Carbon Quaternization of Redox Active Esters and Olefins via Decarboxylative Coupling

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Abstract: The synthesis of quaternary carbons often requires numerous steps and complex conditions or harsh reagents that act on heavily engineered substrates. This is largely a consequence of relying exclusively on conventional polar-bond based retrosynthetic disconnections that in turn require multiple functional group interconversions, redox manipulations, and protecting group chemistry. In fact, the presence of a quaternary center even in seemingly trivial structures can dominate the practitioner's entire retrosynthetic plan (referred to by Corey as a "keying element"). Here we report a simple catalyst and minimal reagents that convert two types of feedstock chemicals—carboxylic acids and olefins—into tetrasubstituted carbons via quaternization of radical intermediates. An iron porphyrin catalyst activates each substrate by electron transfer or hydrogen atom transfer then combines the fragments by an S_H2 reaction. This cross-coupling reduces the synthetic burden to procure numerous quaternary carbon-containing materials from simple chemical feedstocks.

Text: Nitrogen quaternization, a polar bond-forming reaction, originated in the 19th century as one of the earliest examples of C–N bond formation in organic synthesis (Figure 1A).[1] Its inherent simplicity and widespread availability of starting materials stands in stark contrast to the way chemists go about forging quaternary carbon centers.[2] Specifically, most carbon quaternizations utilize polar transformations such as conjugate addition, enolate chemistry, and pericyclic reactions.[3–5] Such processes are complicated by the differing regiochemistries that can result depending on the substrates and conditions employed. For instance, conjugate additions can often lead to undesired 1,2-addition products, enolate C–alkylation often competes with O–alkylation, and pericyclic processes can suffer from regioisomeric mixtures depending on the innate sterics and electronics of the reactants. A simple and predictable method to form carbon-based quaternary centers akin to classic N–quaternization would be an appealing transformation. Previous studies from our labs have demonstrated how radical methods can be leveraged to cross-couple olefins with other olefins or alkyl/aryl halides.[6, 7] In many cases, quaternary center synthesis can be

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achieved through such methods. The cross coupling between two different redox active esters has also been reported but is not generally applicable to quaternary center synthesis.[8, 9] Here we show how a single catalyst can mediate regioselective quaternization of carbon using ubiquitous chemical feedstocks: olefins and carboxylic acids (Figure 1B). An inexpensive Fe-based catalyst in the presence of simple reducing agents can effectively achieve this powerful transformation in a chemoselective fashion with broad substrate scope through a similar mechanistic pathway. It is particularly striking that a single catalyst can both activate distinct functional groups (RAEs and olefins) and mediate bond formation between them. An illustrative demonstration of the power of such a reaction is depicted in Figure 1C wherein the 10-step synthesis of a seemingly trivial structure (**4**)[10] can be truncated into a single step by coupling a primary tosylate-containing RAE **3** with either RAE **1** or olefin **2** with high chemoselectivity in 47% and 42% yield, respectively.

The mechanistic framework outlined in Figure 1B was inspired by key literature precedents outlined in Table 1A. Seminal studies of Hirobe and co-workers showed that Drago-Mukaiyama-type olefin hydration could be achieved using Fe-porphyrins.[11] Indeed, the pioneering studies of Setsune *et al.* identified *sec*-alkyl iron porphyrins formed upon exposure of 1-alkenes to Fe-TPPCl and $NaBH_4$.[12] Fe–H formation and metal hydride hydrogen atom transfer (MHAT) explains the branched-selective hydrometalation.[12] Neta depicted alkyl-Fe^{3+}(TPP) complexes as mesomers with single-electron density localized on carbon, which explained its ferrous phorphyrin-like behavior.[13] Shenvi and co-workers recently utilized this same iron complex along with a silane to catalyze C–C bond formation[14] between benzyl bromides and olefins to form quaternary centers via S_H2 reactions.[15] The Baran group demonstrated that Fe-catalysis could also enable decarboxylative Negishi couplings of RAEs and various aryl-organometallic reagents.[16] Taken together, it seemed reasonable that RAEs might quaternize radicals through catalytic cycles in which Fe(II)porphyrins both *form* and *trap* open-shell carbon intermediates generated from olefins or other RAEs. These two related catalytic cycles would rely on overall reducing conditions (Zn or silane) to produce a pool of Fe(II) that might cleave *N*-hydroxy-phthalimide esters to generate primary and/or tertiary radicals. Due to the instability of *tert*-alkyliron complexes above 0 °C,[17] capture of the primary radical would be preferred, allowing its interception by the tertiary radical in a putative S_H2 reaction.[14] This same tertiary radical may be formed from an alkene with an iron hydride that can regenerate Fe(II) via MHAT or an HER reaction.[18] In contrast to many MHAT reactions, this catalytic cycle would not require turnover by an exogenous oxidant; the RAEs partners would reoxidize Fe(II) to (III). Below we identify conditions to reduce this design to practice and achieve a versatile carbon quaternization that unites ubiquitous bench-stable starting materials (olefins and acids) in a simple and easily scalable fashion.

The realization of this plan is summarized in Table 1B using RAE 5 with either olefin **7** or RAE **8** leading to the same product **6** (see SI for the comprehensive optimization). As illustrated by entries 1–8,15 (olefin-RAE coupling) and 9–14 (RAE-RAE coupling), each reaction variant required simple and similar conditions: the Fe(TPP)Cl complex, a base, a reductant and a 1,2-dichloromethane/ acetone solvent mixture. The choice of base proved crucial as exemplified in entries 2-3 with CsOAc emerging optimal. Increased yields are observed after a simple degassing (bubbling Ar) of the reaction mixture, although the presence of air is not detrimental (entry 4). Exclusion of acetone led to lower yields presumably due to catalyst insolubility (entry 5). Addition of other Fe-sources such as $Fe(acac)_3$ led to diminished conversion (entry 6) as well. As observed in other MHAT transformations, the use of pre-formed Ruben's silane proved beneficial (entries 7-8). Turning to the RAE-RAE coupling, the optimized conditions above only led to 9% yield of

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the desired adduct **6** (entry 9). Increasing the Fe-loading to 20% had a measurable positive effect on conversion (entry 10). The most significant improvement emerged when switching the reductant from a silane to Zn metal (entry 11). A slight change in solvent composition to DCE/acetone 7:4 along with KOAc in place of CsOAc led to a further increase in yield (entries 12-13). The inclusion of a weak acid (Et_3N•HCl) likely serves to activate Zn(0) and results in a 61% isolated yield of **6** (entry 14). Notably, the final optimized conditions for RAE-RAE coupling cannot be applied to the closely related olefin-RAE coupling (entry 15) and vice versa (entry 9). Nevertheless, both conditions employ a simple combination of commercially available reagents and the same Fe(TPP)Cl catalyst.

Significantly, neither Fe-catalyzed decarboxylative coupling (conditions A or B) necessitated O_2 to turn over the catalytic cycle (Fe^{2+} to Fe^{3+}), whereas recent work from our group(s) required an air atmosphere in conjunction with an Fe β-diketonate MHAT catalyst or co-catalyst.[15, 17] In the current work, the single iron(II) porphyrin turns over to iron(III) in the absence of oxygen by reaction with the RAE or its resultant radical: ^{1}H NMR studies demonstrated that Fe(TPP) will complex *n*-pentyl-CO(NHPI) prior to formation of *n*-pentyl–Fe(TPP) (see SI). Fe(TPP) can be formed from its corresponding hydride by either hydrogen evolution or alkene MHAT (see SI).[18] *As a result, Fe(TPP)Cl mimics the polyfunctionality of precious metals in inner-sphere (coordinative) alkene functionalization catalysis, but does so in a unique outer-sphere (non-coordinative) series of elementary steps.* In the case of RAE-RAE coupling, the use of Zn metal is well-precedented to reductively decompose NHPI esters into carbon centered radicals.

The different optimal bases in conditions A/B were determined empirically and likely fulfill different roles: silanes can require Lewis base addition to increase hydridic strength[19] and/or accelerate metal hydride formation[20] en route to MHAT with alkenes. Bases can presumably sequester Lewis acidic metals, e.g. $ZnCl_2$, that might accrue as an RAE is reduced by Zn(0).

With a streamlined set of conditions in hand for the radical quaternization of olefins and carboxylates, the scope was examined as illustrated in Table 2. In general, these highly chemoselective conditions tolerate a range of functional groups including carbamates amides, alkyl halides, epoxides, aryl halides, esters, alcohols, nitriles, tertiary amines, ketones, ureas, and electron-rich/deficient heterocycles. It is particularly noteworthy that alkyl bromides, terminal alkynes as well as an alkyl boronate, remain intact during this quartenization despite their notorious reactivity in both transition-metal catalyzed couplings and radical chemistry. Similarly, aryl iodides and electron-deficient aryl chlorides are left untouched despite their common use in radical cross couplings. In the case of olefins, preferential reactivity can be achieved during the RAE-RAE coupling whereas less reactive olefins are spared when employing the RAE-olefin coupling. Stabilized radicals can also be coupled (α-heteroatom, benzylic) derived from α-heteroatom containing acids. In the case of RAE-RAE couplings of such substrates, FeOEP led to a dramatically increased yield. Complex pharmaceutically relevant structures can be coupled efficiently resulting in quaternary center containing analogs **36**-**40**. The direct installation of all-carbon quaternary centers within saturated heterocycles is a particularly challenging motif to construct by conventional polar bond analysis; this quaternization allows an intuitive coupling from readily accessible heterocyclic fragments (**10**, **11**, **12**, **15**, **16**). The reactions described above are extremely simple and practical to perform using inexpensive reagents, a rapid setup time, and are amenable to gram-scale preparation (see **41** and **34**). The absence of oxygen in conditions A/B (Schlenk or glovebox conditions are not required, just a simple Ar balloon) allowed facile scaling to gram quantities with no change in yield, and pointed to internal oxidative turnover, i.e. an overall redox neutral process (see Table 1A). These features bode well for adoption in a parallel/combinatorial synthesis campaign wherein ubiquitous, bench-stable precursors can

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combine delivering long sought-after complex libraries rich in sp^3 content including quaternary carbons.

The capacity for these new reactions to dramatically simplify the way quaternary-center containing molecules has been exemplified through 11 different case studies (see SI for complete listing), of which six examples are illustrated in Figure 2. Thematically what all of these examples have in common is a near exclusive reliance on polar bond analysis during the planning stages, especially carbonyl chemistry. As a consequence, the conventional routes to these mostly simple structures rely on extensive redox manipulations, function group interconversions, and a variety of pyrophoric reagents for various carbonyl reductions. In contrast, direct carbon quaternarization sidesteps these inefficient tactics through a modular LEGO-like transformations of commercially available building blocks (olefins and acids).

For instance, the simple alkyne **53** was previously prepared (en route to prostaglandin analog synthesis) in an eight-step route of which only one step forges a C–C bond and wherein the key quaternary center was purchased in the form of a dimethyl cyclohexanone **52** whose skeleton was tediously edited.[21] In contrast, commercially available olefin **54** can be coupled with the RAE derived from the simple commercial alkyne-containing acid (**55**) under radical quaternarization conditions to deliver **53** in only 2 steps (48% isolated yield). Ketoaldehyde **56**, a useful building block for steroid analog synthesis, was previously accessed relying on classic carbonyl chemistry, C–C homologation, and a variety of undesirable reagents (Br_2, Mg, OsO_4).[22] Alternatively, the same structure was accessed directly following radical quaternarization of olefin **57** with RAE **58** followed by acidic workup in 45% isolated yield. Substrate **60**, containing two quaternary centers was previously accessed through a laborious 11-step sequence with low ideality commencing from glutaric anhydride **59** again relying on polar bond analysis and carbonyl chemistry.[23–25] Remarkably, diene **61** could be enlisted in a sequential radical cross coupling first by employing olefin-olefin Fe-catalyzed MHAT cross coupling with methylacrylate (72% yield) followed by radical quaternarization of **62** with RAE **63** to deliver the same product **60** in 58% isolated yield obviating the need for 9 inconvenient steps and toxic/pyrophoric reagents ($LiAlH_4$, HBr, KCN). Enyne **65**, used as a substrate in a cycloisomerization study, was previously accessed through a 15-step sequence relying on alkyne hydrometallation, Wittig, carbonyl chemistry, and acetylide addition as the key C–C bond forming steps.[26] This lengthy sequence required the use of protecting groups and extensive redox manipulations (3 instances of $LiAlH_4$ reduction). A more intuitive LEGO-like approach was enabled through radical retrosynthesis. Thus, an Ag-Ni-facilitated decarboxylative alkenylation of commercial acid **66** with vinyl iodide **67**, followed by radical quaternarization with alkyne-containing RAE **68** afforded **65** in only 5-steps without any redox manipulations. Radical quaternarization could also be used to construct scaffolds appearing in natural products. For example, piperidine **70**, featuring a quaternary carbon at the C-3 position, serves as a pivotal scaffold within the madangamine alkaloids. In the previous 7-step synthesis, the construction of the quaternary center again relied on carbonyl chemistry commencing from 2-piperidone.[27] Of those seven steps, two forged C–C bonds with the remainder comprising concession steps (redox, FG, and PG manipulations). Conversely, starting from commercial acid **71**, a simple alkylation followed by radical quaternarization with free alcohol containing RAE **70** enables a 3-step synthesis. Finally, α-tocopherol analog **74**, useful for the modulation of microglial activation, required a 10 step route reliant on classic polar bond analysis.[28] In a complete departure from this strategy, commercially available Trolox (**75**) could be used to efficiently incorporate the

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desired alkanol side chain through radical quaternarization (58% yield) with RAE **72** to deliver analog **74** in only 3 steps.

Conclusion. Quaternary carbons can now be dissected into feedstock precursors, alkenes and carboxylic acids, via radical quaternization. Numerous high fraction sp^3 materials are now available in a fraction of the prior synthetic burden. Indeed, the approach outlined herein represents a complete departure from the mostly carbonyl-focused retrosynthetic analysis (Table 2) historically utilized to forge such systems.[3] In this simple protocol, two substrates classes converge into the same catalytic cycle in which an iron(III) catalyst undergoes reduction to iron(II) by either Zn or a silane/alkene combination, and oxidative capture by a redox-active ester returns the iron(III). Notably, the alkene cross-coupling involves iterative outer-sphere steps to form new C–C bonds using a single catalyst; the RAE cross-coupling exhibits perfect heteroselectivity. In contrast, inner sphere cross couplings that involve weak alkene-metal center complexes to form sp^3-sp^3 linkages (e.g. Heck, Kulinkovich, 1,4-addition) often do not allow chemoselective merger of complex fragments. It has been widely recognized that fragment coupling simplifies retrosynthetic analysis by increasing convergency.[29,30] Simple tools such as the reactions described herein point to a unique conceptual platform[31–35] to decisively solve this vexing problem in organic synthesis.

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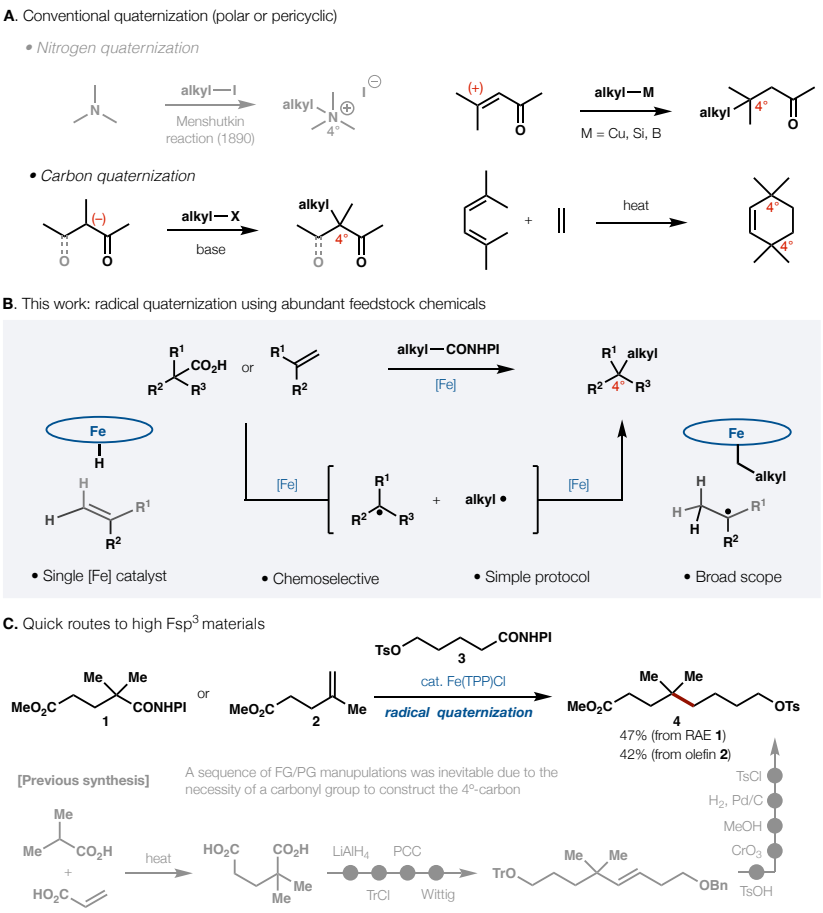

Fig. 1. Carbon quaternization overview and application. (A). Nitrogen quaternization compared to methods for carbon quaternization. (B) Overview of method reported here. (C) Simplification imparted by this cross-coupling strategy compared to traditional multi-step synthesis.

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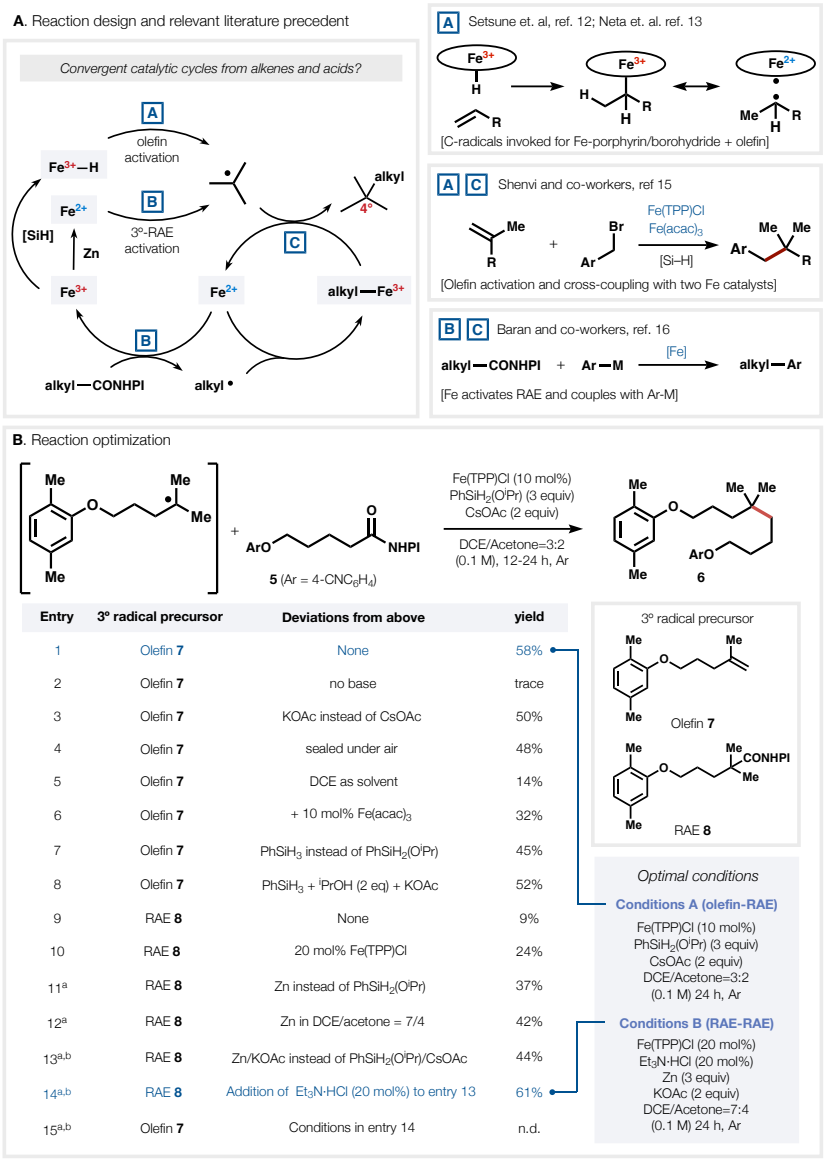

Entry	3° radical precursor	Deviations from above	yield
1	Olefin **7**	None	58%
2	Olefin **7**	no base	trace
3	Olefin **7**	KOAc instead of CsOAc	50%
4	Olefin **7**	sealed under air	48%
5	Olefin **7**	DCE as solvent	14%
6	Olefin **7**	+ 10 mol% $Fe(acac)_3$	32%
7	Olefin **7**	$PhSiH_3$ instead of $PhSiH_2(O^iPr)$	45%
8	Olefin **7**	$PhSiH_3$ + ^{i}PrOH (2 eq) + KOAc	52%
9	RAE **8**	None	9%
10	RAE **8**	20 mol% Fe(TPP)Cl	24%
11[a]	RAE **8**	Zn instead of $PhSiH_2(O^iPr)$	37%
12[a]	RAE **8**	Zn in DCE/acetone = 7/4	42%
13[a,b]	RAE **8**	Zn/KOAc instead of $PhSiH_2(O^iPr)$/CsOAc	44%
14[a,b]	RAE **8**	Addition of Et_3N·HCl (20 mol%) to entry 13	61%
15[a,b]	Olefin **7**	Conditions in entry 14	n.d.

Table 1. Catalytic cycle design and execution. (A). Proposed catalytic cycles in common between redox-active ester (RAE) and olefin coupling parners based on literature precedents. (B) Exploration and optimization identifies similarities and differences between coupling parners.

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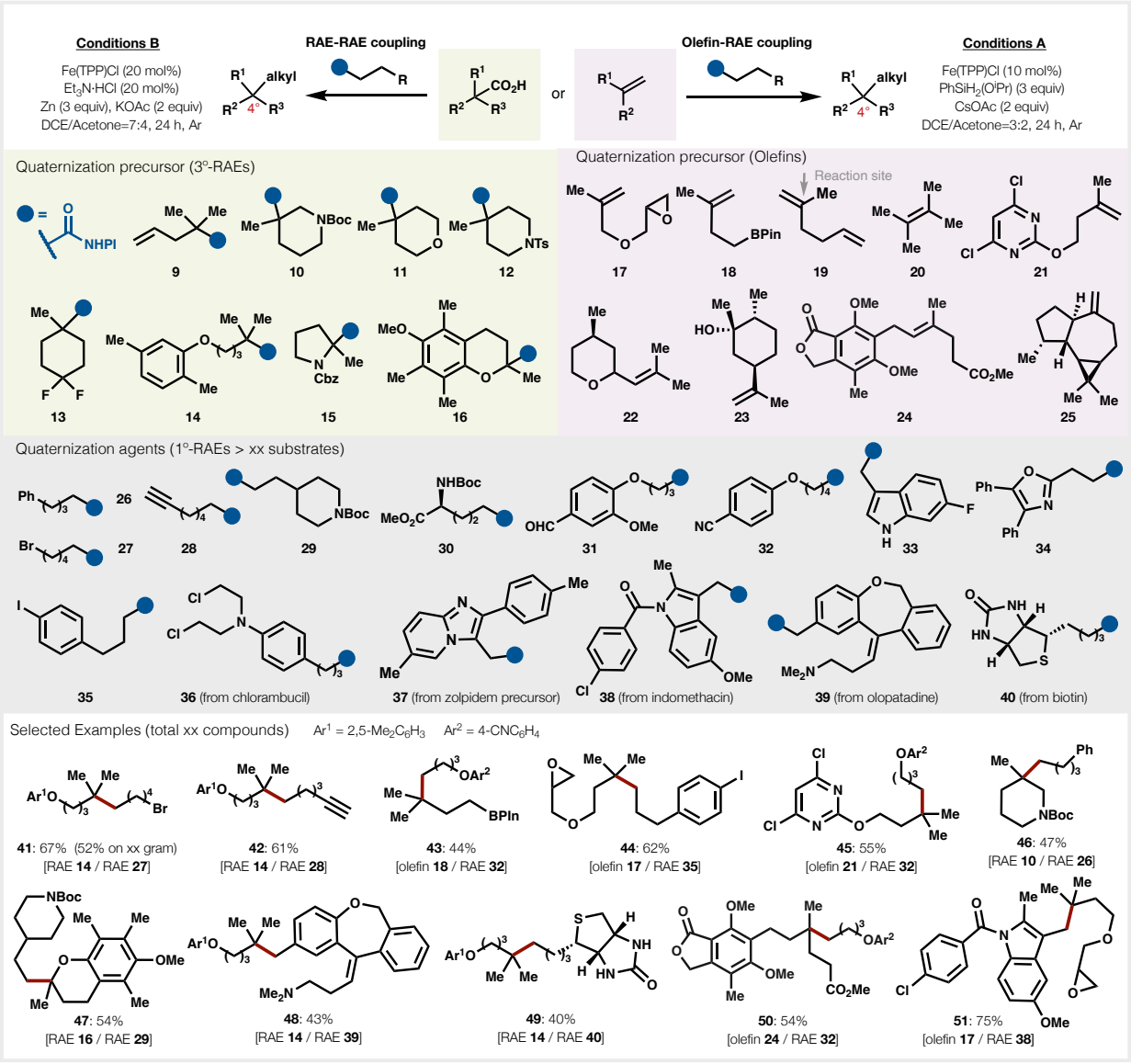

Table 2. Exploration of Scope. Carboxylic acids (tan) and olefins (pink) substrates couple with quaternizing carboxylic acid reagents (gray). Complex fragment couplings to form quaternary carbons under simple conditions are now possible (white).

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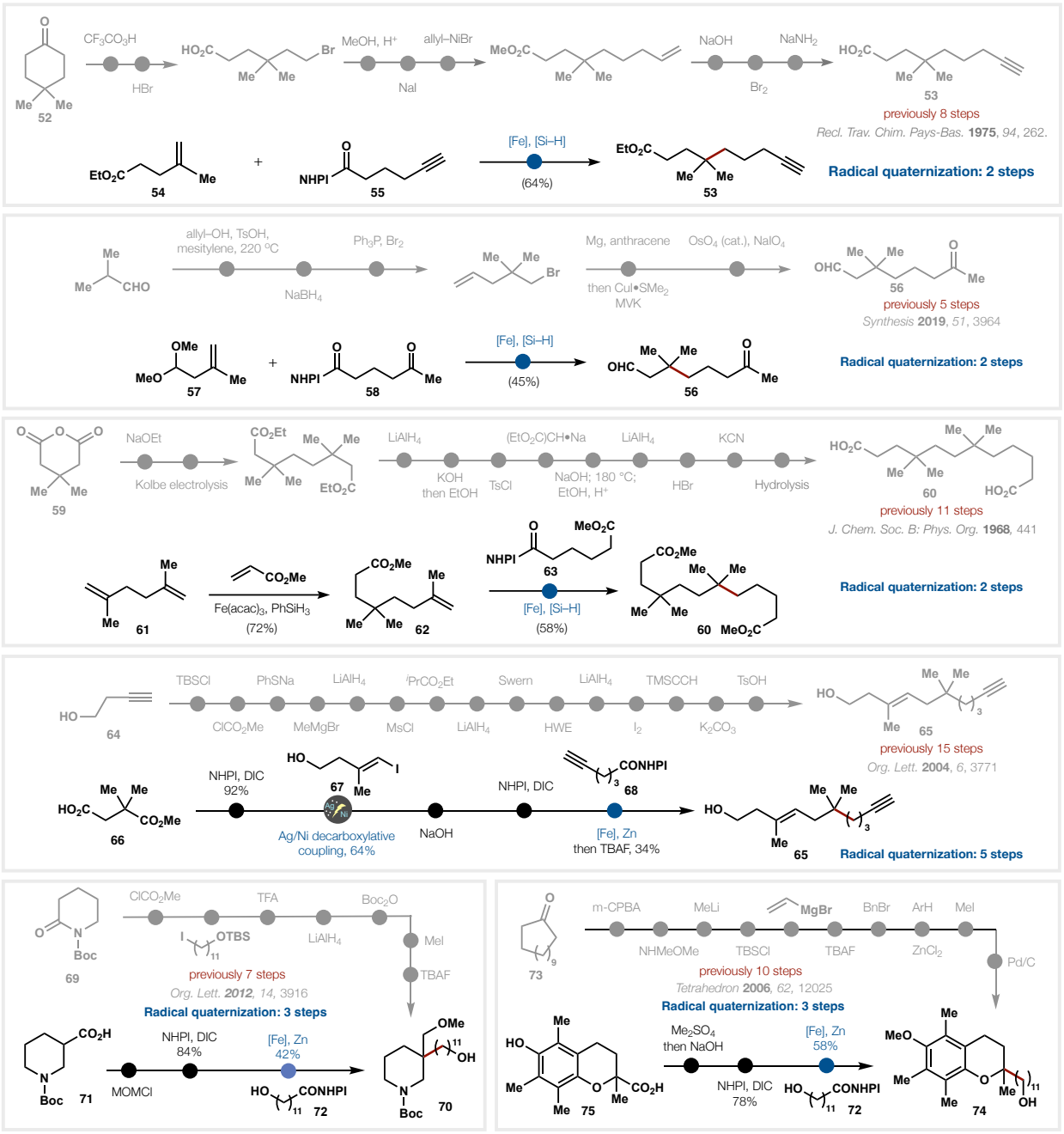

Fig. 2. Examples of simplified syntheses. Lengthy routes to quaternary carbon-containing materials are compressed into short sequences using radical quaternization.

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