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Mn-Mediated α -Radical Addition of Carbonyls to Olefins: Systematic Study, Scope, and Electrocatalysis

Sylvain Charvet, Maurice Médebielle, and Julien C. Vantourout*



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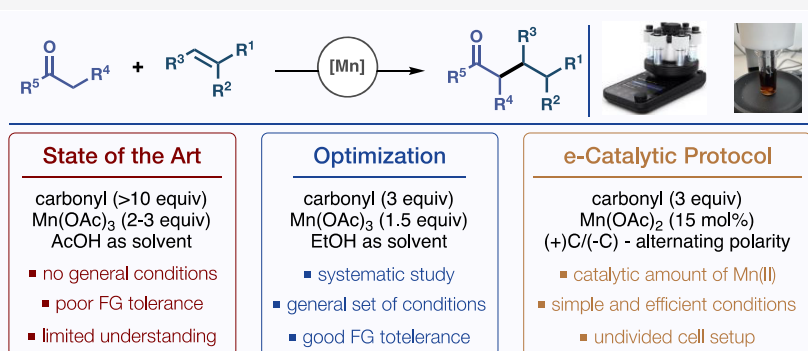
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ABSTRACT: A systematic study of the manganese-mediated α -radical addition of carbonyl groups to olefins is presented. After an in-depth investigation of the parameters that govern the reaction, a first round of optimization allowed the development of a unified stoichiometric set of conditions, which were subsequently assessed during the exploration of the scope. Due to observed limitations, the knowledge accumulated during the initial study was reengaged to quickly optimize promising substrates that were so far inaccessible under previously reported conditions. Altogether these results led to the creation of a predictive model based on the pKa of the carbonyl compound and both the substitution and geometry of the alkene coupling partner. Finally, a departure from the use of stoichiometric manganese was enabled through the development of a robust and practical electrocatalytic version of the reaction.

1. INTRODUCTION

One of the central challenges of our century is the development of sustainable chemical processes.¹ Following this concept, the use of first row transition metals has become essential in catalysis.² Manganese is abundant, inexpensive, and nontoxic and participates in a myriad of transformations due to the wide range of oxidation states it can adopt (from 0 to +7, [Ar]3d⁵4s²).³ In the framework of a new research program dedicated to manganese catalysis, we are particularly interested in the systematic study of reactions previously neglected due to low practicality and lack of mechanistic understanding.

For our first study, we selected the field of α -alkylation of carbonyls as it is a central and well-established transformation in organic synthesis that could still benefit from improvement (Figure 1).⁴ Indeed, the coupling of enolates with nucleofuge-containing molecules under basic conditions is extensively employed, but its low atom-economy makes it often industrially impracticable.⁵ Similarly, modern procedures employing a combination of a metal-based catalyst with directing amines have allowed the use of alkenes as coupling partners, which circumvent any waste generation.⁶ However, the expensive catalysts and/or reagents employed in these protocols make them difficult to implement on scale. Despite the current limitations associated with the Mn-mediated

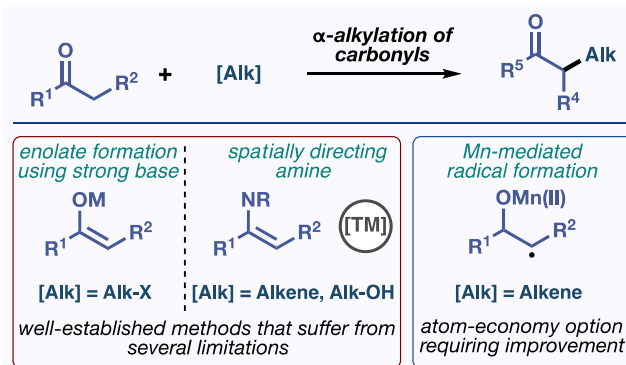


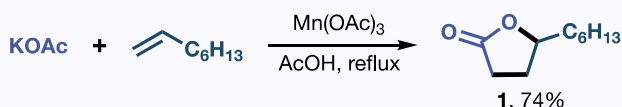
Figure 1. Introduction to α -alkylation of carbonyls.

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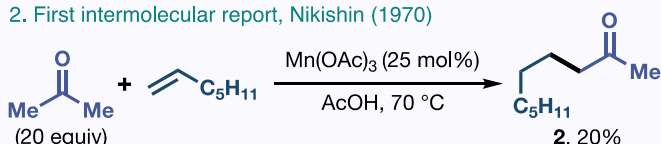
Scheme 1. Introduction: (A) State of the Art and (B) Core of This Study

A. State of the Art

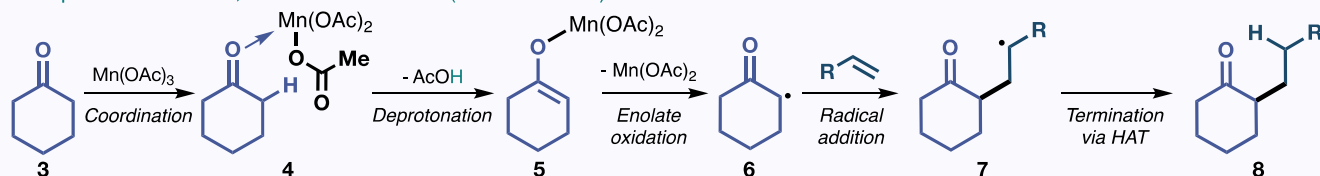
1. First back-to-back reports, Finkbeiner and Heiba (1968)



2. First intermolecular report, Nikishin (1970)

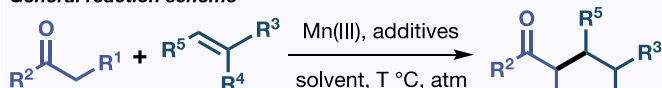


3. Proposed mechanism, Peterson and Snider (1985 and 2009)



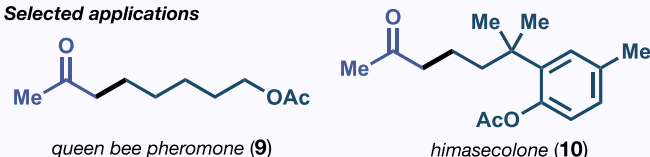
4. Intermolecular stoichiometric approaches

General reaction scheme



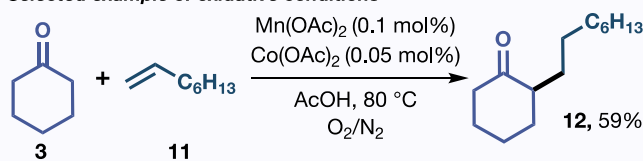
- ubiquitous SM
- applications in synthesis
- manganese
- AcOH as solvent
- large excess of ketone
- high temperature
- limited functional group tolerance
- no general set of conditions
- limited understanding of reaction parameters

Selected applications



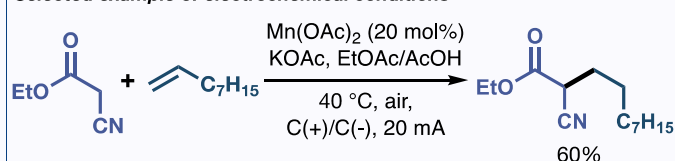
5. Intermolecular catalytic approaches

Selected example of oxidative conditions



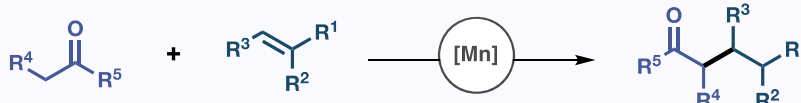
- AcOH as solvent
- large excess of ketone
- co-catalyst needed

Selected example of electrochemical conditions



- divided cell
- no general set of conditions
- use of excess AcOH

B. This Work



Stoichiometric Protocol

carbonyl (3 equiv)
Mn(OAc)₃ (1.5 equiv)
EtOH as solvent

- good understanding of reaction parameters
- EtOH as solvent
- general set of conditions
- good FG tolerance

e-Catalytic Protocol

carbonyl (3 equiv)
Mn(OAc)₂ (15 mol%)
(+)C/(-)C - alternating polarity

- catalytic amount of Mn(II)
- undivided cell
- graphite electrodes
- non-explosive electrolyte
- simple, efficient, and robust conditions

34 carbonyl α -radical addition to olefins (vide infra), we identified
35 this transformation as a full atom-economy alternative to
36 existing enolates and metal-based systems. Therefore, we
37 decided to systematically investigate the parameters that
38 govern this reaction to assemble a general and robust set of
39 conditions that would supplant existing procedures.⁷

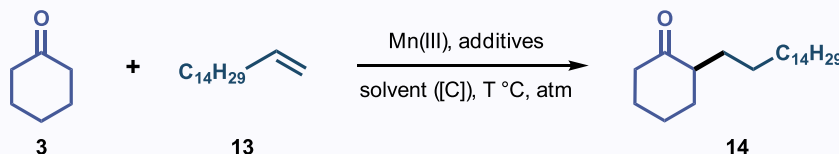
2. STATE OF THE ART

40 Since the seminal 1968 back-to-back publications of
41 Finkbeiner and Heiba, Mn(III) has emerged as an ideal
42 catalyst to promote various oxidative free-radical reactions.^{8,9}
43 In these pioneering reports, a nonactivated olefin reacts with
44 solvent quantities of AcOH in the presence of a stoichiometric
45 amount of Mn(OAc)₃ and KOAc under reflux to afford the
46 corresponding lactone (Scheme 1A.1). After 2 years, the group
47 of Nikishin demonstrated that a large amount of the carbonyl
48 compound (20 equiv) was also able to react with alkenes in an

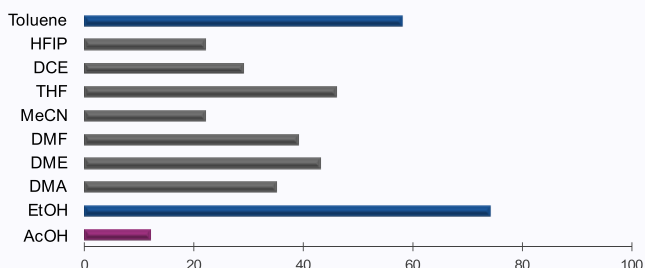
intermolecular fashion to deliver the α -functionalized ketone 2,
albeit in low yield (Scheme 1A.2).¹⁰ Indeed, Mn(III) is able to
oxidize carbonyl compounds to generate an α -keto free radical,
which can subsequently react with an unsaturated substrate to
deliver the desired coupled product.¹¹ The detailed mechanism
of this reaction has been extensively studied and proposed by
Peterson and Snider.^{12,13} It subtly depends on the nature of the
carbonyl starting material but can generally be summarized as
depicted in Scheme 1A.3. It begins with the coordination of
carbonyl 3 onto the Mn(OAc)₃ catalyst to form complex 4,
followed by loss of the α -proton assisted by one of the acetate
groups to generate enolate 5. The latter is oxidized by Mn(III)
to give the free-radical intermediate 6 that subsequently reacts
with the olefin, forging the C–C bond and affording the more
stable radical species 7. This sequence may also be concerted if
the enolate oxidation step is sluggish.¹³ Finally, a termination

Scheme 2. Development of a Unified Stoichiometric Set of Conditions: (A) Study of the Influence of Key Parameters and (B) Optimized Set of Reaction Conditions^a

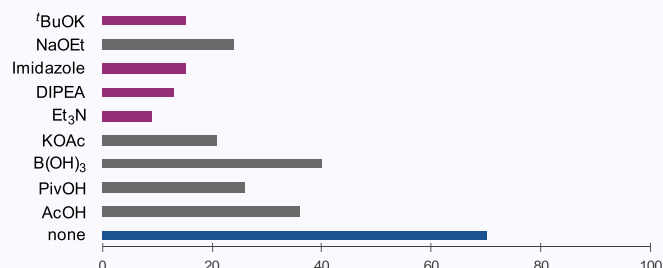
A. Influence of the reaction parameters



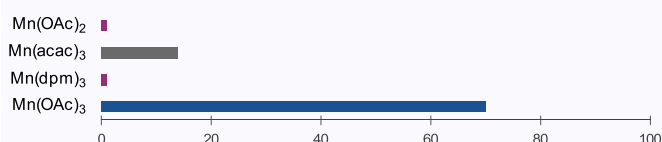
1. Solvent



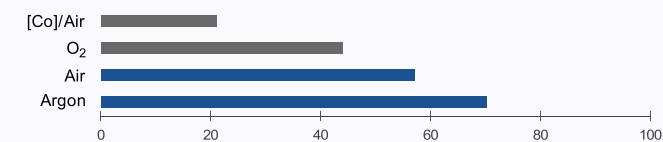
5. Additives



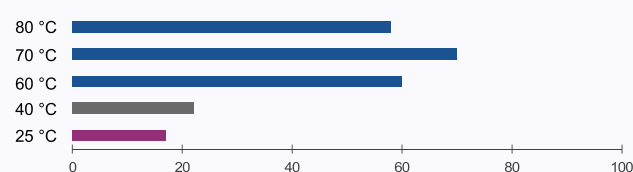
2. Catalyst



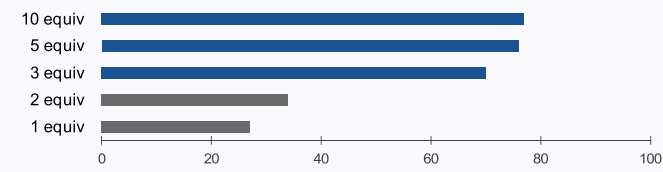
6. Atmosphere



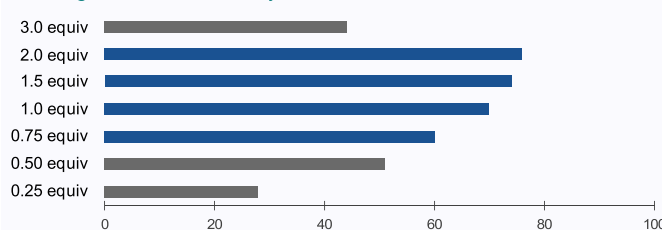
3. Temperature



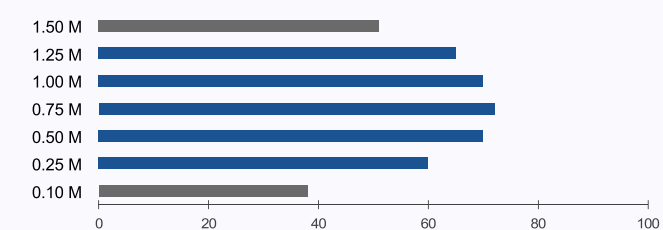
7. Ketone stoichiometry



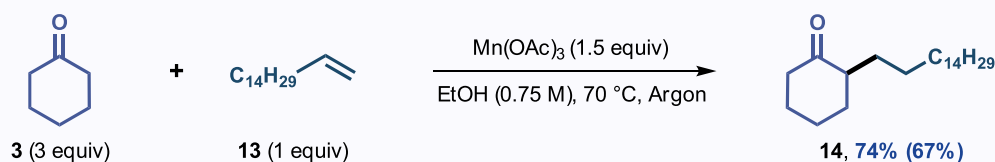
4. Manganese stoichiometry



8. Concentration



B. Optimized reaction conditions



^aReactions were run on a 0.25 mmol scale. A1: cyclohexanone (3 equiv), hexadecene (1 equiv), Mn(OAc)₃ (1.5 equiv), solvent (0.75 M), 70 °C, Ar, 16 h; A2: cyclohexanone (3 equiv), hexadecene (1 equiv), catalyst (1 equiv), EtOH (0.75 M), 70 °C, Ar, 16 h; A3: cyclohexanone (3 equiv), hexadecene (1 equiv), Mn(OAc)₃ (1 equiv), EtOH (0.75 M), temperature, Ar, 16 h; A4: cyclohexanone (3 equiv), hexadecene (1 equiv), Mn(OAc)₃ (equivalents), EtOH (0.75 M), 70 °C, Ar, 16 h; A5: cyclohexanone (3 equiv), hexadecene (1 equiv), Mn(OAc)₃ (1 equiv), EtOH (0.75 M), additive (3 or 5 equiv, see the Supporting Information for details), 70 °C, Ar, 16 h; A6: cyclohexanone (3 equiv), hexadecene (1 equiv), Mn(OAc)₃ (1 equiv), EtOH (0.75 M), atmosphere, 16 h; A7: cyclohexanone (equivalents), hexadecene (1 equiv), Mn(OAc)₃ (1 equiv), EtOH (0.75 M), 70 °C, Ar, 16 h; A8: cyclohexanone (3 equiv), hexadecene (1 equiv), Mn(OAc)₃ (1 equiv), EtOH (concentration), 70 °C, Ar, 16 h. Yields refer to GCMS yields using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are shown in brackets.

65 step via hydrogen atom transfer (HAT) allows the formation
66 of desired product 8.

The reaction tolerates a wide range of ubiquitous carbonyl 67
68 compounds, including ketones, esters, keto-esters, diesters, 68

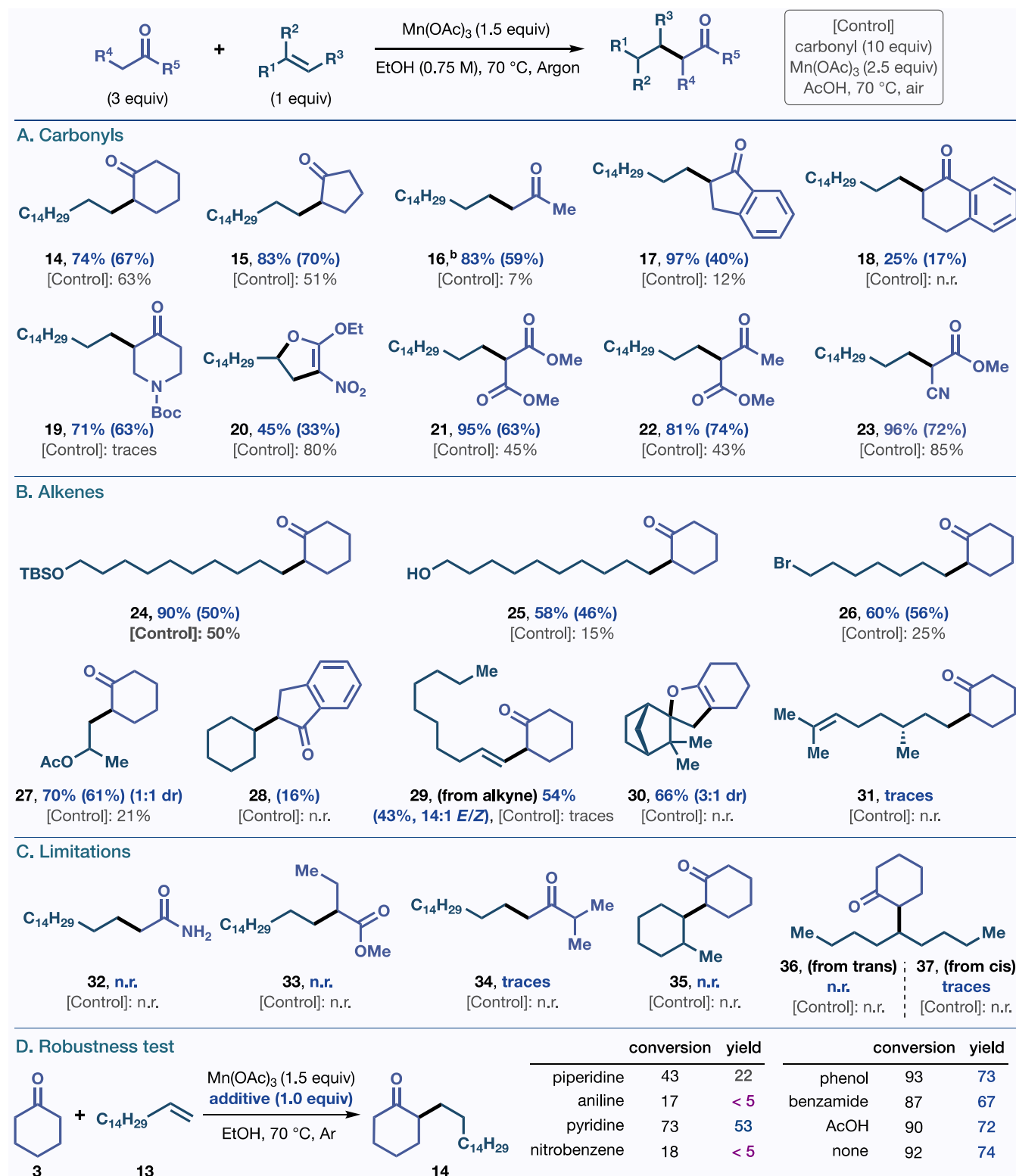
69 aldehydes, and carboxylic acids.¹¹ In addition, the possibility
70 for the carbonyl moieties to react with nonactivated olefins
71 using earth abundant manganese renders this transformation
72 highly attractive and broadly applicable, especially in the
73 context of natural product synthesis (Scheme 1A.4).¹⁴ While
74 the Snider group among others reported several intramolecular
75 polycyclization cascades,¹⁵ the Mamdapur groups applied the
76 intermolecular version of the Mn-mediated α -radical addition
77 of carbonyl groups to olefins as a key step for the synthesis of
78 queen bee pheromone **9** and himasecolone **10**, respectively.¹⁶
79 Despite all the advantages it offers, the intermolecular version
80 of the reaction still suffers from major limitations such as (1)
81 the absence of a general set of conditions; (2) the need for a
82 large amount of the carbonyl starting material to be employed
83 (usually more than 10 equiv); (3) the use of acetic acid as the
84 solvent which lowers the functional group tolerance; and (4)
85 the lack of understanding with regard to some reaction
86 parameters including temperature, concentration, atmosphere,
87 and more importantly, the nature of the alkene coupling
88 partner (Scheme 1A.4). These limitations hamper the
89 widespread use of this powerful transformation. Another
90 significant drawback that reduces the broad application of
91 this reaction is the (over)stoichiometric amount of the
92 Mn(OAc)₃ catalyst often required to afford satisfactory
93 yields.¹¹ Such an excess amount of the manganese catalyst
94 leads to a tedious workup, as exemplified in several studies.^{15c}
95 To overcome this issue, several groups have attempted to run
96 the reaction under oxidative conditions to regenerate Mn(III)
97 from Mn(II).^{11,17} As a selected example, the Ishii group
98 reported the coupling between cyclohexanone **3** and octene **11**
99 to afford desired product **12** in 59% yield (Scheme 1A.5).¹⁸
100 This set of conditions only requires 0.1 mol % of the
101 Mn(OAc)₂ catalyst and 0.05 mol % of the Co(OAc)₂ co-
102 catalyst to be employed under a mixed atmosphere of oxygen
103 and nitrogen. However, the large amount of the ketone starting
104 material and the use of AcOH as the solvent remain two major
105 limitations which reduce the applicability of the reaction. As an
106 alternative to chemical oxidative conditions, it was demon-
107 strated that Mn(II) could be oxidized to Mn(III) under
108 electrochemical conditions (Scheme 1A.5).¹⁹ In these studies,
109 the products are obtained in good yield using low Mn(II)
110 catalyst loadings (down to 10 mol %). Nevertheless, the use of
111 solvent quantities of AcOH, the necessity to run the reaction in
112 a divided cell, and the absence of a general procedure reduce
113 the synthetic value of this catalytic approach.

114 The aforementioned limitations have certainly lowered the
115 uptake of the Mn-mediated α -radical addition of carbonyl
116 groups to olefins,^{11f} and although this reaction has been
117 exemplified multiple times in the literature, it has only been
118 sporadically studied.²⁰ We recognized that if rendered
119 practical, such a reaction could undoubtedly impact the field
120 of carbonyl α -functionalization. Therefore, we decided to (1)
121 investigate the parameters that govern this transformation; (2)
122 assemble a general set of stoichiometric reaction conditions;
123 (3) evaluate the scope and its limitations; (4) reengage the
124 knowledge accumulated during the initial study to quickly
125 optimize low yielding substrates; and (5) depart from the use
126 of stoichiometric manganese with the development of a general
127 electrocatalytic version of the reaction (Scheme 1B).

3. RESULTS AND DISCUSSION

128 **3.1. Systematic Study of the Reaction Parameters.** We
129 began our investigation by studying the parameters that govern

the Mn-mediated α -radical addition of carbonyls to olefins 130
between cyclohexanone **3** and 1-hexadecene **13** (Scheme 2A). 131 s2
As most of the existing intermolecular processes suffer from 132
the requirement for a large amount of the carbonyl compound 133
to be used under oxidative conditions, the excess of ketone **3** 134
was limited to 3 equiv and the reaction was run under argon. 135
Based on previously reported conditions, Mn(OAc)₃ was 136
selected as the stoichiometric catalyst source and the reaction 137
was conducted at 70 °C. Inspired by the elegant Mn(III)- 138
catalyzed intramolecular cyclization study disclosed by the 139
Snider group, where the authors described the impact of the 140
solvent and especially the beneficial effect of using EtOH to 141
enhance the HAT termination step, we initially studied this 142
parameter.²¹ To our surprise, AcOH, which is the preferred 143
solvent for the majority of previously reported conditions, only 144
afforded 14% of desired product **14** (Scheme 2A.1). This is 145
potentially due to the limited amount of ketone (3 equiv) used 146
in the reaction, which cannot compete with the competitive 147
lactone formation reported by Finkbeiner and Heiba (Scheme 148
1A.1). DMA, DME, DMF, MeCN, DCE, and HFIP were also 149
tested but only delivered moderate yields (22–46%, Scheme 150
2A.1). This trend can be rationalized by the reduced ability of 151
these solvents to facilitate the final HAT process as the H-atom 152
source, constraining the ketone starting material or the desired 153
product to serve this role. The subsequent radicals can then 154
result in the formation of unwanted byproducts (see the 155
Supporting Information for details). As expected, based on 156
Snider initial disclosure, out of all the solvents that were 157
screened, EtOH conferred the best result (74% yield), while 158
toluene provided a moderate yield of 58% (Scheme 2A.1).²¹ 159
This result matches Snider initial observation. In each case, the 160
corresponding stabilized α -hydroxy or benzylic radical afforded 161
by the HAT termination step can explain why these solvents 162
offered an improved outcome. The remarkably enhanced 163
conversion observed in EtOH can also be supported by several 164
studies which previously highlighted its ability to enhance the 165
reactivity of manganese-based processes.²² Screening of 166
commercially available catalyst sources was then attempted 167
using EtOH as the solvent (Scheme 2A.2). Unfortunately, 168
Mn(dpm)₃ and Mn(acac)₃ resulted in none and 14% 169
conversion to product **14**, respectively. The steric hindrance 170
engendered by dpm or acac ligands surrounding the metal 171
center obstructs the formation of coordinated intermediate **4**, 172
which impedes product formation. In addition, such ligands 173
could lead to the formation of undesired α -functionalized 174
byproducts. A non-commercially available Mn(pic)₃ catalyst 175
was also tried under the reaction conditions but did not 176
provide a satisfactory yield compared to Mn(OAc)₃ (see the 177
Supporting Information for details). Unsurprisingly, the use of 178
Mn(OAc)₂ did not afford any product as oxidation to Mn(III) 179
is impossible under an argon atmosphere. The influence of 180
temperature on the reaction was also investigated (Scheme 181
2A.3). Temperatures lower than 60 °C considerably 182
diminished the yield as it decreased the solubility of the 183
manganese catalyst, while temperatures higher than 70 °C 184
significantly increased byproduct formation. The impact of the 185
amount of manganese was then studied (Scheme 2A.4). While 186
increasing the number of equivalents from 1 to 1.5 improved 187
the yield of compound **14** from 70 to 74%, lowering the 188
loading from 1 to 0.5 equivalents resulted in a decreased yield 189
of 51%. This result is in accordance with the proposed 190
mechanism where Mn(III) is reduced to Mn(II) to generate 191
keto-radical **6**. Under inert conditions, Mn(II) cannot be re- 192

Scheme 3. Scope of the Reaction: (A) Carbonyls, (B) Alkenes, (C) Limitations, and (D) Robustness Test^a

^aYields refer to GCMS yields using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are shown in brackets. ^bAcetone is used as the solvent.

193 oxidized and a (super)stoichiometric amount of manganese
 194 needs to be employed. Of note, using a large amount of the
 195 manganese catalyst (e.g., 3 equiv) resulted in low conversion to
 196 the desired product (44%), possibly due to precipitation of the
 197 catalyst. Several additives were screened, and their impact on

the reaction efficiency was studied (Scheme 2A.5). Doping the
 reaction with acidic additives such as AcOH, PivOH, and
 199 B(OH)₃ resulted in unexpectedly lower conversions. Unin-
 200 tuitively, adding external bases including KOAc, Et₃N, DIPEA,
 201 imidazole, NaOEt, or ^tBuOK to facilitate the deprotonation 202

203 step did not increase the yield of the reaction and instead
204 considerably hampered conversion. We next turned our
205 attention to the atmosphere under which the coupling reaction
206 was being conducted. Running the reaction under argon
207 provided 70% of desired product **14**, while an atmosphere of
208 oxygen only afforded 44% (Scheme 2A.6). A careful analysis of
209 the byproduct distribution allowed us to explain the drastic
210 differences observed between an inert and oxidizing environ-
211 ment (see the Supporting Information for details). Indeed,
212 under air or oxygen, the ketone starting material is consumed
213 by undesired processes leading to dimeric and α -oxidized
214 species, thus lowering the overall yield of the reaction. Based
215 on the elegant study from the group of Ishii, the impact of
216 using a Co(II) co-catalyst was also reevaluated (vide supra).¹⁸
217 Attempts to apply these conditions to our system resulted in
218 low efficiency and only gave a 21% yield of desired product **14**.
219 A reduction in ketone stoichiometry (1 or 2 equiv) diminished
220 the yield considerably, and compound **14** was only obtained in
221 **27** and 34% yields, respectively (Scheme 2A.7). The use of a
222 large amount of ketone (5 or 10 equiv) delivered high yields,
223 matching with previously reported results from the literature.¹¹
224 Finally, as both the solubility of the manganese catalyst and
225 overall concentration of the ketone starting material appeared
226 to greatly impact the yield of the reaction, we hypothesized
227 that the concentration should also play an important role in the
228 outcome of the transformation (Scheme 2A.8). Moving from a
229 concentration of 0.5 to 0.1 M significantly decreased the yield
230 from 70 to 38%. Similarly, the yield of the reaction was
231 markedly lowered when the concentration was too high due to
232 catalyst insolubility and lower stirring efficiency.

233 3.2. Optimized Stoichiometric Set of Reaction

234 **Conditions.** Using the knowledge gained throughout this
235 in-depth study, a simple and general Mn-mediated α -radical
236 addition of carbonyls to olefins was developed (see the
237 Supporting Information for details). Running the reaction with
238 a slight amount of Mn(OAc)₃ in EtOH at suitable temperature
239 (70 °C) and concentration (0.75 M) under an atmosphere of
240 argon delivered desired product **14** in 67% isolated yield with
241 only 3 equiv of the carbonyl starting material (Scheme 2B).

242 3.3. Scope of the Reaction.

243 With the optimized
244 conditions in hand, we first started to assess the carbonyl
245 scope (Scheme 3A). Ketones such as cyclopentanone, acetone,
246 and indanone delivered compounds **15**, **16**, and **17** in 70, 59,
247 and 40% isolated yields, respectively. Noteworthy, the
248 conversion for compounds **16** and **17** (83 and 97%,
249 respectively) was much higher than the isolated yield due to
250 challenging purification. α -Tetralone, which was known to be
251 unreactive under previously reported conditions, afforded
252 compound **18** in 17% yield. Boc-protected piperidin-4-one
253 afforded desired product **19** in 63% isolated yield. Strikingly,
254 this compound was only obtained in a trace amount following
255 the original literature conditions, which highlights the
256 importance of using EtOH instead of AcOH to improve the
257 functional group tolerance. Nitroacetate did not give the
258 desired linear product but the cyclized compound **20** in a
259 moderate isolated yield of 33%. Other carbonyls including
260 diester, keto-ester, and cyanoacetate proved compatible under
261 the reaction conditions with compounds **21**, **22**, and **23**
262 obtained in good yields (63–74%). Unfortunately, due to
263 higher α -C–H pKa values, amides and esters did not react
264 under the reaction conditions (compounds **32** and **33**, Scheme
3C). Similarly, compound **34** issued from the coupling

between methyl isopropyl ketone (MIPK) and 1-hexadecene
13 was only detected in negligible amounts (traces in GCMS).²⁶⁶

267 Regarding the alkene scope, stabilized disubstituted olefins
268 such as prop-1-en-2-yl acetate when reacting with cyclo-
269 hexanone **3** delivered product **27** in 61% isolated yield.
270 Alkynes were also successfully coupled under the reaction
271 conditions with alkene **29** obtained in 43% yield (14:1 *E/Z*
272 ratio). Functionalization of valuable alkenes such as camphene
273 and (+)- β -citronellene afforded different outcomes with
274 compounds **30** obtained in 66% yield, while only a trace
275 amount of compound **31** was detected. In addition, cyclo-
276 hexene when coupled with indanone delivered compound **28**
277 in 16% isolated yield, highlighting that 1,2-disubstituted
278 nonstabilized olefins are challenging compounds to function-
279 alize. This trend was further confirmed when 1-methylcyclo-
280 hex-1-ene, (*E*)-non-4-ene, and (*Z*)-non-4-ene were used as
281 alkene coupling partners with no desired or trace product
282 formation observed.

283 Regarding functional group tolerance, the optimized
284 reaction conditions proved highly efficient. Indeed, ester
285 (**21**–**23** and **27**), cyano (**23**), nitro (**20**), free (**25**), or TBS
286 (**24**)-protected alcohols, and acetyl groups (**27**) were all
287 tolerated under the reaction conditions and afforded the
288 desired products from moderate to good yields (27–74%).
289 Notably, halogen moieties were also stable under the reaction
290 conditions with bromine containing compound **25** obtained in
291 56% yield. To further assess the functional group tolerance, a
292 robustness test was performed by adding 1 equiv of an additive
293 bearing a specific reactive handle (Scheme 3D).²³ While
294 phenol, amide, and carboxylic acid moieties did not impact the
295 outcome of the reaction, amine- and nitro-based compounds
296 hampered both the conversion and yield. Interestingly,
297 pyridine lowered the conversion (73% instead of 92%) but
298 afforded a serviceable yield (53% instead of 74%).

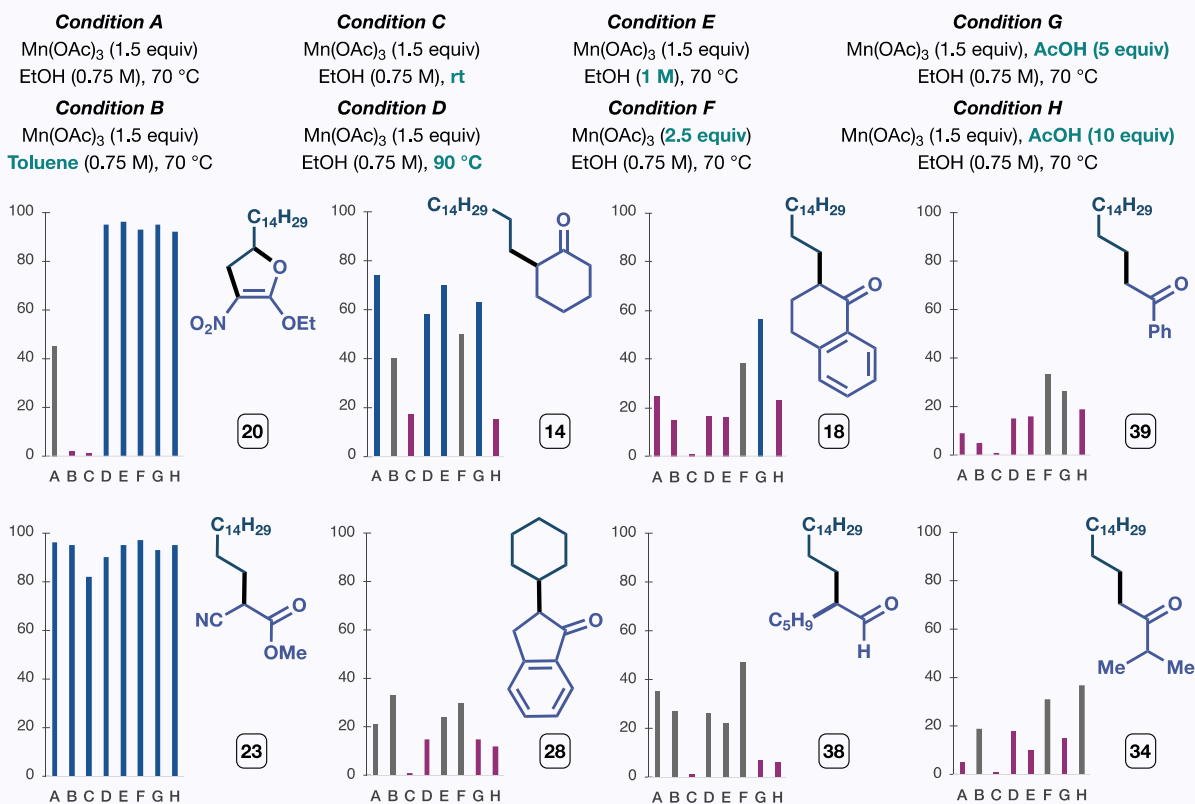
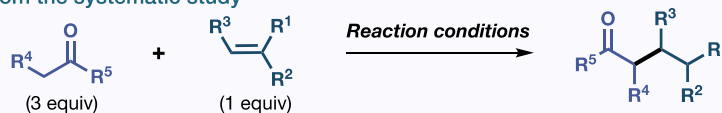
299 All these results can be rationalized based on the nature of
300 the olefin or carbonyl coupling partners. Alkenes that afford
301 secondary radicals are not oxidized by Mn(III) allowing the
302 HAT step to proceed efficiently. However, when they react
303 with highly reactive carbonyl, the secondary radical can engage
304 with the oxygen and then undergo oxidation to give lactones or
305 dihydrofurans such as compound **20**. 1,2-Disubstituted alkenes
306 work poorly since the initial addition is slow. Finally, 1,1-
307 disubstituted alkenes and styrenes are the most reactive
308 alkenes, but the radicals issued from the initial addition step
309 are subsequently oxidized, so there is little or no HAT product
310 as exemplified by compound **30**.

311 Overall, the optimized set of reaction conditions delivered a
312 broad scope, but some unexpected and contrasting results
313 highlighted the difficulty to identify a truly general set of
314 conditions, especially with respect to the alkene coupling
315 partners. To equally compare our newly developed conditions
316 to the previously reported ones, we decided to run a control
317 where 10 equiv of carbonyl was used in AcOH in the presence
318 of 2.0 equiv of Mn(OAc)₃ at 70 °C. Strikingly, except for
319 nitroacetate, our reaction conditions outperformed the control
320 experiments. More importantly, for compounds **18**, **28**, **31**, **34**,
321 and **37**, our conditions always afforded products, while
322 previously reported ones were ineffective. This observation
323 motivated us to try to understand the reaction further to
324 optimize for those low yielding substrates.

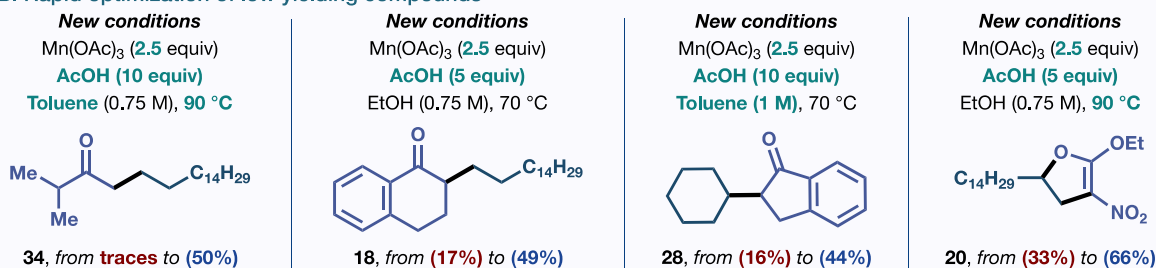
325 **3.4. Rapid Optimization of Low Yielding Substrates.**
326 We envisioned that we could re-apply the knowledge
327 accumulated during our systematic study to identify key

Scheme 4. Broadening the Scope of the Reaction: (A) Reengaging Data from the Systematic Study, (B) Rapid Optimization of Initially Low Yielding Compounds, and (C) Predicting Reaction Outcome^a

A. Reengaging data from the systematic study

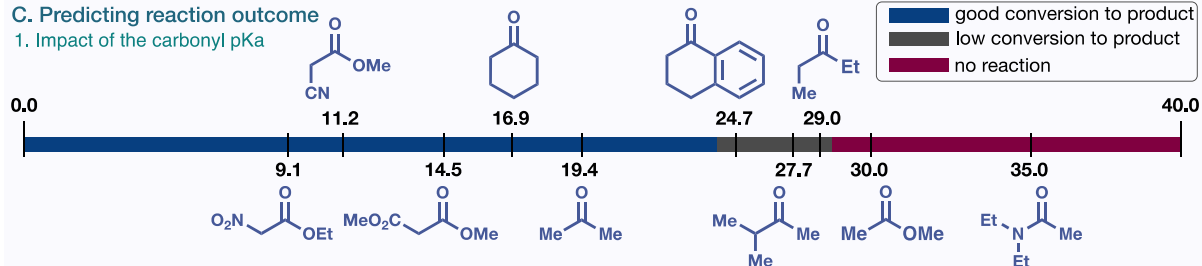


B. Rapid optimization of low yielding compounds

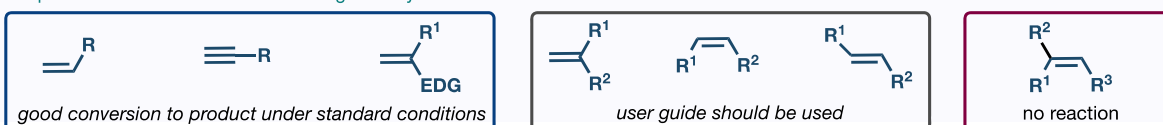


C. Predicting reaction outcome

1. Impact of the carbonyl pKa



2. Impact of the alkene substitution and geometry

^aYields refer to GCMS yields using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are shown in brackets.

parameters that should impact the outcome of the reaction. If successful, this approach would allow the practitioner to quickly identify optimal reaction conditions to give at least some product under the general stoichiometric set of conditions for challenging substrates.

Throughout our initial investigation of the Mn-mediated α -radical addition of carbonyls to olefins, parameters such as solvent, temperature, manganese loading, and concentration were found to dramatically impact the reaction outcome (Scheme 2). Due to its importance in previously reported conditions by the Snider group, AcOH was also a variable that needed to be considered.^{11g} With those parameters in mind, eight sets of conditions were designed and assessed on eight substrates containing seven ketones and two alkenes. Depending on the substrates and the conditions used, huge reactivity differences were observed matching with the observed difficulty to develop a truly general protocol (vide supra). As an example, cyanoester afforded high conversions to desired product **23** under all tested conditions even at room temperature. This extremely high reactivity can explain why it is one of the most frequently used substrates in literature reports.²⁴ Conversely, several changes impacted the conversion to product **20** which results from the coupling between nitroacetate and hexadecene. Running the reaction with more equivalents of manganese (from 1.5 to 2.5 equiv), higher temperature (from 70 to 90 °C), higher concentration (from 0.75 to 1 M), or using AcOH as an additive (5 or 10 equiv) provided better conversions versus the original conditions. The reactivity of α -tetralone, which already delivered reasonable conversion (25%), was enhanced by simply adding 5 equiv of AcOH to afford 56% of desired product **18**. Similarly, compound **38** was obtained in a moderate yield of 43% by increasing the amount of manganese from 1.5 to 2.5 equiv.

While trying to optimize compounds **28**, **34**, and **39** proved more difficult, several conditions still afforded decent conversions (20–50%). Therefore, it was envisioned that the combination of all promising set of conditions could significantly increase the yield of initially low conversion reactions. This merged approach was attempted on several substrates, and the results are highlighted in Scheme 4B. Outstandingly, compounds **34**, **18**, **28**, and **20**, which were initially only observed in trace amounts or isolated in low yields using the initial set of conditions, were obtained in 50, 49, 44, and 66% isolated yields, respectively.

Testing of these simple parameters (manganese loading, temperature, concentration, and AcOH additive) can quickly identify optimized conditions for challenging substrates. However, we thought it would be even better if the practitioner could predict the reaction outcome based on the nature of the carbonyl and the olefin.

3.5. Predicting Reaction Outcome. The systematic optimization, scope evaluation, and the subsequent re-optimization of low yielding compounds afforded copious data on reaction outcomes and allowed for a predictive model that relied on (1) the pKa of the carbonyl and (2) the geometry and substitution of the olefin to be assembled (Scheme 4C).

Several studies have highlighted the importance of steric hindrance and pKa depending on the nature of the carbonyl coupling partner.^{11,25} However, no general trends have been reported due to the complexity of the transformation and the myriad of conditions associated to it. Based on our stoichiometric set of conditions, the reaction outcome can be

predicted by simply using the pKa of the carbonyl starting material (Scheme 4C.1). Carbonyl compounds with a pKa lower than 24 will provide good yields under the optimized stoichiometric conditions. For carbonyls with pKas between 24 and 29, the approach developed for the low yielding compounds should be applied to obtain satisfactory yields. Compounds with pKas higher than 29 such as esters and amides will not deliver the desired product.

As highlighted by several reviews, the impact of the substitution and geometry of the alkene coupling partner has not been deeply studied.¹¹ Indeed, most of the examples reported in the literature focus on the functionalization of terminal nonsubstituted and cyclic olefins. The evaluation of the reaction scope and the optimization of its limitations allowed us to rationalize outcomes based on the nature of the olefin (Scheme 4C.2). Terminal alkenes and alkynes as well as stabilized disubstituted olefins are well tolerated under the reaction conditions and should afford good yields using the standard stoichiometric protocol. For nonstabilized, cyclic, and *cis/trans* alkenes, the eight conditions designed using the systematic study should deliver moderate yields. When the olefin is too encumbered, no desired product should be expected.

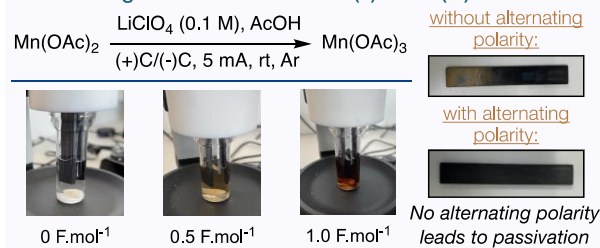
3.6. Development of an Electrocatalytic Set of Conditions. With the stoichiometric set of conditions, the knowledge accumulated from the systematic study, and the ability to predict the reaction outcome, the practitioner will be able to confidently run the Mn-mediated α -radical addition of carbonyls to olefins. However, the need for a stoichiometric amount of Mn(OAc)₃ was still a serious limitation from a sustainability and scalability standpoint. The development of a catalytic version was therefore sought. As mentioned in the Introduction, electrochemical alternatives have been attempted for Mn(III)-mediated reactions but have either not proven general, were not deeply investigated, or suffered from limitations such as the requirement for a divided cell and limited substrate scope.^{15e,19,24b,26} Therefore, the development of a robust electrochemical version of the Mn-mediated carbonyl α -radical addition to olefins was undertaken.

The oxidation of Mn(II) to Mn(III) was first studied in an undivided cell equipped with a graphite anode and cathode (Scheme 5A). The reaction was conducted using Mn(OAc)₂ as the catalyst in AcOH at room temperature under argon. AcOH was selected as the solvent due to the dual role it would ensure through the course of the catalytic reaction. While proton reduction would occur at the cathode, the subsequently generated acetate would assist the regeneration of the Mn(OAc)₃ active catalyst at the anode. After 1 F·mol⁻¹, the formation of Mn(OAc)₃ was clearly detected. However, passivation of the electrodes was also observed due to accumulation of the Mn-based species on the anode surface. Pleasingly, this undesirable phenomenon was easily suppressed by simply applying alternating polarity. Indeed, such a mode allow for the polarity of each electrode to be switched at a defined frequency lowering charge accumulation.

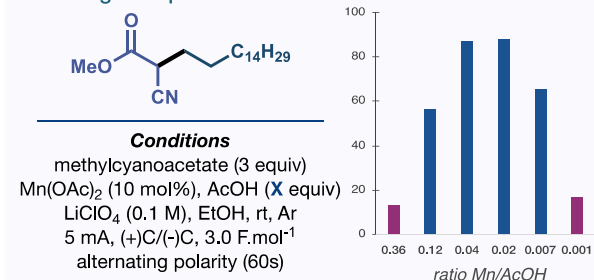
With this proof of concept in hand, the carbonyl starting material was carefully selected. Indeed, cyanoacetate was an ideal coupling partner to start the optimization with as it allowed the reaction to be conducted at room temperature and tolerated the use of AcOH (vide supra, Scheme 4). The excess of carbonyl was maintained at 3 equiv, while the amount of Mn(OAc)₂ was fixed at 10 mol %. Based on our earlier optimization studies, the impact of the [Mn]/[AcOH] ratio on

Scheme 5. Electrochemical Mn-Mediated α -Radical Addition of Carbonyls to Olefins: (A) e-Oxidation of Mn(II) to Mn(III), (B) Optimum [Mn]/[AcOH] Ratio, (C) Optimization, and (D) Scope^a

A. Validating the e-oxidation of Mn(II) to Mn(III)



B. Finding the optimum ratio Mn/AcOH

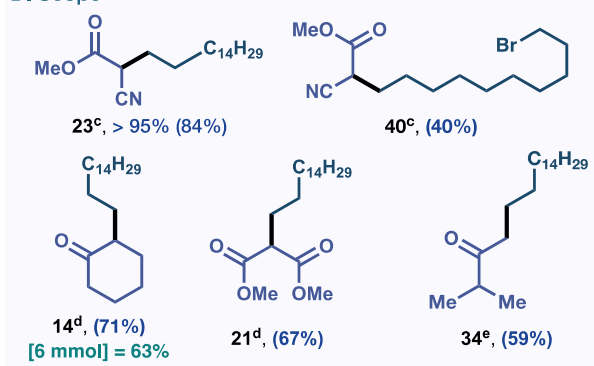


C. Optimization

methylcyanoacetate (3 equiv), Mn(OAc)₂ (15 mol%)
AcOH (7.5 equiv), LiClO₄ (0.1 M), EtOH (0.25 M), rt, Ar
5 mA, (+)C/(-)C, 3.0 F.mol⁻¹, alternating polarity (60s)

deviation from above conditions	yield ^{a,b}
none	> 95%
no AcOH	< 5%
10 mol% Mn(OAc) ₂	88%
no alternating polarity	15%
5 mA, 1.5 F.mol ⁻¹ , 5 h	49%
10 mA, 3.0 F.mol ⁻¹ , 5 h	68%
LiBF ₄ instead of LiClO ₄	90% (77%)
LiBF ₄ instead of LiClO ₄ and 0.5 M	> 95% (84%) ^c

D. Scope



^aReactions were conducted on a 0.6 mmol unless otherwise state.

^bGCMS yields using 1,3,5-trimethoxybenzene as an internal standard.

^cIsolated yields are shown in brackets. ^dReactions were conducted on a 1.2 mmol scale in EtOH (0.5 M) at rt. ^eReactions were conducted on a 1.2 mmol scale in EtOH (0.5 M) at 70 °C. ^fReaction was conducted on a 1.2 mmol scale using 20 equiv of AcOH in toluene/EtOH (1:1, 0.5 M) at 90 °C.

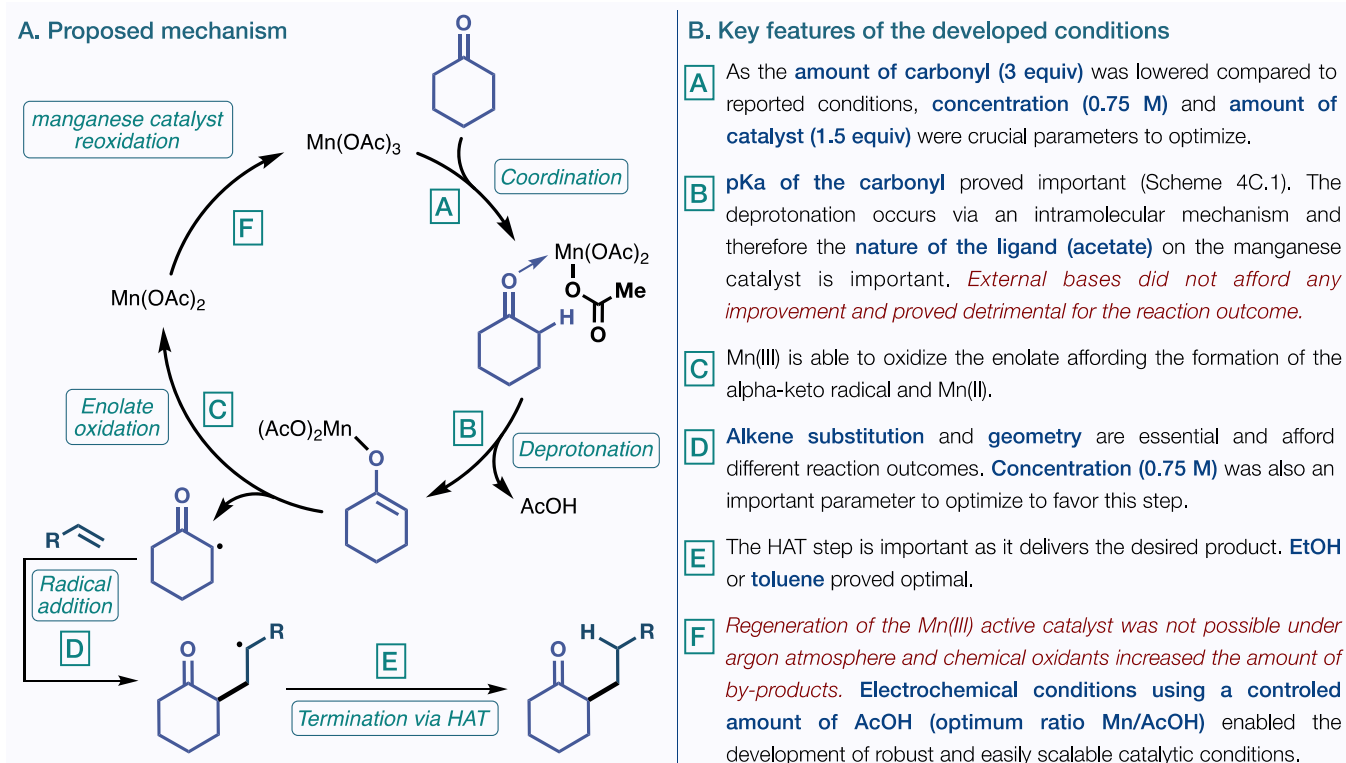
the reaction outcome was first investigated (Scheme 5B). As expected, a high [Mn]/[AcOH] ratio did not lead to sufficient concentration of the active catalyst and afforded the desired product in low yield. Conversely, too much AcOH in the reaction gave a low [Mn]/[AcOH] ratio and reduced the efficiency of the transformation. The optimal [Mn]/[AcOH] ratio was obtained using 7.5 equiv of AcOH which afforded the desired product **22** in 88% yield. With this optimized ratio in hand, we turned our attention to the electrochemical reaction conditions (Scheme 5C). To maximize the conversion, 15 mol % of the Mn(OAc)₂ catalyst was used in the presence of 11.3 equiv of AcOH to maintain the [Mn]/[AcOH] ratio (0.02). Under these conditions, the desired product was obtained in more than 95% yield. A control experiment without AcOH led to extremely low conversion. In the absence of alternating polarity, compound **23** was only obtained in 15% yield, supporting the detrimental impact of electrode passivation on the reaction outcome. Using 1.5 F.mol⁻¹ instead of 3.0 F.mol⁻¹ only delivered 49% of the desired compound, while using 10 mA instead of 5 mA also lowered the yield to 68%. To avoid scalability issues associated with the use of perchlorate-based electrolytes, LiBF₄ was used instead of LiClO₄, which maintained high conversion to product **23** and good isolated yield (77%). Finally, aware of the beneficial effect of running the reaction at high concentration, the electrochemical conditions were concentrated up to 0.5 M (instead of 0.25 M), and compound **23** was isolated in 84% yield.

We then decided to synthesize several molecules to assess the efficiency of the electrochemical protocol (Scheme 5D). Compound **40** bearing a halogen moiety was isolated in 40% yield. As expected, compounds **14** and **21** which usually require higher temperature to proceed in good yield did not give satisfactory results at room temperature. Simply heating these reactions to 70 °C afforded good yields (71% for **14** and 67% for **21**). In addition, the reaction was easily scaled-up to 6 mmol in a single 20 mL ElectraSyn vial by adjusting the current to 25 mA. Finally, the knowledge gained throughout the study was easily transferable to the electrochemical protocol with compound **34** obtained in 59% by using 20 equiv of AcOH in toluene at 90 °C. Altogether, these results not only highlight the efficiency of the optimized paired electrochemical protocol but also demonstrate its scalability.²⁷

4. SUMMARY

The key mechanistic features of the developed conditions are summarized in Scheme 6. To increase the practicality of the Mn-mediated α -radical addition of carbonyls to olefins, the goal of this study was to lower the amount of the carbonyl starting material to 3 equiv. Fixing this parameter impacted the first step of the mechanism where the carbonyl moiety needs to coordinate the Mn-catalyst. Therefore, increasing the concentration (from 0.1 to 0.75 M) was crucial to obtain the desired product in good yield (Scheme 6, panel A). The following loss of proton is afforded through an intramolecular deprotonation process where the presence of the acetate ligands proved essential. Indeed, external bases or additives were detrimental for the reaction to occur with high efficiency (Scheme 6, panel B). The oxidation of the resulting enolate has been extensively studied in the literature and none of the reaction parameters we have investigated improved it (Scheme 6, panel C). Conversely, for the free-radical addition step, our study systematically highlighted the importance of the alkene geometry and substitution (Scheme 6, panel D). The high

Scheme 6. Key Mechanistic Features of the Developed Conditions



515 concentration also favored this step of the mechanism. The use
516 of EtOH instead of AcOH, in addition to increasing the
517 functional group tolerance, positively impacted the final HAT
518 step (Scheme 6, panel E). Finally, the use of electrochemical
519 conditions to reoxidize Mn(II) to Mn(III) allowed the
520 development of a robust and general catalytic set of conditions
521 where a precisely controlled [Mn]/[AcOH] ratio was found to
522 be critical (Scheme 6, panel E).

5. CONCLUSIONS

523 An in-depth study of the Mn-mediated α -radical addition of
524 carbonyls to olefins has been assembled, allowing the
525 development of a new and general set of reaction conditions.
526 A wide range of functional groups including ester, cyano, nitro,
527 free, and TBS-protected alcohols and acetyl groups were
528 tolerated, and several carbonyls and olefins proved competent
529 coupling partners. Understanding the effect of solvent,
530 concentration, temperature, amount of the catalyst, as well as
531 the impact of additives has enabled us to identify a list of eight
532 key experiments that can quickly be performed to optimize
533 challenging reactions. This approach was successfully applied
534 to four different initially low yielding substrates, proved highly
535 efficient, and led to the creation of a predictive model based on
536 the pKa of the carbonyl compound and both the substitution
537 and geometry of the alkene coupling partner. Finally,
538 development of a robust and practical electrocatalytic version
539 of the reaction enabled the departure from stoichiometric
540 manganese loadings. The e-procedure requires only 3 equiv of
541 the carbonyl starting material to achieve good conversions and
542 uses two inexpensive graphite electrodes and a safe electrolyte.
543 Importantly, this paired electrochemical process does not
544 require the use of an undivided cell and was straightforwardly
545 scaled-up to 6 mmol in a single 20 mL vial. Overall, both

stoichiometric and electrocatalytic protocols should find 546
applications in academic and industrial environments and 547
will enable the development of new Mn-based catalytic 548
systems. 549

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at 552
<https://pubs.acs.org/doi/10.1021/acs.joc.2c00054>. 553

Experimental procedures and graphical abstracts for 554
both the stoichiometric and catalytic reactions, inves- 555
tigation of the reaction parameters, optimization of the 556
reaction conditions (stoichiometric and catalytic), 557
optimization of low yielding substrates, analysis, and 558
compound characterization data (PDF) 559

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575 **Author Contributions**

576 The manuscript was written through contributions of all
577 authors. All authors have given approval to the final version of
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579 **Notes**

580 The authors declare no competing financial interest.

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589 ■ **DEDICATION**

590 Dedicated to the memory of Professor Gérard Cahiez for his
591 pioneering work in manganese catalysis.

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