

Nickel-Catalyzed Decarboxylative Coupling of Redox-Active Esters with Aliphatic Aldehydes

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ABSTRACT: The addition of alkyl fragments to aliphatic aldehydes is a highly desirable transformation for fragment couplings, yet existing methods come with operational challenges related to the basicity and instability of the nucleophilic reagents commonly employed. We report herein that nickel catalysis using a readily available bioxazoline (BiOx) ligand can catalyze the reductive coupling of redox-active esters with aliphatic aldehydes using zinc metal as the reducing agent to deliver silyl-protected secondary alcohols. This protocol is operationally simple, proceeds under mild conditions, and tolerates a variety of functional groups. Initial mechanistic studies suggest a radical chain pathway. Additionally, alkyl tosylates and epoxides are suitable alkyl precursors to this transformation providing a versatile suite of catalytic reactions for the functionalization of aliphatic aldehydes.

Cross-coupling reactions have revolutionized the landscape of carbon–carbon bond construction, with extensive application in the synthesis of natural products, pharmaceuticals, agrochemicals, and functionalized polymers.¹ Coupling of Grignard or organolithium reagents with carbonyl compounds remains among the most frequently used synthetic reactions (Figure 1A),² although limitations exist due to the instability, basicity, and lack of functional group compatibility of the requisite highly nucleophilic reagents. Barbier-type reactions³ and Nozaki-Hiyama-Kishi (NHK)⁴ couplings are attractive as they avoid the handling of air- and moisture-sensitive organometallic reagents, and have been employed in many complex settings,⁵ although the reaction scope is often limited in cases where sp^3 alkyl fragments are added to aliphatic enolizable aldehydes.

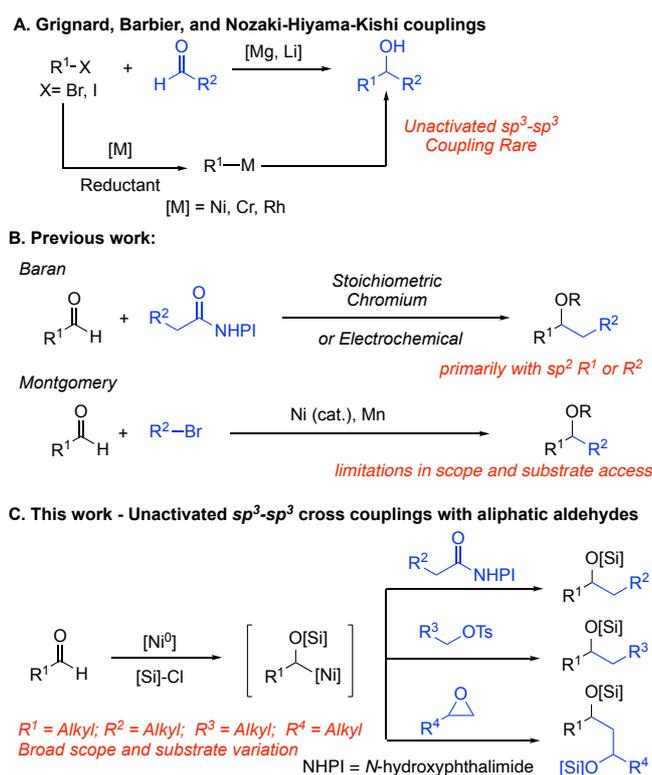
An attractive approach to deliver organohalide feedstocks to carbonyl compounds that obviates the need for preformed organometallic reagents are transition-metal-catalyzed reductive coupling reactions.⁶ To date, the coupling of aldehydes with organohalides using a stoichiometric reducing agent can be catalyzed by Cr,⁷ Rh,⁸ Co,⁹ and Ni,¹⁰ but current systems are often restricted to aryl, allylic or propargylic halides and aromatic aldehydes. The catalytic transformation of aliphatic aldehydes with less-activated sp^3 counterparts remains a synthetic challenge.^{7c-e,11} Aliphatic aldehydes often exhibit attenuated reactivity, and competing enolization reactions lead to side product formation.^{10d} Additionally, compared with sp^2 -hybridized halides, unactivated alkyl halides are less suitable coupling partners due to lower reactivity and undesirable side pathways such as homocoupling or competing β -H eliminations of reactive intermediates.¹²

The wide availability of alkyl carboxylic acids makes this substrate class an attractive coupling partner for processes of this type.¹³ In recent studies, Baran, Weix, and others have extensively explored the utility of redox-active esters (RAEs), as a carboxylic acid-derived radical precursors in a variety of carbon–carbon and carbon–heteroatom bond forming reactions.¹⁴ While the specific combination of aliphatic, enolizable aldehydes with sp^3 alkyl fragments are largely excluded from

past work, Reisman, Blackmond, and Baran recently reported an attractive electrochemical Cr-catalyzed cross-coupling of aldehydes with redox-active esters including two examples of this combination with primary RAEs (Figure 1B),^{11b} but no general approach to the catalytic union of aliphatic aldehydes with simple sp^3 alkyl fragments has been described.

In order to address this gap in the field, our lab recently described a catalytic process involving the reductive coupling of aliphatic aldehydes with alkyl bromides in a pathway proposed to proceed through the intermediacy of α -silyloxyalkylnickel intermediates derived from aldehydes, silyl chlorides, and low-valent nickel (Figure 1B).¹⁵ In order to address limitations of that protocol, including substrate access, scope, and yield, we have now explored the utility of more broadly available substrate classes in catalytic couplings with aliphatic aldehydes (Figure 1C). The main focus of this study is the coupling of aliphatic aldehydes with redox-active esters, providing access to numerous product types derived from simple carboxylic acid precursors. Additionally, preliminary examples of reductive couplings between aldehydes and alkyl tosylates or epoxides^{14w,16} are described. This combination of procedures provides strategies where alkyl fragments are derived from carboxylic acids, alcohols, or alkenes, thus greatly expanding the range of precursors available for aldehyde functionalization processes.

Figure 1. Background and focus of this work.



Our initial investigation geared towards developing the catalytic reductive coupling of aldehydes **1a** with the *N*-hydroxyphthalimide (NHPI) ester **2a** (Table 1). Systematic investigation of the reaction parameters showed that the desired product **3a** was isolated in good yield (91%) with a combination of $Ni(cod)_2$ and bioxazoline (BiOx). Control experiments indicated that a nickel catalyst was necessary for the reaction to proceed, and other nickel sources only led to moderate yield (entries 2, 11 and 12). The ligand (BiOx), reductant (nanopower Zn), 1,5-hexadiene and LiCl also

played a crucial role in successful transformation (entries 3-6). A ligand screen revealed that BiOx is uniquely effective when compared with other common ligands (entries 13-15). Of note, olefin additives can dramatically improve the efficiency, with 1,5-hexadiene proving the most effective (entries 5, 8-10). Furthermore, the particle size of Zn is critical, with the use of nanopowder Zn (40-60 nm) enhancing the yield (entry 7).

Table 1. Optimization of Reaction Conditions

entry	deviation from standard conditions	yield (%) ^a
1	none	94(91)
2	no Ni(cod) ₂	N.R.
3	no Biox	12
4	no Nanopowder Zn	17
5	no 1,5-hexadiene	17
6	no LiCl	31
7	Zn instead of Nanopowder Zn	71
8	1-octene instead of 1,5-hexadiene	83
9	1,7-octadiene instead of 1,5-hexadiene	70
10	(<i>E</i>)-Stibene instead of 1,5-hexadiene	25
11	NiBr ₂ dme instead of Ni(cod) ₂	54
12	NiCl ₂ dme instead of Ni(cod) ₂	47
13	Bpy instead of Biox	13
14	Terpy instead of Biox	0
15	PCy ₃ instead of Biox	0
16	30 min	94

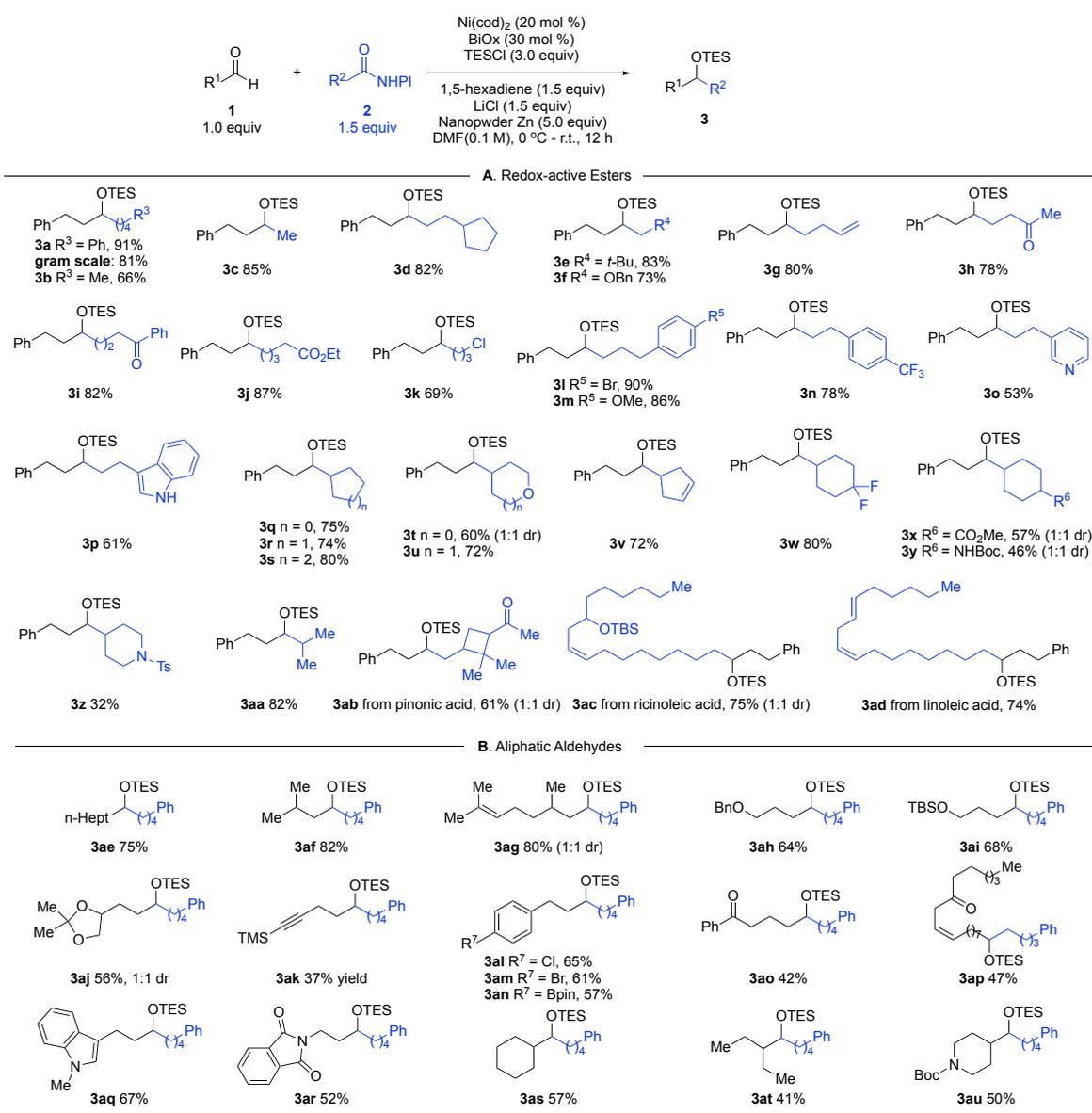
^aYields were determined by GC with *n*-tridecane as the internal standard. Isolated yield is given in parentheses (0.2 mmol scale). Diastereomeric ratios were determined by ¹H NMR analysis. TES = triethylsilyl.

With optimal conditions in hand, we sought to define the reaction scope (Table 2A). Various 1° and 2° carboxylic acids were converted to the corresponding NHPI-esters and coupled efficiently with aldehyde **1a**. A range of functional groups were well tolerated including ketones (**3h**, **3i**, **3ab**), esters (**3j**, **3x**), N-Boc (**3y**), N-tosyl (**3z**), and alkenes (**3g**, **3v**, **3ac**, **3ad**). A simple methyl group can also be added effectively using the RAE **3c** derived from acetic acid. Notably, some potentially reactive functional groups, including alkyl chloride **3k** and aryl bromide **3l** were left intact under current conditions, offering opportunities for subsequent cross-coupling. Protected alcohols (**3f**, **3ac**) and ethers (**3m**, **3t**, **3u**) were also competent coupling partners, allowing for the construction of polyol motifs. Moreover, heterocycles including pyridine (**3o**), and indole (**3p**) were also readily accommodated as were a series of secondary redox-active esters (**3q-3z**). The protocol was scalable to 5 mmol, obtaining the desired product **3a** in 81% isolated yield.

After defining the scope of RAEs, attention then turned to the scope of the aliphatic aldehyde

component (Table 2B). Sterically encumbered aldehydes with β -branching, such as isovaleraldehyde (**3af**) and citronellal (**3ag**) were competent coupling partners. α -Branched aldehydes (**3as-3au**) also delivered the desired products without diminished efficiency. Benzyl ethers (**3ah**), silyl ethers (**3ai**), acetals (**3aj**), alkynes (**3ak**), and phthalimide groups (**3ar**) were also tolerated. Substrates with functional groups known to engage in transition-metal-catalyzed transformations such as aryl chlorides (**3al**), aryl bromides (**3am**) and aryl boronate esters (**3an**), delivered the desired product smoothly without competing reactivity. Notably, heterocycle substrates, such as indole (**3aq**), was likewise suitable for this chemistry. The scope and chemoselectivity of this method in activating aldehydes in the presence of a wide array of reactive functional groups including ketones is thus quite broad, addressing an important limitation of classical methods for carbonyl additions.

Table 2. Scope of Catalytic Couplings of Aldehydes and Redox-active Esters.^a

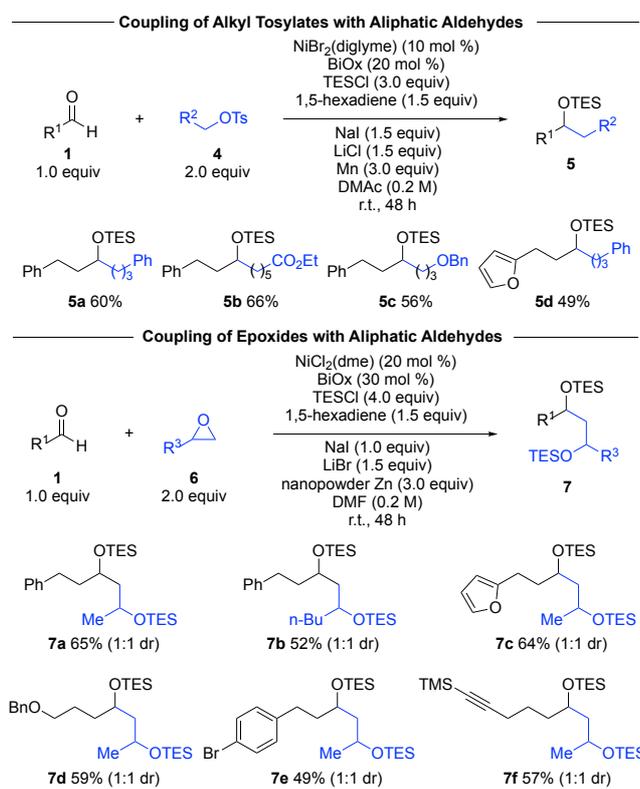


^aReactions run on 0.20 mmol scale unless otherwise noted. Yields are for isolated material. Diastereomeric ratios were determined by ¹H NMR analysis. TES = triethylsilyl. Ts = *p*-toluenesulfonyl.

While this method demonstrates considerable scope with carboxylic acid-derived RAEs, we considered that utilizing alkyl precursors derived from simple alcohols and alkenes would further extend the utility and scope of the strategy (Table 3). To enable the use of alcohol precursors, we explored the use of alkyl tosylates as the coupling partner.¹⁷ With simple modification of the reaction conditions (see SI), our catalytic system can activate the C-O bond of tosylates, delivering the desired product in good yield (Table 3) with attractive functional group compatibility including esters (**5b**), ethers (**5c**), and furans (**5d**).

With an eye towards utilizing alkene feedstocks, we then considered the use of epoxides as the alkyl precursor (Table 3).¹⁸ After extensive investigation of reaction parameters (see SI), an effective method was realized, obtaining the desired silyl-protected 1,3-diols in good yield, tolerating a range of functional groups, such as furans (**7c**), ethers (**7d**), aryl bromides (**7e**), and alkynes (**7f**). This approach further diversifies the range of product types accessible by this method, with 1,3-diols being obtained in the epoxide-based procedure.¹⁹

Table 3. Catalytic Couplings of Aldehydes with Alkyl Tosylates or Epoxides.^a



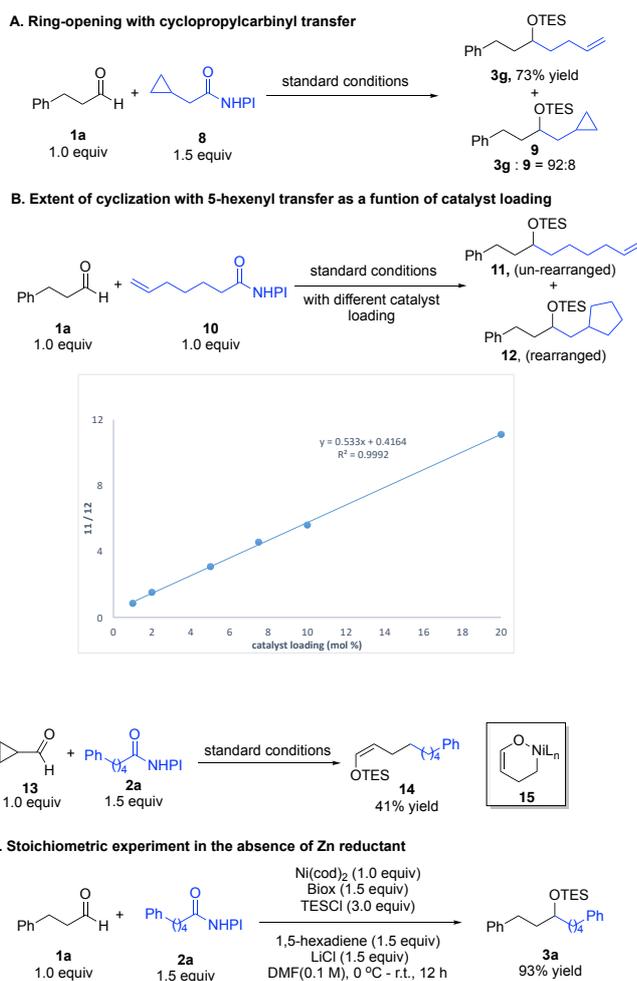
^aReactions run on 0.20 mmol scale unless otherwise noted. Yields are for isolated material.

Diastereomeric ratios were determined by ¹H NMR analysis. TES = triethylsilyl.

A cyclopropane-containing RAE **8** afforded a 92:8 ratio of ring-opened product **3g** and compound **9** with the cyclopropane ring intact (Figure 2A). Additionally, in an experiment involving hexenyl transfer, a direct linear dependence of the ratio of **11/12** on the catalyst loading was observed (Figure 2B). These experiments are consistent with a mechanism involving free-radical intermediates, in analogy to prior studies on nickel-catalyzed processes with both alkyl halides or

redox-active esters.^{14v,20} Similarly, ring opening was observed in couplings of cyclopropanecarboxaldehyde (**13**) leading to product **14** exclusively as the Z-isomer (Figure 2C). In this case, we attribute ring-opening of the cyclopropane unit to a nickel-catalyzed process involving the intermediacy of **15**, potentially involving the initial oxidative addition of a low-valent nickel species to the aldehyde, promoted by Et₃SiCl.^{15,21} An experiment employing stoichiometric Ni(cod)₂ but lacking the zinc reductant resulted in the formation of product **3a** in high yield, suggesting that key organonickel intermediates involved in product formation do not require reduction at the nickel center, but rather that the zinc reductant is involved in catalyst regeneration (Figure 2D).

Figure 2. Mechanistic Experiments



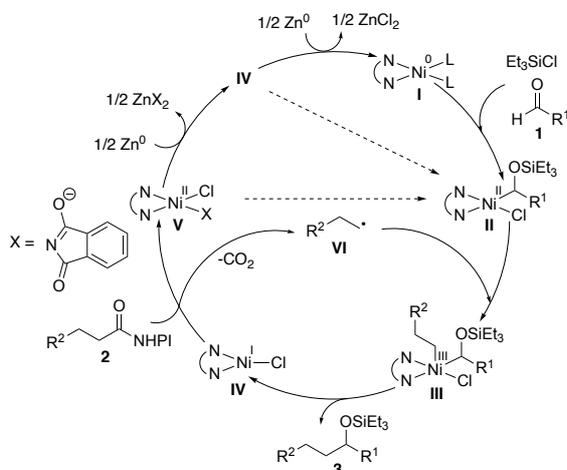
Based on these experiments and insights from prior studies, we propose a mechanistic picture consistent with the above findings (Figure 3). Oxidative addition of aldehyde **1** and silyl chloride to Ni(0) generates Ni(II) silyloxyalkyl complex **II**. Species related to **II** have been previously described,²² and our prior studies of aldehyde – alkyl halide couplings illustrated characteristic byproducts that are best explained by the involvement of **II**. Addition of free radical **VI** to **II** affords Ni(III) species **III**, which undergoes rapid reductive elimination to form product **3** and Ni(I) species **IV**. Combination of **IV** with the RAE **2** results in **V** and the free radical **VI** that recombines with species **II**. The above steps are consistent with the observation that Ni(0) undergoes product

formation in the absence of zinc, illustrating that reduction of intermediate **II** to the corresponding Ni(I) complex is not strictly required for turnover. Additionally, the above evidence (Figure 2A-B) for free radical intermediates derived from the RAE **2** are consistent with this proposed mechanistic pathway.

The conversion of Ni(II) complex **V** to the Ni(II) silyloxyalkyl nickel intermediate **II** requires a net two-electron reduction by zinc and oxidative addition of the aldehyde and silyl chloride. The commonly invoked reduction of nickel complex **V** to Ni(0) complex **I** completes the catalytic cycle, although this possibility must be viewed within the context of recent work from Diao that illustrates that Ni(II) BiOx complexes are more resistant to reduction compared with the corresponding Ni(II) complexes of other commonly employed pyridyl-based ligands.²³ The presence of the phthalimido substituent in **V** and the interaction of **V** with the aldehyde and silyl chloride may affect the facility of this reduction by nanopowder zinc. Given these complexities, the precise nature of the conversion of **V** to **II** will require further investigation.

The generation of free radical **VI** from RAE **2** is depicted (Figure 3) as involving Ni(I) species **IV** in analogy to studies from Baran in the coupling of anhydrides with redox-active esters.^{11a} The efficiency of product formation in the absence of zinc (Table 2D) illustrates that the nickel catalyst is competent in mediating the decomposition of redox-active esters. We observed that zinc and Et₃SiCl rapidly promotes the decomposition of RAE **2**, however, the presence of the nickel catalyst has a protective effect as previously described by Baran, slowing the rate of consumption of **2** compared to control experiments where the nickel catalyst is omitted (see SI). Recent studies from Rousseaux have provided evidence in reductive arylation reactions that TMSCl and Zn promote the formation of free radicals.²⁴ Our studies, which potentially involve effects of the silyl chloride in several steps including aldehyde activation and/or redox-active ester decomposition, have not clearly elucidated the active agent in mediating radical formation from the redox-active ester. Finally, the role of 1,5-hexadiene is not illustrated in the mechanistic scheme since the 4- and 5-coordinate complexes **II** and **III** cannot accommodate the bidentate coordination of this additive. Coordination of this additive likely prevents catalyst decomposition and/or inhibits competing side reactions that lie off the productive catalytic pathway.

Figure 3. Proposed Mechanism



In conclusion, a highly effective decarboxylative alkylation of aliphatic aldehydes with redox-

active esters has been developed. The procedure is broad in scope, tolerant of a wide array of functional groups, high-yielding, experimentally simple, and scalable. This process was extended to include the reductive cross-coupling of alkyl tosylates or epoxides with aliphatic aldehydes, thus providing a broad range of precursors derived from carboxylic acids, alcohols, or alkenes. Preliminary mechanistic experiments on this aldehyde – redox-active ester coupling are consistent with initial aldehyde activation to produce α -silyloxyalkylnickel species as a key intermediate that is captured by free radicals generated from the redox-active ester. Future work will include efforts to further study the mechanism of these transformation and expand the scope in increasingly complex applications.

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