Nickel-Catalyzed Defluorinative Coupling of Aliphatic Aldehydes with Trifluoromethyl Styrenes

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Abstract: A simple procedure is reported for the nickel-catalyzed defluorinative alkylation of unactivated aliphatic aldehydes. The process involves the catalytic reductive union of trifluoromethyl styrenes with aldehydes using a nickel complex of a 6,6'-disubstituted bipyridine ligand with zinc metal as the terminal reductant. The protocol is distinguished by its broad substrate scope, mild conditions, and simple catalytic setup. Reaction outcomes are consistent with the intermediacy of an α-silyloxy(alkyl)nickel intermediate generated by a low-valent nickel catalyst, silyl electrophile, and the aldehyde substrate. Mechanistic findings with cyclopropanecarboxaldehyde provide insights into nature of the reactive intermediates and illustrate fundamental reactivity differences that are governed by subtle changes in ligand and substrate structure.

INTRODUCTION

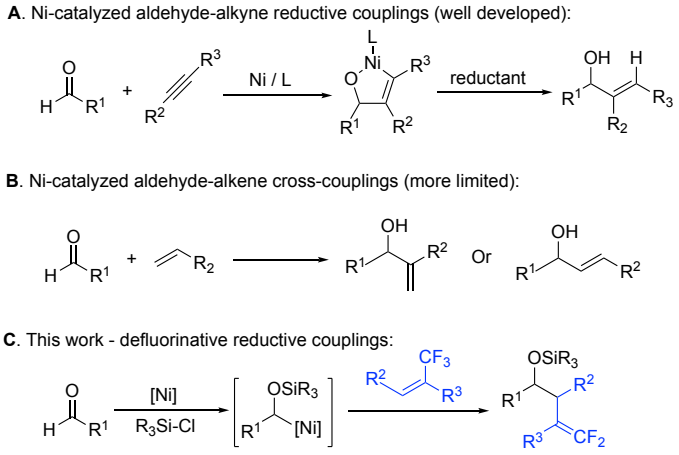
Transition metal-catalyzed reductive coupling reactions that avoid the need for pre-generation of air- and moisture-sensitive organometallic reagents provide an attractive route to highly functionalized synthetic intermediates.[1] Notably, reductive couplings of unsaturated compounds with aldehydes have demonstrated high efficiency for the construction of carbon-carbon bonds in a number of contexts using alkynes,[2] 1,3-dienes,[3] or allenes (Scheme 1A).[4] Couplings of alkenes with aldehydes, however, are more difficult, and methods are often restricted to intramolecular versions,[5] highly activated alkenes such as norbornene[6] and

methylenecyclopropane,[7] or hydroacylations of styrenes.[8] Advances using triethylsilyl triflate as promoter enabled considerable improvements in olefin scope to include alkenes with aromatic aldehydes and tertiary aliphatic aldehydes (Scheme 1B).[9] More recently, cobalt- and chromium co-catalyzed branch-selective coupling of alkenes with aldehydes through an alkyl chromium intermediate further broadened the scope of substrate combinations tolerated.[10] Additionally, iron-catalyzed transfer hydrogenative coupling of alkenes with aromatic and aliphatic aldehydes[11] and Brønsted acid enabled nickel-catalyzed hydroalkenylation of styrene derivatives with unactivated aldehydes provided further advances.[12] Despite these developments, the majority of current methods for aldehyde-alkene reductive coupling are restricted to aromatic aldehydes,[13] and the direct coupling reaction of abundantly available alkenes with unactivated aliphatic aldehydes still presents challenges in many cases.

An alternative approach for functionalization α to oxygen involves the generation and capture of α-oxy radical intermediates, which have been developed as highly useful cross-coupling partners using nickel catalysis.[14] Among these approaches, ketyl radicals offer a versatile platform of reactivity for reversing the traditional electrophilic character of carbonyls and play a pivotal role in numerous bond-forming and bond-breaking processes including ketyl-olefin couplings.[15] The requirement for strong, stoichiometric reductants, however, places practical limits on the synthetic utility of ketyl intermediates generated by classical approaches.[16] Several innovative strategies to generate ketyl radical were recently reported through processes such as concerted proton-coupled electron transfer,[17] Lewis acid-facilitated photocatalytic reduction,[18] redox-neutral photochemical promotion through transient α-acetoxy vinyl iodides intermediate,[19] and electrocatalytic reduction.[20]

Recent efforts in our laboratory have identified the addition of Ni(0) to aliphatic aldehydes through the activation by silyl halides as an alternative strategy for promoting reductive cross couplings of aldehydes either involving cyclization of an ynal with alkylation by an alkyl bromide or through direct coupling of the aldehyde with alkyl electrophiles.[21] By analogy, we envisioned that trifluoromethyl-substituted alkenes might serves as competent electrophiles in cross couplings with aldehydes under reductive conditions. This outcome would enable reactivity that serves as a functional synthetic equivalent of ketyl radicals through activation of the aldehyde by a low-valent nickel species in the presence of a silyl chloride. The 1,1-difluoroalkenes obtained through reductive couplings of aldehydes with trifluoromethyl-substituted alkenes with extrusion of a single fluorine atom are intriguing motifs owing to their presence in a number of biologically active compounds.[22] Due to their resistance to *in vivo* metabolism, *gem*-difluoroalkenes are a promising carbonyl bioisostere owing to their steric and electronic similarity to aldehydes, ketones, and esters, offering new opportunities in the drug discovery pipeline.[23] Commonly, *gem*-difluoroalkenes are typically prepared by synthetic routes involving *gem*-difluoroolefination of diazo or carbonyl precursors,[24] highly reactive organometallic species or strong base-mediated nucleophilic addition to α-trifluoromethyl alkenes,[25] suffering from the limited functional group tolerance and narrow substrates scope, due to the harsh reaction conditions. However, considerable progress has been made with expanded reaction scope in the field of photo-,[26] or transition metal-caralyzed[27] redox-neutral allylic defluorinative cross-coupling reactions. Recently, Wang and other groups have established Ni- and Ti-catalyzed reductive defluorinative couplings between different electrophiles with trifluoromethyl alkenes to further expand the diversity of *gem*-difluoroalkenes,[28] but approaches to *gem*-difluoroalkenes bearing additional functionality are still limited. Herein, we describe efficient nickel-catalyzed defluorinative couplings of trifluoromethyl-

substituted alkenes with aliphatic aldehydes to provide homoallylic alcohols possessing the *gem*-difluoroalkenes structural motif. These advances further establish effective strategies for the nickel-catalyzed functionalization of simple aliphatic aldehydes, and the mechanistic findings presented highlight the impact of subtle modifications of the reactant structure and ligand motif employed.



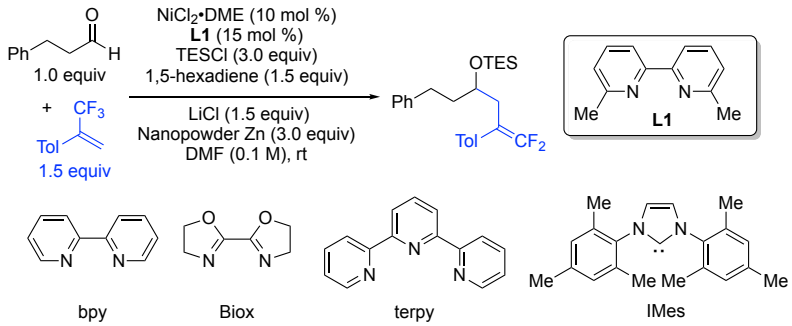
Scheme 1. Nickel-catalyzed additions to alkynes and alkenes.

RESULTS AND DISCUSSION

Initial experiments focused on the coupling of hydrocinnamaldehyde (**1a**) with a trifluoromethyl alkene (**2a**) (Table 1). Through systematic investigation of the reaction parameters, optimal results were found using a combination of $NiCl_2$(DME), 6,6'-disubstituted bipyridine ligand **L1**, LiCl, 1,5-hexadiene, chlorotriethylsilane (TESCl), and nanopowder zinc as sacrificial reductant, providing **3a** in 83% isolated yield (entry 1). Control experiments showed that the nickel source, ligand (**L1**), nanopowder zinc, and 1,5-hexadiene (entries 2-7) each played a pivotal role in this transformation. Although the inclusion of LiCl did not significantly affect yields of the standard product (entry 8), it resulted in modest improvements in yield with other substrates. Importantly, olefin additives can minimize the formation of enol ether (Scheme 1, **9**) and silyl

ether (Scheme 1, **10**) side products, and 1,5-hexadiene provided superior reactivity compared with other olefin additives (entries 9-13).[21b,c] It should be noted $Ni(COD)_2$ had a comparable efficiency to $NiCl_2$(DME), but $NiCl_2$(DME) was employed due to its stability in air and ease of handling (entry 19). Finally, the ligand selection was essential for the reaction outcome, and the 2,2′-bipyridine framework provided optimal results with 6,6'-disubstitution providing further improvements, leading to **L1** (6,6'-dimethyl-2,2'-bipyridine) as the optimal choice from our studies (entries 1, 14). Other nitrogen-based ligands such as Biox, Terpy, phosphines such as PCy_3, or NHC ligands such as IMes led to lower yields (entries 15-18).

Table 1. Optimization of couplings of aldehydes with trifluoromethyl alkenes



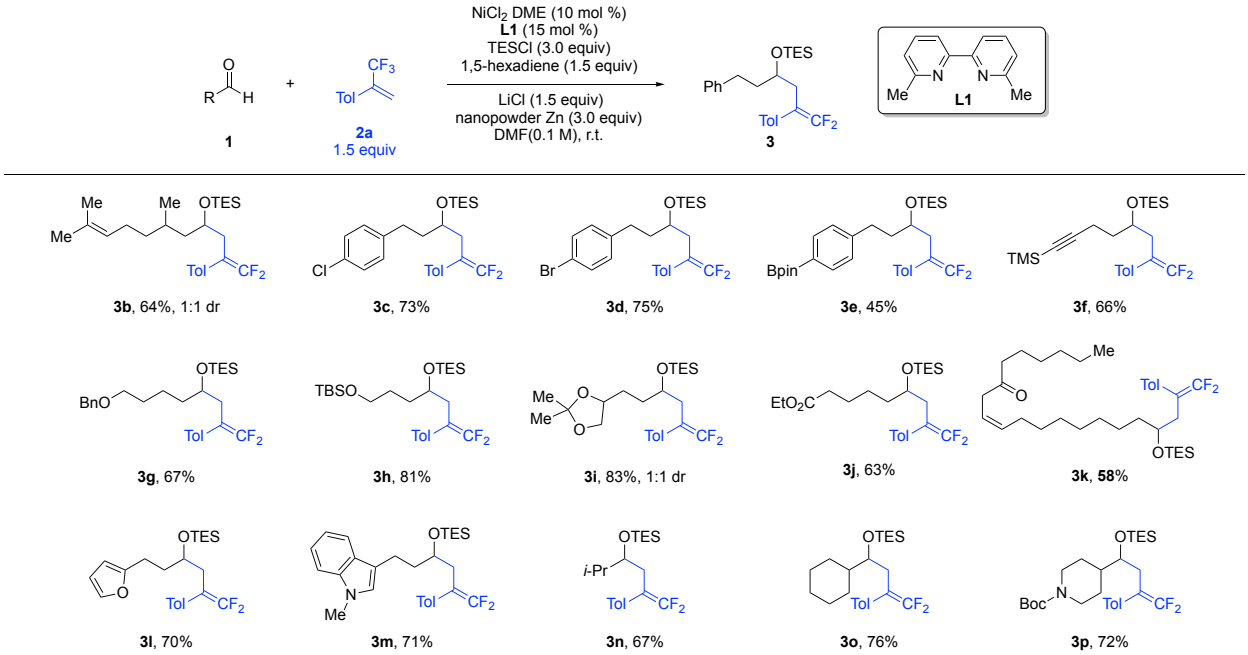
Entry	Deviation from Standard Conditions	% Yield[a]
1	None	86(83)[b]
2	$NiCl_2$•DME omitted	---
3	**L1** omitted	6
4	nanopowder Zn omitted	---
5	Zinc dust[c]	67
6	Mn powder[c]	71
7	1,5-hexadiene omitted	37
8	LiCl omitted	80
9	1,5-cyclooctadiene[d]	49
10	1,7-octadiene[d]	37
11	1,6-heptadiene[d]	67

12	(*E*)-stilbene[d]	68
13	duroquinone[d]	6
14	bpy[e]	80
15	Biox[e]	7
16	Terpy[e]	---
17	PCy_3[e]	---
18	IMes[e]	3
19	$Ni(COD)_2$[f]	86

[a]Yields were determined by GC with *n*-tridecane as the internal standard. [b]Isolated yield from a 0.2 mmol preparative experiment. [c]additive in place of nanopowder zinc. [d]additive in place of 1,5-hexadiene. [e]ligand instead of **L1**. [f]catalyst instead of $NiCl_2$•DME

We next turned our attention to define the substrate scope using the optimized conditions from the above studies. First, we explored an array of aliphatic aldehydes **1** to examine the generality of the coupling with trifluoromethyl alkenes (**2a**) (Table 2). Unhindered aliphatic aldehydes were well tolerated, delivering the corresponding products in good yield (**3c**-**3m**). The presence of β–substituents (**3b**) and α–substituents (**3n**-**3p**) was also tolerated albeit with diminished efficiency. Notably, a number of potentially reactive functional groups were unaffected in the transformation, including aryl chlorides (**3c**), aryl bromides (**3d**), aryl boronate esters (**3e**), and alkynes (**3f**). Benzyl ethers (**3g**), silyl ethers (**3h**), acetals (**3i**), esters (**3j**), and carbamates (**3p**) were also well tolerated. In addition, heterocyclic substrates including furans (**3l**) and indoles (**3m**) were also suitable coupling partners in the process. When the substrate contains both an aldehyde and ketone functional group (**3k**), the reaction is completely selective for aldehydes, leaving the ketone unchanged.

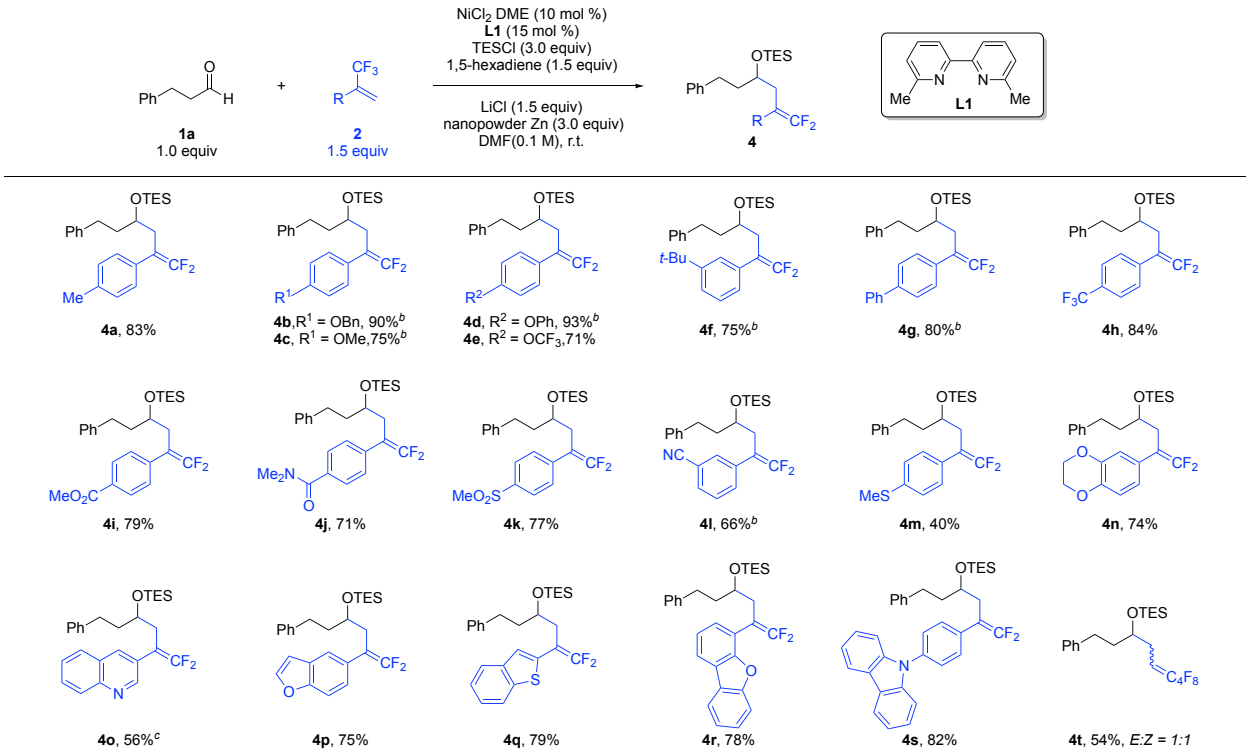
Table 2. Aldehyde scope in couplings with trifluoromethyl alkenes.



[a]Reactions performed on 0.20 mmol scale unless otherwise noted. Yields are for isolated material. Tol = *p*-tolyl.

We next demonstrated the generality of this protocol with respect to the trifluoromethyl alkenes **2a**–**t** (Table 3). Under these mild and base-free conditions, various 1,1-trifluoromethylstyrenes featuring either electron-rich (**4a**-**4e**) or electron-deficient (**4g-4k**) substituents underwent the transformation smoothly, affording the corresponding products in good yields (71-93%). Notably, this reductive protocol is tolerant of a wide range of functionality on the alkene coupling partner, such as esters (**4i**), amides (**4j**), sulfonyl groups (**4k**), nitriles (**4l**), and sulfides (**4m**). Furthermore, heterocycles including quinolone (**4o**), benzofuran (**4p**), benzothiophene (**4q**), dibenzofuran (**4r**), and carbazole (**4s**), are also readily compatible. It is noteworthy that beyond the aryl and heteroaryl system, mono-substituted alkenes, such as 2-nonafluorobutyl-1alkene (**2t**), smoothly proceeded to afford the desired product **4t** in moderate yield.

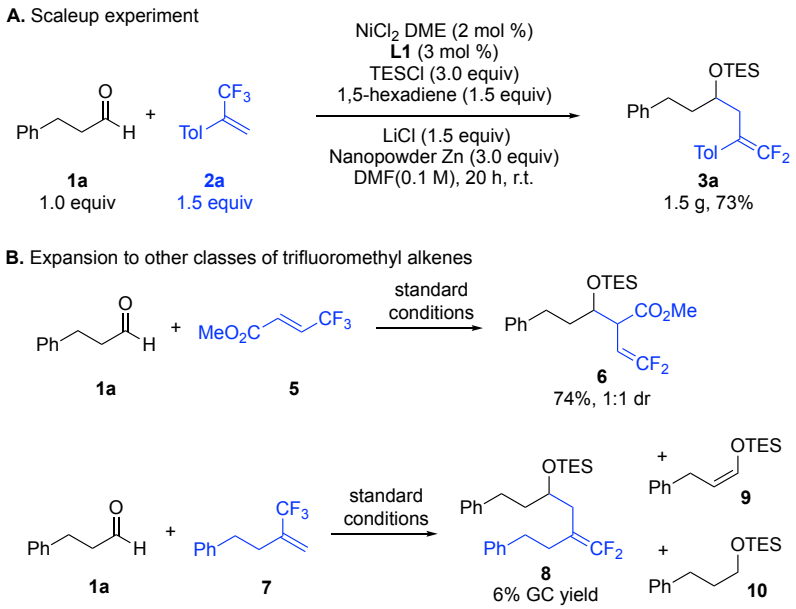
Table 3. Trifluoromethyl alkene scope in couplings with aldehydes.



[a]Reactions performed on 0.20 mmol scale unless otherwise noted. Yields are for isolated material; [b]Reactions performed with 0.40 mmol aldehyde and 0.20 mmol trifluoromethyl alkenes; [c]Reactions performed with 0.24 mmol aldehyde and 0.20 mmol trifluoromethyl alkenes.

To showcase the robustness and practicality of our method, a 5-mmol-scale experiment was conducted under an inert atmosphere using a benchtop setup without glovebox manipulations to provide 1.5 g of the desired product **3a** in 73% yield using only 2 mol% catalyst loading (Scheme 2A). Additionally, the protocol was also expanded to include α-trifluoromethyl enoates. As shown in Scheme 2B, subjecting methyl 4,4,4-trifluorocrotonate (**5**) to this catalytic system exclusively provided the defluorinative alkylation product **6** in high yield, illustrating that the trifluoromethyl group directs regiochemistry of the addition in analogy to the examples provided in Tables 2 and 3. Alkyl-substituted trifluoromethyl alkene (**7**), however, did not participate in the process, and

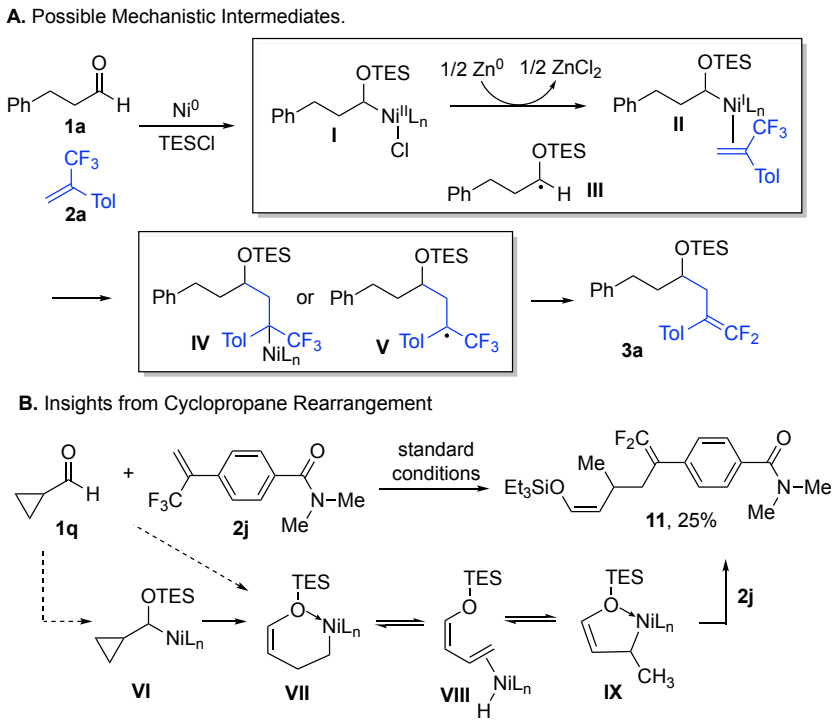
competitive formation of enol ether **9** and reduced silyl ether **10** was observed, with most of trifluoromethyl alkene **7** recovered intact with only 6% yield of the desired product **8** observed by GCMS analysis.



Scheme 2. Scaleup experiment and additional substrate classes.

A related chromium-catalyzed method for the addition of ketyl radicals to trifluoromethyl alkene intermediates was recently described by Wang.[29] Notably, the use of nickel catalysis was described in that study as ineffective in promoting the reaction, illustrating the unique effectiveness of the ligand/additive/reductant combination developed herein. ICP analysis illustrated that trace levels of chromium (0.4 ppm) are present in the commercial samples of $NiCl_2$(DME) that were used in this study. Control experiments, however, illustrated that $CrCl_3$, used in the method of Wang, has little effect on rates or outcomes of our optimal nickel-catalyzed conditions, suggesting that co-catalysis with trace chromium is not involved in the method describe herein (see supporting information for details).

A description of possible reaction pathways is outlined (Scheme 3). The addition of Ni(0), generated from the reduction of the Ni(II) pre-catalyst, to the aldehyde **1a** in the presence of chlorotriethylsilane (TESCl) provides a possible route to Ni(II) intermediate **I**. Intermediate **I** could undergo single electron reduction with Zn to afford the corresponding Ni(I) intermediate **II**. Notably, our recent report of aldehyde couplings with redox-active esters illustrated that stoichiometric $Ni(COD)_2$ in the absence of Zn or Mn reductants led to high yields of product, suggesting that the catalytic process involves catalyst turnover by the terminal reductant and that reduction of intermediates that precede product formation are not strictly required. In couplings of trifluoromethyl alkenes, however, the use of stoichiometric $Ni(COD)_2$ in the absence of a terminal reductant led only to trace product formation (7 % isolated yield). This outcome suggests that the reduction of Ni(II) species **I** to Ni(I) intermediate **II** is likely required in the current protocol. Notably, the redox-active ester protocol requires BiOx as ligand whereas the trifluoromethyl alkene protocol requires **L1**, and a recent study from Diao[30] illustrates that bipyridyl complex of nickel are much more easily reduced than are the corresponding BiOx complexes, which provides a potential rationale for the differing behavior of these catalytic systems.



Scheme 3. Possible intermediates involved in key mechanistic steps.

Free radical species have previously been proposed as intermediates derived from homolytic bond scission of nickel alkyl species in other classes of nickel-catalyzed trifluoromethyl alkene addition reactions,[28g,j] and it is plausible that free ketyl intermediate **III** could potentially be derived from either intermediate **I** or **II**. The observation of product **3a** is consistent with either an organometallic addition of **I** or **II** to provide intermediate **IV**, which would undergo nickel fluoride elimination to afford product **3a**, or from addition of a transiently generated ketyl radical **III** to produce **V**. To gain further insight into the involvement of addition of a free radical or organometallic intermediate to the trifluoromethyl alkene, we examined the catalytic addition of cyclopropanecarboxaldehyde (**1q**) and trifluoromethyl alkene **2j**. Ring opening of either a cyclopropylcarbinyl radical or the corresponding organonickel intermediate **VI** would be expected, but in this case, further rearrangement of the cyclopropane fragment led to the production of

compound **11** in 25% isolated yield. A recent study from Weix[31] illustrates ring-opening processes of cyclopropyl aldehydes and provides deep insight into the mechanism of how intermediate **VII** can be produced directly from **1q** under conditions similar to those described in this report. Additionally, we attributed reactivity of **1a** with redox-active esters to be derived from intermediates similar to **VII** in our recent report of aldehyde / redox-active ester couplings.[21c] The product **11** from the current study, however, is unusual and informative in several respects. First, the putative ring-opened organometallic intermediate **VII** undergoes chain-walking[28g,j,32] through **VIII** to intermediate **IX** prior to capture by **2j**, ultimately forming the branched isomer of product **11**. In contrast, our recent report of aldehyde couplings with redox-active esters led exclusively to ring-opened products but without evidence for chain walking.[21c] We attribute this difference to be the result of the changes in ligand structure between redox-active ester couplings (BiOx) and trifluoromethyl alkene couplings (**L1**). While we originally envisioned that **VII** was likely derived from **VI**, the recent evidence from Weix illustrating the direct formation of **VII** from **1q** is detailed and convincing.[31] Formation of a ketyl radical through homolysis of **VI** would not afford the rearranged constitution of **11** unless recombination of the radical with nickel again leads to intermediate **VII**. Formation of the *Z*-isomer of the enol silane of **11** is consistent with the formation of cyclic intermediates such as **VII** and **IX** where the alkene is constrained within a ring.[33]

Other rearrangements involving Ni(0) catalyzed cyclopropyl ketone rearrangements have been described, but only under much higher temperature conditions with different ligand types.[34] Those studies documenting the formation of intermediates such as **VII** in the absence of silyl electrophiles showed that α,β-unsaturated carbonyl intermediates were produced through this pathway. While this potentially suggests that crotonaldehyde produced from intermediates

analogous to **VII** could be an intermediate in the formation of **1q**, when crotonaldehyde was used in place of aldehyde **1q**, only trace quantities of **11** were observed. On this basis, we favor the pathway depicted in Scheme 3B as the operative mechanism for the production of **11**. Treatment of **1q** and **2j** to conditions using $CrCl_3$ described by Wang[29] afforded no product **11**, providing further evidence that the Ni and Cr procedures fundamentally differ in mechanism. With the insights from the behavior of substrate **1q**, the involvement of organometallic intermediates such as **I**, **II**, and **IV** seem most likely in the reductive couplings described in Tables 2 and 3 rather than ketyl-derived additions directly to the trifluoromethyl alkene.

CONCLUSIONS

In summary, an efficient method for defluorinative cross-couplings of aliphatic aldehydes with trifluoromethyl styrenes has been developed. The facile installation of the difluoromethylene unit to an array of aldehyde structures provides an effective entry to this desirable functional group class. The substrate scope enables wide variation of the aldehyde reaction partner, and the protocol is amenable to gram-scale syntheses. The combination of a hindered 6,6'-disubstituted bipyridine ligand, 1,5-hexadiene as an additive, triethylsilyl chloride, and nanopowder zinc were key components of the optimized procedure. Experiments detailing a ring-opening / chain-walking cascade process with cyclopropanecarboxaldehyde lends support to the involvement of organonickel intermediates as key intermediates involved in C-C bond formation and illustrate important differences in mechanism that result from subtle changes in ligand and substrate structures. This work expands the use of simple alkenes in nickel-catalyzed reductive couplings of aldehydes and illustrates that bipyridine ligand frameworks enable unique reactivity in processes of this type when used in combination with simple diene additives.

ASSOCIATED CONTENT

Supporting Information. Experimental and computational details. This material is available free of charge via the Internet at http://pubs.acs.org. Experimental details, copies of spectra.

AUTHOR INFORMATION

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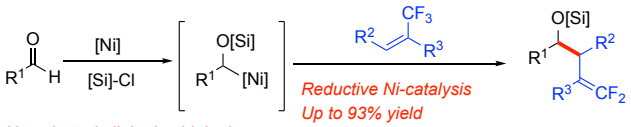
Synopsis TOC



Unactivated aliphatic aldehydes

Reductive Ni-catalysis
Up to 93% yield
High functional group tolerance
Gram-scale efficiency with 2% Ni loading