# Nickel-Catalyzed Reductive Conjugate Addition of Primary Alkyl Bromides to Enones To Form Silyl Enol Ethers

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S *Supporting Information*

ABSTRACT: Conjugate addition of organometallic reagents to enones to form silyl enol ether products is a versatile method to difunctionalize activated olefins, but the organometallic reagents required can be limiting. The reductive cross-electrophile coupling of unhindered primary alkyl bromides with enones and chlorosilanes to form silyl enol ether products is catalyzed by a nickel-complexed *ortho*-brominated terpyridine ligand. The conditions are compatible with a variety of cyclic/acyclic enones and functional groups.
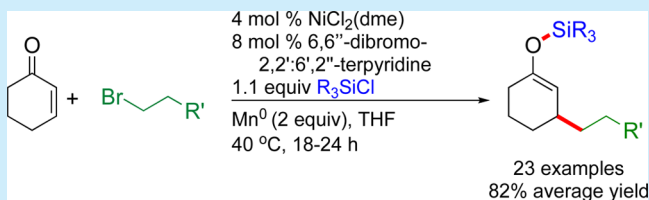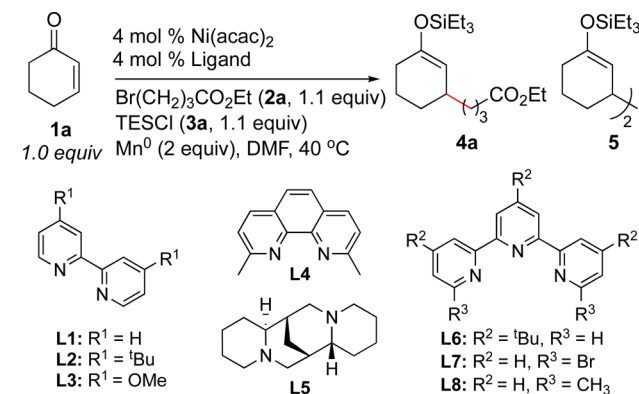
The ability to difunctionalize electrophilic olefins by the nickel- and copper-catalyzed addition of organometallic reagents in the presence of chlorosilanes to form β-alkylated silyl enol ethers has become a standard transformation in organic synthesis,[1] in large part due to the versatility of the resultant products.[2] While widely used, the organometallic reagents required in such processes are usually moisture-, oxygen-, and temperature sensitive.[3,4] We recently reported that aryl, vinyl, secondary alkyl, and tertiary alkyl halides could be coupled with enones and chlorosilanes to form silyl enol ether products in high yield and with strong functional-group compatibility,[5,6] but primary alkyl halides coupled in low yield due to competing dimerization of the alkyl halide. We report herein a new ligand−catalyst combination that solves this challenge and provides high yields of silyl enol ether product with primary alkyl bromides.[7−9]

We had previously found that steric matching between the ligand and substrates could have a large effect on conversion;[5a] therefore, we began by examining a variety of bidentate and tridentate ligands (Table 1). While most ligands formed little to no cross-coupled product **4a** (entries 1−4 and 6), we found that reactions run with sparteine[10] and 6,6″-dibromo-2,2′:6′,2″-terpyridine (entries 5 and 7) gave moderate product yields (see the Supporting Information for a full list of ligands examined). We focused our efforts on terpyridine **L7**. Although this ligand is commercial and can be synthesized in a single step,[11] it has not previously been applied to transition-metal-catalyzed organic synthesis.[12] Considering that the C−Br bonds on **L7** could react with nickel and be alkylated under these reaction conditions,[13,14] we examined 6,6″-dimethyl-2,2′:6′,2″-terpyridine (**L8**) as a ligand but found that reactions with it formed almost no product (entry 8).[15]

Switching the solvent to tetrahydrofuran (THF) and the nickel source to NiCl₂(dme) improved the yield and avoided the challenges of using amide solvents (Table 2, entries 1−3). We found that higher yields and less of enone dimer byproduct **5** were obtained using an excess of ligand (entries 4 and 5). As

Table 1. Ligand Screen of Reductive Coupling of Cyclohexenone with Ethyl 4-Bromobutyrate[a]
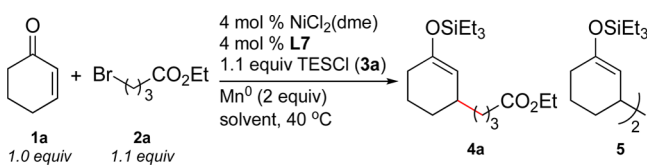

entry	ligand	yield of 4a[b] (%)	yield of 5 (%)
1	L1	9	66
2	L2	0	90
3	L3	0	47
4	L4	0	84
5	L5	31	53
6	L6	0	71
7	L7	41	44
8	L8[c]	0	0
9[d]	none	2	18

[a]Reactions were run on a 0.5 mmol scale in 1 mL of solvent for 18−24 h. [b]Corrected GC yields vs internal standard (dodecane). [c]Both starting materials remained after 36 h at either 1:1 or 1:2 Ni/**L7** in DMF and THF. [d]Reaction time after 48 h.

we had previously found, zinc was a less effective reductant than manganese (entry 6).[2] Upon reexamining tridentate ligands

Table 2. Optimization of Reductive Coupling of Cyclohexenone with Ethyl 4-Bromobutyrate[a]

entry	solvent	yield of 4a[b] (%)	yield of 5 (%)
1	DMF	46	43
2	DMA	34	46
3	DME	51	39
4	THF	73	13
5[c]	THF	82	0
6[d]	THF	18	40
7[e]	THF	72	19

[a]Reactions were run on a 0.5 mmol scale in 1 mL of solvent for 18−24 h. [b]Corrected GC yields vs internal standard (dodecane). [c]8 mol % of ligand. [d]Zn[0] used in place of Mn[0]; reaction time was 48 h. [e]8 mol % of L6.

under the optimized reaction conditions, L6 was found to be a similarly effective ligand (entry 7).

Given the contrast between this result and those in Table 1, we reoptimized the reaction to confirm that Ni/L ratio and solvent change were required (see Table S2). This is a stark example of how small changes in initial conditions and reagents can influence ligand screening efforts.[16]

A wide variety of silylating reagents and α,β-unsaturated ketones are tolerated under optimized reaction conditions (Scheme 1). Several less hindered silicon reagents can be coupled with 2-cyclohexen-1-one (1a) and ethyl 4-bromobutyrate (2a) to form silyl enol ether products (4a−c) in excellent yields (69−98%). Larger silicon reagents, such as *tert*-butylchlorodimethylsilane and chlorotriisopropylsilane, resulted in lower yields. Tri-*n*-propylsilyl enol ethers proved more

Scheme 1. Chlorosilane and Enone Scope[a]
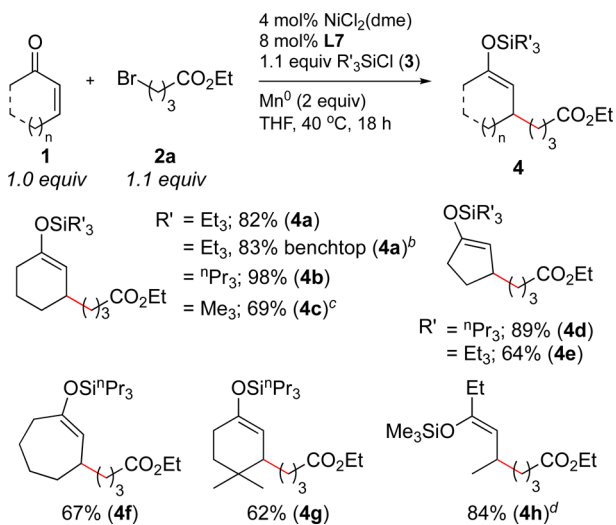
[a]Reactions were run at a 1.0 mmol scale in 2 mL of THF. Yields are after isolation and purification. [b]Reaction was set up on the benchtop in a 50 mL round-bottom flask and run on a 6.0 mmol scale to provide 1.63 g of 4a. [c]Yield of deprotected ketone product after treatment with KF in MeOH for 1 h. See the Supporting Information for deprotection procedure. [d]Isolated as a 3.8:1 mixture of Z and E isomers.

stable to column chromatography and gave higher yields than triethylsilyl ethers in most cases (98% vs 82% yield for cyclohexenone and 89% vs 64% yield for cyclopentenone, respectively). Cycloalkenones with a variety of ring sizes (4d−f) and substitution patterns worked well (4g), but the formation of all-carbon quaternary centers proceeded in low yield (<40%, data not shown). Although standard conditions provided a low yield with an acyclic enone, switching to a less hindered silicon reagent provided 4h in 84% yield. These reactions were assembled in a nitrogen-filled glovebox, but a gram-scale reaction set up and run on the benchtop in a round-bottom flask provided the same yield as a milligram-scale reaction set up in the glovebox (83% vs 82% yield).

We also examined the scope of primary alkyl bromides in this coupling reaction (Scheme 2). While a wide variety of alkyl

Scheme 2. Primary Alkyl Bromide Scope[a]
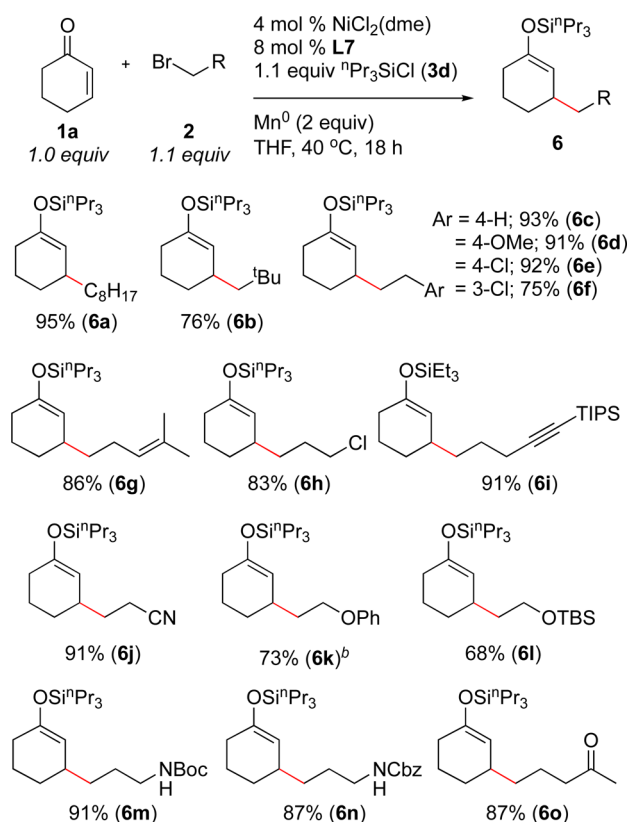
[a]Reactions were run on a 1.0 mmol scale in 2 mL of THF. Yields are after isolation and purification. [b]2.0 equiv of alkyl bromide.

bromides provided high yields, alkyl iodides, including methyl iodide, provided lower yields and alkyl chlorides did not couple. Both unhindered and hindered primary alkyl halides coupled in high yield (6a and 6b), and the yield with neopentyl bromide was a large improvement over the yield previously reported with neopentyl iodide (76% vs 54%).[5a] A variety of functional groups were tolerated, including ethers, aryl chlorides, olefins, alkyl chlorides, nitriles, protected alkynes, silyl ethers, ketones, and common nitrogen protecting groups. Trialkylamine and unprotected alkynes were not tolerated in substrates. In addition, activated alkyl halides, such as cinnamyl chloride and propargyl bromide, did not provide a high yield of product.

A variety of these products would be difficult to synthesize by conjugate addition of organometallic reagents and demonstrate

the utility of this new method. For example, products **6k** and **6l** would be derived from β-oxy-organometallics that are prone to β-elimination. The free N−H bonds in **6m** and **6n** would also be problematic due to their acidity.

Although the solvent and ligand differ, we propose that the mechanism of this reaction is the same as that proposed previously for more hindered alkyl halides and aryl halides. This is supported by the similarities in side products and reaction conditions.[5b] In those previous studies, $(\mathbf{L})Ni(\eta^3$-1-trialkylsilyloxyallyl)Cl was found to react with a variety of alkyl and aryl halides, presumably by one of the mechanisms reported for stoichiometric reactions of organonickel(II) reagents with organic halides.[17,18] This reaction can be viewed as catalytic version of Mackenzie's stoichiometric chemistry.[4]

In conclusion, the use of a more hindered terpyridine ligands has enabled the first reductive cross-electrophile coupling of primary bromoalkanes with enones and chlorosilanes to form silyl enol ether products. The synergistic combination of ligand concentration and ethereal solvent increased yield and eliminated homodimer formation. The good yields and high functional group compatibility, particularly with substrates for which the corresponding organometallic would decompose, should be of benefit to the synthesis of complex molecules. We are currently examining enantioselective versions of this transformation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03509.

> Additional tables of experimental data, full experimental procedures, and product characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(18) Initial studies suggest a radical intermediate is likely. When 6-bromo-1-hexene was reacted with cyclohexenone under standard reaction conditions, the formation of both alkene (unrearranged) and cyclopentylmethyl (5-*exo-trig* cyclized, rearranged) products were observed.