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Trisubstituted olefin synthesis *via* Ni-catalyzed hydroalkylation of internal alkynes with non-activated alkyl halides†

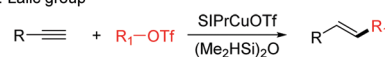
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The stereoselective synthesis of tri-substituted alkenes is challenging. Herein, we report a Ni-catalyzed regio- and stereo-selective hydroalkylation of internal alkynes with non-activated alkyl halides. This method does not use any sensitive organometallic reagents and shows good functional group compatibility, which enables the efficient synthesis of many tri-substituted olefins from readily available coupling partners. It also provides a straightforward method for the modification of bioactive organic molecules.

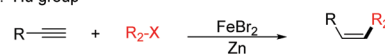
Alkenes are one of the most widely occurring and important class of organic compounds, which are widely used in the chemical, materials, and pharmaceutical industries.¹ Over the past century, numerous methods, such as elimination reactions, the reduction of alkynes, Wittig-type reaction, and the Julia–Kocienski, have been developed for the synthesis of olefins. In addition, many significant catalytic methods using transition metals have been reported, for example, the Heck reaction, the semi-hydrogenation of alkynes, olefin metathesis, and the cross-coupling reactions of alkenyl metal reagents or alkenyl halides.² Recently, intermolecular hydrocarbonation reactions between alkynes and electrophilic reagents have been considered as one of the most attractive methods for the synthesis of alkenes because these can synthesize a diverse array of substituted alkenes by controlling the regio- and stereoselectivity. However, most of the hydrocarbonation reactions of alkynes use π -electrophiles.^{3–8} Hydrocarbonation cross-coupling reactions of alkynes with alkyl electrophiles are less. In 2015, the Lalic group reported the copper-catalyzed hydroalkylation of terminal alkynes with alkyl triflates (Scheme 1a).⁹ The Hu group has reported the iron-catalyzed reductive coupling of terminal aryl alkynes with alkyl halides (Scheme 1b).¹⁰ In 2016, Fu realized the Ni-catalyzed Markovnikov hydroalkylation of alkynes with alkyl

Previous work

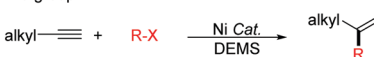
a. Lalic group



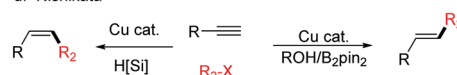
b. Hu group



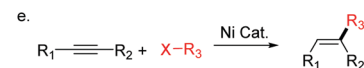
c. Fu group



d. Nishikata



This work



$\text{R}_1 = \text{aryl}$ & $\text{R}_2 = \text{alkyl}$ or $\text{R}_1 = \text{R}_2 = \text{alkyl}$

Scheme 1 The hydroalkylation of alkynes with alkyl electrophiles.

halides (Scheme 1c).¹¹ The Nishikata group has reported that Cu-catalyzed tandem reactions enable *trans*- and *cis*-hydro-tertiary-alkylations (Scheme 1d).¹² However, these elegant studies can only utilize terminal alkynes in the hydroalkylation reaction to afford di-substituted olefins.¹³

Tri-substituted alkenes are in high demand, and the efficient regio- and stereoselective synthesis of tri-substituted alkenes bearing three different carbon-linked groups presents a particular challenge in modern organic synthesis. Over the past few decades, transition metal-catalyzed cross-coupling reactions of tri-substituted alkenyl halides or tri-substituted alkenyl metal reagents are regarded as a versatile and straightforward method for the synthesis of tri-substituted alkenes.¹⁴ These coupling partners need to have the corresponding stereo-configurations. However, the stereoselective synthesis of these coupling partners is difficult.¹⁵ Herein, we report the first example of a nickel-catalyzed regio- and stereo-selective hydroalkylation of non-functionalized internal alkynes with non-activated alkyl halides (Scheme 1e). Not only aryl-alkyl substituted

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alkynes, but also alkyl-alkyl substituted alkynes can be successfully transformed into the desired products. This method does not use any sensitive organometallic reagents and both of the starting materials are readily available, thus enabling the efficient synthesis of many tri-substituted alkenes. Due to the mild reaction conditions, this new approach shows good functional group compatibility. In addition, it provides a method to modify complex organic molecules.

We began our study by choosing the commercially available 1-phenyl-1-propyne (**1a**) and iodocyclohexane (**2a**) as the model substrates (Table 1). On the basis of the previous study on the Ni-catalyzed hydroalkylation of alkynes with alkyl halides, we first examined the previously reported catalytic conditions used for the reaction.¹¹ Gratifyingly, we obtained the product in a moderate yield (entry 1). The results showed that the previously reported conditions were not suitable. Next, we examined other bidentate nitrogen ligands such as the phenanthroline family of ligands (L1–L2) and pyrox family of ligands (L3–L4). Disappointingly, these ligands did not increase the yield. Then, we used tri-nitrogen ligands instead of the bidentate nitrogen ligands (L5–L7). However, the yields obtained for the desired

product remained very poor. We also tested some phosphine ligands (L8–L9). Disappointingly, the reactions did not afford any desired product. Consequently, we screened a series of bases (entries 11–14). Gratifyingly, when K₂CO₃ was used as a base, we obtained the optimal reaction conditions (85% GC yield and 81% isolated yield, entry 14, product ratio >30:1). Finally, the control experiments indicated that the reaction almost shut down without the use of a nickel catalyst (entry 15).

With the optimized conditions in hand, we explored the scope of the hydroalkylation reaction of internal alkynes. As shown in Table 2, our protocol exhibited excellent regio- and stereoselectivity (product ratio >25:1, as determined by GC and ¹H-NMR spectroscopy). The coupling partners with different functional groups can be successfully converted into the desired products in modest to excellent yields. Both cyclic and acyclic alkyl halides can be transformed. Due to the mild reaction

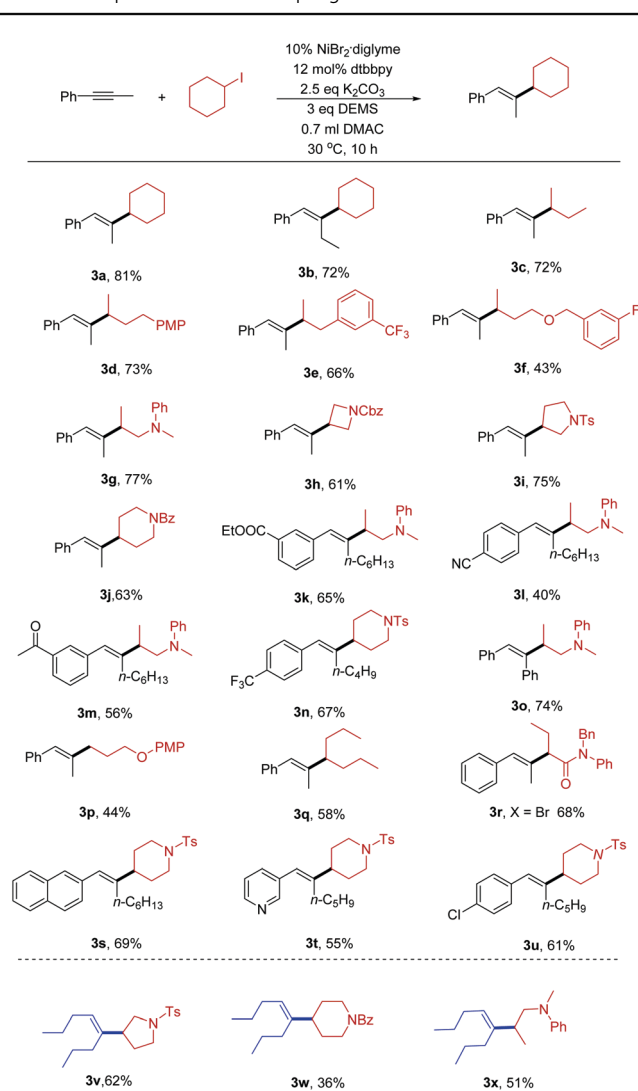
Table 1 Optimization of the reaction conditions



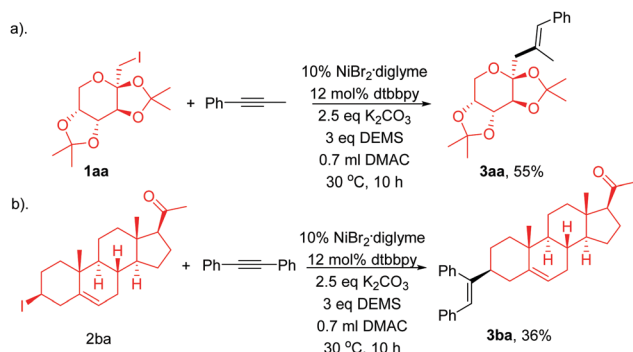
Entry	Cat. (10 mol%)	Ligand (12 mol%)	Base (2.5 eq.)	Solvent (0.6 mL)	Yield (%) 3a ^a
1	NiBr ₂ ·diglyme	dtbbpy	CS ₂ CO ₃	DMAC	32
2	NiBr ₂ ·diglyme	L1	CS ₂ CO ₃	DMAC	5
3	NiBr ₂ ·diglyme	L2	CS ₂ CO ₃	DMAC	Trace
4	NiBr ₂ ·diglyme	L3	CS ₂ CO ₃	DMAC	4
5	NiBr ₂ ·diglyme	L4	CS ₂ CO ₃	DMAC	8
6	NiBr ₂ ·diglyme	L5	CS ₂ CO ₃	DMAC	7
7	NiBr ₂ ·diglyme	L6	CS ₂ CO ₃	DMAC	5
8	NiBr ₂ ·diglyme	L7	CS ₂ CO ₃	DMAC	4
9	NiBr ₂ ·diglyme	L8	CS ₂ CO ₃	DMAC	Trace
10	NiBr ₂ ·diglyme	L9	CS ₂ CO ₃	DMAC	Trace
11	NiBr ₂ ·diglyme	dtbbpy	NaOAc	DMAC	15
12	NiBr ₂ ·diglyme	dtbbpy	CsF	DMAC	38
13	NiBr ₂ ·diglyme	dtbbpy	LiOMe	DMAC	50
14	NiBr₂·diglyme	dtbbpy	K₂CO₃	DMAC	85(81)^c
15 ^b	—	dtbbpy	K ₂ CO ₃	DMAC	Trace

^a The reaction was carried out at 30 °C for 10 h under an Ar atmosphere. 3 equiv. of diethoxymethylsilane was used as a hydride donor. The yields were determined by GC analysis using biphenyl as an internal standard (the average of two GC runs). ^b Performed without NiBr₂·diglyme. ^c The yield of isolated product. DMAC = *N,N*-dimethylacetamide.

Table 2 Scope of the cross-coupling reaction^a



^a The reactions were conducted on a 0.2 mmol scale at 30 °C. The yields of the isolated products after 10 h. Bz = benzoyl, DEMS = diethoxymethylsilane and Ts = 4-toluenesulfonyl.

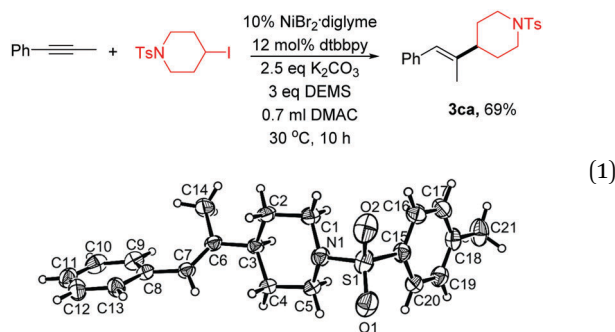


Scheme 2 The modification of complex molecules.

conditions, the hydroalkylation of internal alkynes is compatible with lots of synthetically relevant functional groups such as trifluoromethyl (**3e**), amine (**3g**), fluoride (**3f**), amide (**3h**, **3j**), and sulfonamide (**3i**). Some base-sensitive functional groups such as ester (**3k**) and nitrile (**3l**) groups can be well tolerated. Even more active groups, such as ketone (**3m**), were compatible in the reaction. The success of the reaction inspired us to apply them to the cross-coupling of primary alkyl halides. For example **3p**, we successfully obtained product when using a primary alkyl halide as the substrate. Activated secondary α -bromo amide (**3r**) was also a good substrate except alkyl iodides. Furthermore, heterocycles, such as pyrrolidine (**3i**), piperidine (**3j**), naphthalene (**3s**), and pyridine (**3t**) are tolerated in either of the two coupling substrates. Aryl-Cl bonds (**3u**) did not hinder the reaction.

Next, we examined whether alkyl-alkyl substituted alkynes with lower activity could participate in the reaction. Fortunately, the present conditions were applicable for these substrates. Alkyl halides bearing sulfonamide (**3v**), amide (**3w**), and amine (**3x**) groups react under these conditions to afford the desired products in moderate yields.

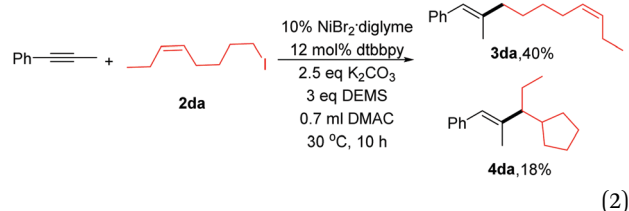
We next demonstrated the efficiency of this regio- and stereoselective hydroalkylation of internal alkynes in the late-stage modification of complex active molecules (Scheme 2). Modification of fructose derivative (**1aa**), which is of great interest in life sciences, with **1ba** results in the formation of **1ca** in a moderate yield (Scheme 2a). Treatment of pregnenolone derivative (**1ab**), tolerating ketone and alkenes, with **2ab** afforded the product **3aa** in a moderate yield (Scheme 2b).



Single-crystal XRD analysis of **3ca** confirmed the regio- and stereoselectivity of the hydroalkylation of internal alkynes (eqn (1)).

The reaction provides an efficient method for the synthesis of many of the single configuration tri-substituted alkenes.

To explore the reaction mechanism, several experiments were conducted. Initially, when we added 1.0 equiv. 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), the reaction was completely inhibited. Next, we performed an experiment between **2da** and phenyl-1-propyne (eqn (2)). A mixture of linear coupling product (**3da**) and ring-cyclized product (**4da**) was obtained. The abovementioned results were consistent with a radical-type mechanism of alkyl halides.^{10,16} However, the detailed reaction process was not clear at this point. Our preliminary view is that the reaction goes through the L_nNiH intermediate, and then, the intermediate reacts with the internal alkyne *via* a *cis*-addition. The detailed mechanism is under study.



In summary, we have developed nickel-catalyzed regio- and stereoselective hydroalkylation of non-functionalized internal alkynes with non-activated alkyl halides for the first time. This method does not use sensitive organometallic reagents, and both of the starting materials are readily available, thus enabling the efficient synthesis of many single configuration tri-substituted alkenes. Due to the mild reaction conditions, this new approach shows good functional group compatibility. Not only aryl-alkyl substituted alkynes, but also alkyl-alkyl substituted alkynes can be successfully converted into the desired products.

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Conflicts of interest

There are no conflicts to declare.

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