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Nickel-Catalyzed Stereospecific Alkylation of Vinylsiloxanes Using Pyridinium Salts

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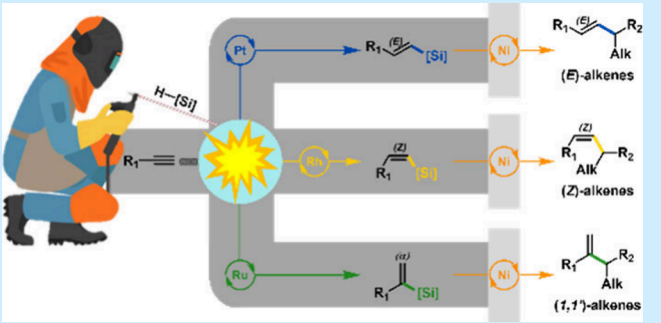
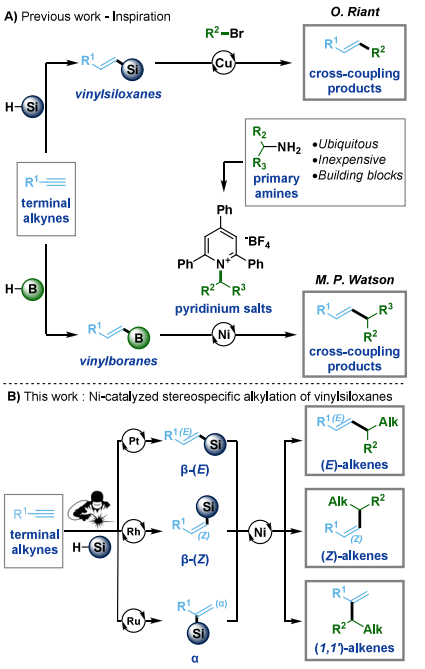
ABSTRACT: A methodology for radical cross-coupling with vinylsiloxanes and pyridinium salts under nickel catalysis is described. Easily implemented from inexpensive and abundant primary amines and terminal alkynes, this Hiyama coupling provides efficient access to (*E*), (*Z*), and (*1,1′*)-alkenes with selectivity control. Operating under mild conditions, this robust strategy applies to a broad range of functional groups with diverse double bond stereochemistries. This versatile reaction is scalable and straightforward, accommodating both secondary and primary alkyl groups.



Metal-catalyzed cross-coupling of organosilicon derivatives provides an efficient route for C−C bond formation, owing to their accessibility, stability, low toxicity, and affordability.[1] Palladium-catalyzed Hiyama coupling, in particular, presents numerous advantages that can surpass those of traditionally used organometallic or organometalloid compounds.[2] The versatility of silicon chemistry enables a wide range of organosilicon reagents, with vinylsiloxanes being especially valuable for introducing unsaturated bonds into complex molecules. In 2014, our group developed copper-catalyzed Hiyama coupling of vinylsiloxanes with carbon-based electrophiles under mild conditions, ensuring high chemical compatibility and complete control over the stereochemistry of the double bond. (Scheme 1A).[3]

Radical cross-couplings (RCC) have recently emerged as a key strategy for C−C bond formation, complementing traditional two-electron methods.[4] This innovative approach has unveiled a diverse array of partners derived from inexpensive building blocks, to generate alkyl radicals. These include halides,[5a,b] carboxylic acids,[5c] redox-active esters,[5d−f] sulfones,[5g] dihydropyridines,[5h] silicates,[5i,j] and Katritzky salts.[5k−m] These pyridinium salts, synthesized in one step from primary amines using commercial pyrylium salts, are bench-stable and redox-active (Scheme 1A).[6] Alkyl amines are inexpensive, widely available, and commonly found in biologically active natural products, making them valuable for RCC to form new C−C bonds. In 2017, Watson and co-workers demonstrated that pyridinium salts serve as effective electrophiles in nickel-catalyzed Suzuki−Miyaura reactions with aromatic boronic acids.[7] Since then, this reaction was extended to numerous coupling partners,[8a−g] including vinylboranes (Scheme 1A).[8h,i]

Scheme 1. A) Cu Catalyzed Hiyama Cross-Coupling and Ni Catalyzed Suzuki−Miyaura Reactions Alkenes; B) Ni Catalyzed Stereospecific Alkylation of Vinylsiloxanes Using Pyridinium Salts



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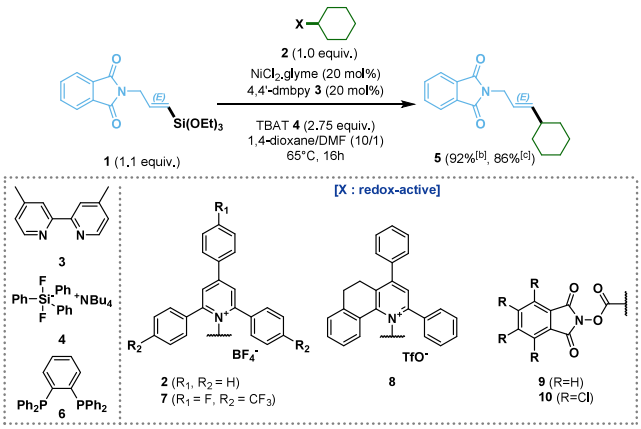
Formed *in situ* by hydroboration of terminal alkynes or commercially available, these organoboron compounds have been coupled with benzylic or secondary alkyl radicals. Inspired by this work, we envisioned merging the chemistry of organosilicon vinylsiloxane compounds in nickel-catalyzed radical cross-coupling with alkylpyridinium salts (Scheme 1B). Our approach would involve an initial atom-economic step of terminal alkyne hydrosilylation using Pt,[9a−c] Rh,[9d] and Ru[9e,f] catalysts highly selective for β-(*E*), β-(*Z*), and α-isomers. This crucial step would weld the double bond stereochemistry, ensuring its preservation through to the cross-coupling products. This work would represent a significant advancement in nickel-catalyzed Hiyama reactions by combining these two elements, an area that has received little attention in the literature.[10] Additionally, this methodology would offer a new pathway to disubstituted alkenes, particularly (*Z*)-olefins, whom synthesis is often less straightforward.[11]

Our study began with the comprehensive optimization of a model alkylation reaction using β-(*E*)-vinylsiloxane **1** (see Supporting Information). After investigating various parameters such as nickel sources, ligands, solvents, and redox-active species, we found that vinylsiloxane **1** efficiently undergoes deaminative alkylation with the classic pyridinium salt **2**, yielding product **5**, which was isolated with an 86% yield (Table 1). The final conditions closely resemble the pioneering work by Watson and Baran on nickel-catalyzed radical cross-couplings with aromatic boronic acids.[8c,12] The optimal catalytic system consists of a 1:1 ratio of $NiCl_2$.glyme, a bench-stable Ni^{II} precursor and 4,4′-dmbpy **3**, although other bipyridyl and phenanthroline also produced good yields.

However, unlike for organoboron chemistry, our method does not require a large excess of valuable vinylsiloxanes, with dimerization being less frequently observed. A 10% yield decrease was noted when a 1:1 ratio was used (Table 1, entry 1). Increasing the temperature to 75 °C gave similar results (entry 2) and a satisfactory yield was achievable at room temperature (entry 3). Subsequently, we evaluated the quantity and nature of fluoride sources commonly used in cross-couplings involving silicon derivatives (entries 4−7). Tetrabutylammonium triphenyldifluorosilicate **4** (TBAT),[13] an anhydrous organic fluoride source, remains the activating agent of choice for vinylsiloxane couplings, consistent with methodologies previously developed by our group.[3] Substituting with tetrabutylammonium bifluoride ($TBAHF_2$)[14] at 75 °C also produced excellent yields (entry 6). Switching solvents to 1,4-dioxane or DMF slightly reduced the yield (entries 8−9). Substituting the Ni source with Cu or Fe, commonly used in radical cross-couplings, did not yield product **5**.[15] Additionally, using a Ni^0 source had a detrimental effect (entry 13). Product **5** is formed somehow (33%) most likely by *in situ* formation of Ni^I. Pyridinium salts with lower redox potentials, due to electron-withdrawing groups or steric hindrance, were found unsuitable for the reaction (entries 14−15).[15a] NHP esters **9**-**10**, with lower potentials than **2**, were also found inappropriate for this radical coupling (entries 16−17). Triethyl-substituted silanes, being more inert, remained intact under the reaction conditions (entry 18).

With the optimized conditions in hand, we then explored the stereospecific nature of this radical alkylation reaction on vinylsiloxanes (Scheme 2).

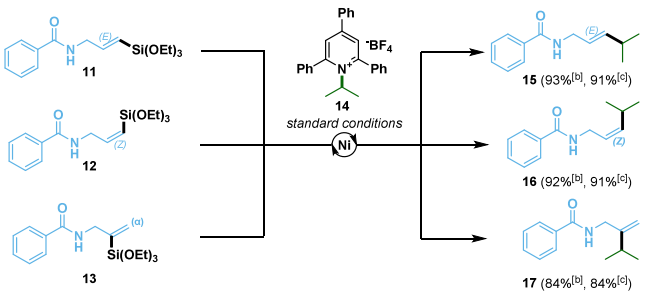
Table 1. Optimization of the Reaction Conditions[a]



entry	variation	yield (%)[b]	entry	variation	yield (%)[b]
1	1.0 equiv. **1**	82	10	w/o [Ni] or **3**	n.d.
2	75 °C	88	11	$[Cu(MeCN)_4]PF_6$	<1
3	25 °C	47	12	$Fe(acac)_3$, **6**	n.d.
4	2.2 equiv. **4**	62	13	$Ni(COD)_2$	33
5	CsF or TBAF	n.d.	14	X = **7**	n.d.
6	$TBAHF_2$, 75 °C	82	15	X = **8**	30
7	w/o **4**	n.d.	16	X = **9**	n.d.
8	1,4-dioxane	80	17	X = **10**	n.d.
9	DMF	85	18	$-SiEt_3$	n.d.

[a]All reactions performed on a 0.20 mmol scale. [b]NMR yield using dimethylsulfone as an internal standard. [c]Yield of isolated product after purification by flash chromatography. n.d. = not determined. See Supporting Information for additional details.

Scheme 2. Evaluation of the Stereospecificity of the Optimized Alkylation Reaction on Different Vinylsiloxane Stereochemistries



[a]All reactions performed on a 0.20 mmol scale. [b]NMR yield using dimethylsulfone as an internal standard. [c]Yield of isolated product after purification by flash chromatography.

To achieve this, β-(*E*) **11**, β-(*Z*) **12**, and α **13** silicon derivatives were prepared *via* catalytic hydrosilylation using low catalytic loadings of Pt, Rh, and Ru, respectively. These reactions are highly robust and atom-economical, allowing access to the three stereopure isomers in a single step. Once the double bond welded, the isomers (**11**-**13**) were subsequently engaged under the previously optimized conditions. Despite the radical mechanism, the double bond stereochemistry was preserved, yielding (*E*), (*Z*), and (*1,1′*)-disubstituted alkenes with excellent yields. Compounds **15** and **16** were each isolated with yields of 91%. The sterically demanding (*Z*)-stereochemistry did not impact the yields,

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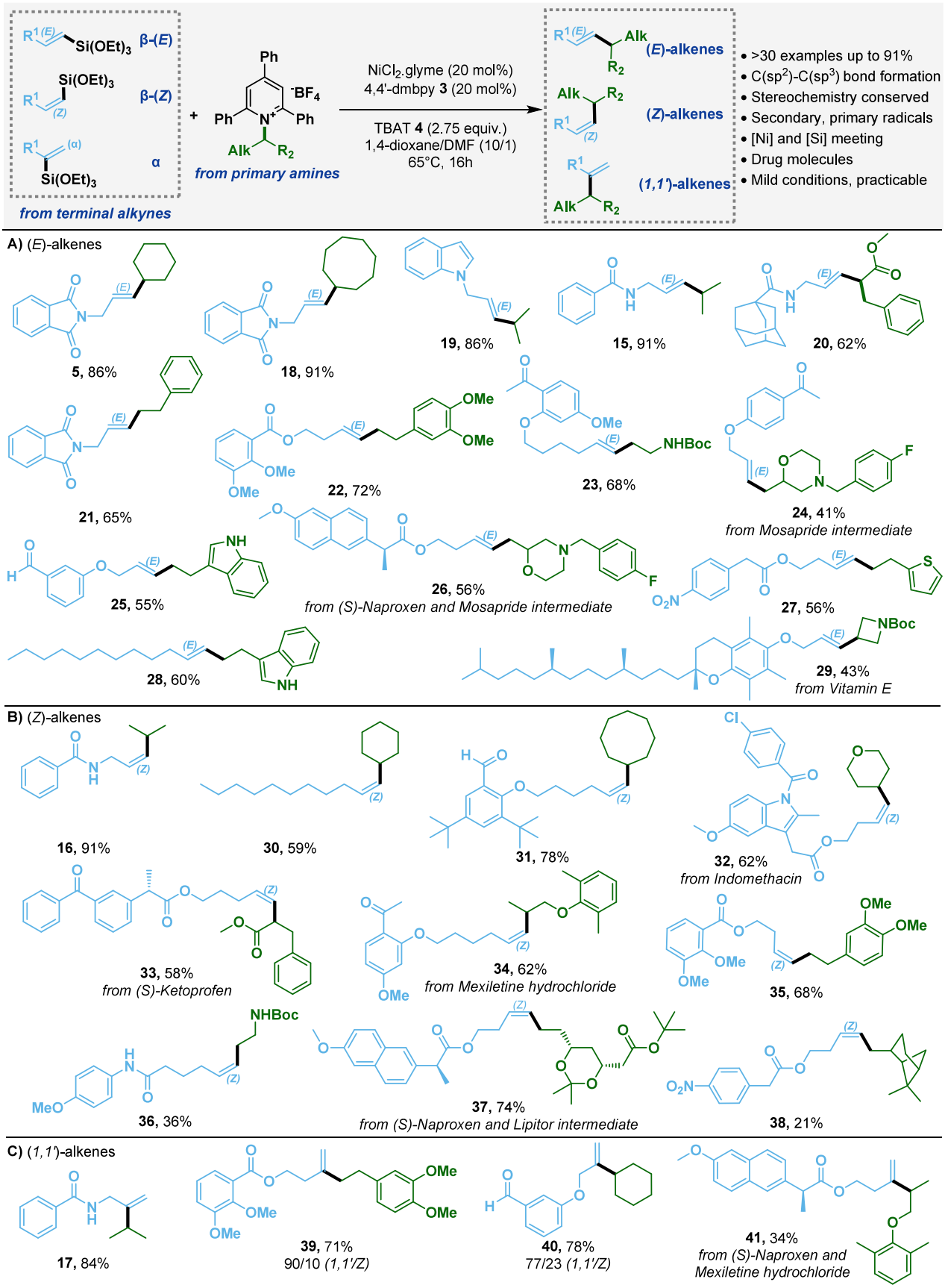
Scheme 3. Substrate Scope of Stereospecific Alkylation of Vinylsiloxanes Using Pyridinium Salt



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while a slight decrease was observed for derivative **17**, isolated with an 84% yield. Importantly, the reaction employs the same conditions regardless of the double bond stereochemistry, thus eliminating the need for further specific optimization. These results paved the way for exploring the scope of this stereospecific alkylation reaction of vinylsiloxanes.

Reactions were carried out on a 0.20 mmol scale. Reaction conditions: Vinylsiloxane (1.1 equiv), pyridinium salt (1.0 equiv), $NiCl_2$.glyme (20 mol %), 4,4′-dmbpy **3** (20 mol %), TBAT **4** (2.75 equiv) in 1,4-dioxane/DMF (10/1) at 65 °C for 16 h.

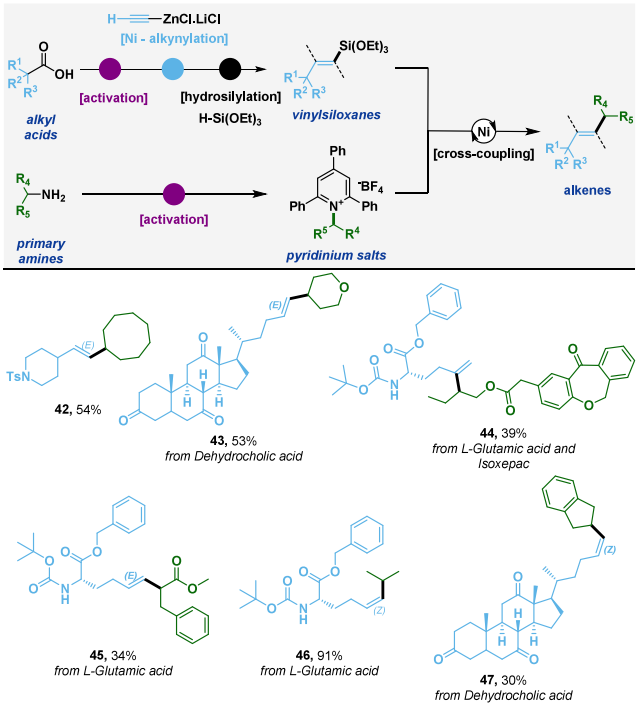
The reaction accommodates modifications to both coupling partners and double-bond stereochemistry, with over 30 examples shown in Scheme 3. Initial studies using (*E*)-alkenes and secondary alkyl radicals (**5**, **15**, **18**−**20**) achieved excellent yields up to 91% (Scheme 3A). The scope was further expanded to primary alkyl radicals, incorporating diverse functional groups like esters (**22**, **26**, **27**), amides (**15**, **20**), ketones (**23**, **24**), aldehydes (**25**), and heterocycles (**25**, **27**, **28**), with yields of 41%−72%. This method selectively modifies the silicon-containing moiety while preserving other functional groups postalkylation.

Having demonstrated the efficiency of the reaction on *β*-(*E*)-vinylsiloxanes, we proceeded to apply to (*Z*)-stereoisomers (Scheme 3B). The alkylation yielded various (*Z*)-compounds without isomerization, preserving the initial stereochemistry. Leveraging the versatility of pyridinium salts, we achieved good yields with pharmaceutical intermediates and derivatives, including the antiarrhythmic drug mexiletine (**34**), lipitor intermediate (**37**), and nonsteroidal anti-inflammatory drug derivatives such as indomethacin (**32**), ketoprofen (**33**), and naproxen (**37**). Encouraged by these results, we further explored *α*-vinylsiloxanes (Scheme 3C). Similarly, the alkylation proceeded effectively across various functional groups with yields independent of the stereochemistry. The ratios (*1,1′*/*Z*) observed for compounds **39** and **40** were attributed to the upstream Ru-catalyzed *α*-hydrosilylation. Notably, the method is highly practical, requiring no preformation of the nickel complex, enabling direct use of reagents in coupling reactions. However, limitations arise with high steric hindrance or unstable radicals (see Supporting Information).

To demonstrate the applicability of the methodology, Scheme 4 illustrates its direct use with readily accessible amines and carboxylic acids. The Ni-catalyzed decarboxylative alkynylation of carboxylic acids, developed by Baran in 2017, is a powerful method to obtain terminal alkynes in two steps *via* activation into redox-active esters.[16]

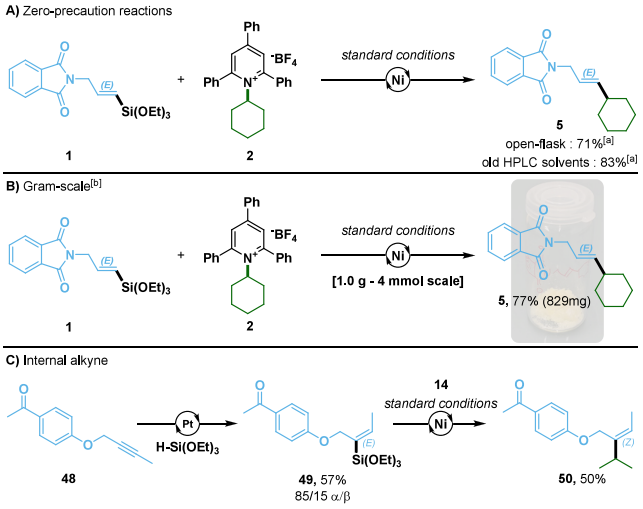
Hydrosilylation completes the synthesis, leading to silicon-based synthetic linchpins. Cross-coupling reactions with pyridinium salts derived from primary amines enabled the addition of 6 examples of functionalized olefins with five derived from natural products. The first example involves an *N*-protected piperidine **41** with a yield of 54%. Dehydrocholic acid, a cholesterol derivative, was efficiently alkylated, yielding stereoisomers (*E*) **42** and (*Z*) **46** with yields of 53% and 30%, respectively. A glutamic acid derivative was successfully coupled with a phenylalanine derivative, producing an amino acid dimer **44** in 34% yield. Additionally, the amino acid was coupled with an isopropyl fragment in (*Z*) stereochemistry **45** in 91% yield. Moreover, the (*1,1′*)-disubstituted olefin with isoxepac **43** was obtained in 39% yield.

Scheme 4. Synthetic Extensions from Decarboxylative Alkynylation of Carboxylic Acids and Amine Activations



To demonstrate the robustness of the alkylation reaction, we conducted two experiments under less stringent conditions (Scheme 5A). The model reaction was performed under ambient air, yielding a coupling product in 71% yield. When nonanhydrous solvents were used, the yield slightly decreased to 83%. Scalability was also evaluated, achieving an isolated yield of 77% on a theoretical scale of 1 g of final product (**5**, Scheme 5B). This methodology was extended to trisubstituted alkenes starting from an internal alkyne (**48**, Scheme 5C). Pt-catalyzed hydrosilylation of **48** resulted in a mixture of

Scheme 5. A) Reactions Performed Opened to Air or with Non-Anhydrous Solvents; B) Reaction Carried out at Gram Scale; C) Application on Internal Alkyne



[a]NMR yield using dimethylsulfone as an internal standard. [b]Reaction carried out with HPLC solvents.

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regioisomers in an 85/15 α/β ratio that could not be separated. Subsequent Ni-coupling conditions led to the compound **50**, separable from the other regioisomer, leaving the ketone intact with a 50% isolated yield.

To summarize, we present a novel association of silicon and nickel in a stereospecific alkylation reaction using pyridinium salts. This method shows broad tolerance for various double bond stereochemistries and functionalized scaffolds, including pharmaceuticals and natural products. It offers a mild, efficient approach to synthesizing disubstituted alkenes via modern Hiyama radical cross-coupling.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c00098.

Experimental procedures, optimization study, graphics, spectroscopic data, and NMR spectra. (PDF)

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Author Contributions

Logan Salamone: Conceptualization, Methodology, Investigation, Visualization, Original draft, Funding Acquisition. Xavier Vanderbiest: Investigation. Olivier Riant: Conceptualization, Methodology, Project Administration, Supervision, Review and Editing, Funding Acquisition.

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Notes

The authors declare no competing financial interest.

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