ORGANIC LETTERS
2011
Vol. 13, No. 10
2766–2769

Reductive Conjugate Addition of Haloalkanes to Enones To Form Silyl Enol Ethers

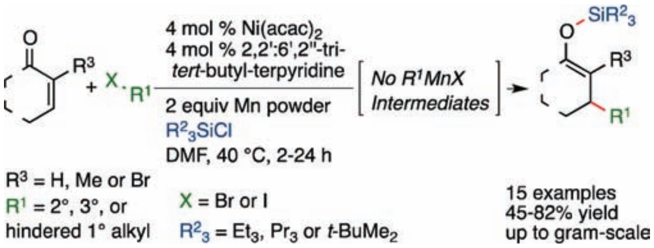
Ruja Shrestha and Daniel J. Weix*

Department of Chemistry, University of Rochester, Rochester, New York 14627-0216, United States

daniel.weix@rochester.edu

Received April 4, 2011

ABSTRACT



A new method is presented for tandem reductive conjugate addition and silyl enol ether formation from cyclic and acyclic enones and enals in the presence of a Mn reductant, a Ni(terpyridine) catalyst, and a trialkylchlorosilane. The addition of secondary, tertiary, and hindered primary haloalkanes is demonstrated. Preliminary studies on the mechanism show that the intermediacy of L1(Ni)(η^3-1-triethylsilyloxyalkenyl)X or in-situ-formed RMnX is unlikely.

The conjugate addition of preformed organometallic reagents to electrophilic olefins is a key bond-forming reaction in modern synthesis.[1] Among the most useful variants are tandem conjugate addition–enolate trapping reactions to form silyl enol ethers. These products are versatile intermediates for further C–C bond formation or functionalization.[2] Several conditions for tandem conjugate addition–silyl enol ether formation have been developed; however, most[3] share the requirement of a preformed organometallic reagent (R—M = R$_2$Zn, RZnX, RMgBr, R$_3$Al). These organometallic reagents are generally not commercially available, and their synthesis often requires cryogenic temperatures and rigorous exclusion of air and moisture, which complicates synthetic routes.

Although great strides have been made in the synthesis of functionalized organometallic reagents,[4] direct use of the corresponding haloalkane would eliminate the need for a preformed organometallic reagent and avoid many of the associated problems. In contrast to traditional conjugate addition reactions with selectivity built into the reagents themselves, *the major challenge associated with a direct reductive approach is selectivity for cross-coupling over competing dimerization reactions*. For example, our envisioned reductive approach requires the ordered coupling of three different electrophiles: a haloalkane, an α,β-unsaturated ketone, and a trialkylchlorosilane reagent. Mackenzie reported a stepwise stoichiometric-nickel approach that tolerates β-substitution on the enone.[5a] Other methods which are stoichiometric in nickel or copper have also been

---

(1) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. Cu: (b) Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308. (c) Taylor, R. J. K. *Synthesis* **1985**, 364. (d) Nakamura, E. *Synlett* **1991**, 539. (e) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 186. Ni:(f) Ashby, E. C.; Heinsohn, G. *J. Org. Chem.* **1974**, *39*, 3297. (g) Bagnell, L.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1975**, *28*, 817. (h) Loots, M. J.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045. (i) Kobayashi, Y. Reaction of Alkenes and Allyl Alcohol Derivatives. In *Modern Organonickel Chemistry*, Tamaru, Y., Ed.; Wiley-VCH: Weinheim, 2005; p 56.

(2) See ref 1a, 1c, and Kobayashi, S.; Manabe, K.; Ishitani, H.; Matsuo, J.-I. *Sci. Synth.* **2002**, *4*, 317.

(3) Selected alternative strategies: Radical additions: (a) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377. (b) Rowlands, G. J. *Tetrahedron* **2009**, *65*, 8603. Alkenes or alkynes in place of organometallic reagents: (c) Trost, B. M.; Surivet, J.-P.; Toste, F. D. *J. Am. Chem. Soc.* **2001**, *123*, 2897. (d) Li, W.; Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2009**, *131*, 17024. (e) Ho, C.-Y.; Schleicher, K.; Chan, C.-W.; Jamison, T. *Synlett* **2009**, 2565.

(4) *Handbook of Functionalized Organometallics: Applications in Synthesis*. Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005.

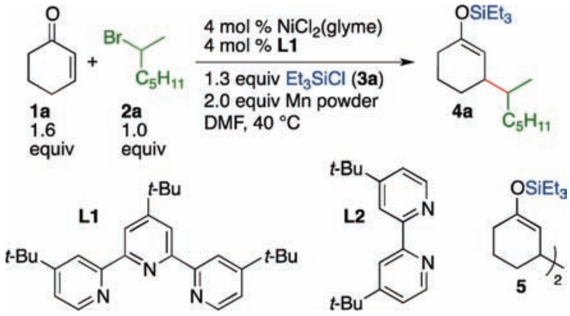
10.1021/ol200881v

reported,[5] but previous studies on the reductive conjugate addition with nickel[6] and cobalt[7] catalysts were limited to electrophilic olefins without β-substitution or with two activating groups.[8] Montgomery reported a conjugate addition–aldol reaction,[6f,g] but the analogous silyl enol ether formation has not been reported. Finally, the use of haloalkanes as substrates also introduces the additional challenge of β-hydride elimination,[9] and only a few examples have been published.[10]

Herein we report an approach to direct reductive conjugate addition reactions (Table 1) that addresses these challenges. Preliminary mechanistic studies suggest a general strategy for the development of cross-selective reductive coupling reactions.

In preliminary studies,[11] the best yields of silyl enol ether **4a** were obtained from reactions containing Ni/**L1** catalyst, chlorotriethylsilane (**3a**), and DMF solvent (Table 1, entry 1).[12] Reactions conducted without ligand **L1** (2,2′:6′,2″-tri-*tert*-butyl-terpyridine) resulted in the slow consumption of starting materials (entry 2). The use of pyridine or bipyridine (**L2**) in reactions instead of **L1** resulted in the formation of large amounts of dimer **5** (entries 3 and 4 respectively). Reactions conducted without TES-Cl (**3a**) consumed both 2-cyclohexen-1-one (**1a**) and 2-bromoheptane (**2a**) but produced only small amounts of the corresponding ketone product (entry 5). Lastly, reactions conducted with a slight excess of either the enone (**1a**) or the haloalkane (**2a**) provided similar results (entries 9 and 10 respectively). Thus, the less costly component may be used in excess.

Table 1. Reductive Coupling of Cyclohexenone with 2-Bromoheptane[a]



entry	change from optimized conditions	yield **4a**[b] (%)	yield **5** (%)
1	None	76	26
2	No ligand (omit **L1**)	6[c]	6
3	4–12 mol % pyridine in place of **L1**	5–7	23
4	4 mol % **L2** in place of **L1**	15	74
5	No chlorotriethylsilane (**3a**)	4[c,d]	0
6	No nickel	3[c]	0
7	$Ni(acac)_2$ in place of $NiCl_2$(glyme)[e]	77	38
8	No Mn powder	NR	NR
9	1.2–1.4 equiv of **1a** to 1.0 equiv of **2a**	66–74	25–36
10	1.2–1.6 equiv of **2a** to 1.0 equiv of **1a**	65–68	21–25
11	1 mol % $NiCl_2$(glyme) and **L1**	77[f]	16
12	10 mol % $NiCl_2$(glyme) and **L1**	33	59

[a] Reactions were run on 0.5 mmol scale in 2 mL of DMF for 14–24 h. [b] Uncorrected GC yield vs dodecane internal standard, mixture of regio- and stereoisomers. See Supporting Information for details. [c] Both starting materials remained (76–87% by GC). [d] Ketone product obtained instead of enol ether **4a**. [e] $Ni(acac)_2$ is 17¢/mmol vs \$2.88/mmol for $NiCl_2$(glyme). [f] Reaction time was 36 h.

The scope of our new reductive coupling process is summarized in Scheme 1 (next page). Several different silicon reagents were effective promoters for reactions of 2-bromoheptane (**2a**) with 2-cyclohexen-1-one (**1a**), providing silyl enol ether products **4a–c** which possess a range of stabilities.[11]

A variety of haloalkanes (**2**) reacted with enone **1a** to provide silyl enol ethers (**4d–j**) in good yield (Scheme 1). 2-Iodoheptane reacted much faster than 2-bromoheptane (2 h vs 18 h), and 2-chloroheptane was unreactive under these conditions. The conjugate addition–enolate trapping reaction tolerates a variety of cyclic haloalkanes, including a tetrahydropyran, (**4d**, **e**, **j**), and ester (**4h**), or nitrile (**4i**) functionality. 2-Bromocyclohexenone provides a high yield of product **4m** without loss of the vinylic bromide.

Even a tertiary haloalkane, *tert*-butyl bromide, coupled to form product **4g** with adjacent tertiary and quaternary carbons in high yield and without detectable isomerization to the *iso*-butyl product.[13] Only a few examples of the use

---

(5) Stoichiometric: Ni: (a) Johnson, J. R.; Tully, P. S.; Mackenzie, P. B.; Sabat, M. *J. Am. Chem. Soc.* **1991**, *113*, 6172. (b) Manchand, P. S.; Yiannikouros, G. P.; Belica, P. S.; Madan, P. *J. Org. Chem.* **1995**, *60*, 6574. (c) Bonjoch, J.; Solé, D.; Garcia-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230. (d) Nicolaou, K. C.; Roecker, A. J.; Follmann, M.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2107. Cu: (e) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149. (f) Shen, Z.-L.; Cheong, H.-L.; Loh, T.-P. *Tetrahedron Lett.* **2009**, *50*, 1051 and references cited therein.

(6) Nickel-catalyzed: Review: (a) Condon, S.; Nédélec, J.-Y. *Synthesis* **2004**, 3070. Chemical reductants: (b) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Ronchi, A. U. *J. Organomet. Chem.* **1986**, *301*, C62. (c) Lebedev, S. A.; Lopatina, V. S.; Petrov, E. S.; Beletskaya, I. P. *J. Organomet. Chem.* **1988**, *344*, 253. (d) Sustmann, R.; Hopp, P.; Holl, P. *Tetrahedron Lett.* **1989**, *30*, 689. (e) Yu, S.; Berner, O. M.; Cook, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7827. (f) Subburaj, K.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 11210. (g) Chrovian, C. C.; Montgomery, J. *Org. Lett.* **2007**, *9*, 537. (h) Gong, H.; Andrews, R. S.; Zuccarello, J. L.; Lee, S. J.; Gagné, M. R. *Org. Lett.* **2009**, *11*, 879. (i) Kim, H.; Lee, C. *Org. Lett.* **2011**, *13*, 2050–2053. Electrochemical methods: (j) Gosden, C.; Pletcher, D. *J. Organomet. Chem.* **1980**, *186*, 401. (k) Condon-Gueugnot, S.; Léonel, E.; Nédélec, J.-Y.; Périchon, J. *J. Org. Chem.* **1995**, *60*, 7684.

(7) Co-catalyzed: Chemical: (a) Shukla, P.; Hsu, Y.-C.; Cheng, C.-H. *J. Org. Chem.* **2006**, *71*, 655. (b) Amatore, M.; Gosmini, C.; Périchon, J. *J. Org. Chem.* **2006**, *71*, 6130. (c) Amatore, M.; Gosmini, C. *Synlett* **2009**, 1073. Electrochemical: (d) Scheffold, R.; Dike, M.; Dike, S.; Herold, T.; Walder, L. *J. Am. Chem. Soc.* **1980**, *102*, 3642. (e) Ozaki, S.; Nakanishi, T.; Sugiyama, M.; Miyamoto, C.; Ohmori, H. *Chem. Pharm. Bull.* **1991**, *39*, 31. (f) Gomes, P.; Gosmini, C.; Nédélec, J.-Y.; Périchon, J. *Tetrahedron Lett.* **2000**, *41*, 3385.

(8) Generally only acrylates, methyl vinyl ketones, fumarates, or maleates produce high yields. For a single coupling in 20% yield with ethyl crotonate, see ref 6k.

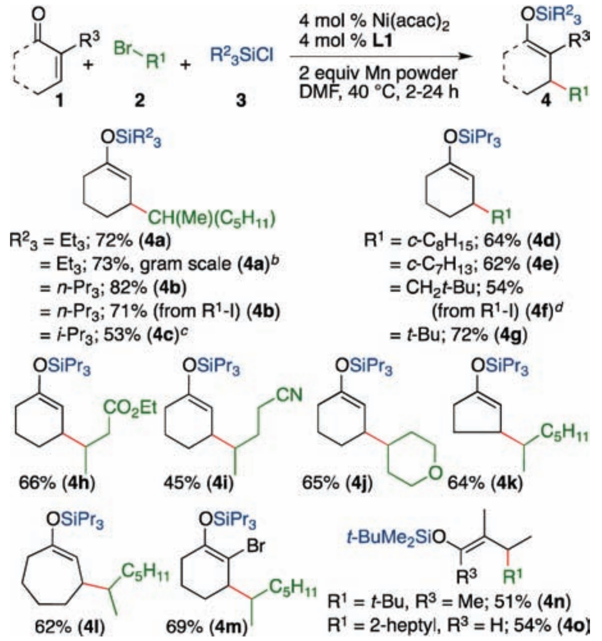
(9) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656.

(10) See refs 6c (2 examples), 6d (3 examples), 6h (glycosyl bromides only), 7a (13 examples), 7d (intramolecular), and 7e (intramolecular).

(11) See Supporting Information for Tables S1 (more detailed optimization table), S2 (solvent effects), and S3 (effect of silicon reagent) as well as details for the TDAE and stoichiometric studies.

(12) Trialkylchlorosilane reagents accelerate copper-mediated conjugate addition reactions: (a) See ref 1d. (b) Lipshutz, B. H.; Dimock, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283. (c) Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288.

Scheme 1. Scope of Conjugate Addition Reaction[a]



[a] Reactions were run on 1.0 mmol scale in 2 mL of DMF. For products **4a**–**e**, **4i**, and **4k**–**o** the ratio of reactants **1**:**2**:**3** = 1.6:1.0:1.3, for **4f**–**h** and **4j** the ratio was 1.0:2.0:1.3. Yields are isolated yields, average of two runs, mixture of isomers. [b] Single run. [c] Silyl triflate was used. [d] Yield of deprotected ketone product. Crude product was deprotected by treatment with 1 M HCl at 40 °C for 8 h.

of tertiary haloalkanes in metal-catalyzed coupling reactions have been published.[14] In addition, neopentyl iodide coupled in good yield (**4f**). Less hindered primary haloalkanes and benzylic secondary haloalkanes do not form product **4** because of rapid dimerization.[15]

A variety of cyclic and acyclic alkenones participate in the reaction (**4k**–**o**), including substrates with 2-substitution (**4m**–**o**) and an aldehyde substrate (**4o**). Acyclic alkenones without 2-substitution provide lower yields under these conditions (33% yield for 3-penten-2-one). Finally, the reaction to form **4a** could be scaled to 10 mmol without complication.

Several mechanistic possibilities exist for reactions involving the reductive coupling of electrophiles. We considered three general mechanisms for our reductive conjugate addition reaction (Figure 1): (1) in situ formation of an organometallic reagent (e.g., RMnBr) followed by conventional conjugate addition (Mechanism A),[1f–i,16,17] (2) disproportionation of two different organonickel intermediates (Mechanism B), and (3) sequential reactions of electrophiles at a single metal center (Mechanisms C[5a] and D[15]).

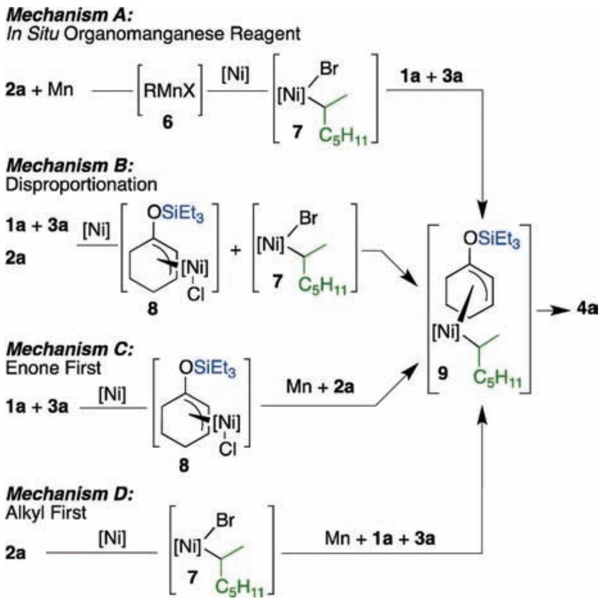


Figure 1. Potential mechanisms.

Our results strongly argue against Mechanism A: (1) a reaction run in the presence of *p*-tolualdehyde did not produce any product from the addition of "RMnX" to the aldehyde;[11,18] (2) reactions conducted using manganese (66% yield), zinc (52% yield), and tetrakis(dimethylamino)-ethylene (TDAE)[19] (44% yield) as reducing agents provided similar yields of **4a**.[11,20] Thus, nickel is the only metal required, and the mechanism is distinct from that of traditional conjugate addition reactions.[5–7]

To evaluate Mechanisms B and C (Figure 1), we conducted a series of stoichiometric studies on isolated (pyridine)Ni(η^3-1-triethylsilyloxycyclohexenyl)Cl (**10**) (Table 2).[21] We disfavor mechanism B at this time for

---

(13) Isomerization with related complexes: Ni: (a) Breitenfeld, J.; Vechorkin, O.; Corminboeuf, C.; Scopelliti, R.; Hu, X. *Organometallics* **2010**, *29*, 3686. Fe: (b) Vela, J.; Vaddadi, S.; Cundari, T. R.; Smith, J. M.; Gregory, E. A.; Lachicotte, R. J.; Flaschenriem, C. J.; Holland, P. L. *Organometallics* **2004**, *23*, 5226.

(14) Representative examples: Pd: (a) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, *21*, 691. Co:(b) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137. (c) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem.—Eur. J.* **2004**, *10*, 5640. (d) Reference 7a. Ag: (e) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 969. (f) Someya, H.; Yorimitsu, H.; Oshima, K. *Tetrahedron Lett.* **2009**, *50*, 3270. (g) Mitamura, Y.; Someya, H.; Yorimitsu, H.; Oshima, K. *Synlett* **2010**, 309. Cu:(h) Sai, M.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1194. Ni: (i) Reference 6d.

(15) Bromooctane yields only **5** and hexadecane. Observation of rapid formation of alkyl dimers from [(**L1**)Ni(R)]I: (a) Jones, G. D.; McFarland, C.; Anderson, T. J.; Vicic, D. A. *Chem. Commun.* **2005**, 4211. Reductive dimerization of alkyl halides catalyzed by (**L1**)NiX$_2$: (b) Goldup, S. M.; Leigh, D. A.; McBurney, R. T.; McGonigal, P. R.; Plant, A. *Chem. Sci.* **2010**, 383. (c) Prinsell, M. R.; Everson, D. A.; Weix, D. J. *Chem. Commun.* **2010**, *46*, 5743.

(16) Organomanganese reagents in conjugate addition reactions: (a) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1986**, *27*, 569. (b) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1989**, *30*, 3541.

(17) For a nickel-catalyzed reductive conjugate addition that is proposed to proceed by in situ formation of organozinc reagents, see ref 6h.

(18) Organomanganese reagents add to aldehydes rapidly at rt: Cahiez, G.; Normant, J. F. *Tetrahedron Lett.* **1977**, *18*, 3383.

(19) (a) Kuroboshi, M.; Tanaka, M.; Kishimoto, S.; Goto, K.; Mochizuki, M.; Tanaka, H. *Tetrahedron Lett.* **2000**, *41*, 81. (b) Wiberg, N. *Angew. Chem., Int. Ed.* **1968**, *7*, 766.

(20) We previously used a similar experiment to establish a similar point: Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920.

two reasons: (1) attempts to form product **4a** by combining isolated complex **10** with a mixture of Ni(cod)$_2$, **L1**, and 2-bromoheptane (**2a**) provided only cyclohexenone dimer **5** and heptenes (entry 1, below);[22] (2) selectivity for cross-coupled product **4a** is improved at lower catalyst loadings (Table 1, entries 1, 11, and 12).

Table 2. Stoichiometric Studies with Nickel-Allyl **10**[a]

entry	conditions	yield **4a** (%)[b]	ratio **4a**:**5**:**11**[c]
1	Premixed solution of Ni(cod)$_2$, **L1**, and 2-bromoheptane (**2a**)[d]	nd[e]	00:100:00
2	**2a**	68	81:5:14
3	**2a** and Mn	30	35:nd:65
4	**2a** and **L1**	8	8:56:36
5	**1a**, **2a**, and **L1**	6	7:89:4
6	**L1**, TES-Cl (**3a**), and enone **1a**	nd[e]	nd:100:nd
7	**L1**, **1a**	nd[e]	nd:100:nd
8	**L1**	nd[e]	nd:100:nd

[a] Reactions conducted at 0.05 M in DMF at 40 °C for 17–21 h with equimolar amounts of all reagents. [b] Uncorrected GC yield vs dodecane internal standard. [c] Ratio of products by GC analysis, uncorrected; nd = not detected. [d] Ni(cod)$_2$ and **L1** were premixed until homogeneous, followed by sequential addition of **2a** and **10**. [e] Dimer **5** was formed quantitatively.

The remaining two mechanisms, C and D, differ only in the order of oxidative additions of the electrophiles, alkenone[5a] or haloalkane[15] first (Figure 1). As expected from Mackenzie's studies, pyridine-ligated complex **10** reacted with 2-bromoheptane (**2a**) to form product **4a** in the absence of any added ligand or reductant (Table 2, entry 2).[5a] However, *reactions conducted in the presence of L1 led primarily to dimeric product 5 and reduction product 11* (entry 4). Finally, competition studies of **10** with both 2-bromoheptane (**2a**) and 2-cyclohexen-1-one (**1a**) produced only small amounts of product **4a** and large amounts of dimer **5** (entry 5).

Formation of dimer **5** from the combination of complex **10** and ligand **L1**, even in the absence of enone **1a** and TES-Cl (Table 2, entries 6–8), suggests that the dimer product is derived from disproportionation of 2 equiv of complex **8** (Figure 1). Given that ligand **L1** is required for high yields of **4a** (76% with **L1**, 7% with pyridine; see Table 1), the results from these stoichiometric studies suggest that complex **8** is not an intermediate and Mechanism C leads to the formation of dimer **5**, but not product **4a**.

These stoichiometric studies and our optimization data suggest that the cross-selectivity originates from a catalyst that (1) primarily reacts with one of the two electrophiles first (in this case, the haloalkane) and (2) is slow to dimerize the electrophile that reacts first (dimerization of 2° haloalkanes is slow with **L1**/Ni at 40 °C[15]). In this specific case, we propose that the tridentate terpyridine ligand **L1** favors the formation of the 4-coordinate [(**L1**)Ni(2-heptyl)]Br[23] (**7** in Figure 1) over the 6-coordinate (**L1**)Ni(η^3-1-triethylsilyloxycyclohexenyl)Cl (**8**).[24] Under these mild conditions, [(**L1**)Ni(2-heptyl)]Br (**7**) is slow to react further with more haloalkane but can react with 2-cyclohexen-1-one (**1a**) and chlorotriethylsilane (**3a**) to form product (**4a**). Further studies on the mechanism of this transformation and the application of these design principles to the development of other reductive coupling reactions are in progress.

In conclusion, we report here a strategy to form the products of conjugate addition and enolate trapping by the reductive coupling of a haloalkane, a trialkylchlorosilane, and an electrophilic olefin. The reaction conditions are mild, do not require specialized techniques (assembled on benchtop, no special precautions to exclude air), and proceed in good yield. Future work will elaborate this method further, including expanding substrate scope and investigating stereoselective methods.

Acknowledgment. This work is supported by the University of Rochester. Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund for partial support of this research. Analytical data were obtained from the CENTC Elemental Analysis Facility at the University of Rochester, funded by NSF CHE-0650456. We thank Dr. William W. Brennessel (University of Rochester) for X-ray analysis of complex **10** and Dr. Sandip Sur (University of Rochester) for his assistance with low temperature NMR analysis of complex **10**.

Supporting Information Available. Full experimental procedures, copies of NMR spectra, X-ray data (CIF file), supplementary stoichiometric studies, and supplementary tables of optimization data. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(21) Synthesized in analogy to similar complexes found in ref 5a. See Supporting Information for procedure and full characterization.

(22) Attempts to isolate nickel complex **7** and study its reactivity have been hindered by its relative instability. See ref 15a.

(23) A related [(**L1**)Ni(Me)]I complex has been structurally characterized. Its reduction product, (**L1**)Ni(Me), is a postulated intermediate in Ni-catalyzed Negishi coupling reactions: (a) ref 15a; (b) Jones, G. D.; Martin, J.; McFarland, C.; Allen, O.; Hall, R.; Haley, A.; Brandon, R.; Konovalova, T.; Desrochers, P.; Pulay, P.; Vicic, D. *J. Am. Chem. Soc.* **2006**, *128*, 13175. (c) Lin, X.; Phillips, D. *J. Org. Chem.* **2008**, *73*, 3680.

(24) [(**L1**)Ni(2-heptyl)]Br would be a 16 electron square-planar species, while (**L1**)Ni(η^3-1-triethylsilyloxycyclohexenyl)Cl would be either an 18-electron, 5-coordinate complex or an even less stable 20-electron, octahedral complex. The CSD contains only 19 examples of 18-electron, 5-coordinate LNi(allyl) out of > 900 [Ni](allyl) structures. CSD Version 5.31, accessed Dec. 14th, 2010.