Supplementary Table 1.

Mechanistic studies. See Supplementary Figures 1 and 2 (isotopic labeling experiment), Supplementary Figure 3 (intermediates analysis and oxidation of olefin isomers), and Supplementary Figure 4 and 5 (interception of radical intermediate).

Data availability

We declare that the data supporting the findings of this study are available within the article and Supplementary Information file or from the corresponding author upon reasonable request.

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Author contributions

B.L., P.H., F.X., L.C. and M.T. performed and analyzed the experiments. W.H. conceived and supervised the project. B.L., P.H. and W.H. wrote the manuscript.

Additional information

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