

Nickel-Catalyzed Sonogashira Reactions of Non-activated Secondary Alkyl Bromides and Iodides**

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Alkynes are recurring structural motifs in a variety of natural products, bioactive molecules, and functional materials.^[1] Among the many methods for the synthesis of substituted alkynes, the transition-metal-catalyzed Sonogashira coupling has proven to be one of the most popular and efficient.^[2] While early studies focused on canonical C(sp)–C(sp²) bond formation, recent attention has been paid to the C(sp)–C(sp³) coupling of terminal alkynes with non-activated alkyl electrophiles. In a pioneering study Fu et al. discovered that N-heterocyclic carbene ligands could promote palladium-catalyzed Sonogashira coupling of primary alkyl bromides and iodides.^[3] Later on Glorius and co-workers extended the work of Fu to even more challenging substrates, that is, non-activated secondary alkyl halides.^[4] The work of the group of Glorius represents an extraordinary example in palladium chemistry, because palladium catalysts can usually promote the coupling of primary, but not secondary alkyl electrophiles.^[5]

In comparison to palladium, nickel is more often used to mediate the cross-coupling of secondary alkyl electrophiles. Extensive recent studies have described nickel-catalyzed Suzuki–Miyaura,^[6] Negishi,^[7] Hiyama,^[8] Kumada,^[9] Stille,^[10] and Heck^[11] reactions of secondary alkyl halides. It is surprising that a nickel-catalyzed Sonogashira reaction of non-activated secondary alkyl halides with terminal alkynes has not been reported. Even for the nickel-catalyzed Sonogashira coupling of primary alkyl halides, there is only one prior report by Hu et al. who used pincer ligands.^[12,13] In continuation of our studies on transition-metal-catalyzed cross-coupling reactions of aliphatic electrophiles,^[14] we now report

the first nickel-catalyzed Sonogashira coupling of non-activated secondary alkyl bromides and iodides. This reaction uses readily available bis(oxazoline) ligands and shows good functional-group compatibility, thus enabling efficient synthesis of a variety of substituted alkynes. Furthermore, we achieved highly diastereoselective C(sp)–C(sp³) cross-couplings of terminal alkynes with 1,3- and 1,4-substituted cyclohexyl iodides.

We started with the coupling of 1-octyne with iodocyclohexane (Table 1). The protocol by Hu et al. was tested first, and it did not afford any desired product (entry 1).^[12] The failure of the Ni^{II} pincer complex **L1** was attributed to the bulky NMe₂ groups. Thus we tested a terpyridine ligand (**L2**) which bears three planar N atoms.^[14a] The desired product was observed albeit in a low yield of 10% (entry 2). This finding encouraged us to test bis(oxazoline) ligands. Gratifyingly *i*Pr-PyBox (**L3a**) and Me-PyBox (**L3b**) improved the yield to 25 and 31%, respectively (entries 3 and 4). After the side chain of oxazoline was completely removed (**L4a**), the yield increased to 39% (entry 5). We then screened the solvent, base, and nickel catalyst (entries 9–11). Under the optimal reaction conditions the GC yield reached 95% with a yield of 88% upon isolation (entry 11). We also tested **L4a**, having different *para*-substituents (**L4b–c**), a bis(oxazoline) with a small bite angle (**L5**), and a bidentate oxazoline ligand (**L6**), but the yield did not improve (entries 12–15). Furthermore, the reaction temperature could be lowered to –20°C while maintaining the yield at 90% (entry 16). Finally, control experiments revealed that the reaction completely shut down without the addition of nickel (entry 17), whereas the yield fell to 15% if CuI was not added (entry 18).

Table 2 shows the scope of the new reaction. Many non-activated secondary alkyl bromides and iodides can be successfully converted into the desired products with modest to high yields (32–89%) at room temperature. Both alkyl and aryl alkynes are good substrates. Both cyclic and acyclic alkyl halides can be transformed. Furthermore, heterocycles such as thiophene, carbazole azetidine, pyrrolidine, and piperidine are tolerated in either of the two coupling partners.

The reaction is compatible with many synthetically relevant functional groups such as ether, fluoride, ketal, amide, sulfonamide, carbamate, and amine groups. The reaction can also tolerate some base-sensitive functional groups such as ester, silyl, and nitrile groups. Some olefin-containing substrates can afford the desired cross-coupling products, and surprisingly, an unprotected OH group (**3w**) can be tolerated in the reaction. An interesting substrate is **3k**, which contains a boronate ester group, and it undergoes the nickel-catalyzed C(sp)–C(sp³) coupling with its C–B bond

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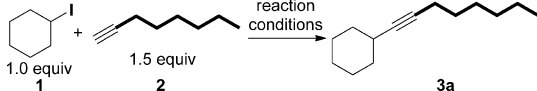
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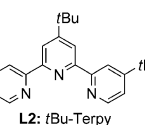
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Table 1: Nickel-catalyzed coupling of iodocyclohexane with 1-octyne.

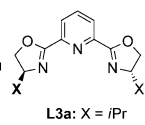




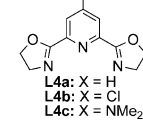
L1: [(MeNN₂)NiCl]



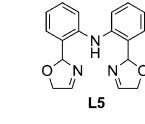
L2: tBu-Terpy



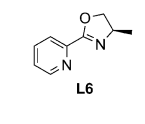
L3a: X = iPr
L3b: X = Me



L4a: X = H
L4b: X = Cl
L4c: X = NMe₂



L5



L6

Entry	Ni catalyst (10 mol %)	Ligand (15 mol %)	Base (2.0 equiv)	Solvent (2 mL)	3 a Yield [%] ^[a]
1	L1 complex	—	Cs ₂ CO ₃	1,4-dioxane	trace
2	NiBr ₂ -diglyme	L2	Cs ₂ CO ₃	1,4-dioxane	10
3	NiBr ₂ -diglyme	L3 a	Cs ₂ CO ₃	1,4-dioxane	25
4	NiBr ₂ -diglyme	L3 b	Cs ₂ CO ₃	1,4-dioxane	31
5	NiBr ₂ -diglyme	L4 a	Cs ₂ CO ₃	1,4-dioxane	39
6	NiBr ₂ -diglyme	L4 a	Cs ₂ CO ₃	DMAc	32
7	NiBr ₂ -diglyme	L4 a	Cs ₂ CO ₃	DMAc/1,4-dioxane ^[b]	45
8	NiBr ₂ -diglyme	L4 a	Cs ₂ CO ₃	DMAc/DME ^[c]	53
9	NiBr ₂ -diglyme	L4 a	Cs ₂ CO ₃	DMAc/DME ^[d]	68
10	NiBr ₂ -diglyme	L4 a	LiOtBu	DMAc/DME ^[d]	82
11	[Ni(cod) ₂]	L4 a	LiOtBu	DMAc/DME ^[d]	95 (88 ^[e])
12	[Ni(cod) ₂]	L4 b	LiOtBu	DMAc/DME ^[d]	52
13	[Ni(cod) ₂]	L4 c	LiOtBu	DMAc/DME ^[d]	67
14	[Ni(cod) ₂]	L5	LiOtBu	DMAc/DME ^[d]	55
15	[Ni(cod) ₂]	L6	LiOtBu	DMAc/DME ^[d]	20
16 ^[f]	[Ni(cod) ₂]	L4 a	LiOtBu	DMAc/DME ^[d]	90
17	—	L4 a	LiOtBu	DMAc/DME ^[d]	trace
18 ^[g]	[Ni(cod) ₂]	L4 a	LiOtBu	DMAc/DME ^[d]	15

[a] The reaction was carried out at room temperature for 24 h. Iodocyclohexane (0.5 mmol) was added into 2 mL solvent with 2 mol % CuI. Yields determined by GC analysis. [b] 0.4 mL DMAc and 1.6 mL 1,4-dioxane. [c] 0.4 mL DMAc and 1.6 mL DME. [d] 0.2 mL DMAc and 1.8 mL DME. [e] Yield of isolated product. [f] Temperature = −20 °C. [g] Without CuI. cod = cyclo-1,5-octadiene, DMAc = *N,N*-dimethylacetamide, DME = dimethoxyethane.

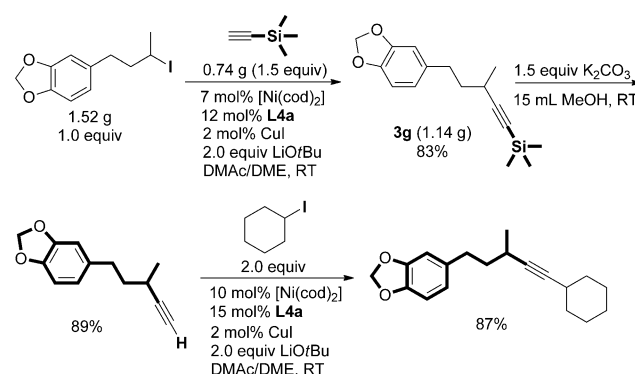
intact. In addition, we observed selective intermolecular cross-coupling of a secondary alkyl iodide over of an intramolecular primary C(sp³)–Cl group (**3f**). These features make additional functionalization reactions possible at either the C–B or C–Cl bond.

A trimethylsilyl-capped alkyne can be readily converted into a terminal alkyne under mild reaction conditions. Thus by using ethynyltrimethylsilane as the starting material (Scheme 1), we could sequentially conduct two alkylation reactions to synthesize a nonsymmetric alkyne having two secondary alkyl substitutions. This particular process expands the scope and flexibility of alkyne synthesis. Scheme 1 also shows that the new nickel-catalyzed C(sp)–C(sp³) coupling could be conducted on gram scale.

The success of the above reactions inspired us to examine their application to the cross-coupling of primary alkyl halides (Table 3). Such cross-couplings may exhibit better functional-group tolerance compared to that under the traditional reaction of primary alkyl halides with alkynyl anions in

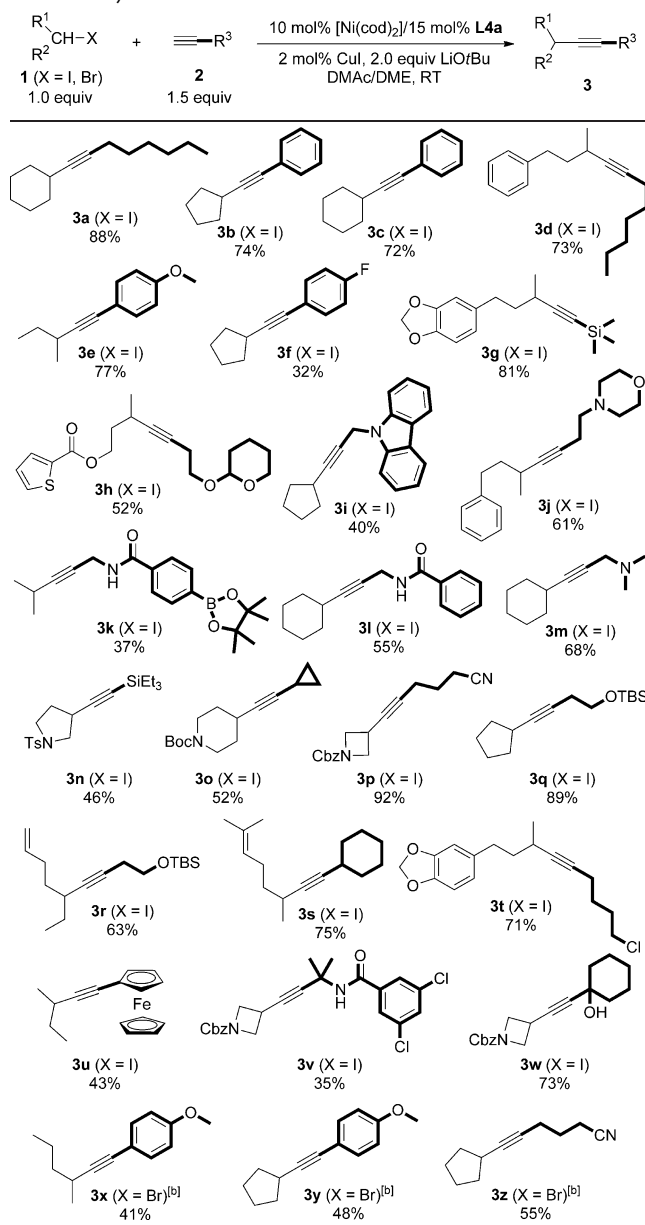
liquid ammonia.^[15] Our tests showed that by using **L4a** as a ligand, many primary alkyl bromides and iodides could be coupled to terminal alkynes in modest to good yields (47–90 %) at room temperature. By comparison, the reaction conditions of Hu et al. for primary alkyl bromides required 100 °C.^[12] Our catalyst system could convert some previously challenging substrates into the desired products. For instance, Hu et al. reported that propynamine was not suitable for nickel-catalyzed Sonogashira reaction of alkyl halides.^[12] Under our reaction conditions **4a** was obtained in 65 % yield. Hu et al. also found that thioether and the 2-H of an indole were not tolerated in their reactions, however, **4b** and **4c** were successfully obtained here.^[12] In addition, a primary alkyl bromide could selectively be converted in the presence of a primary C(sp³)–Cl or a secondary C(sp³)–Br bond. The reaction could also tolerate an aryl chloride or bromide. As to the functional group compatibility, amine, thioether, nitrile, silyl, ether, ketone, and ester groups were tolerated. Primary alkyl iodides were also good substrates for the reaction. Finally, when CH₃I was used (**4p**, **4q**), the reaction could be employed for the methylation of a terminal alkyne.^[16]

Recently Knochel et al. reported palladium-catalyzed diastereoselective cross-coupling of alkynyl bromides with substituted cyclohexylzinc which produced stereochemically defined alkynes with 1,3- or 1,4-remote stereocontrol.^[17] Inspired by the work of Knochel et al. we examined the stereocontrol of the present nickel-catalyzed C(sp³)–C(sp) cross-coupling. Thus 4- or 3-substituted cyclohexyliodides, the thermodynamically preferred *cis*-1,3-disubstituted cyclohexanes were obtained with high diastereoselectivities (92:8 to 99:1). Finally, by using 3β-iodo-5-cholestene as substrate we obtained the alkynylation product **5j** in 63 %



Scheme 1. Synthesis of disubstituted alkynes.

Table 2: Reaction scope with respect to the secondary alkyl halide and terminal alkyne.^[a]



[a] 0.2 mL DMAc and 1.8 mL DME were used. The reactions were conducted on a 0.5 mmol scale. Yields of isolated products after 24 h reaction time. [b] Reaction conditions: 0.5 mmol alkyl bromides, 2 equiv alkynes, 0.5 equiv KI, 0.6 mL DMF and 1.4 mL DME were used. The reaction was carried out at 60°C. Yields of isolated products after 24 h reaction time. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, TBS = *tert*-butyldimethylsilyl, Ts = 4-toluenesulfonyl.

yield as a single diastereomer, whose structure was confirmed by X-ray.

To examine the mechanism of the nickel-catalyzed Sonogashira cross-coupling of alkyl halides, we tested the reaction between 6-iodoheptene with hex-5-ynenitrile [Eq. (1)]. We obtained 15% of the linear coupling product **8a**, while the major product **8b** (50% yield upon isolation) revealed the involvement of a 5-*exo* cyclization process.^[18] Subsequently we also tested the cross-coupling of (bromo-

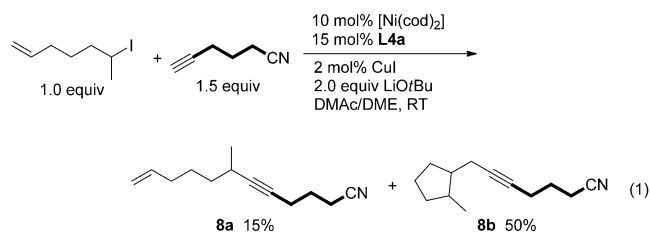
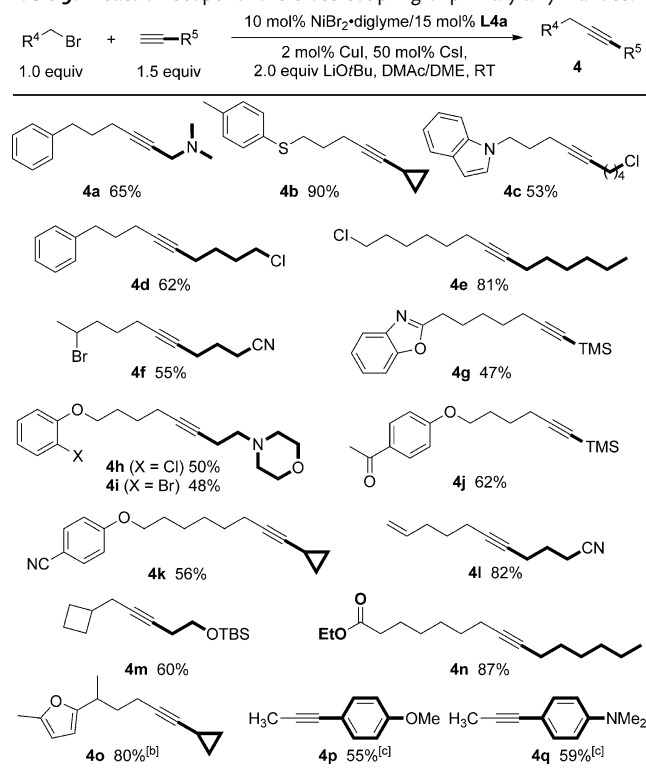


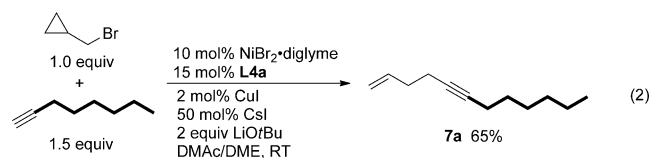
Table 3: Reaction scope for the cross-coupling of primary alkyl halides.^[a]



[a] 0.4 mL DMAc and 1.6 mL DME were used. 0.5 mmol alkyl bromide was used. Yields of isolated products after 24 h reaction time.

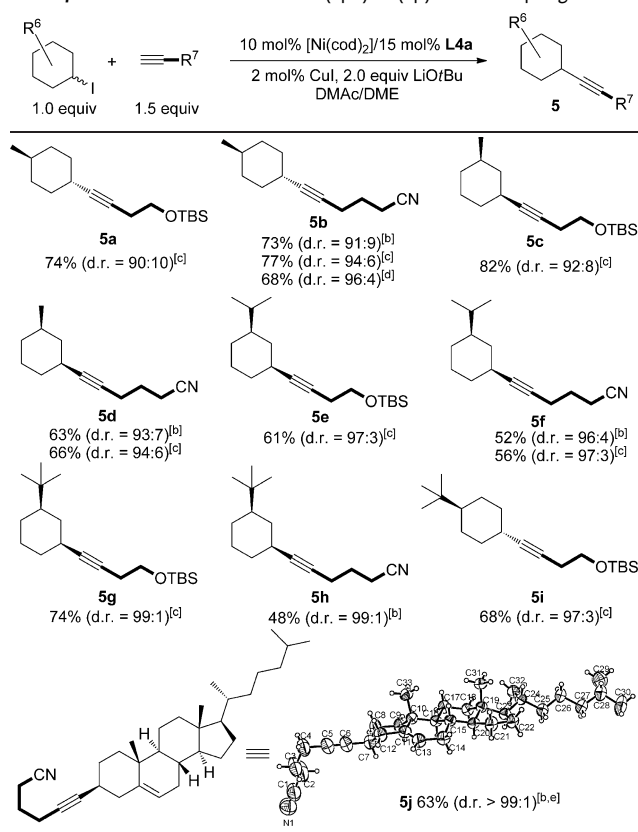
[b] 0.5 mmol alkyl iodine was used. No CsI was added. [c] 2.0 equiv MeI and 1.0 equiv alkynes were used. No CsI was added. Yields were based on the alkynes. TMS = trimethylsilyl.

methyl)cyclopropane [Eq. (2)]. In this reaction we only obtained the ring-opening product **7a** in 65% yield upon isolation.^[19]



The above observations are consistent with a radical-type mechanism which has been proposed for nickel-catalyzed cross-coupling reactions.^[20] In this mechanism, an alkynyl-Ni^I complex is generated first, and then reacts with an alkyl halide through a one-electron, ligand-based redox event to generate a Ni^{II} species. An oxidative radical addition ensues to afford the Ni^{III} complex, which undergoes reductive elimination to generate the desired product, leaving a Ni^I complex to enter

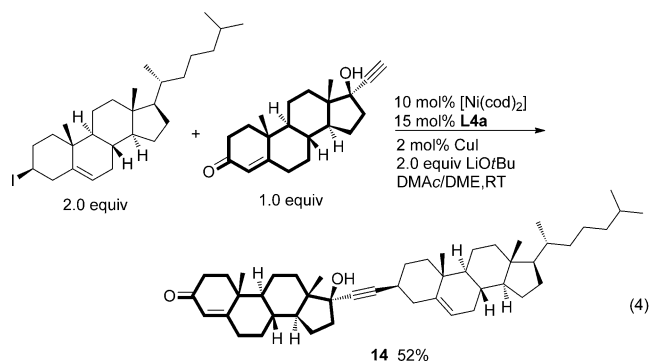
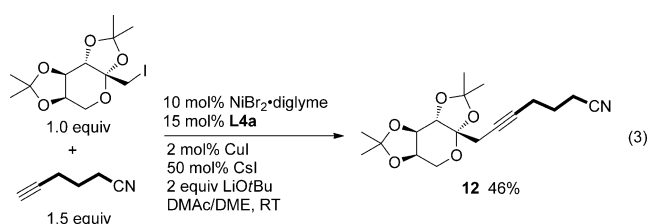
Table 4: Remote stereocontrol in C(sp³)–C(sp) cross-coupling.^[a]



[a] 0.2 mL DMAc and 1.8 mL DME were used. The reactions were conducted in 0.5 mmol scale. Yields of isolated products after 24 h reaction time. The diastereoselectivities were measured by GC. [b] Reaction at RT. [c] Reaction at 0 °C. [d] Reaction at –20 °C. [e] The thermal ellipsoids are displayed in 30% probability.^[21]

the next catalytic cycle. This radical-type mechanism is consistent with the stereochemistry observed in the C(sp)–C(sp³) cross-couplings of terminal alkynes with 1,3- and 1,4-substituted-cyclohexyl iodides. Furthermore, when TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) was added as a radical trap, the present reaction with either a primary or secondary alkyl halide was completely shut down.

Finally, to use nickel-catalyzed C(sp)–C(sp³) coupling for the modification of biologically interesting compounds, we tested the alkynylation of 1-deoxy-1-iodo-diacetonefructose [Eq. (3)]. The desired product was isolated in 46% yield. In addition, we tested the cross-coupling of ethisterone with 3β-iodo-5-cholestene [Eq. (4)], and the desired product was obtained in 52% yield despite the presence of unprotected alcohol, ketone, and olefin groups in the reactants.



To summarize, in the present study we developed the first practical procedure for nickel-catalyzed Sonogashira cross-coupling of terminal alkynes with non-activated secondary alkyl iodides and bromides. This new reaction provides a useful approach to the synthesis of substituted alkynes (in particular, dialkylated asymmetric alkynes) from readily available substrates. The bis(oxazoline) family of ligands was found to be effective for mediating nickel-catalyzed C(sp)–C(sp³) cross-couplings of both secondary and primary alkyl halides under fairly mild reaction conditions (room temperature to –20 °C). The new reaction exhibited good compatibility with a variety of synthetically important functional groups and therefore, could be used for the synthesis and modifications of biologically relevant molecules. Furthermore, high diastereoselectivities were observed in C(sp)–C(sp³) cross-couplings of terminal alkynes with 1,3- and 1,4-substituted cyclohexyl iodides. Our next challenge is to optimize the ligand to induce enantioselectivity in the nickel-catalyzed C(sp)–C(sp³) cross-coupling reactions of secondary alkyl halides.

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- [21] CCDC 962572 (5j) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif