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Merging carboxylic acids with metal-catalyzed hydrogen atom transfer (MHAT) chemistry via alkene-functionalized redox-active esters†

Laura G. Rodríguez,  Aina Serra, Josep Bonjoch  and Ben Bradshaw *

The development of general methods for radical bond formation remains a central goal in organic synthesis, particularly those that enable diverse transformations from simple, abundant starting materials. Here, we report a unified approach that merges carboxylic acid activation with metal-catalyzed hydrogen atom transfer (MHAT) to enable the generation and selective functionalization of open-shell intermediates under a single catalytic system. Key to this strategy is the design of a redox-active ester bearing an internal alkene "trigger" that undergoes regioselective MHAT using $\text{Fe}(\text{acac})_3$ and phenylsilane, leading to decarboxylative radical formation under mild conditions. This platform supports the synthesis of a wide array of products via C–C, C–heteroatom, and C–H bond-forming processes, accessed solely by varying the radical acceptor. Notably, it enables the formation of linear coupling products—previously inaccessible under conventional MHAT conditions—via access to primary radical intermediates. We anticipate that this conceptually distinct mode of activation will find applications in modular synthesis, late-stage functionalization, and the generation of medically relevant analogs.

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Introduction

The ability to transform simple, abundant functional groups into structurally and functionally diverse products using a single, unified reaction framework represents a long-standing aspiration in synthetic chemistry.¹ Strategies that decouple substrate identity from reaction outcome – by applying a common set of conditions across structurally distinct inputs – offer powerful platforms for modular synthesis, minimizing the need for case-by-case optimization. Such versatility is particularly valuable in complex molecule construction, where it enables route flexibility in natural product synthesis by accommodating diverse starting materials and bond-forming modes and accelerates medicinal chemistry efforts by providing rapid access to analogs from shared intermediates—ideal for structure–activity relationship studies and parallel synthesis workflows (Fig. 1A).

Efforts to achieve such unified reactivity frameworks have increasingly turned to radical chemistry – a field that, while once regarded as niche and difficult to control, has matured into a powerful and mainstream strategy in modern synthesis.² The ability to harness single-electron reactivity has unlocked new frontiers in chemical space, enabling unique disconnections and novel reaction pathways that are inaccessible through

traditional two-electron mechanisms.³ Beyond these strategic advantages, radical processes also offer significant practical benefits: broad functional group tolerance, orthogonal reactivity profiles, and a reduced reliance on protecting group strategies. These features make radical methodologies particularly well-suited for modular platforms that prioritize flexibility, diversity, and late-stage functionalization. The exploration of new chemical space has further accelerated with the emergence of metal-catalyzed hydrogen atom transfer (MHAT) as a powerful strategy for the hydrofunctionalization of alkenes through open-shell intermediates (Fig. 1B).⁴ This reaction proceeds via a metal hydride species, generated *in situ* from an earth-abundant first-row transition metal and a suitable hydride source. This species adds selectively to the least hindered end of the alkene, generating a radical intermediate that can be intercepted by a wide variety of acceptors.⁵ There are many inherent advantages to this methodology, including chemoselectivity,⁶ chemofidelity,⁷ site-selectivity,⁸ low toxicity,⁹ and compatibility with diverse activation modes.¹⁰ These benefits, together with novel disconnection possibilities, have established MHAT as a powerful platform for constructing natural products.¹¹ Our group has been active in the development of MHAT chemistry over recent years, expanding its utility through a variety of new bond-forming transformations. These include the synthesis of tertiary alcohols^{8b} and amines,¹² alkylated products,¹³ heterocycles,¹⁴ and *cis*-electron-deficient alkenes.¹⁵ Through these efforts, we began to recognize that two defining features of classical MHAT reactions – the reliance on alkenes as radical precursors and their intrinsic Markovnikov selectivity –

Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, Universitat de Barcelona, 08028, Spain. E-mail: benbradshaw@ub.edu

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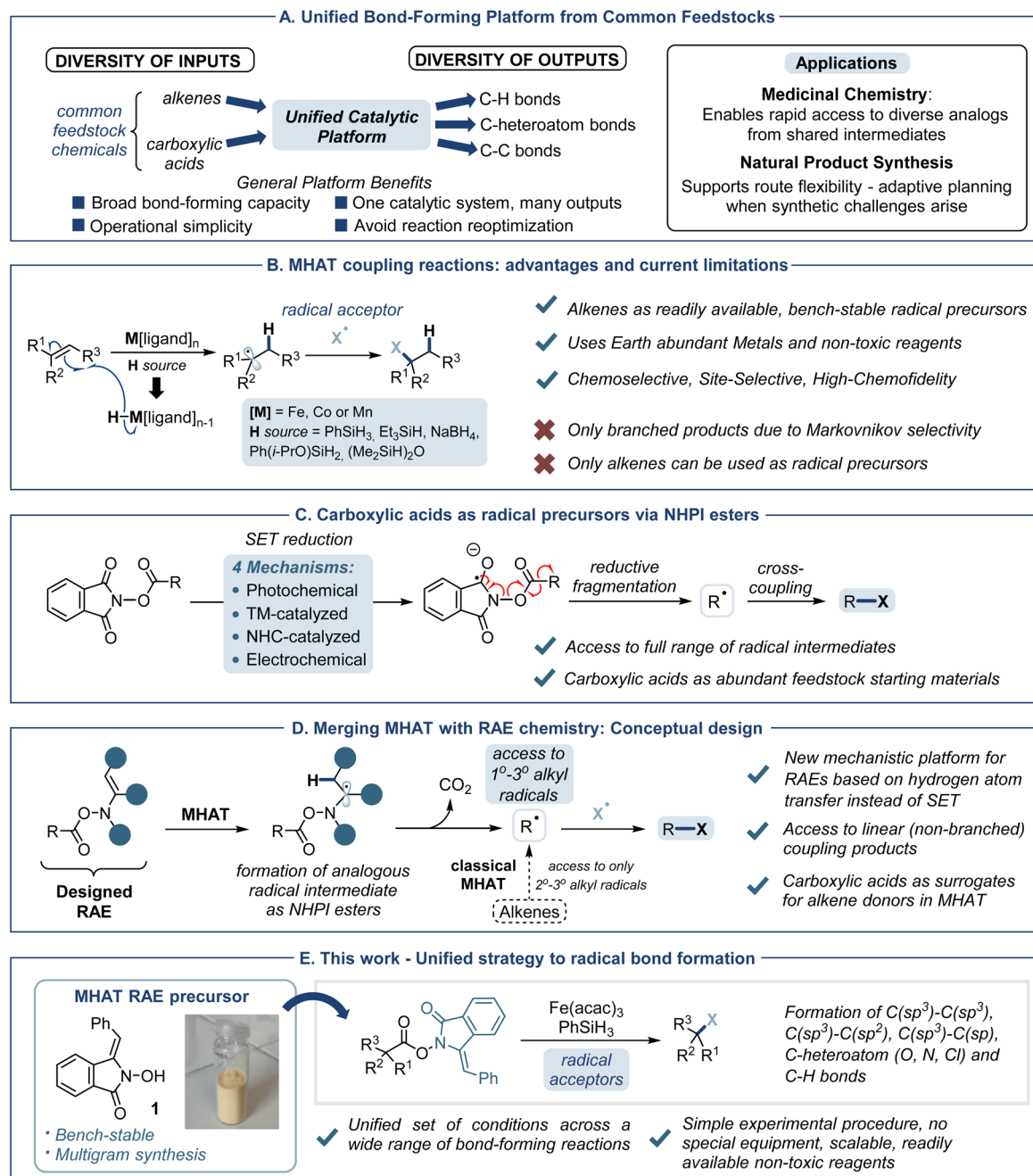


Fig. 1 (A) Benefits of a unified bond-forming platform from abundant feedstock chemicals (B) MHAT coupling reactions overview and current limitations (C) carboxylic acids as radical precursors via NHPI esters (D) conceptual strategy to merge MHAT with RAE chemistry (E) this work: unified strategy to MHAT radical bond formation via use of an alkene-substituted RAE.

can also impose important limitations. While alkenes are among the most abundant and accessible feedstocks, the chemical space accessible through MHAT cross-couplings is inherently constrained by their structural diversity. In addition, the Markovnikov selectivity that underpins traditional MHAT chemistry, although valuable for constructing branched products¹⁶ and sterically congested centers as demonstrated in our synthesis of the tricyclic core of (–)-4-*epi*-presilphiperfolan-8-ol,¹⁷ precludes the generation of primary radicals and thus limits access to linear coupling products. Overcoming these

constraints would significantly broaden the scope and synthetic utility of MHAT catalysis.

In contrast, decarboxylative radical chemistry offers a mechanistically orthogonal route to a broader radical landscape. Upon conversion to redox-active esters (RAEs), these acids can serve as versatile radical precursors under a range of activation strategies, including photoredox, electrochemical, NHC-catalyzed, and metal-mediated single-electron transfer processes (Fig. 1C).¹⁸ These approaches offer access to primary, secondary, and tertiary radicals, and have transformed



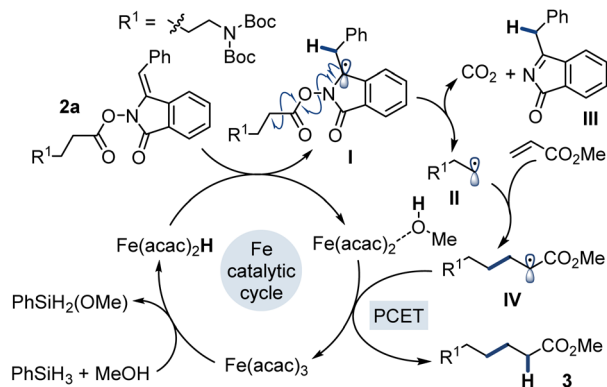


Fig. 2 Proposed mechanism for the reaction.

Table 1 Optimization and control reactions

Entry ^a	Deviation from optimum conditions	Yield ^b
1	No deviation	93
2	60 °C instead of rt, EtOH as solvent	55
3	EtOH as solvent	74
4	2a' instead of 2a	—
5	2a' instead of 2a and 1.0 equiv. Fe(acac) ₂	—
6	DCE instead of THF/MeOH	2
7	10 equiv. of acceptor instead of 5.0 equiv.	35
8	2.0 equiv. of acceptor	74
9	0.25 equiv. of Fe(acac) ₃	89
10	0.5 equiv. of Fe(acac) ₃	90
11	Mn(dpm) ₃ instead of Fe(acac) ₃	4
12	Co(Sal ^{tBu})Cl instead of Fe(acac) ₃	—
13	1.0 equiv. of PhSiH ₃	64

^a All reactions were carried out on a 0.20 mmol scale except the final optimized reaction which was carried out on a 1.0 mmol scale (91% on a 0.20 mmol scale). ^b All yields are isolated.

carboxylic acids into central building blocks in radical chemistry.¹⁹ However, they remain mechanistically distinct from MHAT catalysis, and integration of acid-derived radicals into MHAT logic has not yet been realized. Although a precedent exists from the work of Shenvi and Baran, which employed NHPI esters in an Fe-catalyzed S_H2-type radical-radical coupling,²⁰ this approach operates *via* a non-classical MHAT mechanism. Specifically, it relies on Fe(TPP)Cl – a porphyrin-based iron complex that cleaves the NHPI ester and sequesters the resulting primary radical for direct attack by another radical species. This precludes interception by external

acceptors, making the system unsuitable as a general platform for MHAT hydrofunctionalization.

We therefore sought a general and operationally simple strategy that would enable carboxylic acids to serve as direct surrogates for alkenes in MHAT reactions, without modifying the existing catalytic platform (Fig. 1D). To this end, we proposed the design of a specialized RAE bearing an integrated alkene “trigger” which under standard MHAT conditions would generate a radical adjacent to the N–O bond, analogous to NHPI esters. This intermediate should spontaneously fragment to furnish the corresponding decarboxylated radical, which could be intercepted downstream by a broad range of radical acceptors. After considering various designs for the alkene-functionalized RAE in terms of stability, accessibility, and reactivity (see ESI†), we opted for using the phenylethylene-substituted phthalimide derivative **1**²¹ which could be prepared in multigram batches as a bench-stable solid.

Herein, we report the development of a unified MHAT-based activation strategy that enables carboxylic acids to serve as direct radical precursors across a broad spectrum of C–H, C–C, and C–heteroatom bond-forming reactions (Fig. 1E). This approach proceeds *via* a redox-active ester and operates under a single, operationally simple catalytic system. By accessing primary, secondary, and tertiary radicals from structurally diverse acids – and circumventing the Markovnikov bias inherent to classical MHAT – this platform significantly expands both the scope and synthetic potential of MHAT chemistry.

Results and discussion

To evaluate the generation of different radical species from carboxylic acids under MHAT conditions, we selected the Giese coupling reaction²² as a representative platform to demonstrate the breadth of accessible radical types. Since primary radicals are inaccessible under conventional MHAT conditions from alkenes, we began our investigation with compound **2a**, designed to showcase the unique ability of this system to access such species. Using methyl acrylate as a model acceptor, we found that the desired product **3** could be obtained in excellent yield (93%) using 10 mol% Fe(acac)₃ as the catalyst and 2.5 equivalents of PhSiH₃ as the hydride source in THF, with 10 equivalents of MeOH as an additive at room temperature (entry 1). The use of heating and EtOH as the solvent led to a significant formation of the transesterification product **3'** (entries 2 and 3). To rule out that classical *N*-hydroxyphthalimide esters could be used in this reaction, the NHPI ester **2a'** was synthesized and exposed to the coupling conditions (entry 4).²³ However, no coupled or decarboxylated products were observed, including with the addition of 1.0 equivalent of Fe(acac)₂ under the same conditions (entry 5).^{20b} Replacing EtOH with DCE as the solvent (entry 6) to avoid the transesterification product yielded only traces of **3**, indicating that an alcoholic solvent is essential for the reaction.²⁴ Modifying the amount of acceptor (entries 7 and 8) proved detrimental to the reaction, while the amount of iron catalyst had little effect on the yield (entries 9 and 10), which improved slightly under lower loadings.



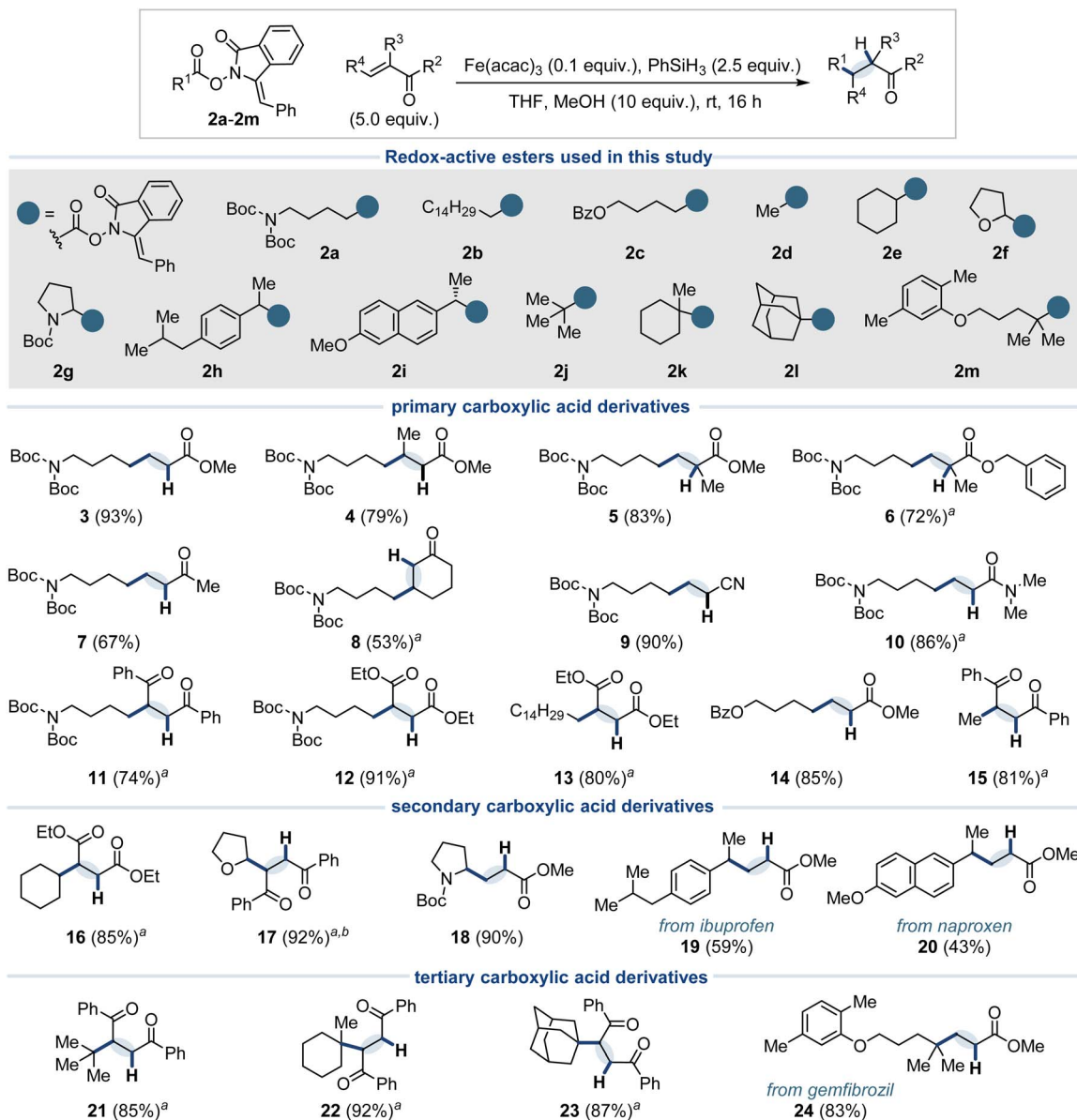


Fig. 3 Scope of electron-deficient alkenes and novel *N*-(acyloxy)phthalimide derivatives. ^a2.0 equivalents of the acceptor were used. ^bIsolated as a mixture of diastereoisomers.

Attempts to use alternative catalysts such as $\text{Mn}(\text{dpm})_3$ or $\text{Co}(\text{Sal}^{\text{tBu,tBu}})\text{Cl}$ (entries 11 and 12) were unsuccessful. Finally, reducing the amount of PhSiH_3 lowered the yield (entry 13).

Our proposed mechanism^{22c,25} for the reaction starts with the formation of an iron hydride species, which then adds to the alkene of the *N*-(acyloxy)phthalimide derivative **2a** (Fig. 2). This results in the formation of **I** with a radical adjacent to the nitrogen atom, which initiates the decarboxylation sequence to give the primary radical species **II** along with carbon dioxide and **III**. Coupling of the generated radical with the acceptor gives **IV**, which is reduced by the $\text{Fe}(\text{II})$ species and a molecule of MeOH in a proton-coupled electron transfer process (PCET)²⁴ to yield **3**. This step is supported by deuterium labeling studies with MeOD , which led to deuterium incorporation at the expected position in the product. In this process, $\text{Fe}(\text{II})$ is also

oxidized back to $\text{Fe}(\text{III})$, completing the catalytic cycle. Evidence for the MHAT mechanism comes from Table 1 entries 4 and 5, which clearly demonstrate that the radical does not form either *via* SET process or direct fragmentation of the N-O bond.

With the optimum conditions in hand, we started to investigate the scope of the reaction (Fig. 3). The coupling was found to be compatible with a broad range of Michael acceptors bearing assorted electron-withdrawing groups, including esters with different substitution patterns (3–6), ketones (7–8), nitriles (9), and amides (10). Acceptors bearing two electron-withdrawing groups also proved to be viable coupling partners (11–12). Finally, other primary radical donors were evaluated with good results (13–15). The methyl radical donor **2d** is of particular note as the introduction of the methyl unit is highly prized in medicinal chemistry due to the profound



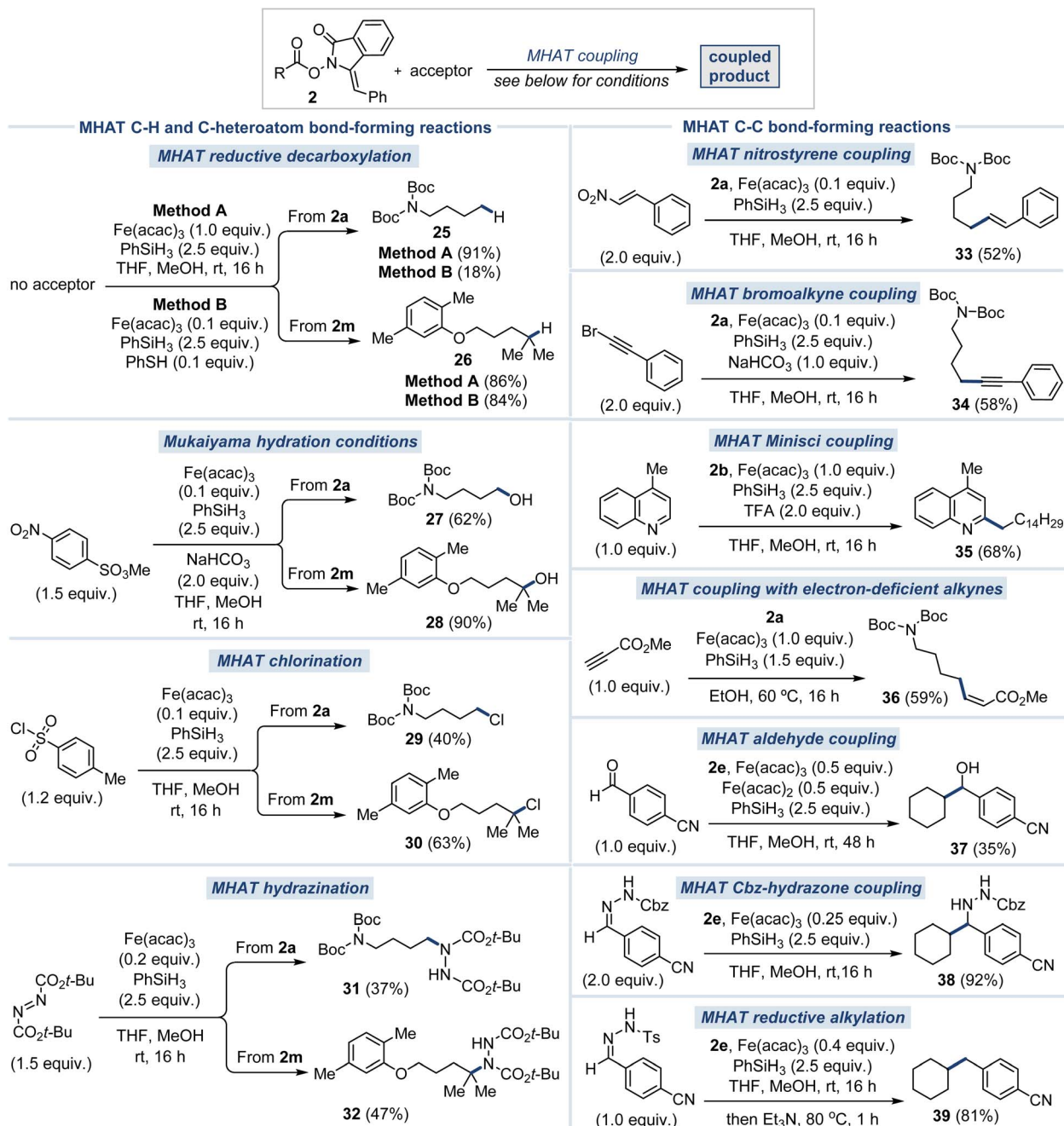


Fig. 4 Evaluation of novel *N*-(acyloxy)phthalimide derivatives in a broad cross-section of established MHAT reactions^a all reactions are unoptimized. For detailed conditions, see ESI.† One equivalent of RAE was used in each case.

pharmacological effects it can exert *via* the “magic methyl” effect.²⁶ Next, a range of secondary radical precursors (**2e–i**) were assessed. In cases where the product was predicted to be volatile, methyl acrylate was replaced with an acceptor bearing two electron-withdrawing groups. Cyclohexane carboxylic acid, tetrahydro-2-furoic acid, and *N*-boc proline derivatives (**2e–g**) were all coupled in excellent yields, giving **16–18**, respectively. The presence of a stabilizing heteroatom was found to benefit the coupling process and did not necessitate the use of alternative iron catalysts such as $\text{Fe}(\text{dibm})_3$, which are required when using alkenes as radical precursors.^{18b} In comparison, the

yield of the benzylic radicals was somewhat lower, with the derivatives from ibuprofen (**2h**) and naproxen (**2i**) giving **19** and **20** in 59% and 43% yields, respectively. All tertiary radical precursors studied (**2j–m**) showed excellent results, allowing the coupling of the *tert*-butyl group (**21**), methylcyclohexane (**22**), and adamantane (**23**) fragments.

Finally, the pharmaceutical gemfibrozil derivative **2m** could be coupled with methyl acrylate to give **24** in 83% yield.

We next evaluated the generality of this radical platform across a range of previously reported MHAT-type reactions, spanning C–H, C–heteroatom and C–C bond formation, using



structurally distinct RAEs without modification to the catalytic system (Fig. 4). Treatment of **2a** and **2m** in the absence of an acceptor and with stoichiometric Fe(acac)₃ (Method A) gave excellent yields of the decarboxylated compounds **25** and **26**, respectively, providing an operationally simple way to perform Barton-type decarboxylations under mild conditions.²⁷ A catalytic version using 10% PhSH²⁸ as an additive was also developed (Method B), with the yield for **2m** being almost identical to that of the stoichiometric version. However, **2a** gave only an 18% yield of the desired decarboxylation product **25**, which was attributed to competitive quenching of the highly reactive primary radical by the metal hydride species.

Next, Studer's Mukaiyama-type hydration employing methyl 4-nitrobenzenesulfonate as the acceptor²⁹ afforded good yield of the corresponding alcohol product **27**, and excellent yield of **28**. Notably, such direct access to alcohols is not achievable through conventional radical decarboxylation strategies, which typically require pre-functionalization to a boron species³⁰ or trapping with TEMPO,³¹ followed by an additional hydrolysis step. Next, Carreira's hydrochlorination³² and hydrazination³³ methods, both originally developed using cobalt catalysis with TsCl and di-*tert*-butyl azodicarboxylate as radical acceptors, respectively, were successfully adapted under our MHAT conditions. These reactions furnished chlorides **29** and **30**, and nitrogen-containing derivatives **31** and **32**, demonstrating the broad compatibility of our platform with such radical functionalizations without requiring catalyst modification.

To illustrate the broad versatility of our strategy in C–C bond formation, we explored coupling with a variety of acceptors, enabling access to diverse products featuring sp³-, sp²-, and sp-hybridized carbon centers under our MHAT conditions. Beginning with Cui's nitrostyrene³⁴ and bromoalkyne³⁵ couplings utilizing RAE **2a**, this approach afforded the linearly coupled alkene **33** and alkyne **34**, respectively, thereby enabling access to compounds previously unattainable under the original methodologies. The intermolecular Minisci coupling reaction of **2b** with lepidine, applying conditions developed in our studies of isocyanides,¹⁴ gave the substituted heterocycle **35** in 68% yield, and our recently developed coupling to electron deficient alkynes gave alkene **36** in 59% yield primarily as the *cis* isomer.¹⁵ Finally, based on our previous work using aldehydes,³⁶ Cbz-hydrazones,¹² and Ts-hydrazones¹³ as acceptors in MHAT reactions with alkenes, the cyclohexyl radical derived from **2e** was coupled to give alcohol **37**, hydrazine **38**, and the alkylation product **39**, respectively.³⁷

Conclusions

In summary, we have developed a redox-active ester that allows carboxylic acids to act as surrogates for alkenes in a wide range of MHAT transformations, operating through a novel activation mode that is mechanistically distinct from conventional SET processes. In contrast to the intrinsic Markovnikov selectivity of traditional alkene-based MHAT, this approach allows for the formation of linear coupling products for the first time. By expanding both the scope of accessible radical precursors and the types of bond constructions enabled, this strategy

significantly broadens the synthetic potential of MHAT catalysis. Moreover, by integrating carboxylic acid activation into classical MHAT logic, this work establishes a unified reaction platform capable of accommodating structurally diverse substrates under a single catalytic regime. Ongoing studies in our group are aimed at extending this platform to new classes of transformations and applications.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

L. G. R. contributed to the experimental work and writing of the paper; A. S. contributed to the experimental work; J. B. contributed to the writing of the paper; B. B. contributed to the ideation and writing of the paper.

Conflicts of interest

There are no conflicts to declare.

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especially difficult due to the reversible and slow nature of the process, while addition to imines, though irreversible, suffers from sluggish kinetics. In contrast, secondary and tertiary radicals engage more effectively with these acceptors under MHAT conditions. Further mechanistic insight and optimization are needed to overcome these challenges for primary radicals.

