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Direct construction of high-value pyridine scaffolds through manganese-promoted alkene dicarbofunctionalization

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The direct construction of high-value pyridine scaffolds through manganese-promoted alkene dicarbofunctionalization starting from ubiquitous carbonyls and heterocyclic compounds is reported. This protocol provides an efficient platform for constructing a wide array of γ -heterocyclic ketone derivatives, which are useful bioactive scaffolds, with high atom economy and controlled regioselectivity. An intramolecular approach was also developed to efficiently synthesize α -tetralones, tetrahydroquinolines, and benz[h]isoquinolines which have garnered significant attention due to their potential applications in medicinal chemistry but also in materials science. In addition, a complementary electrochemical protocol has also been developed to avoid the use of stoichiometric amounts of Mn(III)-salts. Finally, several control experiments allowed a proposed mechanism to be assembled, thus rationalizing the crucial role of *N*-methoxypyridinium salts.

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Introduction

The synthesis of complex nitrogen-containing heterocycles remains a cornerstone in modern organic chemistry, particularly due to their prevalent role in pharmaceutical development and natural product synthesis.^{1,2} Among these privileged scaffolds, γ -heterocyclic ketones, α -tetralones, tetrahydroquinolines, and benz[h]isoquinolines stand out as exceptionally valuable structural motifs. In addition to being known as muscle relaxants,^{3,4} γ -heterocyclic ketones represent essential intermediates in the synthesis of complex heterocyclic systems, offering unique reactivity patterns that enable selective functionalization. α -Tetralones, with their fused bicyclic framework, not only serve as versatile synthetic intermediates but also appear in various natural products exhibiting significant biological activities in the context of antimalarial,⁵ antidepressant,⁶ and Alzheimer treatments.⁷ The tetrahydroquinoline scaffold, ubiquitous in both natural and synthetic bioactive compounds, has proven indispensable in drug discovery, appearing in treatments for conditions ranging from cardiovascular diseases to cancer.⁸ Perhaps most intriguingly, benz[h]isoquinolines, with their extended aromatic system, have garnered significant attention due to their potential appli-

cations in medicinal chemistry⁹ but also in materials science.^{10–12}

The strategic significance of these heterocyclic scaffolds in pharmaceutical development and materials science underscores the critical need for robust synthetic methodologies. Despite their fundamental importance, current synthetic approaches to accessing these valuable compounds suffer from significant limitations. Existing methods involve multiple synthetic steps, resulting in poor atom economy and environmental concerns.^{13,14} Moreover, these approaches frequently deliver unsatisfactory yields, exhibit limited functional group tolerance, and lack the versatility needed for late-stage functionalization.^{15–17} The restricted substrate scope further hampers their broad applicability in both academic research and industrial settings. This compelling gap in synthetic methodology presents an urgent need for the development of a more efficient, selective, and sustainable method that can deliver these crucial heterocyclic compounds with improved yields, broader scope, and enhanced practicality for large-scale applications.

Within the framework of our research program dedicated to manganese catalysis, we have been intrigued by a few studies reporting the dicarbofunctionalization of non-activated alkenes starting from carbonyls and *N*-heterocycles using Mn(OAc)₃ as metal source.^{16–24} In these reactions, the α -carbonyl-C-centered radical intermediate is electrophilic due to SOMO- π delocalization.^{25–27} Thus, it subsequently reacts with an unsaturated substrate to afford a γ -ketoalkyl radical which is less electrophilic.^{27,28} This radical *umpolung* along the reaction allows for a multicomponent radical cascade to take place,

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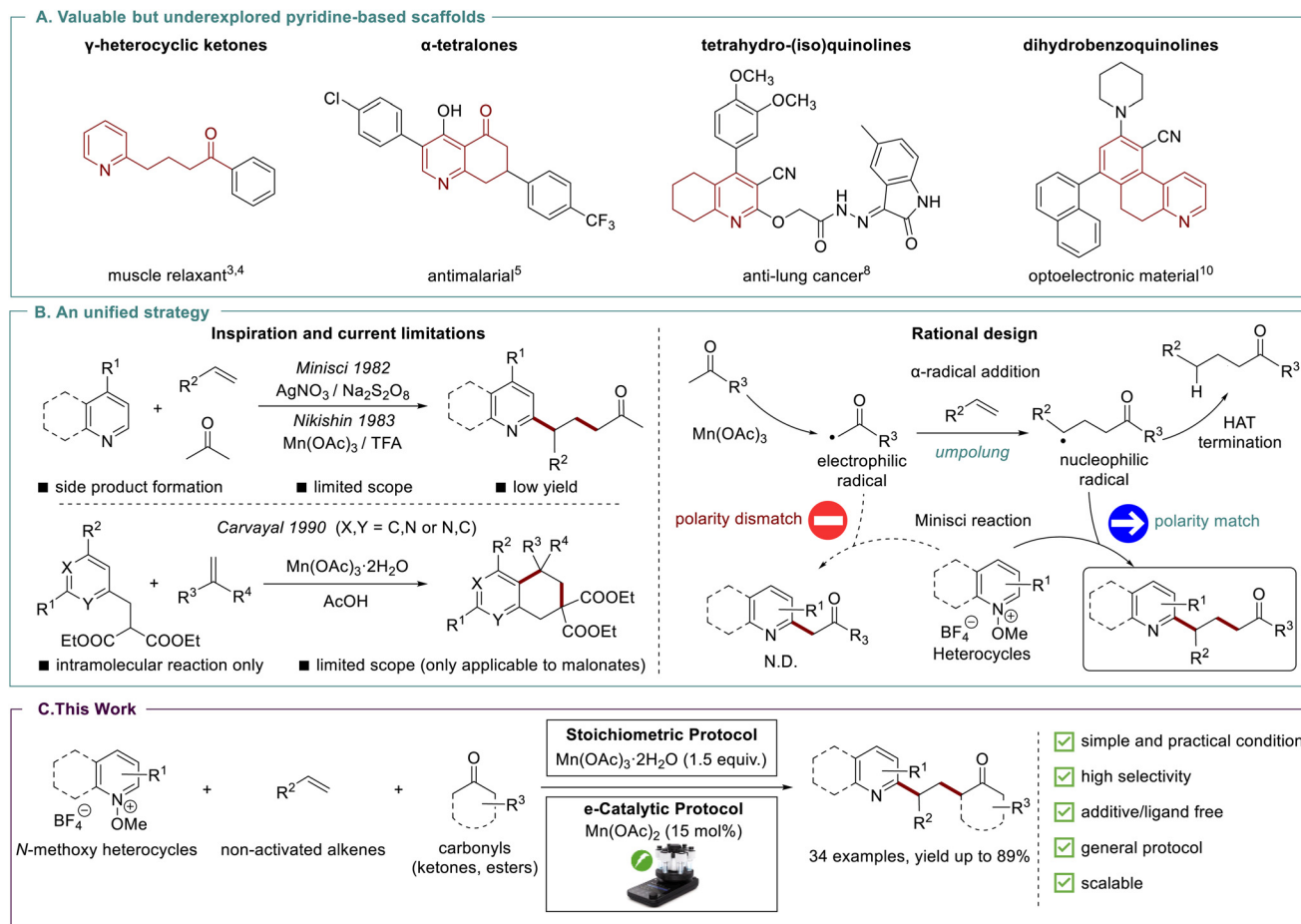


Fig. 1 Direct construction of high-value pyridine scaffolds through manganese-promoted alkene dicarbofunctionalization starting from ubiquitous carbonyls and heterocyclic compounds.

sharing similarities with an inter/intramolecular Minisci-type reaction as illustrated in Fig. 1B. Indeed, the *in situ* generated nucleophilic γ -keto alkyl radical undergoes faster $S_{\text{H}}\text{Ar}$ with an appropriate heteroarene (polarity match), such as pyridine or quinoline, than the corresponding α -carbonyl radical (polarity mismatch), as displayed in Fig. 1B. This one-pot cascade ultimately delivers the desired γ -pyridyl ketone derivatives. However, while these early reports clearly highlight the potential of such a tactic to access this important class of compounds, the reaction displayed several limitations including: (i) the absence of a general set of conditions; (ii) the limited substrate scope where only acetone or specific malonate derivatives underwent the desired transformation; (iii) the low yields obtained and the large amount of carbonyl starting materials required for the intermolecular processes; (iv) the use of stoichiometric amount manganese (Fig. 1A and B).

Herein, we report a manganese-mediated dicarbofunctionalization of unactivated alkenes that employs readily available carbonyl compounds and strategically activated heteroarenes, fundamentally addressing the limitations of existing methodologies (Fig. 1C). This powerful transformation enables rapid access to structurally diverse γ -heterocyclic

ketone derivatives under mild conditions with exceptional functional group tolerance. Through strategic molecular design, we extended this methodology to an intramolecular variant, achieving efficient synthesis of complex α -tetralones, tetrahydroquinolines, and benz[*h*]isoquinolines – structures that have historically posed significant synthetic challenges. Notably, we developed a sustainable electrochemical protocol that dramatically reduces manganese loading to catalytic quantities while maintaining high efficiency, thereby enhancing the practical utility of our strategy (Fig. 1C). Comprehensive mechanistic investigations, including key control experiments, revealed the critical role of *N*-methoxy-pyridinium salts in the reaction pathway, providing crucial insights that rationalize the observed reactivity and selectivity patterns.

Results and discussion

Optimization of the reaction conditions

The investigation started with the selection of *N*-methoxy-4-methylquinolinium tetrafluoroborate (**1a**), oct-1-ene (**2a**) and

pinacolone (**3a**) as model substrates (Fig. 2A). The reaction between the carbonyl (5.0 equiv.), the alkene (1.5 equiv.), and the *N*-methoxy-heterocyclic tetrafluoroborate (1.0 equiv.) in the presence of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (1.5 equiv.) in AcOH at 70 °C afforded the desired difunctionalized product in 61% isolated yield, whose structure was unambiguously confirmed by ^1H NMR, ^{13}C NMR and HRMS. Fig. 2A summarizes the influence of each parameter that governs the transformation. First, the nature of the heterocyclic acceptor, and more precisely the modulation of its electronic properties *via N*-functionalization,

was investigated. Modification of the nitrogen activating group led to a dramatic decrease in yield (Fig. 2A, **1b–1e**). This trend matches with reported rate constants for the addition of alkyl radicals on heteroarene derivatives depending on their *N*-substitution.^{22,29}

Therefore, in addition to their air-stability, *N*-methoxy heterocyclic compounds were selected for their enhanced reactivity. Then, the ideal number of equivalents for each starting material was assessed (Fig. 2A, middle). While reducing the amount of ketone (3.0 equiv.) or alkene (1 equiv.) lowered the overall reaction efficiency, using a large amount of ketone (10.0 equiv.) or alkene (2.0 equiv.) delivered slightly higher yields than standard conditions, matching with previously reported results from the literature.^{20,21,30} To avoid such excess of reactants, the ideal quantities for ketone and alkene starting materials were determined to be 5.0 equiv. and 1.5 equiv. respectively. Then, the impact of the amount of Mn ($\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ was examined. Increasing the number of equivalents from 0.5 to 1.5 improved the yield from 44% to 66%. However, increasing the loading above 1.5 equiv. resulted in decreased yields likely due to solubility issues.

Next, the influence of the temperature was investigated (Fig. 2A, middle). While temperatures lower than 50 °C considerably diminished the yield, temperatures higher than 70 °C improved the yield but reduced the selectivity affecting the purification of the desired product. Next, the impact of solvent was examined (Fig. 2A, middle). As previously described in the literature, AcOH is the solvent of choice for this transformation.^{20,30} Lower yields were obtained when using MeCN, benzene, toluene, ethanol, trifluoroethanol, and pinacolone itself (Fig. 2A, entries 1–7). No reaction was observed when replacing the AcOH by ether, ester, chlorinated and other non-polar solvents (Fig. S7). The specific role of AcOH was previously attributed to its ability to solubilize and dissociate Mn salts.^{20,30} Interestingly, a 2 to 1 mixture of AcOH/HFIP improved the yield up to 82% (Fig. 2A, entry 8). However, this positive outcome was not transferable to other substrates. Based on promising pioneering contributions, Co(II) or Cu(II) salts were used as co-catalysts to try to enhance the activity of our Mn-based system.^{20,31,32} However, adding $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ or $\text{Cu}(\text{OAc})_2$ proved to be detrimental for both selectivity and yields (Fig. 2A, entries 9 and 10). Similarly, the addition of NaOAc or KOAc, known to provide advantageous effect on the Mn-mediated oxidation, almost completely inhibited the reactivity (Fig. 2A, entries 11 and 12).³³

Finally, robustness tests were performed by adding acids, water and bases. While the reaction outcome was not affected by acid or water contents (Fig. 2A, entries 13 and 14), addition of basic additives hampered both the conversion and yields (Fig. 2A, entries 15 and 16). The impact of the solvation and acidic conditions on the reaction outcome may be associated to the narrow E-pH stability domain of Mn(III) species as suggested by the Mn-water Pourbaix diagram, in which Mn(III) is only accessible for pH below -2 and potential above 1.5 V vs. SHE. In parallel, due to the low cost and easy sourcing of acetone, its use as both reactant and component of a binary

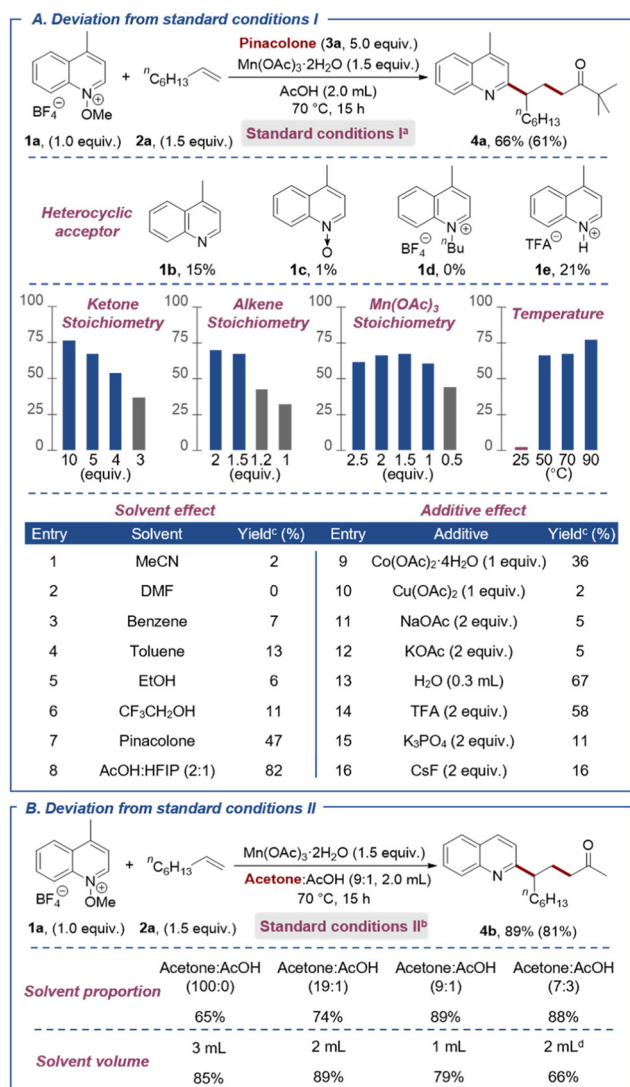


Fig. 2 Optimization of reaction conditions. ^aStandard reaction conditions I are as follows: pinacolone (0.63 mmol, 5.0 equiv.), oct-1-ene (0.19 mmol, 1.5 equiv.), *N*-methoxy-4-methylquinolinium tetrafluoroborate (0.13 mmol, 1.0 equiv.), $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (0.19 mmol, 1.5 equiv.), AcOH (2.0 mL), 70 °C, 15 h; ^bStandard reaction conditions II are as follows: oct-1-ene (0.19 mmol, 1.5 equiv.), *N*-methoxy 4-methylquinolinium tetrafluoroborate (0.13 mmol, 1.0 equiv.), $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (0.19 mmol, 1.5 equiv.), acetone:AcOH (9:1, 2.0 mL), 70 °C, 15 h; ^cGC yields determined by gas chromatography/mass spectrometry using 1,3,5-trimethoxybenzene or hexadecane as an internal standard; ^dAcetone (0.63 mmol, 5.0 equiv.) and AcOH (2.0 mL) were used.

solvent system with AcOH was evaluated (Fig. 2B). In pure acetone, the reaction delivered the expected product in 65% yield, though $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ was not fully dissolved. Using a 9 : 1 mixture of acetone/AcOH enables not only to fully solubilize the Mn salt but also to improve the yield up to 89%. Under this set of conditions, the volume of solvent was also examined. While concentration does not seem to considerably impact the reaction efficiency, running it at too high concentration lowered the yield, probably due to partial solubility of the Mn salts and low stirring efficiency (Fig. 2B, bottom). Using reduced amount of acetone (5.0 equiv.) in AcOH lowered the yield due to acetone evaporation (Fig. 2B, bottom).

Substrate scope

Carbonyl derivatives. With the optimized conditions in hands, the scope of the Mn-mediated dicarbofunctionalization of non-activated alkenes was investigated starting by evaluating several carbonyl derivatives (Fig. 3A). We initially examined the reactivity of acetone as the simplest carbonyl derivative. In this case, the desired product was isolated in an 81% yield (**4b**). α -Monoalkyl substituted carbonyls also performed in high efficiency (**4c–4f**). Based on previous reports, this trend is remarkable as 2-methylbutanone was previously reported to hardly provide the α -keto free radical.²¹ Notably, no product resulting from the activation of the disubstituted α -C–H position could be identified, suggesting the good chemoselectivity of the oxidation between primary and secondary α -carbonyl substituents (Fig. S20). Further substitution on the α -position as in 2,2-dimethylbutanone resulted in a 78% isolated yield (**4f**). Cyclic ketones such as cyclohexanone were also amenable to this protocol, delivering the desired product **4g** in a 70% yield. Pleasingly, acetophenone also afforded the desired product **4h** in a moderate yield of 30%. Finally, β -diesters, such as malonate, were also compatible with the reaction conditions delivering the desired product **4i** in 50% yield. Limitations regarding the structure of carbonyl derivatives have been encountered as described in the SI. Amides and esters did not react under the reaction conditions due to their high α -C–H $\text{p}K_{\text{a}}$ values (Fig. S20).³⁰ In additions, β -dicarbonyls and classes of carbonyl derivatives that display low α -C–H $\text{p}K_{\text{a}}$ values were not compatible with the reaction conditions. In these cases, HAT termination products are mainly generated, as characterized by GC-MS (Fig. S20). However, in the case of acetylacetone, the targeted product **4j** was isolated in 29% yield. Finally, aldehydes such as acetaldehyde were evaluated. In this case, both the activation of aldehydic hydrogen and α -C–H of carbonyl are competitive leading to complex mixtures (Fig. S20). Of note, in absence of the carbonyl substrates, the methoxy adduct **4k** was isolated in 59% yield. As discussed, hereafter the MeO group originates from the cleavage of the heterocycle *N*-methoxy substrate.

Alkenes. Substituted alkenes bearing alkyl, halogen, methoxy, cyanide, phenyl, acetoxy, ester, amide and benzodioxole substituents were all successfully converted in good yields to their corresponding dicarbofunctionalized products (Fig. 3B, **5a–5i**, 42–86%), demonstrating a good functional

group tolerance on this coupling partner. Regarding halogenated alkenes, chlorinated compound such as **5b** was obtained in 86% yield. In contrast, bromo-containing compounds could not be isolated due to the formation of quinolinium salts (Fig. S21). Finally, the reactivity of cyclic alkenes, such as cyclohexene was also examined. The resulting compound **5j** was isolated in a 56% yield when coupled with acetone. Though moderate, this yield highlights the ability of this methodology to functionalize 1,2-disubstituted non-activated alkenes. Furthermore, the reaction proved selective towards the formation of 1,2-*trans* isomer in a 14 : 1 ratio. Some limitations of this methodology were unveiled when attempting to couple alkynes, α,α -disubstituted alkenes, α,α,β -trisubstituted alkenes, and highly sterically hindered alkenes. In most cases, due to the complexity of product mixtures, the desired difunctionalized product could not be isolated and fully characterized (Fig. S21).

Heterocycles. Within the quinoline series, the outcome of the reaction does not depend on the substitution pattern of the 4-position (Fig. 3C, **6a–6d**) and the reaction also proceeds smoothly using isoquinoline (Fig. 3C, **6e**). 2-Substituted quinolines, such as 2-methylquinoline, afforded desired product **6f** in moderate yield (Fig. 3C). A variety of substituted pyridines, such as 4-phenylpyridine and 2,6-lutidine, were readily converted to targeted products **6g** and **6h** in excellent yields (Fig. 3C). In addition, some polycyclic aromatic hydrocarbons (PAHs), such as pentahalide and acridine, also successfully delivered the desired products **6i** and **6j** in acceptable yields, displaying excellent chemo-selectivity. The only observed limitation is related to the 4-nitropyridine scaffold for which our methodology proved ineffective (Fig. S22).

Methodology applications, electrochemical adaptation and mechanistic study

Intramolecular cascade

Building on the success of our intermolecular alkene difunctionalization system to efficiently synthesize diverse γ -heterocyclic ketone cores, we strategically expanded our investigation to more challenging intramolecular radical cascades, enabling unprecedented access to α -tetralone, tetrahydroquinoline, and benz[*h*]isoquinoline frameworks.

As illustrated in Fig. 4A, we rationally designed three distinct substrate classes that incorporate two of the three essential reaction components, allowing direct and efficient access to each target scaffold. When subjected to optimized conditions with the third complementary coupling partner, these substrates underwent the proposed cascade reaction, generating valuable and previously challenging-to-access pyridine-tethered polycyclic derivatives (**7a–7f**) in yields significantly superior to existing methods (Fig. 1A and C). Notably, our methodology demonstrates exceptional functional group tolerance in accessing 5,6,7,8-tetrahydroisoquinoline and 9,10-

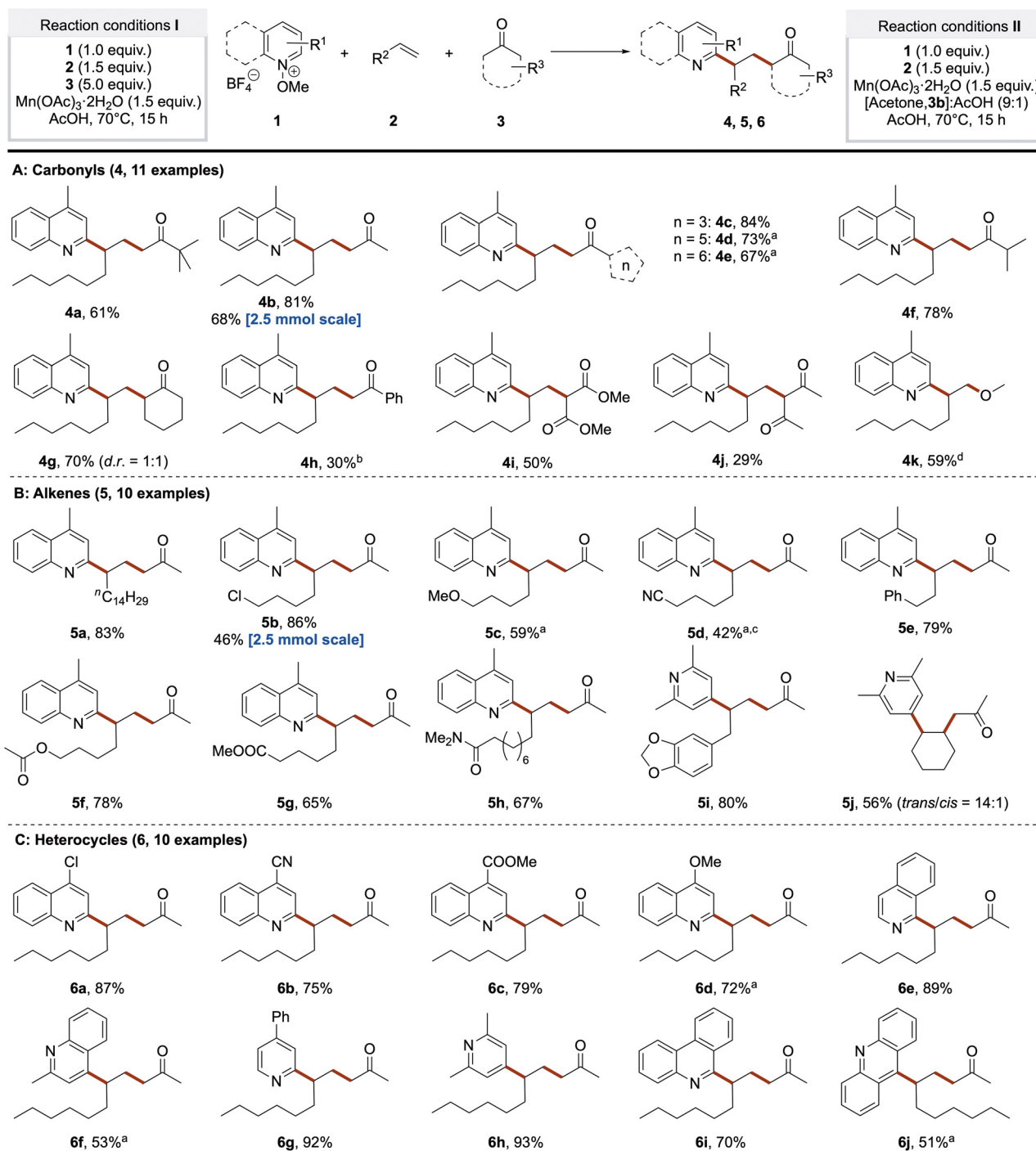


Fig. 3 Substrate scope. ^aReaction proceeded under argon; ^bAcetophenone (10 equiv.) was used; ^cReaction proceeded at 90 °C; ^dWithout using carbonyls.

dihydro-2-phenantrolines – a feat that has proven particularly challenging using conventional synthetic approaches.

Electro-catalytic adaptation

To avoid using stoichiometric amounts of Mn(OAc)₃, which is a clear limitation from a sustainability and scalability standpoints, the development of a reliable electrochemical system

for oxidation of Mn(II) to Mn(III) was initiated.²¹ The reaction was conducted using 15 mol% of Mn(OAc)₂ in acetone/AcOH/H₂O at 70 °C under air in an undivided cell equipped with a graphite anode and cathode (Fig. 4B). AcOH was selected as the solvent due to its ability to solubilize Mn salts and to promote the regeneration of the Mn(OAc)₃ at the anode. Under these conditions with an applied current of 3 mA using alter-

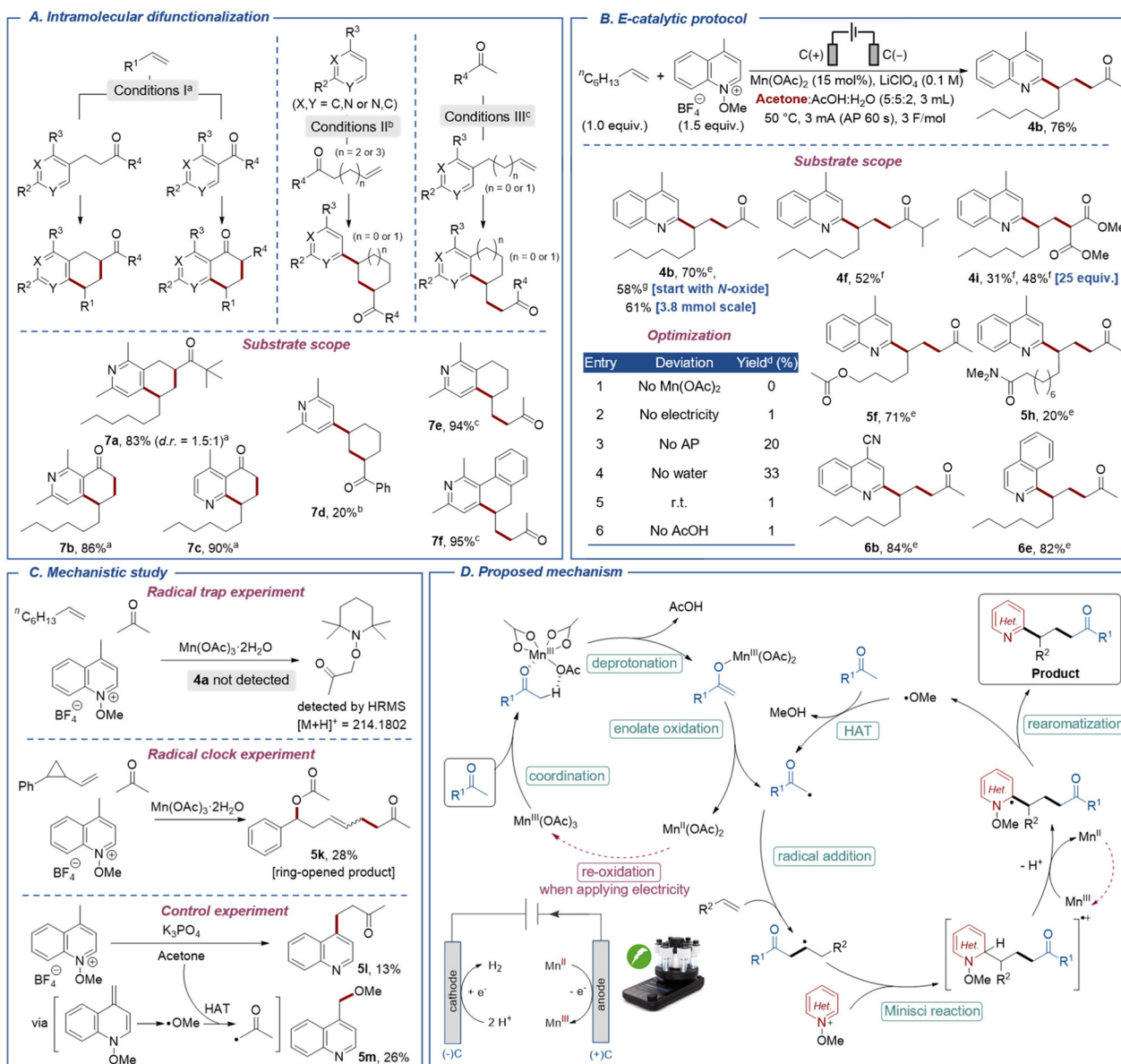


Fig. 4 Methodology applications, electrochemical adaptation and mechanistic study. ^aStandard reaction conditions I are as follows: *N*-methoxy-heterocyclic tetrafluoroborate (0.25 mmol, 1.0 equiv.), alkene (0.38 mmol, 1.5 equiv.), Mn(OAc)₂·2H₂O (0.38 mmol, 1.5 equiv.), AcOH (4.0 mL), 70 °C, 15 h; ^bStandard reaction conditions II are as follows: alkene (1.25 mmol, 5.0 equiv.), *N*-methoxy-heterocyclic tetrafluoroborate (0.25 mmol, 1.0 equiv.), Mn(OAc)₂·2H₂O (0.38 mmol, 1.5 equiv.), AcOH (4.0 mL), 70 °C, 15 h; ^cStandard reaction conditions III are as follows: *N*-methoxy-heterocyclic tetrafluoroborate (0.25 mmol, 1.0 equiv.), Mn(OAc)₂·2H₂O (0.38 mmol, 1.5 equiv.), acetone : AcOH (9 : 1, 4.0 mL), 70 °C, 15 h; ^dStandard reaction conditions IV for optimization are as follows: oct-1-ene (0.13 mmol, 1.0 equiv.), *N*-methoxy-4-methylquinolinium tetrafluoroborate (0.19 mmol, 1.5 equiv.), Mn(OAc)₂ (0.013 mmol, 0.15 equiv.), LiClO₄ (0.1 M), acetone : AcOH : H₂O (5 : 5 : 2, 3.0 mL), (+)C/(−)C, 3 mA (AP 60 s), 3 F mol^{−1}, 50 °C, yields determined by GC-MS; ^eStandard reaction conditions V are as follows: alkene (0.25 mmol, 1.0 equiv.), *N*-methoxy-heterocyclic tetrafluoroborate (0.38 mmol, 1.5 equiv.), Mn(OAc)₂ (0.025 mmol, 0.15 equiv.), LiClO₄ (0.1 M), acetone : AcOH : H₂O (5 : 5 : 2, 3.0 mL), (+)C/(−)C, 3 mA (AP 60 s), 3 F mol^{−1}, 50 °C; ^fStandard reaction conditions VI are as follows: carbonyls (1.25 mmol, 5.0 equiv.), alkene (0.25 mmol, 1.0 equiv.), *N*-methoxy-heterocyclic tetrafluoroborate (0.38 mmol, 1.5 equiv.), Mn(OAc)₂ (0.025 mmol, 0.15 equiv.), LiClO₄ (0.1 M), AcOH : H₂O (5 : 1, 2.4 mL), (+)C/(−)C, 3 mA (AP 60 s), 3 F mol^{−1}, 70 °C; ^g4-Methylquinoline-*N*-oxide was used instead of *N*-methoxy-4-methylquinolinium tetrafluoroborate.

nating polarity, compound **4b** was obtained in 76% yield. The optimization campaign is depicted in Fig. 4B. The absence of Mn(OAc)₂, electricity, temperature or AcOH resulted in no conversion (Fig. 4B, entries 1–4). Severe Mn passivation on the anode surface was observed in conjunction with low yield

when not using alternating polarity (Fig. 4B, entry 5). Adding water to the reaction mixture significantly improved the yield of this electrochemical transformation by enhancing the solubility of the manganese catalyst (Fig. 4B, entry 6). With the optimized conditions in hands, the applicability of the electro-

chemical protocol was evaluated towards the synthesis of targeted compounds **4b**, **4f**, **5f** and **6e** which were isolated in good yields. In the case of **4i** 25 equiv. of the malonate were required to achieve a yield similar to the one obtained under the stoichiometric condition. To our delight, *N*-oxide heterocycles, which were incompatible with stoichiometric amounts of manganese, can be straightforwardly used as starting heterocyclic precursors affording the desired compounds in good yields (Fig. 4B, **4b**). Importantly, the reaction between *N*-methoxy-4-methylquinolinium tetrafluoroborate and oct-1-ene in a mixture of acetone/AcOH/H₂O was easily scaled-up to 3.8 mmol to deliver the corresponding difunctionalized product **4b** in 61% yield (Scheme S1). Altogether, these results not only highlight the efficiency of the optimized electrochemical protocol but also demonstrate its tolerability.

Radical trap experiment

To probe the reaction mechanism, a radical trap experiment was performed. The desired alkene difunctionalization reaction was completely inhibited in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO; 3.0 equiv.). The corresponding TEMPO adduct was detected in the reaction mixture by high-resolution mass spectrometry (HRMS) (Fig. 4C, top), suggesting the intermediacy of an α -keto radical along the reaction pathway.³⁴ However, considering the oxidizing character of TEMPO and its ability to bind to metal centers which could inhibit the reaction, we performed less perturbative radical clock experiments.

Radical clock experiment

A radical clock experiment was conducted using a cyclopropane derivative under standard reaction conditions.³⁵ 1-Phenyl-2-vinyl-cyclopropane is a highly sensitive radical probe based on the (*trans*-2-phenylcyclopropyl)carbinyl radical rearrangement timed by Newcomb at $k = 1.8 \times 10^{11} \text{ s}^{-1}$ at 25 °C.³⁶ The ring-opened product **5k** that originates from successive radical addition, ring opening and acetate quench was isolated in 28% yield. This reaction further supports the radical pathway of the reaction mechanism (Fig. 4C, middle).

Control experiments

We hypothesized that the enhanced reactivity of *N*-methoxy-heterocyclic salts derives from the methoxy radical generated during the reaction which then initiates a radical chain mechanism. To verify this assumption, control experiments were conducted by treating *N*-methoxy-4-methylquinolinium tetrafluoroborate (**1a**) with K₃PO₄ in acetone. Based on previous reports,^{37,38} the methoxy radical can be generated from homolysis of the N–O bond after deprotonation of the *N*-methoxy salts by K₃PO₄. To our delight, two products were isolated from the reaction mixture after completion, 4-methyl quinoline acetone adduct **5l** and 4-methyl quinoline methoxy adduct **5m**. This observation indicated that the methoxy radical propagates the radical chain mechanism by undergoing a HAT process with acetone to deliver the corresponding α -keto free radical (Fig. 4C, bottom).

Proposed reaction mechanism

On the basis of the mechanism investigation and literature precedents,^{22–24} a proposed mechanism for this Mn-mediated alkene dicarbon functionalization was assembled (Fig. 4D). Starting from Mn(OAc)₃ and the carbonyl derivative, the Mn-keto adduct can be formed upon coordination and then undergoes deprotonation by one acetate to generate Mn-enolate adduct. Mn-enolate adduct can be subsequently oxidized by Mn(III) to afford the α -keto radical. In presence of alkene, radical addition forges the C–C bond and delivers the less electrophilic γ -keto alkyl radical. This radical can then be captured by the electro-deficient heterocycle to provide the γ -heterocyclic ketone radical cation intermediate. Rearomatization occurs by deprotonation followed by elimination of a methoxy radical that contributes to the radical chain propagation. This step shares similarities with the mechanism of the photoinduced demethoxylation of *N*-methoxypyridinium salts.^{39–41} This interpretation of the role played by the methoxy group also explains the influence of *N*-substitution on the reaction outcome.

Conclusions

In conclusion, we have developed a versatile manganese-mediated strategy that addresses long-standing challenges in heterocyclic synthesis. Our methodology enables efficient access to pharmaceutically relevant γ -heterocyclic ketones, α -tetralones, tetrahydroquinolines, and benz[*h*]isoquinolines through a dicarbofunctionalization approach. This transformation stands out for its exceptional functional group tolerance, operational simplicity, and broad substrate scope – key advantages that significantly advance the state of the art in heterocycle synthesis. The development of an electrochemical variant using catalytic manganese quantities further enhances the sustainability profile of our approach, making it particularly attractive for large-scale applications. Mechanistic insights gained through detailed investigations not only rationalize the observed reactivity but also provide a foundation for future methodology development. Given the prevalent role of these heterocyclic scaffolds in pharmaceutical development, natural product synthesis, and materials science, we anticipate this methodology will find broad application in both academic and industrial settings. This work represents a significant step forward in sustainable heterocycle synthesis and opens new avenues for accessing high-value pyridine scaffolds.

Author contributions

M.-Y. C. performed the experiments and analysed the results. All authors contributed to the writing and revision of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The primary data associated with this work can be found in the Supplementary information (SI). Supplementary information is available and comprises: general information, optimization details, mechanistic investigation, preparation of substrates and other reagents, general procedures and characterization of products, references and NMR spectra. See DOI: <https://doi.org/10.1039/d5qo01424g>.

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