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Nickel-Catalyzed Reductive Conjugate Addition to Enones via Allylnickel Intermediates

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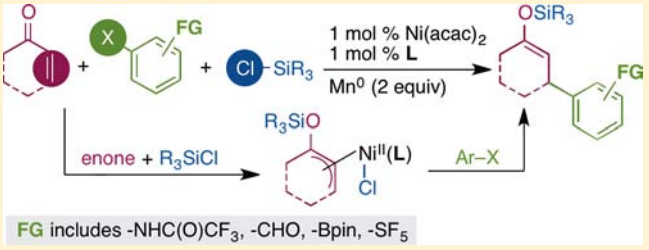
Supporting Information

ABSTRACT: An alternative method to copper-catalyzed conjugate addition followed by enolate silylation for the synthesis of β-disubstituted silyl enol ether products ($R^1(R^2)HCCH{=}C(OSiR^4_3)R^3$) is presented. This method uses haloarenes instead of nucleophilic aryl reagents. Nickel ligated to either neocuproine or bipyridine couples an α,β-unsaturated ketone or aldehyde ($R^2HC{=}CHC(O)R^3$) with an organic halide ($R^1{-}X$) in the presence of a trialkylchlorosilane reagent ($Cl{-}SiR^4_3$). Reactions are assembled on the benchtop and tolerate a variety of functional groups (aldehyde, ketone, nitrile, sulfone, pentafluorosulfur, and *N*-aryltrifluoroacetamide), electron-rich iodoarenes, and electron-poor haloarenes. Mechanistic studies have confirmed the first example of a catalytic reductive conjugate addition of organic halides that proceeds via an allylnickel intermediate. Selectivity is attributed to (1) rapid, selective reaction of LNi^0 with chlorotriethylsilane and enone in the presence of other organic electrophiles, and (2) minimization of enone dimerization by ligand steric effects.



1. INTRODUCTION

The conjugate addition of aryl and vinyl nucleophiles to an α,β-unsaturated ketones has been important to organic synthesis for over half a century.[1] The potential to functionalize two adjacent carbons via conjugate addition and trapping of the resultant enolate has proven especially powerful in synthesis (Figure 1A).[1c,d,2,3] Trapping with chlorosilanes to form silyl enol ethers enables subsequent regioselective vinylnonaflate formation,[4] enolate formation,[2] α-arylation,[5] α-alkylation,[6] aldol reaction,[2] Michael addition,[2] α-oxygenation,[7] and α-amination.[7b] While the conjugate addition reaction has been continually expanded and refined over the intervening years, a fundamental weakness of the approach, the need for preformed organometallic reagents, has remained.

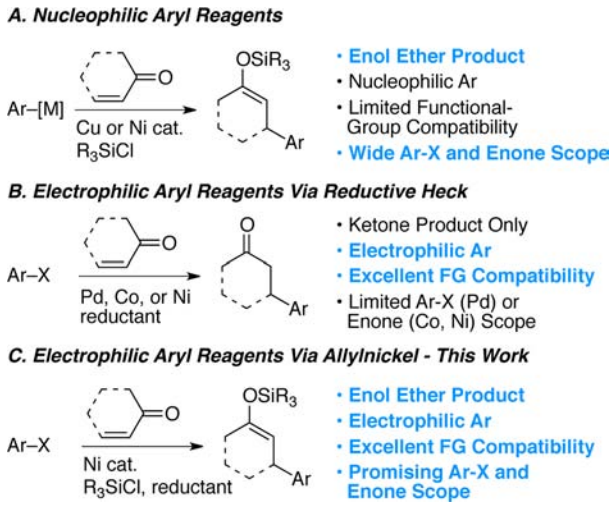


Figure 1. Comparison of three approaches to conjugate addition reactions that highlights the advantages of this study (C).

Although great progress has been made in the synthesis and conjugate addition of less reactive carbon nucleophiles, such as organozinc, organotin, or organoboron compounds,[8] functional group compatibility remains a challenge, and few of these carbon nucleophiles are commercially available. Of these approaches, the Rh[9]- and later Pd[10]-catalyzed conjugate addition of arylboronic acids has proven to have the broadest functional-group compatibility, but trapping of the enolates has not been demonstrated.[11] Additionally, 10−1000 times fewer arylboronic acids than haloarenes are commercially available.[12] As a consequence, extra synthetic steps may be required to synthesize a molecule of interest due to the formation of the organometallic reagent or because of protection and deprotection steps.

The reductive Heck reaction avoids the use of nucleophilic carbon reagents; however, trapping of the resultant enolate has not been demonstrated (Figure 1B). It would be a great advantage in complex molecule synthesis to have a method for conjugate addition that combines the mildness of the Heck reaction with the ability to form silyl enol ether products.

We report our development of a reaction that satisfies these needs (Figure 1C). In addition, our studies explain the cross-selectivity observed and shed light on a mechanism for the reductive conjugate addition of organic halides.

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2. BACKGROUND

The Pd-catalyzed reductive Heck reaction, pioneered by Cacchi nearly 30 years ago, is the most developed approach toward conjugate addition without preformed organometallic reagents (Figure 1B).[13] Intermolecular, intramolecular, and even stereoselective intramolecular applications have been reported by a number of groups. While good substrate scope has been demonstrated for the Michael acceptor, all of the intermolecular approaches suffer from the same limitations: only electron-rich aryl iodides provide high yields, and no addition/enolate trapping sequences have been reported.

Nickel[14]- or cobalt-catalyzed[15] reductive Heck reactions have broader haloarene scope, but only Michael acceptors without β-substitution provide high yields. Ronchi, Beletskaya, and Nédélec demonstrated that the nickel-catalyzed reactions tolerated electron-poor haloarenes, which was an important advance over the palladium-catalyzed methods. While acrylates, vinyl ketones, and acrylonitrile provide good yields of product, β-substituted α,β-unsaturated ketones are rarely used as substrates. For example, the addition of bromonaphthalene to ethyl crotonate provided only 20% of the conjugate addition product.[14h] Finally, although Montgomery has shown that iodoarenes can be added to acrylates with trapping of the resultant enolate by an aldehyde,[14f,g] no examples of trapping with silicon reagents are known. In fact, the addition of chlorotrimethylsilane has been reported to favor biaryl formation over conjugate addition product.[15b] In contrast, a host of literature has demonstrated that the conceptually related addition of alkynes and alkenes to enones in the presence of silicon reagents can form silyl enol ether products with broad functional group compatibility.[16]

The limitations of the reductive Heck approaches appear to be related to their common mechanism (Figure 2). Migratory

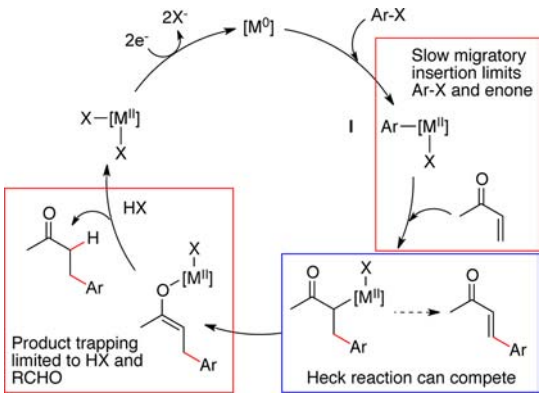


Figure 2. The reductive Heck consensus mechanism and its relationship to the limitations of the methods.

insertion of the arylmetal intermediate (**I**) into the acceptor is inefficient, resulting in poor results with electron-poor haloarenes (Pd) or less electrophilic Michael acceptors (Ni, Co). β-Hydride elimination from the metal enolate can result in the formation of Heck reaction products. Finally, trapping of the metal enolate intermediate is inefficient with chlorosilanes or the chlorosilanes cause undesired reactivity. While adjustment of conditions or catalysts could be envisioned to overcome these problems, overcoming these limitations may require a reaction with a fundamentally different mechanism (Figure 3).

Precedent for a different approach can be found in the stoichiometric reactivity of nickel(0) with enones and chlorosilanes.[17] Mackenzie showed that allylnickel(II) reagents can be formed

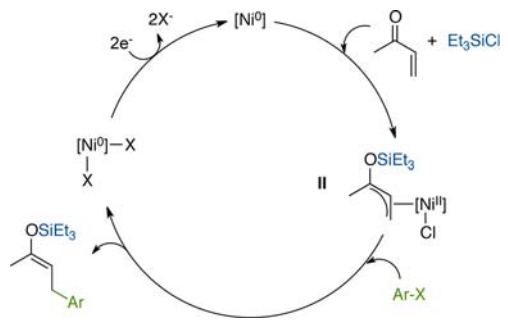
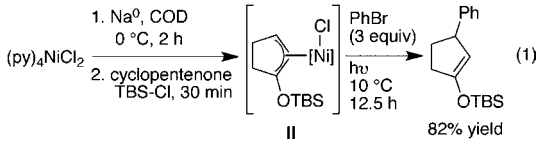


Figure 3. A hypothetical reductive conjugate addition mechanism with an allylnickel(II) intermediate (**II**).

by the reaction of Ni^0 with an enone and a chlorosilane and that these allylnickel intermediates will react with aryl bromides when irradiated with UV light (eq 1).[17a,b] Allylnickel(II) species are versatile reagents, which react with a variety of electrophiles,[18] presumably via a single-electron transfer mechanism involving nickel(I) intermediates.[19] If Mackenzie's approach could be made catalytic, it would avoid the two problematic steps in the reductive Heck reaction: (1) migratory insertion and (2) enolate trapping.



The catalytic applications of this proposed approach have not been reported;[20] however, the use of Lewis acids or chlorosilanes to facilitate the oxidative addition of enones to nickel(0) and palladium(0) has been shown by a number of groups. Mackenzie reported an allylnickel mechanism to be operative for the nickel-catalyzed conjugate addition of organostannanes to enones.[21] In this case, transmetalation between an allylnickel(II) complex and a nucleophilic carbon reagent (e.g., $ArSnMe_3$), followed by reductive elimination, forms the silyl enol ether product. This inverse mechanism has been leveraged by Morken,[22] Yorimitsu, and Oshima[23] in the reaction of enones with organoboranes as well. Last, palladium was shown to behave similarly by Ogoshi and Kurosawa,[24] and this has enabled unconventional conjugate additions of carbon nucleophiles.[25]

While this prior work establishes the viability of each individual step in a potential "enone-first" catalytic cycle (Figure 3), it was not clear if each step could be accomplished in the presence of the other reagents. For instance, if the iodoarene reacted with nickel(0) faster than enone and chlorosilane, then a reductive Heck mechanism would result. On the other hand, formation of allylnickel(II) complexes could result in bis-allyl dimers.[19d,20b] Thus, formation of the conjugate addition product requires oxidative addition of the enone first, followed by preferential reaction of allylnickel **II** with iodoarene over enone or another equivalent of **II**.

We recently reported the reductive conjugate addition of secondary, tertiary, and neopentyl halides to enones with trapping as the silyl enol ether (eq 2), but were unable to confirm the mechanism by which the products were formed.[26]

While we were able to rule out the intermediacy of AlkylMnBr intermediates, both the reductive Heck (Figure 2) and "enone-first" (Figure 3) mechanisms were considered. While **L1** was required for the chemistry, stoichiometric studies on in situ-formed

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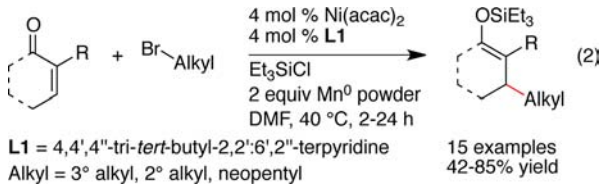
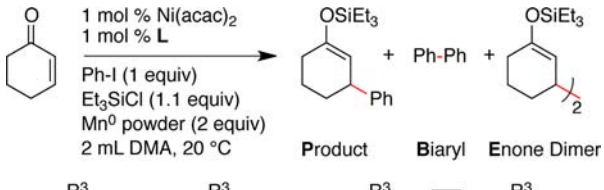


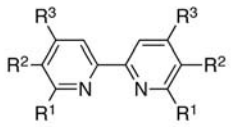
(**L1**)Ni^{II}(η^3-1-triethylsilyloxycyclohexenyl)Cl (like **II** in Figure 3) did not match the selectivity observed under catalytic conditions. Because of the instability of (**L1**)Ni(alkyl)X complexes (like **I** in Figure 2),[27] we were unable to directly test for the viability of a reductive Heck mechanism. The poor selectivity observed with **L1**-ligated allylnickel led us to favor a reductive Heck mechanism.

Our previous study, while promising because the reductive conjugate additions were not previously possible, was limited to unactivated alkyl halides. Attempts to use the same catalyst to couple vinyl and aryl halides provided low yields of product (vide infra, Table 1, entry 3). Furthermore, the demonstrated functional-group tolerance was limited to an ester and a nitrile. Finally, the limited mechanistic understanding limited our ability to further improve the scope of the reaction.

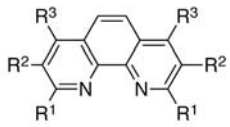
We report here a new catalyst system that broadens the scope of reductive conjugate addition/enolate trapping to include aryl and vinyl halides (eq 3). New mechanistic studies on reactions conducted with aryl and alkyl halides reveal a general mechanism for reductive conjugate addition. Finally, these studies also illuminate the factors that govern cross-selectivity for these new reactions.

Table 1. Ligand Effects on Reductive Conjugate Addition[a]





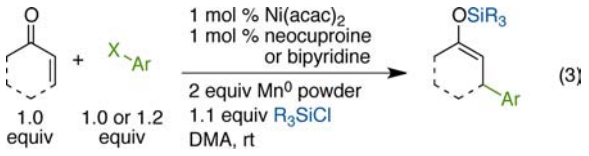
L2: R^1 = R^2 = R^3 = H
L3: R^1 = R^2 = H, R^3 = *t*-Bu
L4: R^1 = R^2 = H, R^3 = OMe
L5: R^1 = R^3 = H, R^2 = Me
L6: 2,2'-biquinoline



L7: R^1 = R^2 = R^3 = H
L8: R^1 = R^2 = H, R^3 = Ph
L9: R^1 = H, R^2 = R^3 = Me
L10: R^1 = Me, R^2 = R^3 = H

entry	ligand (**L**)	*t* (h)	**P** (%)	**B** (%)	**E** (%)	PhH (%)
1	none	24	28[b]	6	19	1
2	py (1 equiv)	15	39[c]	3	14	4
3[d]	**L1**	18	24	42	98	10
4	**L2**	24	67	13	51	6
5	**L3**	24	41[c]	16	38	10
6	**L4**	24	41[e]	36	54	11
7	**L5**	72	60	0	34	0
8	**L6**	24	41[c]	19	47	11
9	**L7**	24	28[c]	12	44	11
10	**L8**	24	34[f]	24	46	11
11	**L9**	24	43[e]	34	36	9
12	**L10**	2	99	0	13	4

[a]See the Supporting Information for full experimental details. Yields for **P**, **B**, and Ph−H are corrected versus internal standard (dodecane). Yields of **E** are uncorrected. [b]>50% of both enone and PhI remained. [c]>10% of both enone and PhI remained. [d]Reaction run with 10 mol % [Ni] and **L1** in DMF. [e]>10% of enone remained. [f]>10% of PhI remained.



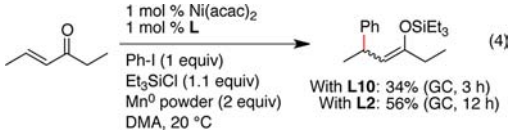
3. RESULTS

3.1. Ligands. Initial reaction development was focused on finding a catalyst that would be selective for the cross-coupling of iodobenzene with cyclohexenone in the presence of chlorotriethylsilane (Table 1). The combination of three electrophiles could result in multiple byproducts, but we primarily observed biphenyl (**B**), benzene (Ph−H), and silylated enone dimer (**E**). Notably, we did not observe the formation of desilylated ketone product or products from a Heck-like addition/β-hydride elimination process.

Consistent with previous studies using cobalt and nickel,[28] reactions of cyclohexenone with iodobenzene did not produce much product in the absence of a ligand (Table 1, entry 1). When pyridine was used in excess to nickel, selectivity was improved but reactivity remained low (entry 2). Reactions with smaller amounts of pyridine provided only trace amounts of product. Our previous studies with haloalkanes[26] had demonstrated the ability of nickel ligated to a tridentate nitrogen ligand (4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine, **L1**) to favor conjugate addition over competing dimerization processes; however, this catalyst primarily formed biaryl and dimerized enone products in reactions with haloarenes (entry 3).

The observation of strong ligand effects for other reductive coupling reactions[29] prompted us to examine various bidentate nitrogen-based ligands (**L2**−**L10**). While the series of ligands did provide a wide range of selectivities, the electronics of the ligands appeared to play only a small role (entries 5 vs 6, 9 vs 10). Substitution, even substitution remote from the metal center, decreased the amount of enone dimer (**E**) formed (entries 5−8 and 9−12). Of the ligands surveyed, 2,9-dimethyl-1,10-phenanthroline (neocuproine, **L10**) provided the highest yield of product, the best selectivity, and the fastest reaction (complete in 20 min vs >18 h).[30]

Application of the best conditions for cyclohexenone to an *E*-acyclic substrate, 4-hexen-3-one, produced a low yield of product (<40% yield after 3 h, SM consumed). The low selectivity appears to be related to sterics because we found that the least hindered ligand, 2,2′-bipyridine (**L2**) provided the best results (eq 4).



3.2. Other Reaction Conditions. As we had seen with the conjugate addition of haloalkanes to enones, the presence of nickel, reductant, and trialkylchlorosilane was essential for reactivity. Reactions conducted without any one of these individual components did not consume iodoarene or enone after 30 min of reaction time. Amide and urea solvents provided the highest yields of product (DMA ≈ NMP ≈ DMPU > DMF > DMI ≈ THF, see

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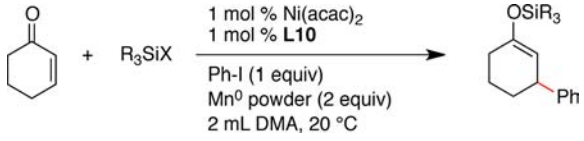
Table S1 in the Supporting Information). Finally, manganese powder was a more effective electron source than zinc.[31] Reactions run with zinc produced more hydrodehalogenated products.

A variety of silicon reagents were tested under our optimized reaction conditions (Table 2). Reactions conducted with the

Table 2. Silicon Reagent Reactivity[a]



entry	silicon reagent	yield (%)[b]
1	Me_3SiOTf (TMS−OTf)	48
2	Me_3SiCl (TMS−Cl)	48
3	$(Me_3Si)_2NH$ (HMDS)	0
4	$(Me_3Si)NHCHOSiMe_3$ (BSA)	0
5	$Et(Me)_2SiCl$	66
6	n-$Bu(Me)_2SiCl$	79
7	Et_3SiCl (TES−Cl, as in Table 1)	94
8	Et_3SiOTf (TES−OTf)	73
9	i-$Pr(Me)_2SiCl$	77
10	n-Pr_3SiCl	95
11	t-$Bu(Me)_2SiCl$ (TBS−Cl)	84
12	t-$Bu(Me)_2SiOTf$ (TBS−OTf)	66
13	i-Pr_3SiCl (TIPS−Cl)	36
14	i-Pr_3SiOTf (TIPS−OTf)	27
15	t-$Bu(Ph)_2SiCl$ (TBDPS−Cl)	0

[a]Reactions conducted as in Table 1. [b]Yield is an uncorrected GC yield versus internal standard (dodecane).

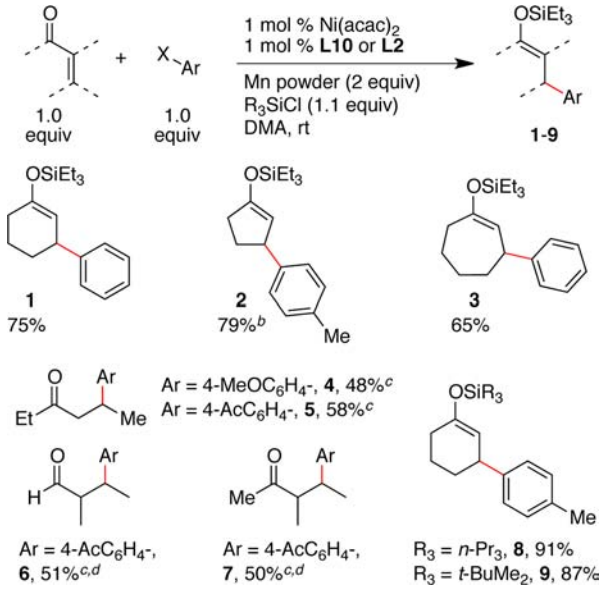
trimethylsilyl donors provided only modest yields of product (entries 1−4), and similarly poor results were obtained with very large silicon groups: triisopropylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) (entries 13−15). Most other silicon reagents with moderate reactivity and steric bulk formed product in reasonable yield (66−95% yield, entries 5−12). Because chlorotriethylsilane (TES-Cl) was among the most effective reagents and it is available at low cost, we conducted the majority of our reactions in the following sections with TES-Cl. If less reactive silyl enol ether products would be an advantage in synthesis, n-Pr_3Si−Cl or TBS−Cl can be used with only a small change in yield (entries 10 and 11, respectively).

3.3. Enone and Silicon Reagent Scope. A variety of α,β-unsaturated ketones and an α,β-unsaturated aldehydes formed conjugate addition products under our optimized conditions (Scheme 1). Five-, six-, and seven-membered $\alpha\beta$-unsaturated cycloalkenones, as well as linear alkenones, provided products **1**−**9** in reasonable yields. The acyclic silyl enol ethers **4**−**7** were formed with modest *E*:*Z* ratios (2:1 to 3:1), so the ketone products were isolated instead of the silyl enol ethers.[32,33] As noted above, *tert*-butyldimethylsilyl and tri-*n*-propylsilyl enol ethers could also be obtained in good yield (**8** and **9**).

3.4. Haloarene Scope. A major advantage of reductive conjugate addition is the large substrate pool and the potential for broad functional-group compatibility. Given the problems observed in Pd-catalyzed reductive Heck reactions with electron-poor arenes, we first examined the effect of electronics on the outcome of these conjugate addition reactions (Scheme 2).

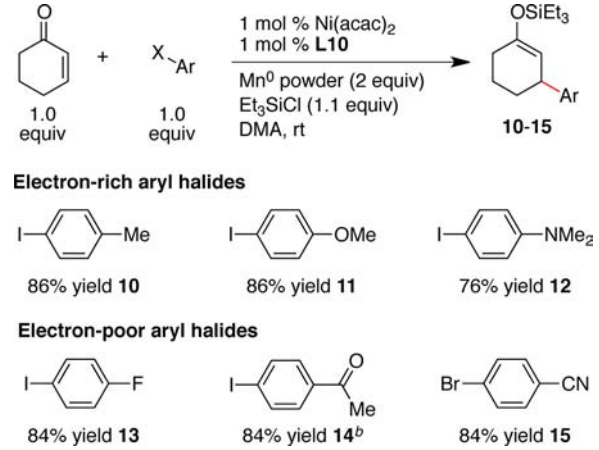
Electron-poor and electron-rich aryl halides coupled equally well, but only electron-poor aryl bromides coupled in high yield. Reactions with bromobenzene, for example, primarily

Scheme 1. Acceptor and Silicon Reagent Scope[a]



[a](a) Ratio of enone:Ar−I:R_3Si−Cl:catalyst was 1.0:1.0:1.1:0.01. Yields reported are of isolated, pure material (average of two runs). (b) Reaction temperature was 40 °C. (c) With ligand **L2** and after deprotection by KF in methanol. Yield reported is for two steps. (d) Products isolated as mixtures of diastereomers: **6**, 1:1; **7**, 6:1.

Scheme 2. Aryl Halide Electronic Effects[a]



[a](a) Reactions conducted as in Scheme 1. (b) With Ar−Br, 58% yield.

produced silyl enol ether dimer **E** (Table 1).[34] This limitation is complementary to reductive Heck reactions, which are limited to electron-rich aryl halides. Despite the poor reactivity with electron-neutral and electron-rich bromoarenes, the commercially available substrate pool is vastly expanded as compared to reactions with Grignard reagents or arylboronic acids.

Reactions with *ortho*-substituted aryl halides resulted in lower yields (Scheme 3). While methoxy and nitrile substituents on the ortho position were tolerated to form **16** and **17**, respectively, reactions run with *o*-iodotoluene and *o*-iodoacetophenone did not form product when ligand **L10** was used. Anticipating that this was due to a steric mismatch similar to what we observed with *E*-alkenones, we briefly explored the less hindered ligands **L2** and **L3**. Consistent with our hypothesis, the reaction conducted with ligand **L3** formed product **18** in better yield than with ligand **L10**. Further improvements for the

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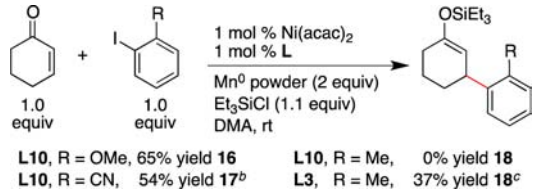
Scheme 3. Ortho-Substituted Arenes[a]

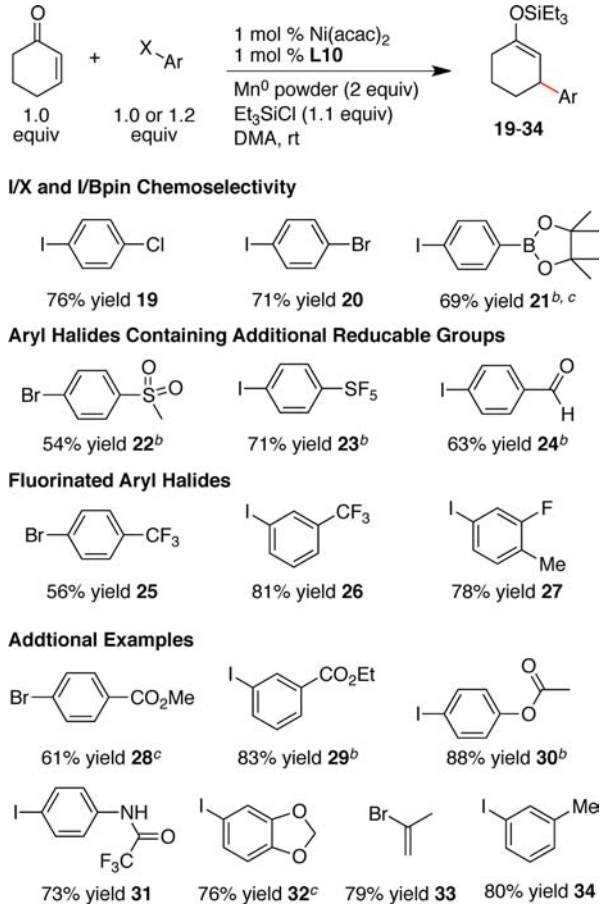


[a](a) Reactions conducted as in Scheme 1. (b) With Ar−Br, 44% yield. (c) Yield based on a single run.

addition of sterically hindered haloarenes are required, but these results demonstrate that ligand design can potentially solve this problem.

Functional-group compatibility is further demonstrated in Scheme 4. While 1 equiv of aryl halide was generally sufficient,

Scheme 4. Functional-Group Compatibility[a]



[a](a) Reactions conducted as in Scheme 1. (b) 1.2 equiv of aryl iodide was used instead of 1 equiv. (c) Product contaminated with a small amount of hydrodehalogenated arene.

a small improvement in yield could be obtained for reactions of aryl iodides when a slight excess of Ar−I was added (1.2 equiv). This improvement was not observed for reactions of aryl bromides.

The lower reactivity of aryl bromides and chlorides as compared to aryl iodides enabled the chemoselective coupling of 4-chloro and 4-bromo-1-iodobenzene (**19** and **20**, respectively). In addition, a pinacolato boronic acid ester was not reactive under these conditions (**21**). As we have found previously, reductive coupling conditions are complementary to reactions that utilize mild carbon nucleophiles, such as boronic acid esters.[29]

Because of the reducing nature of the reaction conditions, we were concerned that high-oxidation-state functional groups would present a challenge. Although nickel and metal reductant combinations have been reported to reduce or cross-couple high oxidation-state sulfur compounds,[35] the sulfone and pentafluorosulfur products (**22** and **23**, respectively) were obtained in high yield. The pentafluorosulfur group has found increasing application in electronics and pharmaceutical applications due to its interesting electronic and steric parameters,[36a,b] but few catalytic reactions have been demonstrated to tolerate its presence. Indeed, the synthesis of derivatives remains the "Achille's heel"[36a] of the SF_5 group. In this case, the corresponding boronic acid is not commercially available and is difficult to synthesize.[36c]

The pinacol coupling of aldehydes and ketones[37] is reported to be catalyzed by nickel under reducing conditions, and manganese dust has been shown to reduce aldehydes to alcohols,[38] but we did not observe these side reactions in the formation of products **14** and **24**. Both products bear differentially protected carbonyls and would be difficult to synthesize directly by any other method.[39] While a few remarkable reports of zinc[40] and copper[41] reagents bearing aldehydes have appeared in the literature, none have been shown to participate in conjugate addition reactions selectively.

Fluorinated arenes are important in the pharmaceutical industry, but their electron-poor nature would prevent their use in reductive Heck reactions for their addition to enones. The expected products **25**−**27** were formed in good yields under our standard conditions.

Aryl halides that could be easily hydrolyzed, such as an aryl ester and a trifluoroacetamide, coupled in high yields to form **30** and **31**, respectively. Conditions that utilize strong nucleophiles (cuprates) or basic aqueous conditions (Rh-catalyzed conjugate addition) could be problematic for these substrates. Additionally, the N−H proton on the *N*-aryltrifluoracetamide is reported to have a pK_a of 12.6 in DMSO[42] and can readily protonate most organometallic reagents.

Finally, a vinyl halide, 2-bromopropene, reacted to form product **33** in good yield. The corresponding boronic acid is reported to be thermally unstable.[43]

Although the reaction demonstrated good substrate scope and broad functional group compatibility, we observed two notable limitations. First, reactions with 4-iodo-nitrobenzene provided none of the conjugate addition product. In fact, we found 10 mol % of 4-iodo-nitrobenzene to be inhibitory to reactions with other iodoarenes. This is probably related to the ease with which the nitroarene accepts electrons. Inhibition by nitroarenes has also been proposed as evidence for radical-chain-like reaction mechanisms.[19] We have observed this limitation in other reductive coupling reactions.[29] Second, reactions with halogenated heteroarenes (pyridine, thiophene) did not produce acceptable yields of product and resulted in large amounts of heteroarene dimerization.

3.5. Oxidative Addition to Nickel(0). Given the strong precedent for both arylnickel (**I**) and allylnickel (**II**) intermediates (Figures 2 and 3), we studied the rate at which iodobenzene, enone, and chlorotriethylsilane react with (**L10**)-Ni^0(cod) by monitoring the disappearance of the MLCT band at 450 nm (Figure 4).[44] The results clearly show that iodobenzene reacts much slower than chlorotriethylsilane and enone, consistent with the "enone-first" mechanism (Figure 3).

While no detailed mechanistic study on the Mackenzie allylnickel formation has been reported, Kurosawa studied the

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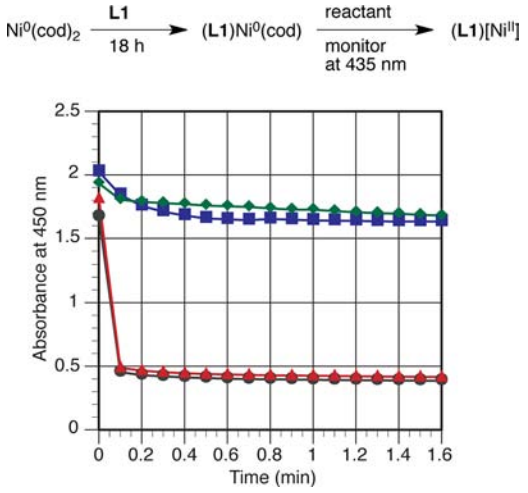
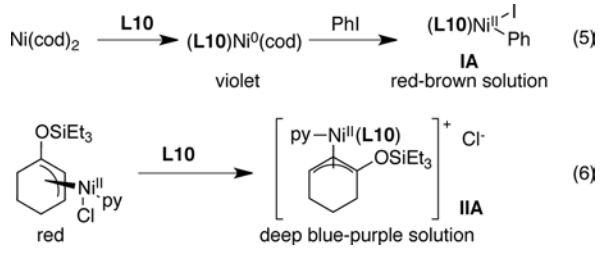


Figure 4. Reaction of (**L10**)Ni(cod) with Ph–I (green ◆), cyclohexenone + Et_3SiCl (red ▲), Et_3SiCl (●), and cyclohexenone (blue ■) as monitored by UV–vis at 450 nm. For full UV–vis spectra and expanded plots of all four reactions, see Figures S1–S3 in the Supporting Information.

formation of allylpalladium by the addition of Lewis acids to enone–palladium complexes.[24] Kurosawa's results suggested that the chlorosilane could react with a nickel–enone complex to form the allylnickel intermediate. While we observe rapid coordination of the enone to (**L10**)Ni^0(cod) (**6**) in the absence of chlorosilane (Figure 4, small shift in UV–vis spectrum, complete in about 30 s), **6** also reacts rapidly with Et_3SiCl in the absence of enone to form a single new yellow species. This product appears to be paramagnetic based upon the broadened ^1H NMR peaks and large chemical shifts observed (Figure 4 and Figures S4, S5 in the Supporting Information). While square-planar nickel(II) complexes are diamagnetic, tetrahedral nickel(II) complexes are paramagnetic and display chemical shifts in this range. These results could represent a rare example of rapid Si–Cl bond activation.[45]

3.6. Synthesis and Stability of Potential Organonickel Intermediates. Although the allylnickel intermediate was formed faster than the arylnickel intermediate, either complex could still be on-cycle if the oxidative addition reactions were reversible. Before examining the reactivity of arylnickel (**I**) and allylnickel (**II**) intermediates, we studied their formation and the relative stability of the two complexes (eqs 5 and 6).



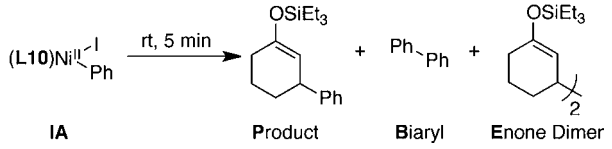
A solution of red-brown complex (**L10**)Ni^{II}(Ph)(I) (**IA**) was generated in situ by adding PhI to a prestirred, violet solution of **L1** and Ni(cod)$_2$ (1:1 ratio), in analogy to preparations reported by Yamamoto (eq 5).[46] A solution of blue-purple complex (py)(**L10**)Ni(η^3-1-triethylsilyloxycyclohex-2-enyl)Cl (**IIA**) was generated in situ by the addition of **L10** to a red solution of (py)Ni(η^3-1-triethylsilyloxycyclohex-2-enyl)Cl[26] (eq 6).

We made some effort to characterize the complexes in solution by ^1H NMR spectroscopy. Although complete assignment of all protons proved difficult (Figures S6 and S7 in the Supporting Information), clear changes to the ^1H chemical shifts of ligand **L10** could be observed in each case, consistent with **L10** coordination with the pyridine-ligated nickel-allyl complex to form **IIA** and the oxidative addition of Ph–I to the (**L10**)Ni^0(cod) complex to form **IA**.

The solutions of **IA** and **IIA** were stable for at least 10 min at room temperature before significant decomposition into yellow solutions[47] containing aryl or allyl dimer was observed (monitored by GC analysis). Experiments in the next sections used freshly generated solutions of **IA** and **IIA**, which were prestirred for 10 min before use[48] and monitored for decomposition by their characteristic color changes.

3.7. Stoichiometric Reactivity of Organonickel Intermediates IA and IIA. After the stability of **IA** and **IIA** was established, the reactivity of each of these reagents was examined in a series of stoichiometric studies (Tables 3 and 4).

Table 3. Stoichiometric Reactivity of Arylnickel IA[a]



	conditions[b]				yield		
entry	enone	Et_3SiCl	Mn^{0c}	PhI	**P** (%)	**B** (%)	**E** (%)
1	0	0	0	0	0	10	0
2	100	110	0	0	0	116	0
3	100	110	200	0	0	86	>100[d]
4	1.0	1.1	1.0	200	0	95	0
5[e]	1.0	1.1	1.0	200	97	96	0
6	catalytic reaction with Ni(acac)$_2$ and **L10**				99[f]	0	13[f]

[a]Nickel complexes were generated in situ at a concentration of 2.5 mM in DMA and reacted with the noted reagents. Analysis at 5 min provided the stated yields (GC, corrected). Yields are calculated with respect to **IA** unless otherwise noted. [b]Equivalents with respect to [Ni]. [c]Mn^0 powder was prestirred with Et_3SiCl. [d]Yield was 37% when calculated with respect to enone. [e]Reaction monitored at 20 min instead of 5 min. [f]Uncorrected GC yield calculated using dodecane as internal standard, with respect to enone as the limiting reagent (0.5 mmol).

The stoichiometric reaction of in situ-generated arylnickel **IA** with cyclohexenone and chlorotriethylsilane exclusively formed biphenyl (**B** in Table 3, entries 1 and 2). When an excess of reagents and a reductant were added, biphenyl was formed in the first turnover, followed by enone dimer (**E**) or product (**P**) formation in subsequent turnovers (entries 2 vs 3 and 4 vs 5). In comparison, the standard catalytic reaction produces no measurable biphenyl (entry 7), making the intermediacy of **IA** in the catalytic reaction unlikely.

In contrast, analogous reactions of allylnickel **IIA** with iodobenzene selectively provided the silyl enol ether product (**P**), albeit in low yield (Table 4, entries 2 and 3). Increased yield and selectivity were observed when Mn preactivated with chlorotriethylsilane was employed with either excess or equimolar amounts of iodobenzene (entries 4 and 5). Selectivity for product formation over biaryl formation is consistent with the catalytic reaction (entry 7). Of the two potential intermediates, only allylnickel **IIA** formed the correct product and showed selectivity consistent with the catalytic reaction.

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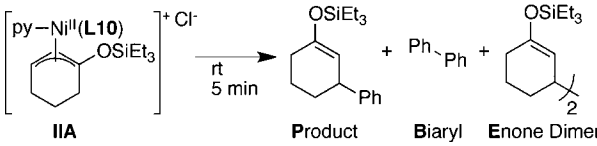
Table 4. Stoichiometric Reactivity of Allylnickel IIA[a]

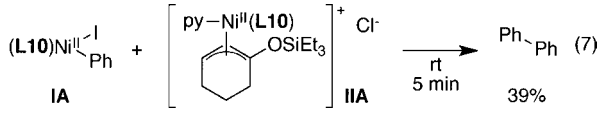


	conditions[b]			yield		
entry	PhI	Mn^{0}[c]	Et_3SiCl	P (%)	B (%)	E (%)
1	0	0	0	0	0	0
2	100	0	0	12	0	0
3	100	0	110	7	0	0
4	100	110	200	71	0	0
5	1.0	110	200	28	0	0
6	100	0[d]	0	26	0	0
7	catalytic reaction with $Ni(acac)_2$ and **L10**			99[e]	0	13[e]
8	Catalytic reaction with $Ni(acac)_2$, **L10**, and pyr			69[e]	0	14[e]

[a]Nickel complexes were generated in situ at a concentration of 2.5 mM in DMA and reacted with the noted reagents. Analysis at 5 min (GC, corrected) provided the stated yields. For stoichiometric reactions (1–6), the yield is calculated from starting nickel complex **IIA**. [b]Equivalents with respect to [Ni]. [c]Mn^0 powder was prestirred with Et_3SiCl. [d]TDAE = tetrakis(dimethylamino)ethylene. [e]Yield calculated from the amount of enone added to catalytic reactions (0.5 mmol).

3.8. Kinetic Competence of IA and IIA. To investigate if the observed stoichiometric reactivity is relevant to the catalytic reactions, we compared reactions catalyzed by **IA** and **IIA** with reactions catalyzed by several other nickel precursors ($Ni(acac)_2$, $Ni(cod)_2$, $NiCl_2(dme)$). Both **IA** and **IIA** were catalytically competent and formed product with rates and selectivities comparable to our standard reaction conditions (Figure S8 in the Supporting Information). Close examination of reactions catalyzed by **IA** revealed that biphenyl is formed at early time points. This is in contrast to reactions catalyzed **IIA** or the other nickel precursors, where biphenyl is not observed until significant amounts of product have been formed (Tables S3–S7 in the Supporting Information).

3.9. Potential Transmetalation Mechanism. In analogy to Osakada's mechanism for biaryl formation,[49] we considered whether product could be formed by a transmetalation event between **IA** and **IIA** followed by reductive elimination of product. We observed only biaryl products from the reaction of a 1:1 mixture of **IA** and **IIA**, suggesting that transmetalation between the two different nickel complexes is slower than disproportionation of **IA** (eq 7).[50]



3.10. Potential Organomanganese Intermediates. With manganese metal as the terminal reductant, the potential exists for the intermediacy of arylmanganese reagents. Reactions conducted without nickel but with 1.1 equiv of chlorotriethylsilane did not consume aryl iodide over a period of 24 h (Figures S9 and S10 in the Supporting Information). As compared to our reaction conditions, the synthesis of arylmanganese iodide reagents is reported to require different additives, higher temperatures, and longer reaction times.[51] Further evidence against the intermediacy of ArMnI is that the reaction of **IIA** with iodobenzene and an organic reductant, tetrakis(dimethylaminoethylene) (TDAE), produced more product than the reaction without any reductant (Table 4, entry 6 vs 2). Additionally, organomanganese sensitive functional groups, such as a free aldehyde and trifluoroacetamide, were also tolerated (Scheme 4, products **24** and **31**, respectively).

3.11. Mechanism of Reactions With Alkyl Halides. In light of the results of our studies showing that allylnickel(II) intermediates are key for the conjugate addition of aryl halides, we chose to revisit our mechanistic studies on the conjugate addition of alkyl halides that used terpyridine ligand **L1** (eq 2).

We first examined the rate at which 2-bromoheptane, chlorotriethylsilane, and cyclohexenone reacted with (**L1**)Ni^0(cod) in a manner identical to our studies with ligand **L10**. The results, shown in Figure 5, show that (**L1**)Ni^0(cod) reacts much faster

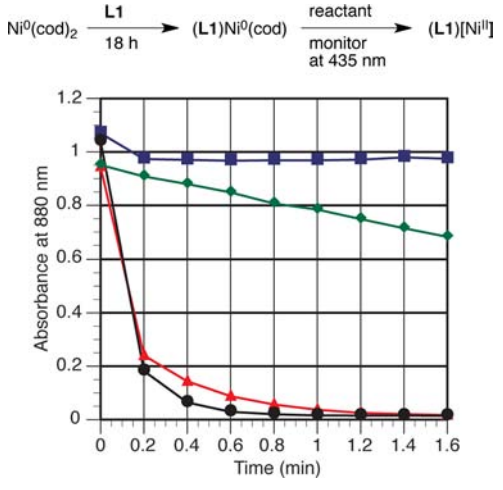
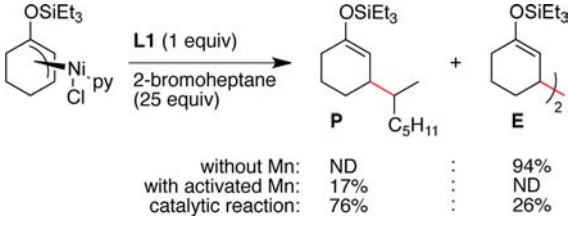


Figure 5. Reaction of (**L1**)Ni(cod) with 2-bromoheptane (green ◆), cyclohexenone + Et_3SiCl (red ▲), Et_3SiCl (●), and cyclohexenone (blue ■) as monitored by UV–vis at 880 nm. For full UV–vis spectra and an expanded plot of all four reactions, see Figures S11 and S12 in the Supporting Information.

with enone and silyl chloride than with 2-bromoheptane. This suggests the "enone-first" mechanism is operative for reactions with alkyl halides as well, in disagreement with our previous report.[26]

Finally, we revisited the reaction of the in situ formed (**L1**)$Ni^{II}(\eta^3$-1-triethylsilyloxycyclohex-2-enyl)Cl with 2-bromoheptane (Scheme 5). Our previous study[26] had shown that

Scheme 5. Reaction of (L1)Ni^0(allyl) with 2-Bromoheptane[a]



[a]See the Supporting Information for full details. Yields of stoichiometric reactions are based upon the amount of nickel; yields of catalytic reaction are based upon the amount of 2-bromoheptane. Yields are uncorrected versus dodecane internal standard.

predominantly enone dimer (**E**) was formed when this complex was reacted with 2-bromoheptane (56% **E** vs 8% **P** with 1 equiv,[26] 94% **E** vs 0% **P** with 25 equiv in Scheme 5), leading us

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to doubt the relevance of allylnickel intermediates. However, the addition of manganese powder activated with Et_3SiCl made a large difference in reactivity and resulted in a reaction that favored product formation over dimer formation. While the yield is modest, this result, along with the oxidative addition studies (vide supra), support the existence of an allylnickel intermediate in the catalytic cycle.

4. DISCUSSION

4.1. Ligand Effects. A major finding of these studies is that the conjugate addition of organic halides to enones can be improved by ligand choice (Figure 6). This study, combined with

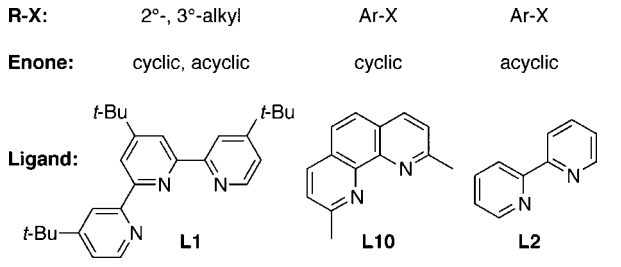

Figure 6. Optimal ligand for different substrate combinations.

our previous communication,[26] demonstrates that a complementarity between substrate and ligand sterics must exist for high yields.

In the context of an allylnickel mechanism (Figure 3), neocuproine (**L10**) enables high yields of product by disfavoring enone homocoupling. Reactions conducted with other ligands produce product and homocoupled enone at earlier time points, followed by eventual biaryl formation. This difference appears to be related to the steric hindrance of the ligand, even on the periphery. As noted in Table 1, substitution on any position of bipyridine or phenanthroline decreases enone homocoupling. In these reactions, more steric hindrance improved selectivity and yield.

The reaction of an (*E*)-enone with iodobenzene (eq 4) or a (*Z*)-enone with a hindered aryl iodide (Scheme 3) demonstrated that too much steric encumbrance at the nickel center could prevent product formation. In both cases, yields could be improved by changing to a less hindered ligand. Simple bipyridine (**L2**) suffices for (*E*)-enones because enone dimerization is slower than for (*Z*)-enones. The reaction of a hindered aryl iodide with a (*Z*)-enone requires a ligand with enough bulk on the periphery to slow enone dimerization, but no steric bulk near the nickel center (**L3**). These results lay the foundation for the design of second-generation ligands with increased generality and selectivity.

Finally, reactions conducted with neocuproine (**L10**) were remarkably fast (~30 min with 1 mol % catalyst at room temperature), and this rate advantage was observed for both (*Z*)- and (*E*)-enones. At this time, the origin of this dramatic effect is unclear.

4.2. Role of Silicon Reagents. As we observed in our studies on the conjugate addition of haloalkanes to enones catalyzed by (**L1**)Ni complexes, silicon reagents are required for the conjugate addition reaction to proceed. Unlike our previous studies, most silicon reagents of moderate steric bulk worked well.

The low reactivity observed without added chlorosilane can be explained by its two roles. One role is in the activation of the Mn surface, which became evident in our stoichiometric studies. Additionally, we could observe small amounts of $Et_3Si{-}O{-}SiEt_3$ formed at early time points in catalytic reactions, suggesting that the silicon reagent is removing an oxide layer from the Mn.

The second role is to completely change the order of reactivity of the two electrophiles and the mechanism of the reaction. The chlorosilane and enone react more rapidly with nickel(0) than organic halides. The enone, which alone reacts slowly with the nickel(0) complex, is activated by the silane to change the order of reactivity; this reactivity is not limited to neocuproine complexes: examination of the selectivity data for reactions in Table 1 over time shows that, regardless of the ligand, aryl dimerization remains slow in the presence of both chlorosilane and enone. Only when enone and chlorosilane have been consumed does significant biaryl formation occur. Although the propensity of Lewis acids and chlorosilanes to allow for the oxidative addition of enones to both Ni[17a,b] and Pd[24] is well documented in the literature, this is the first time that the relative magnitude of this effect has been reported and exploited for reaction design.

Our UV–vis data (Figures 4 and 5) and NMR data (Figures S4 and S5) suggest that the chlorosilane alone can react with the nickel(0) complex, resulting in a new, paramagnetic species. At this time, the structure of this putative complex and its role in the catalytic cycle is unclear. It is important to note that the rapid oxidative addition of a chlorosilane Si–Cl bond is rare.[45] We are currently studying this reaction and will report our results in due course.

4.3. Functional-Group Compatibility and Synthetic Utility. These studies show, for the first time, the potential of reductive conjugate addition reactions for the formation of functionalized silyl enol ether products from the union of organic halides, enones, and chlorosilanes. Functional-group tolerance and chemoselectivity are promising. For example, the reaction is highly selective for reaction at the iodine–carbon bond over nearly all other electrophiles, including C–X and C–O bonds, acidic protons, and carbonyls. As compared to copper-catalyzed reactions, the primary method of forming the same silyl enol ether products, functional group compatibility is superior.

Rh-catalyzed methods using arylboronic acids have seen wide application in synthesis[9c] due in part to excellent functional-group compatibility and broad Michael acceptor scope.[52] The nickel-catalyzed reductive conjugate addition has just as great potential in synthesis because it combines the functional-group tolerance of the Rh-catalyzed reactions with (1) a broader pool of aryl substrates and (2) the ability to form silyl enol ether products.

The products in Schemes 1–4 are mostly 3-arylcyclohexanone derivatives, a frequent motif found in the pharmaceutical patent literature.[53] Despite their prevalence, relatively few examples of the silyl enol ethers of these valuable intermediates have been reported (24 examples, no patents), and we expect that they would be useful for drug design.

Finally, the ability to form TBS or TES silyl enol ethers provides some flexibility in synthetic planning because the TBS ethers are much more resistant to cleavage under acidic conditions.[54] Because the electrophilicity and steric size of the silicon reagent are easily tuned, the choice of silicon reagent could be used to match or differentiate the reactivity of two different substrates or improve selectivity of poorly selective reactions.

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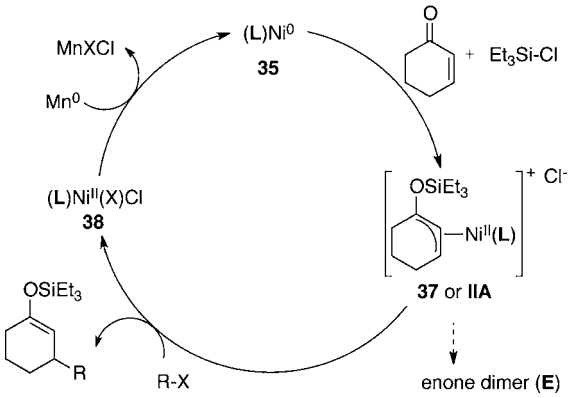
4.4. Mechanism. All previous reports on nickel-, cobalt-, and palladium-catalyzed reductive conjugate addition reactions proposed, and in many cases provided strong evidence for, reductive Heck-like mechanisms (Figure 2). As compared to these previous reactions, our new nickel-catalyzed conditions provide different products (silyl enol ethers), better results with β-substituted enones than other Ni- or Co-catalyzed methods, and better results with electron-poor aryl halides than the Pd-catalyzed methods. Our hypothesis was that these improvements could be the result of a change in mechanism to one involving an allylnickel intermediate (Figure 3), but our previous studies on the conjugate addition of alkyl bromides had proven inconclusive.

Our new results point to a new unified, "enone-first" mechanism that contains an allylnickel intermediate (Scheme 6)

Scheme 6. Unified Mechanism



and a revision of our earlier suggestion that an alkyl-first mechanism was likely for reactions of alkyl halides.[26] The key evidence in support of this result is: (1) allylnickel intermediates are formed faster than either arylnickel or alkylnickel species, and (2) only the allylnickel intermediates react to form the observed products with the correct selectivity.

While allylmetal intermediates have been postulated in nickel- and palladium-catalyzed conjugate additions of various organometallic reagents to enones,[21−25] they have never been demonstrated to be an intermediate in catalytic coupling reactions of organic halides with enones.[55]

At this time, we do not have firm evidence for the mechanism by which the allylnickel(II) intermediate **37** reacts with iodoarene to form product. From the literature, two proposals exist for the reaction of allylnickel complexes with electrophiles. Hegedus showed that stoichiometric reactions of allylnickel(II) reagents proceed via a complex radical-chain-like process involving reactive nickel(I) and nickel(III) intermediates as well as less reactive nickel(0) and nickel(II) intermediates.[19d] The other proposal is a single-electron reduction of allylnickel(II) to allylnickel(I), followed by oxidative addition of R−X, and reductive elimination of product, but no supporting data are available.[55−57]

Differentiating between these mechanisms will require further studies, but a few observations are worth noting. Stoichiometric reactions of allylnickel **IIA** provided more product in the presence of added reductant (Table 3, entries 11−13), consistent with either mechanism, but the formation of small amounts of product without added reductant is harder to explain with an allylnickel(I) intermediate. We have looked for radical intermediates using a radical trap, 1,4-cyclohexadiene, but results were inconclusive.

Hegedus noted that stoichiometric reactions of allylnickel(II) reagents were accelerated by the addition of reductant (sodium naphthalenide), irradiation with a tungsten lamp, or the addition of excess $NiBr_2$.[19d] Mackenzie reported on stoichiometric reactions of allylnickel(II) reagents generated from enones and silyl chlorides, which required UV irradiation to react with electrophiles.[17a,b] Consistent with the manganese powder initiating the reaction or reducing an allylnickel intermediate, a reaction conducted in the dark proceeded the same as reactions run in the light. Similar to Hegedus's observations, we also found that 10 mol % of 4-nitroiodobenzene significantly inhibited product formation.

4.5. Selectivity. The ordered coupling of three electrophiles, enone, trialkylchlorosilane, and organic halide, requires selectivity at two different stages. Our results show that selectivity is achieved because (1) in the presence of a trialkylchlorosilane, (**L**)Ni^0 reacts more rapidly with enone than with iodoarene; and (2) proper ligand substitution slows the reaction of the allylnickel species with more enone and facilitates selective formation of product. Our results demonstrate that the selectivity and reactivity in the second step is the weakest point of the current catalysts, and further improvement in catalyst design has the potential to allow the use of more hindered substrates and less reactive organic halides.

5. CONCLUSIONS

The reductive conjugate addition of haloarenes, vinyl halides, and alkylhalides to α,β-unsaturated ketones or aldehydes forms silyl enol ether products in good yield. The only other methods that can form these products require preformed organometallic reagents (R−MgX, R−Ti$(OR)_3$, R−ZnX). These other reactions have limited functional-group compatibility, usually require cryogenic temperatures, and almost always require the synthesis of the organometallic reagent. This new reductive conjugate addition displays superior functional group compatibility to Cu-catalyzed methods and is comparable to the mildest conjugate addition approaches that cannot form silyl enol ether products (Rh-catalyzed conjugate addition of arylboronic acids,[9] and Pd-catalyzed addition of iodoarenes[13]). We expect that further studies by our group and others will be able to further expand the scope of the Michael acceptor and render the reaction enantioselective. Encouragingly, the choice of ligand has a profound affect on the selectivity and reaction rate, presenting a clear focus for these future efforts.

In contrast to all previous reports on reductive conjugate addition reactions, our studies support a mechanism involving an allylnickel intermediate. Allylnickel(II) intermediates have proven versatile in the conjugate addition of various organometallic reagents, enabling unconventional reactivity.[21−25] Our own results show that the Mackenzie allyl intermediates[17] allow the use of substrates that were unreactive for reductive-Heck conjugate addition reactions (β-substituted enones,[13] electron-poor aryl halides[14,15]). Interestingly, we have shown that the oxidative addition of an enone to nickel(0) in the presence of Et_3SiCl is an order of magnitude faster than the oxidative addition of iodobenzene. The chlorosilane reagent activates the enone substrate and enables selective cross-coupling with other reactive electrophiles in a catalytic process. Given the broad, selective stoichiometric reactivity of allylnickel reagents with a wide variety of electrophiles,[18] we expect that a correspondingly wide variety of electrophile conjugate-addition reactions will soon be possible.

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6. EXPERIMENTAL SECTION

Representative Procedure. For the synthesis of triethyl((1,4,5,6-tetrahydro-[1,1′-biphenyl]-3-yl)oxy)silane (**4a**), no precautions were taken to exclude air or moisture besides using anhydrous-grade *N*,*N*-dimethylacetamide (DMA) and oven-dried 1-dram vials and stir-bars. On the benchtop, $Ni(acac)_2$ (2.56 mg, 0.01 mmol), neocuproine (2.08 mg, 0.01 mmol), and manganese powder (110 mg, 2.00 mmol) were weighed directly into a 1-dram vial equipped with a Teflon-coated stir bar. DMA (3 mL), 2-cyclohexen-1-one (96.8 μL, 1.00 mmol), iodobenzene (111 μL, 1.00 mmol), and chlorotriethylsilane (185 μL, 1.10 mmol) were added using an automatic pipet. The vial was then capped with a PTFE-faced silicone septum, and stirred at 1200 rpm at room temperature. Upon completion, the reaction mixture was purified using silica gel column chromatography on deactivated silica gel (1% EtOAc in hexanes). Silyl enol ether **4a** was obtained as a faint yellow oil (221 mg, 77% yield).

■ ASSOCIATED CONTENT

Supporting Information

Supplementary Tables S1−S7, Figures S1−S10, detailed experimental procedures, and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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