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A Radical Approach to Anionic Chemistry: Synthesis of Ketones, Alcohols, and Amines

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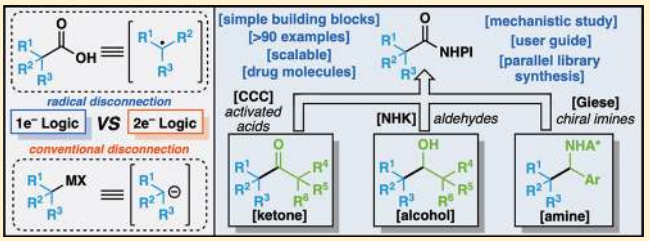
Supporting Information

ABSTRACT: Historically accessed through two-electron, anionic chemistry, ketones, alcohols, and amines are of foundational importance to the practice of organic synthesis. After placing this work in proper historical context, this Article reports the development, full scope, and a mechanistic picture for a strikingly different way of forging such functional groups. Thus, carboxylic acids, once converted to redox-active esters (RAEs), can be utilized as formally nucleophilic coupling partners with other carboxylic derivatives (to produce ketones), imines (to produce benzylic amines), or aldehydes (to produce alcohols). The reactions are uniformly mild, operationally simple, and, in the case of ketone synthesis, broad in scope (including several applications to the simplification of synthetic problems and to parallel synthesis). Finally, an extensive mechanistic study of the ketone synthesis is performed to trace the elementary steps of the catalytic cycle and provide the end-user with a clear and understandable rationale for the selectivity, role of additives, and underlying driving forces involved.



INTRODUCTION

Roughly 120 years ago, Grignard invented his eponymous reaction that converts alkyl halides into nucleophilic organomagnesium reagents that engage electrophilic C=O bonds.[1] This reaction forms one of the foundational reactions of organic synthesis and although the precise mechanism of carbonyl addition is not fully understood, it is generally regarded (and taught to undergraduates) as a two-electron (anionic) process.[2] Grignard reagents and related species are routinely used to generate some of the most useful functional groups such as ketones (via addition to activated ester or amide derivatives), alcohols (via addition to aldehydes), and amines (via addition to imines), as depicted in Figure 1.[3] Notwithstanding its indisputable utility and broad scope, it bears with it a restricted window of chemoselectivity—certain functional groups are simply not compatible with the highly basic and nucleophilic properties of the reagents. Additionally, alkyl halides are often inconvenient to prepare and scarcely available compared to other feedstock functional groups such as olefins and carboxylic acids.[4] Thus, the search for Grignard-like reactivity that is milder and more tolerant of air and moisture continues to the present day.[5] Indeed, groundbreaking findings from Lipshutz, Buchwald, Krische, and Miura have opened up a realm of mild nucleophilic additions beginning with olefin precursors.[6] We and others have also explored how Mukaiyama-type reactivity can be harnessed on olefins to add to carbonyl groups.[7]

In the quest for practicality, alkyl carboxylic acids are perhaps the most ubiquitous functional group from the

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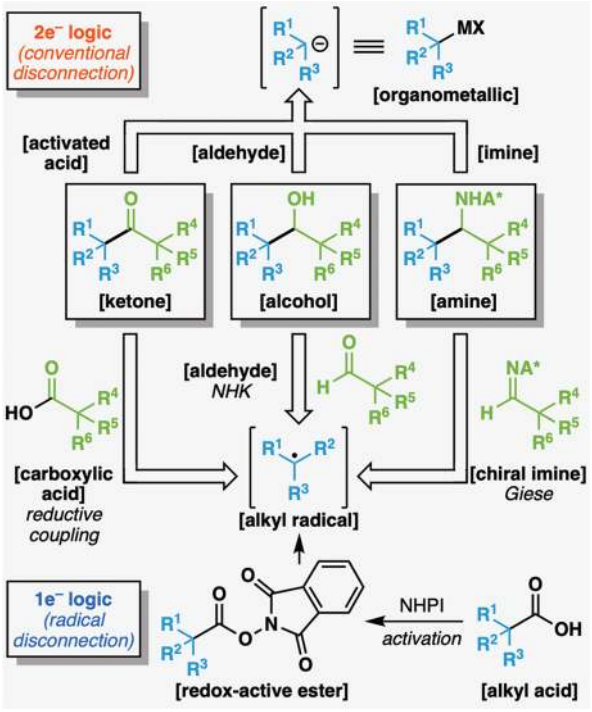

Figure 1. Polar-bond disconnections via conventional 2e⁻ logic vs newly explored radical processes for ketone, alcohol, and amine synthesis. NHPI = *N*-hydroxyphthalimide.

standpoint of commercial availability.[8] They are uniquely modular building blocks in that they can be easily diversified at the alpha-position using anionic chemistry and then disassembled to lose CO_2 and afford a carbon-centered radical. Radicals derived in this way have a storied history dating back to Kolbe and Barton's legendary findings.[9] More recently, we and others have explored how such radicals could be generated in the same way that alkyl halide-derived radicals have been for decades using transition metals.[10] Thus far, most recent studies in this area have been focused on the canonical chemistry of radicals such as their use in cross-coupling and trapping with radicalophiles.[11]

The focus of this work was to see if carboxylate-derived radicals could be engaged in reaction manifolds that have historically been within the purview of anionic (Grignard) chemistry. This Article describes the invention, full scope and limitations, and detailed mechanism of methods for harnessing radicals derived from redox-active esters (RAEs) for reactions with electrophilic C═X bonds to generate ketones, alcohols, and amines.

BACKGROUND AND HISTORICAL CONTEXT

The generation of radicals and subsequent interception with transition metals for the specific purpose of adding to C═X bonds is not new (Figure 2). In fact, this area has a long history dating back to the late 1970s. Figure 2 outlines the key precedents in this area that have laid the strategic and mechanistic basis for the current studies. Early work in this area focused on the use of electrochemical techniques to generate alkyl-M species (M = Cd and Mg) that could be

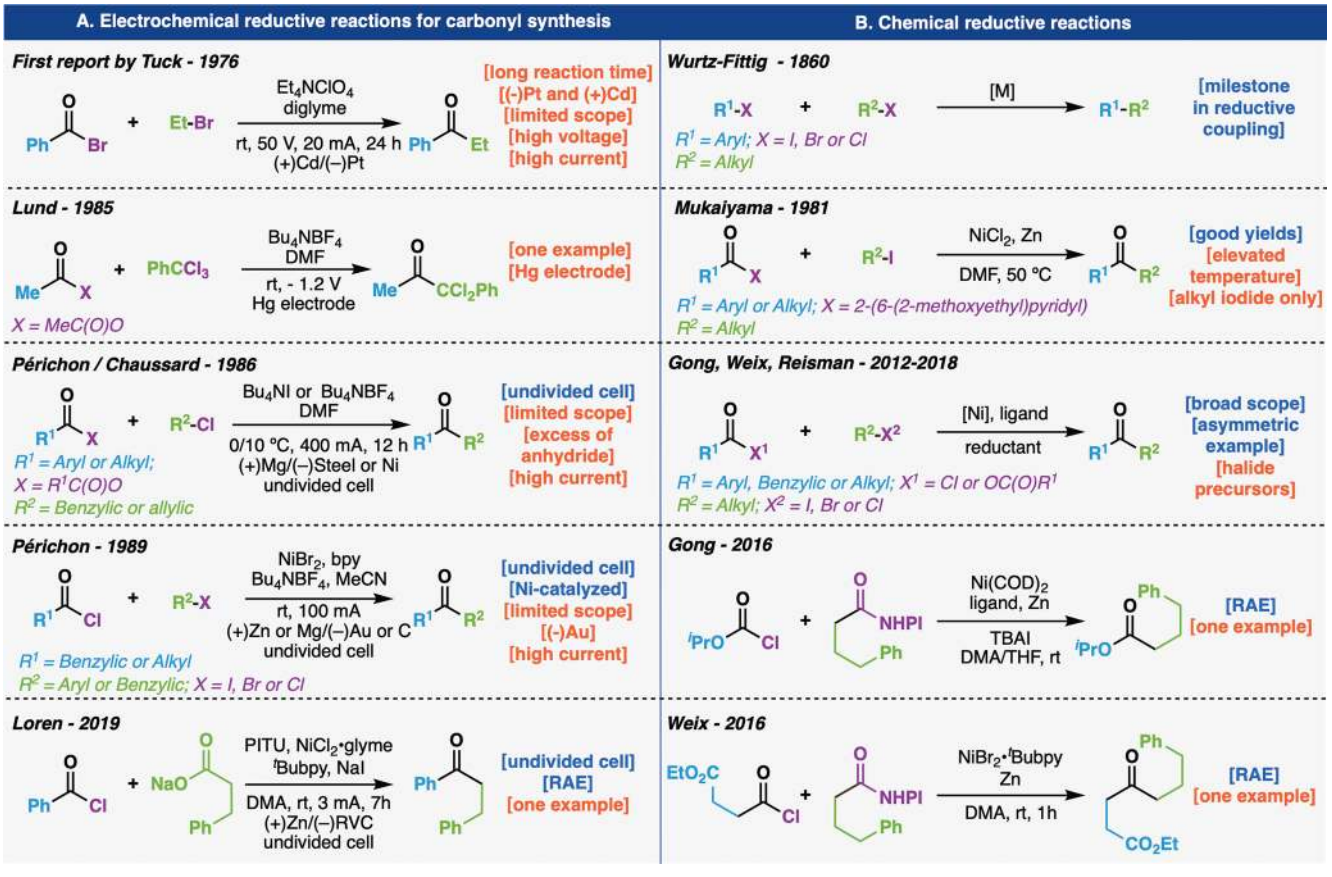

Figure 2. Radical methods for accessing carbonyl compounds: historical perspective. NHPI = *N*-hydroxyphthalimide.

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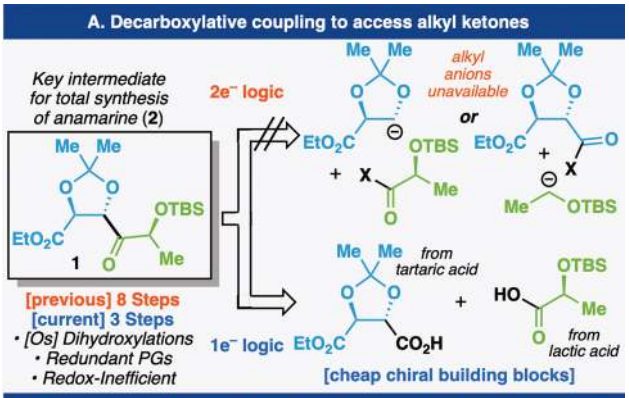
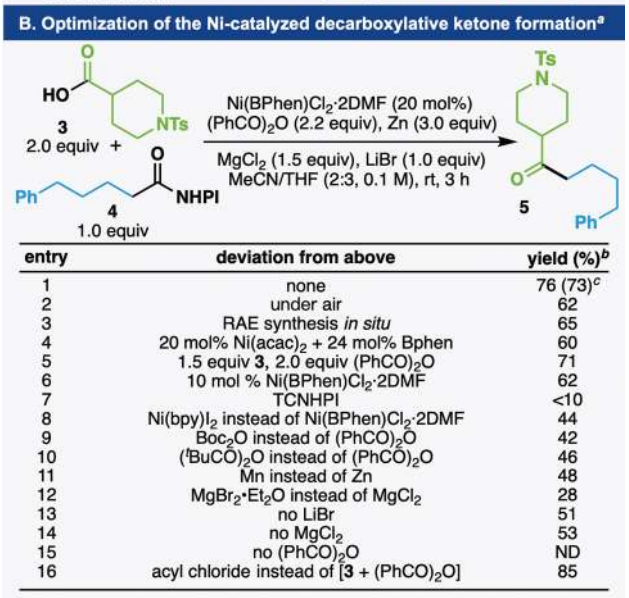
directly added to acyl halides *in situ*.[12] Lund and co-workers subsequently demonstrated that anhydrides were also suitable electrophiles in this transformation.[13] One of the key breakthroughs in this area can be traced to a report by Périchon who laid some of the groundwork for the cross-electrophile couplings of the modern era.[14] In that work, a sacrificial anode such as zinc was utilized in an undivided cell along with catalytic nickel in the presence of a diamine ligand (bpy) to couple simple alkyl and acyl halides to form ketones. In parallel to these electrochemical studies, Mukaiyama and co-workers demonstrated a similar transformation by embedding the ligand for Ni onto the ester (2-pyridyl ester derivatives) rather than using an acyl halide.[15] Moving to the modern era, the field of reductive/cross electrophile couplings, specifically those between alkyl halides and acyl halides/anhydrides, has flourished with impactful contributions from the Martin, Gong, Weix, and Reisman groups among many others.[16] Finally, the Gong, Weix, and Loren teams have reported single examples of the use of RAEs in place of alkyl halides for ester (Gong) or ketone (Weix and Loren) synthesis.[17] This backdrop of precedent places our studies in a proper context.

KETONE SYNTHESIS VIA CROSS-CARBOXY COUPLING: DEVELOPMENT AND SCOPE

Retrosynthetic considerations for the synthesis of complex ketones inspired our explorations in this area. For example, as illustrated in Figure 3A, ketone fragment **1** was enlisted as a key intermediate in a total synthesis of anamarine **2**. Prior routes to this ketone, which conveniently maps onto readily available tartaric acid, relied on $2e^-$ logic and thus could not easily take advantage of this inexpensive building block because anionic chemistry of the type shown in Figure 3A is not workable.[18] Therefore, an olefin-based route was pursued requiring two asymmetric dihydroxylations with Os along with extraneous redox fluctuations and PGs (8 steps overall). In contrast, $1e^-$ logic pointed to a simple (3-step) means of utilizing feedstock chiral pool materials: tartaric and lactic acid. The development of the necessary chemistry to achieve this simplification was accomplished using model substrates **3** and **4** as outlined in Figure 3B. In its fully optimized manifestation, a 73% isolated yield of ketone **5** was obtained from RAE **4** and acid **3** using a carefully engineered set of reagents in concert with a Ni catalyst: (1) benzoic anhydride as activating agent for the carboxylic acid, (2) Zn powder as reducing agent, and (3) magnesium- and lithium-based Lewis acids ($MgCl_2$ and LiBr). The experimental simplicity is worth pointing out: all components are simply added to a flask followed by addition of solvent, and after 3 h of stirring at room temperature the reaction is stopped. Deviations from the conditions prescribed above are certainly tolerated.

For instance, the following set of modifications resulted in only 5−15% decrease in yield: running the reaction under air (entry 2), generating either the RAE (entry 3) or catalyst (entry 4) *in situ*, reducing the equivalents of acid and anhydride (entry 5), or lowering the catalyst loading (entry 6). Key parameters for the success of this reaction include the specific identity of the RAE (entry 7), Ni-bound ligand (entry 8), anhydride (entries 9 and 10), reductant (entry 11), and Lewis acids employed (entries 12−14). Unsurprisingly, inclusion of the anhydride was found to be required for product formation (entry 15). In addition, the use of an acyl chloride in place of the *in situ* combination of carboxylic acid and anhydride led to even higher conversion (entry 16). For





entry	deviation from above	yield (%)[b]
1	none	76 (73)[c]
2	under air	62
3	RAE synthesis *in situ*	65
4	20 mol% $Ni(acac)_2$ + 24 mol% Bphen	60
5	1.5 equiv **3**, 2.0 equiv $(PhCO)_2O$	71
6	10 mol % $Ni(BPhen)Cl_2$·2DMF	62
7	TCNHPI	<10
8	$Ni(bpy)I_2$ instead of $Ni(BPhen)Cl_2$·2DMF	44
9	Boc_2O instead of $(PhCO)_2O$	42
10	$(^tBuCO)_2O$ instead of $(PhCO)_2O$	46
11	Mn instead of Zn	48
12	$MgBr_2$·Et_2O instead of $MgCl_2$	28
13	no LiBr	51
14	no $MgCl_2$	53
15	no $(PhCO)_2O$	ND
16	acyl chloride instead of [**3** + $(PhCO)_2O$]	85

Figure 3. (A) Inspiration for a mild ketone and chemoselective ketone synthesis and (B) development and optimization of CCC. [a] 0.1 mmol. [b] Yield determined by LC-MS with 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield. See Supporting Information for details. NHPI = *N*-hydroxyphthalimide, TCNHPI = *N*-hydroxytetrachlorophthalimide, bpy = 2,2'-bipyridine, BPhen = bathophenanthroline, ND = not detected.

the sake of experimental simplicity and to enable parallel library synthesis (*vide infra*), the *in situ* protocol was adopted as the standard protocol. An extensive list of parameters screened can be found in the Supporting Information (SI), and the role of each component will be discussed in the Mechanistic Inquiry section (*vide infra*).

With a set of optimized conditions in hand the scope and versatility of ketone synthesis was systematically explored employing a range of different carboxylic acids (Table 1). This "cross-carboxy coupling" (CCC) tolerates a range of 1°, 2°, 3°, and aromatic carboxylic acids to deliver unsymmetrical ketones in an operationally simple, chemoselective, and scalable way. 1° RAEs were coupled to 1° (**6**, **7**, **9**, **11**, and **13**), 2° (**5**, **8**, **10**, **12**, **14**−**17**, **19**, **20**, **22**, and **23**), and bridged 3° (**21**) carboxylic acids in good yields. A large variety of functional groups including esters (**6**), ketones (**7**−**9**, **11**, **12**, and **19**), *N*-Boc (**9**, **14**, **16**, and **23**) or *N*-tosyl (**5**, **8**, **10**, **12**, **14**−**17**, and **20**) protected amines, amides (**22** and **23**), ethers (**7** and **17**), and halogens (**10**, **13**, **15**, **20**, **22**, and **23**) were tolerated under the reaction conditions. In addition, successful functionalization of fenbufen and indomethacin was achieved to afford

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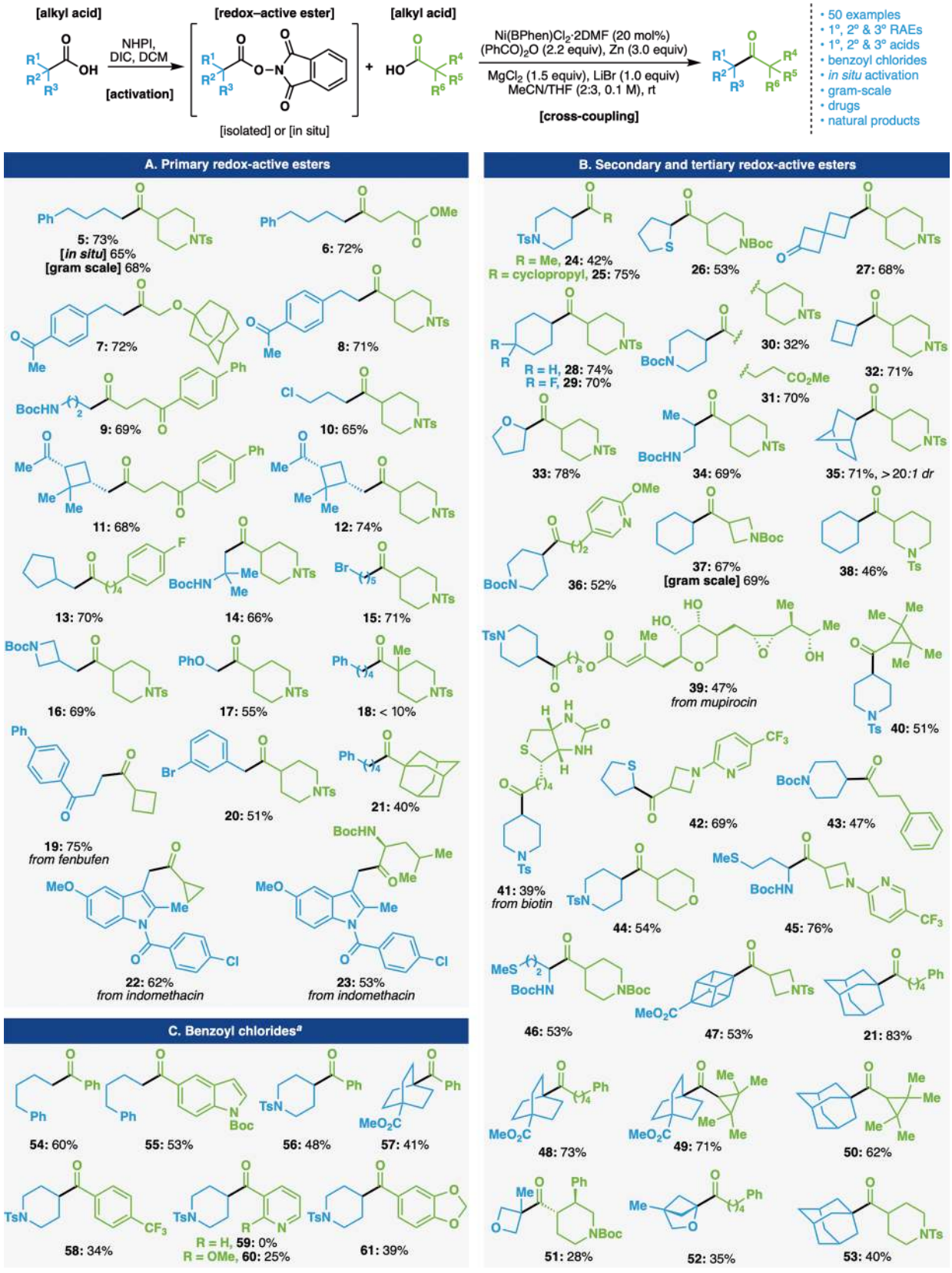
Table 1. Scope of the CCC Ketone Synthesis



[a]Using benzoyl chlorides (2.0 equiv) instead of [acid + $(PhCO)_2O$]. DIC = *N*, *N*′-diisopropylcarbodiimide. Yields of isolated products are indicated in each case. Standard reaction conditions: RAE (1.0 equiv), carboxylic acid (2.0 equiv), Ni(BPhen)Cl_2·2DMF (20 mol %), Zn (3.0 equiv), $(PhCO)_2O$ (2.2 equiv), $MgCl_2$ (1.5 equiv), LiBr (1.0 equiv), MeCN/THF (2:3, 0.1 M), rt, 3 h.

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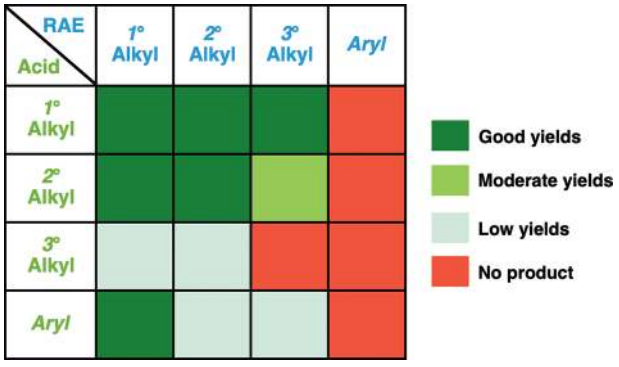
compounds **19**, **22**, and **23** in 75%, 62% and 53% yield, respectively. 2° and 3° RAEs were also coupled to a broad range of 1° (**21**, **24**, **31**, **36**, **39**, **41**, **43**, **48**, and **52**) and 2° (**25**−**30**, **32**−**35**, **37**, **38**, **40**, **42**, **44**−**47**, **49**−**51**, and **53**) carboxylic acids with similarly exceptional levels of chemoselectivity, including a diol, an epoxide, and a Michael acceptor found on mupirocin (**39**). Although bridged 3° carboxylic acids and RAEs were well tolerated, lower yields were observed in the case of exceedingly sterically encumbered moieties (**18**). It is worth noting that the diversification of biotin,[19] a highly polar and oft installed structure in chemical biology was also successful (**41**). Strikingly, almost 90% of the compounds illustrated in Table 1 have never been prepared before, thereby illustrating the capability CCC to access new chemical space. For example, the successful coupling of bridged compounds such as cubane **47** and 2-oxabicyclo[2.1.1]hexane **52** provides a versatile entry into these useful phenyl ring bioisosteres.[20] Pleasingly, the developed conditions were easily translated to gram scale experiments affording compounds **5** and **37** in 68% and 69%, respectively.

When attempting CCC on aryl carboxylic acids, minimal product formation was observed (see SI for optimization details). In this instance, modification of the coupling partner to acyl chlorides, as pioneered by Weix and Loren,[17] afforded the desired products in suitable yields (**54**−**58**, **60**, and **61**). Tolerance of protected indole, amine, and ester functionality was observed (**55**, **56**, and **57**, for example), although an ortho-methoxy group was required in the case of a pyridine-based substrate (**59** and **60**).

The range of conceivable coupling partners in CCC is vast and thus from a practitioner's perspective it may not be intuitive as to which acids serve the role of electrophile/nucleophile. For instance, substrate **21** can be prepared in either fashion (see SI for additional examples). Thus, Table 2 presents a convenient user guide for CCC based on the 16 possible combinations of cross coupling based on empirical findings. For example, in the case of 1° and 2° couplings, the starting acids can be used in either form (free acid or RAE) whereas benzoyl chlorides are best employed as the free carboxylic acid component in all couplings. Returning to the original inspiration for the development of this method, Figure 4 outlines a series of applications that serve to simplify synthesis. As depicted in Figure 4A, building block **1**, previously prepared through an 8-step sequence relying on olefin functionalization,[18] could now be accessed in 3 steps commencing from tartrate-derived acid **62**. Subjecting this acid to CCC using commercial lactate-derived acid **63** delivered **1** in 52% yield as a single stereoisomer. It should be noted that in the CCC stereoselectivity of the RAE fragment is usually eroded via the planar radical intermediate, however in this case selectivity is guided by the conformation of the starting material. In a similar vein, muscone **64**, a widely employed fragrance additive, has previously been prepared through RCM/hydrogenation of diene **65**.[21] The preparation of this simple ketone commences from a relatively expensive alcohol **66** (by fragrance industry standards) and employs three reactions to generate one new C−C bond with the correct ketone oxidation state. In contrast, 10-undecenoic acid **67** is roughly an order of magnitude less expensive and can be smoothly converted to the same building block **65** in 68% yield upon CCC with citronellic acid **68**. This 1-step process avoids halide waste, water-sensitive Grignard reagents, and excess chromium waste (employed solely for the purpose of alcohol oxidation). The experimental simplicity of this method makes it perfectly suited to a parallel library synthesis workflow. Thus, a curated set of diverse building blocks from the Pfizer collection were chosen and subjected to ketone synthesis using 1-cyclopentane carboxylic acid-derived NHPI ester **69**. All reagents, with the exception of zinc, were added as stock solutions to facilitate parallel execution in plate format. HPLC analysis indicated that 19 of the 20 substrates (**70**−**89**) successfully underwent CCC, while 17 provided sufficient material after isolation (>1.0 mg) for submission to standard bioactivity assays. Compound **81** was not isolated presumably due to the basic work up procedure used to facilitate isolation. The resulting ketones possess drug-like properties, conforming with Lipinski's "rule of five" (mean molecular weight 371, mean ClogP 4.4, mean hydrogen bond acceptor count 2.5) and include a range of common heterocycles.[22] This protocol is particularly well-suited for fragment-based drug discovery (FBDD),[23] or as a diversity incorporating event in multistep parallel library construction (e.g., with subsequent reductive amination).

Table 2. An Empirically Derived User Guide for CCC



■ ASYMMETRIC SYNTHESIS OF BENZYLIC AMINES

Compelled by ongoing medicinal chemistry projects at Pfizer, attention then turned to how the putatively nucleophilic species generated from RAEs under Ni catalysis could be engaged by other electrophilic species such as imines.[24] Prior studies from our laboratories (Figure 5A) focused on the synthesis of enantiopure amino acids using the glyoxyl-derived chiral sulfinyl imine reagent **90**.[11n] That chemistry exhibits remarkable substrate scope and utilizes a TCNHPI-based RAE in concert with an inexpensive reducing agent (Zn) and catalyst [$Ni(OAc)_2 \cdot 4H_2O$]. Translation of those exact conditions using the less electrophilic aryl sulfinyl imines in order to generate enantiopure benzylic amines furnished only trace product (Figure 5B, entry 1). Thus, a thorough re-examination of conditions was pursued culminating in the identification of a mild and robust set of conditions (entry 3). Three key modifications relative to prior studies were an increased concentration (0.2 vs 1.0 M, entry 10), use of NHPI instead of TCNHPI as the RAE (entry 6) and a more reactive reducing agent (standard zinc powder vs zinc nanopowder, entry 8). This unique form of zinc, available from Sigma-Aldrich, was also found to be critical in radical couplings in DNA-encoded library synthesis.[11k] Similar to ketone synthesis via CCC, the reaction tolerates air/moisture (entry 4) and the RAE can be made *in situ* to enable parallel synthesis endeavors (entry 5). Attempts to utilize the corresponding Ellman imine

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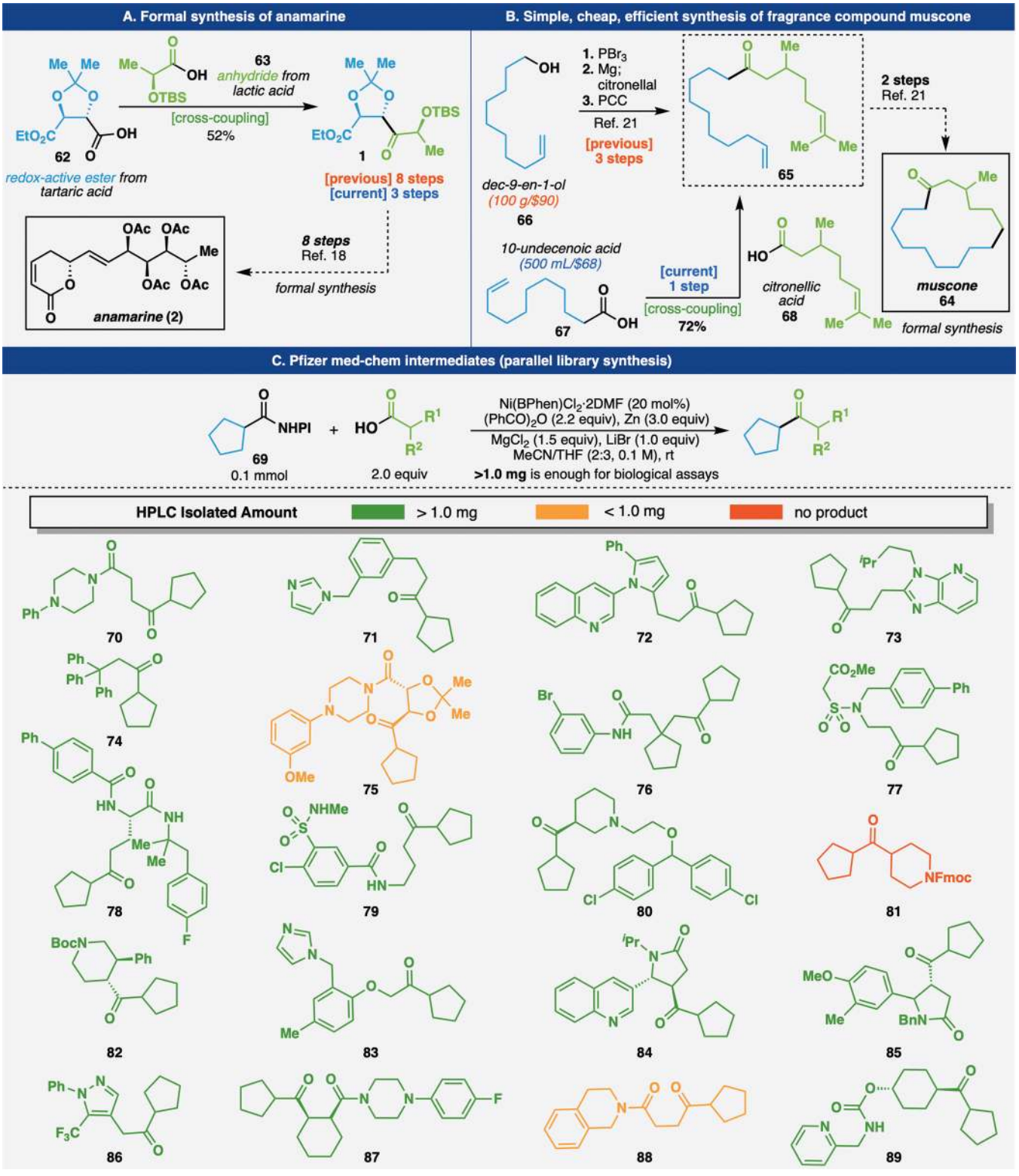

Figure 4. Applications of CCC to the formal synthesis of anamarine (A) and muscone (B), and parallel library synthesis (C). NHPI = *N*-hydroxyphthalimide.

(R = ^{t}Bu) failed due to competitive reduction of the sulfinimine (entry 2). Interestingly, unlike previous studies, where low yields of product were observed in the absence of Ni catalyst, the current reaction completely shuts down without it (with nearly quantitative imine recovery, entry 7).

With this new set of conditions in hand a range of 1°, 2°, and 3° carboxylic acids could be coupled with imine **92** via the corresponding RAE to rapidly provide a range of chiral benzylic amines in good yield and high dr (Table 3). Ethers (**95** and **104**), esters (**98**−**100** and **103**), Boc- and Ts-protected amines (**93**, **96**, **101**, **102**, **105** and **106**), pyridines

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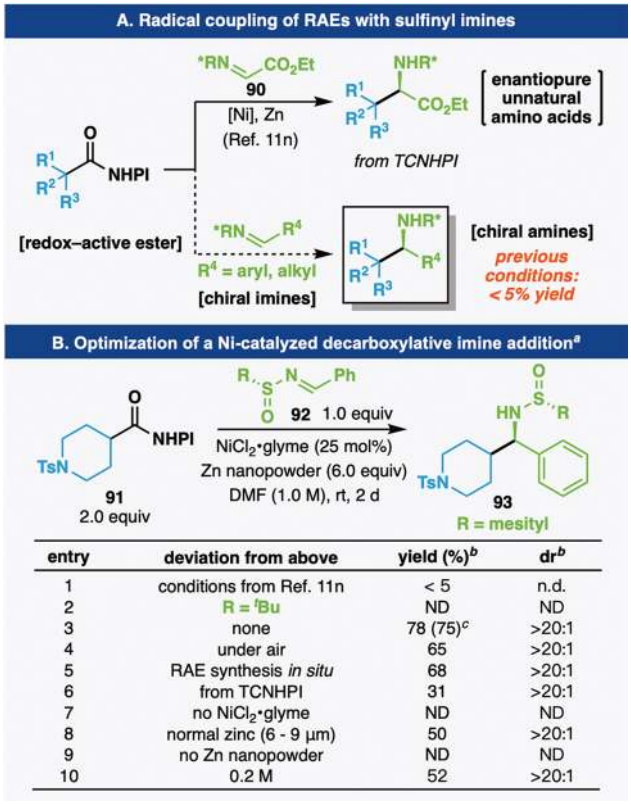
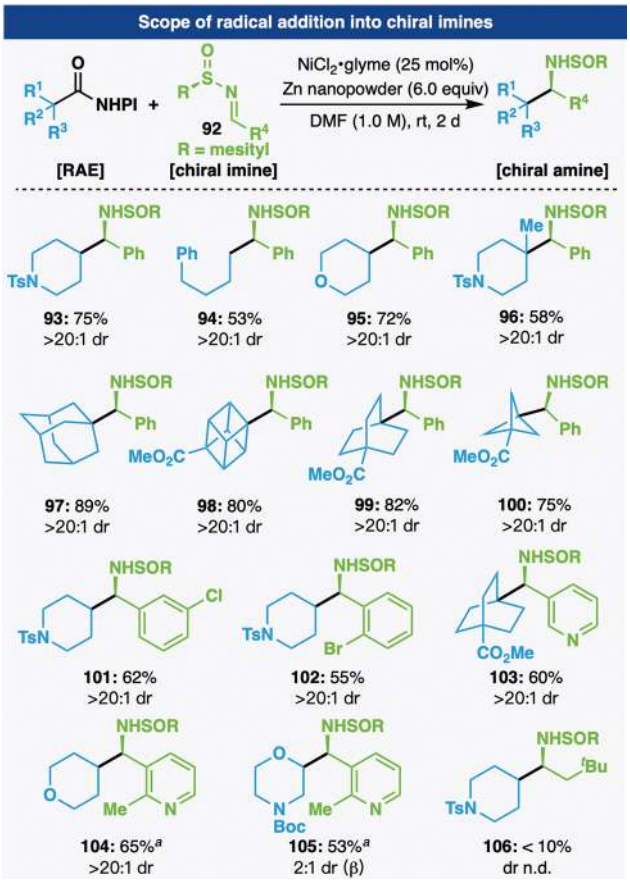


entry	deviation from above	yield (%)[b]	dr[b]
1	conditions from Ref. 11n	< 5	n.d.
2	R = ^{t}Bu	ND	ND
3	none	78 (75)[c]	>20:1
4	under air	65	>20:1
5	RAE synthesis *in situ*	68	>20:1
6	from TCNHPI	31	>20:1
7	no $NiCl_2$·glyme	ND	ND
8	normal zinc (6 - 9 μm)	50	>20:1
9	no Zn nanopowder	ND	ND
10	0.2 M	52	>20:1

Figure 5. (A) Synthesis of amines from RAEs previously limited to amino acid synthesis and (B) an alternative protocol to access benzylic amines. [a] 0.1 mmol, Zn nanopowder: 40-60 nm particle size. Aldrich catalog no. 578002. [b] Yield and dr determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield. See Supporting Information for details. NHPI = *N*-hydroxyphthalimide, TCNHPI = *N*-hydroxytetrachlorophthalimide, ND = not detected, n.d. = not determined.

Table 3. Scope of the Radical Addition into Chiral Imines



[a]See SI for reaction conditions. Standard reaction conditions: RAE (2.0 equiv), sulfinimine (1.0 equiv), $NiCl_2$·glyme (25 mol%), Zn nanopowder (6.0 equiv), DMF (1.0 M), rt, 2 d. NHPI = *N*-hydroxyphthalimide.

(**103**−**105**), and aryl halides (**101** and **102**) were all tolerated. Of the substrates screened, the most rapid and high yielding reactions involved bridgehead RAEs (**97**−**100**, and **103**) presumably due to the increased stability and nucleophilicity of the putative radical intermediates. A notable limitation of this work is that alkyl sulfinyl imines are not viable coupling partners. The majority of products in Table 3 are novel (including their deprotected analogs). In the case of substrate **93**, the deprotected racemic amine is expensive (from Sigma-Aldrich, ca. $1/mg).[25] The deprotected analog of **94** has been prepared in racemic form during the search for new kinase inhibitors by way of isonipecotic acid through a classical 3-step sequence (Weinreb amide, Grignard, reductive amination).[26]

EXTENDING THE SCOPE OF NUCLEOPHILIC RAE CHEMISTRY: ALKYL NHK REACTIVITY

The addition of standard 2e$^-$-based nucleophiles to aldehydes is often beleaguered with competing enolization/polymerization problems (Figure 6A). The alkyl Nozaki−Hiyama−Kishi (NHK) reaction provides a viable solution to this issue but still requires an alkyl halide precursor.[27] Shenvi and coworkers recently reported an impressive departure from this requirement by utilizing olefin-derived radicals in a HAT/Cr system to deliver branched products from terminal olefins.[28] At this juncture it is now self-evident that RAEs represent viable surrogates for alkyl halides in a myriad of different reactions under Ni-, Fe-, Co-, Cu-, Ru-, Pd-, and Ir-based catalysis.[29] The use of alkyl halides in the classic NHK reaction is rare, and within the theme of utilizing RAEs to add to C═X bonds, this seemed like a useful reaction to explore (Figure 6A).[30] Access to such reactivity via RAEs versus olefins could provide a complementary solution to give linear rather than branched products.

The execution of a RAE-based alkyl NHK was straightforward and optimized conditions simply involved the addition of RAE to aldehyde in the presence of $CrCl_2$ and TMSCl (Figure 6B). This is exemplified using model RAE **4** and aldehyde **107** to deliver TMS-protected alcohol **108** in 79% isolated yield. Although the RAE could be generated *in situ* to give a similar yield (entry 2), the reaction is sensitive to air (entry 3) and should be conducted using an Ar or N_2 balloon. NHPI is the preferred RAE (entry 4) and Cr is clearly essential for the reaction (entry 5). The free alcohol could also be obtained in the absence of TMSCl, albeit in diminished yield (entry 6).[31] Unlike the original alkyl NHK using alkyl halides, low-valent transition metal mediators such as CoPc or Ni have no effect on conversion (entries 7 and 8).[30] However, excess Cr is still required (2.0 equiv leads to diminished yield, entry 9). Although reversing the stoichiometry of substrates had no effect, a lower yield was observed with 1 equiv of RAE (entries 10 and 11). The RAE-based alkyl NHK has admirable scope (Table 4) with regard to functional group compatibility

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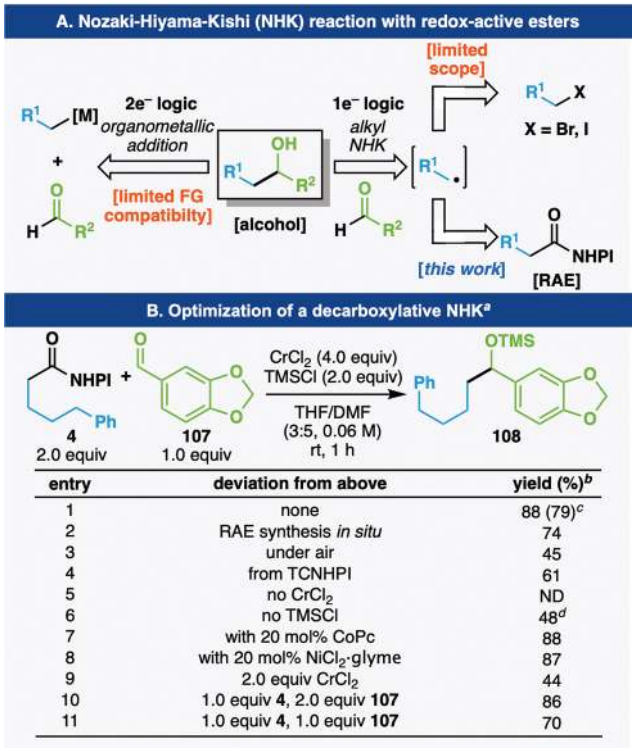


entry	deviation from above	yield (%)[b]
1	none	88 (79)[c]
2	RAE synthesis *in situ*	74
3	under air	45
4	from TCNHPI	61
5	no $CrCl_2$	ND
6	no TMSCl	48[d]
7	with 20 mol% CoPc	88
8	with 20 mol% $NiCl_2$·glyme	87
9	2.0 equiv $CrCl_2$	44
10	1.0 equiv **4**, 2.0 equiv **107**	86
11	1.0 equiv **4**, 1.0 equiv **107**	70

Figure 6. (A) Alcohol synthesis through conventional and radical means and (B) the development of an alkyl-NHK reaction employing RAEs. [a] 0.1 mmol. [b] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield. See Supporting Information for details. [d] Isolated yield of the corresponding alcohol. NHPI = *N*-hydroxyphthalimide, TCNHPI = *N*-hydroxytetrachlorophthalimide, ND = not detected.

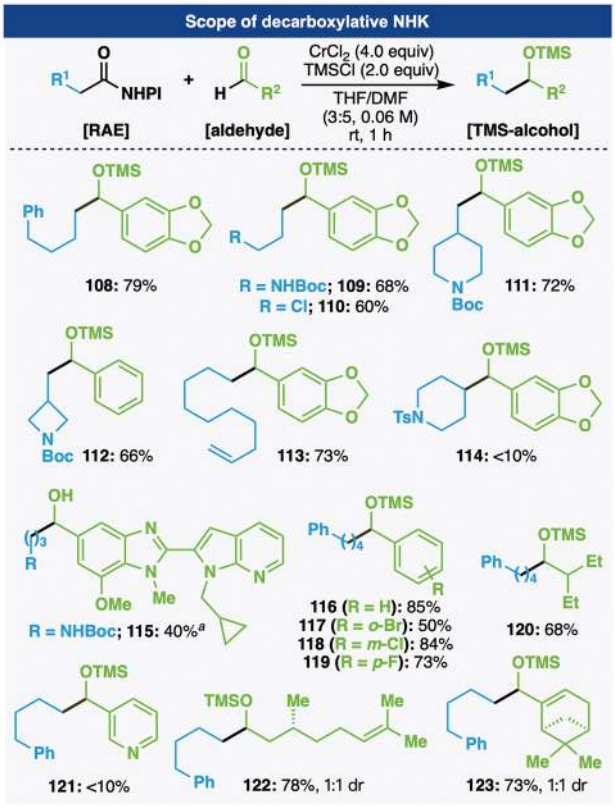
tolerating *N*-Boc-protected amines (**109**, **111**, **112**, and **115**), halogens (**110** and **117**−**119**), and alkenes (**113** and **122**). Heterocyclic motifs such as azaindole and benzimidazole were also tolerated under the reaction conditions and compound **115** was afforded in 40% yield. Moreover, it is worth noting that selective addition at the 1,2 position was observed in the case of enone compound **123**. However, only primary RAEs provide synthetically useful yields thus mirroring the historic limitations of alkyl-halide based NHK. In addition, pyridine-containing building blocks did not afford synthetically useful yields (**121**).

MECHANISTIC INQUIRY

The synthetic utility of RAEs to function as nucleophilic (Grignard-like) reagents for the addition to C═X bonds presents an exciting opportunity to interrogate this unique chemical reactivity. For this purpose, the CCC described above was chosen for in-depth study.[32] Figure 7A outlines the complete mechanistic picture of this transformation supported by kinetics, radical-clock studies, UV spectroscopy, isotopic labeling, and byproduct analysis.[33]

A catalytic cycle that is fully consistent with the data (Figure 7A, see high level summary) consists of initial oxidative addition by the electrophilically activated (anhydride or acyl chloride) carboxy group (R_1-CO_2H) to a ^{t}Bubpy-ligated Ni(0) species **I**. Here, $MgCl_2$ serves to facilitate the formation of a mixed anhydride species as verified in control studies outlined in inset A.[34] The critical oxidative addition step occurs rapidly to furnish acyl-bound Ni(II)-carboxylate species **II**. Indeed,

Table 4. Scope of the Alkyl NHK Reactions with RAEs



[a]See SI for reaction conditions. Standard reaction conditions: RAE (2.0 equiv), aldehydes (1.0 equiv), $CrCl_2$ (4.0 equiv), TMSCl (2.0 equiv), THF/DMF (3:5, 0.06 M), rt, 1 h. TMS = trimethylsilyl. NHPI = *N*-hydroxyphthalimide.

zero-order kinetics in acid/anhydride were measured, as evidenced in the kinetic orders, Figure 7. Selective insertion by **I** into the desired C−O bond is likely dictated by electronics, wherein the electron-rich alkyl component better stabilizes electron-deficient Ni(II) species **II**.[35] This step was confirmed through the discrete preparation of Ni(0) complex **I** (see insets B and C) and exposure to either a symmetrical anhydride or acyl chloride which both resulted in near instantaneous oxidative addition to complexes **II** and **III**, respectively.[36] Subsequent ligand exchange (carboxylate for chloride) then occurs as supported by UV−vis spectroscopy wherein the addition of $MgCl_2$ appears to convert **II** to **III**.[37] It is also important to note that control studies with complex **I** and the RAE **127** lead to radical-based decomposition pathways rather than OA products (see SI). Competition experiments between RAE **127** and acyl chloride in the presence of complex **I** show complete consumption of the acyl chloride to the OA complex **III** (see SI). As aided by the persistent radical effect,[38] complex **III** captures a radical derived from the RAE (R^2-CONHPI) to deliver Ni(III) intermediate **IV** that undergoes rapid reductive elimination to provide the ketone product and Ni(I) complex **V**.[39] The observation of small amounts of dimerized and decarboxylated byproducts from the RAE indicates that transient radical $R^{2\bullet}$ is captured by persistent metalloradical complex **III** (see "Byproduct analysis", Figure 7A and SI). Support for these two steps stems from the direct reaction of either complex **II** or **III** with RAE **127** (insets D and E). Presumably due to the

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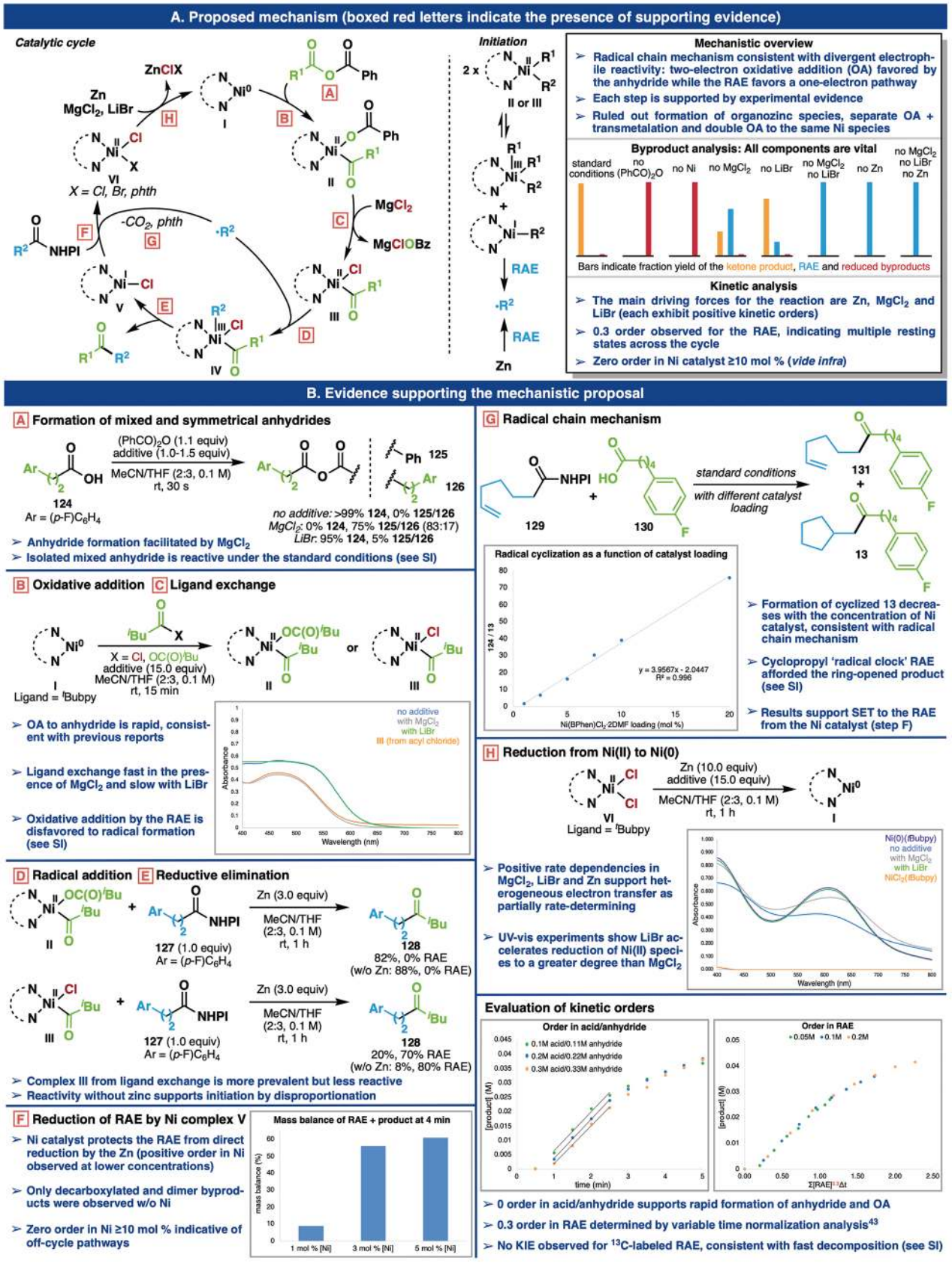

Figure 7. CCC: complete mechanistic picture and supporting experiments. phth = phthalimide.

differences in disproportionation rates for **II** and **III**, carboxylate complex **II** does not require the presence of a reductant whereas chloride complex **III** does (see "Initiation", Figure 7A).[40] Thus, either complex may exist in the reaction mixture and both of them can participate in the catalytic cycle. The Ni(I) complex **V** produced can then engage another

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molecule of RAE to perpetuate the cycle and generate Ni(II) species **VI**.[41] Alternative pathways to RAE decomposition (to produce $R^{2\bullet}$) can be rationalized through disproportionation or via a Ni/Zn-mediated process (see "Initiation", Figure 7A).[42] To deconvolute the role of Ni and Zn in the reductive cleavage of RAEs, the kinetics of this step were studied (inset F). Strikingly, if a RAE is exposed to standard reaction conditions in the absence of Ni, it undergoes rapid decomposition to a mixture of dimerized and decarboxylated products without any ketone product (see "Byproduct analysis", Figure 7A and the SI for the kinetic profile). The chart in inset F illustrates the "buffering" effect of Ni to slow down Zn-induced RAE consumption and increase product formation as the catalyst loading is increased. This creates a complex kinetic picture with slight positive orders in Ni at low catalyst loading and saturation kinetics observed at higher loadings (>10%) possibly indicative of off-cycle pathways. These data, combined with that mentioned in insets D and E, support a Ni-based pathway for radical formation from the RAE. A positive kinetic order of 0.3 in the concentration of RAE is observed, suggesting it is involved in one of multiple rate-determining in this complex mechanistic pathway (see "Evaluation of kinetic orders", Figure 7B).[43]

The key evidence for a radical chain pathway came from analysis of the extent of cyclization upon exposure of RAE **129** and acid **130** to the standard reaction conditions (see inset G).[44] The direct linear relationship between concentration of nickel catalyst and the ratio of **131** to **13** forges a mechanistic picture that is consistent with radical formation from complex **V**, diffusion of $R^{2\bullet}$ out of the solvent cage (wherein cyclization is proposed to occur) before capture by complex **III**.[7d] The addition of more Ni catalyst to the reaction mixture shortens the lifetime of the radical in solution resulting in diminished cyclization. Ni(II)-species **VI** is then reduced by Zn to afford complex **I** and complete the cycle. The observation of positive kinetic orders in Zn, $MgCl_2$, LiBr indicate this step may be partially rate determining and supports the crucial role that is experimentally observed for the additives (see SI for complete kinetic analysis). Indeed, a complete shutdown of reactivity occurs in the absence of Zn or both $MgCl_2$ and LiBr (see "Byproduct analysis", Figure 7A and SI). To evaluate the effects of each additive on the reduction from complex **VI** to complex **I**, a solution of $NiCl_2$(^{t}Bubpy) (inset H, orange line) was stirred in the presence of Zn for an hour. The UV spectra (inset H, blue line) clearly demonstrate formation of Ni(0)(^{t}Bubpy) complex **I** (inset H, purple line). However, addition of $MgCl_2$ (inset H, gray line) or LiBr (inset H, green line) accelerated the reduction from Ni(II) to Ni(0), LiBr to a greater extent. Thus, $MgCl_2$ serves a triple role in facilitating anhydride formation (as a Lewis acid), ligand exchange (via salt metathesis), and Ni reduction.

To summarize, although the mechanistic picture outlined above is complex, each elementary step is supported, and the role of each essential additive is justified. The studies outlined above help in rationalizing the empirically generated user guide in Table 2 (*vide supra*) and should aid in the troubleshooting of difficult couplings or the large-scale implementation of CCC.

CONCLUSION

Barton's pioneering studies taught the community that there is much value in using carboxylic acids as precursors to a realm of new chemical space via C−C breaking radical fragmentations rather than simple dehydrations (to make amides or esters). Barton esters,[9c] Okada's NHPI esters,[11a,b] and other RAEs (e.g., TCNHPI, -OAt, or -OBt) as well as redox-active pyridiniums[45] and sulfones[46] all provide a useful way of breaking bonds in order to modularly install new ones in a versatile way. This study centered on the use of RAEs to access products that have heretofore resided within the scope of two-electron retrosynthetic disconnections. In accessing common functional groups like ketones, alcohols, and amines, students are generally taught that polar bond analysis should lead to nucleophilic and electrophilic starting materials. Implementing radical retrosynthetic logic to the same targets results in the use of RAEs in an unusual way. Thus, these three functional groups can now be accessed commencing from readily available carboxylic acids via RAEs (which become the "nucleophilic" component) with mixed anhydrides, acyl halides, imines, or aldehydes (the canonical electrophilic component). Although certain limitations were encountered (Figure 8), these mild methods offer enhanced scope and orthogonal access to the same functionality previously accessed through two-electron chemistry and are amenable to parallel synthesis. In some cases, the enabled reactivity permits access to disconnections completely unavailable to the two-electron world (i.e., Figure 4).

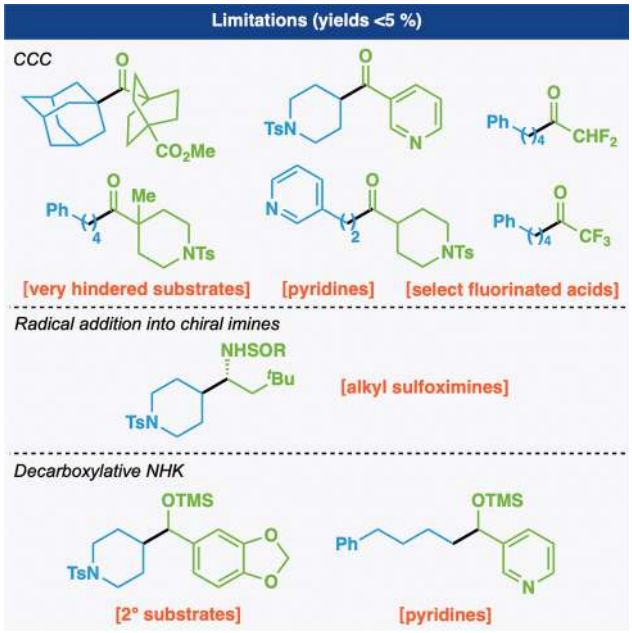

Figure 8. Limitations of the described methodologies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b02238.

Detailed experimental procedures and analytical data (PDF)

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Authors for this paper from independent organizations have all collaborated with the Baran lab independently on this work but are not collaborating with one another.

Notes

The authors declare no competing financial interest.

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NOTE ADDED AFTER ASAP PUBLICATION

Due to a production error, Table 4 was misrepresented in the version published on April 16, 2019 and has been corrected. Associated compound numbers in the text have been adjusted accordingly; this reposted on April 24, 2019.

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