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Authors

Xiao-Yu Lu, * Mei-Lan Hong, Hai-Pin Zhou, Yue Wang, Jin-Yu Wang, Xiu-Tao Ge

Affiliations

a: School of Materials and Chemical Engineering, ChuZhou University, Chu Zhou, 239000, China.

b: School of Chemistry and Chemical Engineering, AnHui University, He Fei, 230601, China.

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Trisubstituted Olefine Synthesis via Ni-Catalyzed Hydroalkylation of internal Alkynes with non-activated Alkyl Halides

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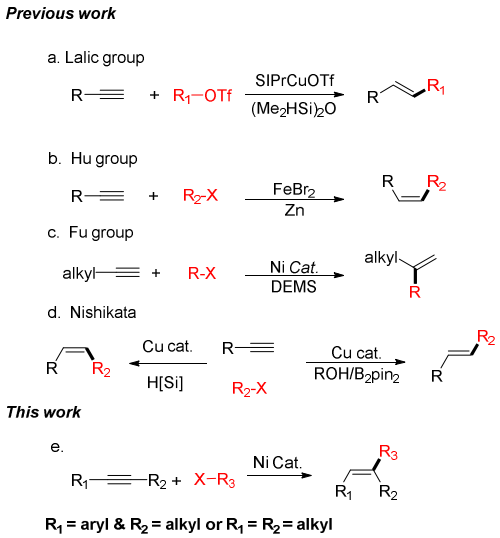
The stereoselective synthesis of tri-substituted alkenes is challenging. Here, we report a Ni-catalyzed regio- and stereo-selective hydroalkylation of internal alkynes with non-activated alkyl halides. This method without using sensitive organometallic reagents and shows good functional group compatibility, and enabling efficient synthesis of many tri-substituted olefines 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 classes of organic compounds, which are widely used in chemical, materials, and pharmaceutical industries.[1] In the past century numerous methods of synthesis of olefins have been developed, such as elimination reactions, the reduction of alkynes, Wittig-type reaction and the Julia–Kocienski. In addition, many significant transition metal catalytic methods have also been reported, for example, Heck reactions, the semi-hydrogenation of alkynes, olefin metathesis, and cross-coupling reactions of alkenyl metal reagents or alkenyl halides.[2] Recently, intermolecular hydrocarbonation reactions between alkynes and electrophilic reagents are considered as one of the most attractive methods for the synthesis of olefins. Because this method can synthesize a diverse array of substituted olefins by controlling the regio- and stereo-selectivity. However, most of the hydrocarbonation reactions of alkynes are π-electrophiles.[3-8] Hydrocarbonation cross-coupling reactions of alkynes with alkyl electrophiles are less. In 2015, Lalic group reported copper-catalyzed hydroalkylation of terminal alkynes with alkyl triflates (Scheme 1a).[9] Hu group reported the iron-catalyzed reductive coupling of terminal arylalkynes with alkyl halides (Scheme 1b).[10] In 2016, Fu realized Ni-catalyzed Markovnikov hydroalkylation of alkynes with alkyl halides (Scheme 1c).[11] Nishikata group reported Cu-catalyzed tandem reactions enable trans- and cis-hydro-tertiary-alkylations (Scheme 1d).[12] However, these elegant works can only realize terminal alkynes hydroalkylation reaction, which afford di-substituted olefins.[13]



Scheme 1 Hydroalkylation of Alkynes with Alkyl Electrophiles

The tri-substituted alkenes have a 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 decades, transition metal catalyzed cross-coupling reactions of tri-substituted alkenyl halides or tri-substituted alkenyl metal reagents have regarded as a versatile and straightforward method for their synthesis.[14] These coupling partners need to have the corresponding stereo-configurations. However, stereoselective synthesis of these coupling partners is difficult.[15] Here, we report the first example of nickel-catalyzed regio- and stereo-selective hydroalkylation of non-functionalized internal alkynes with non-activated alkyl halides (Scheme 1e). Not only aryl-alkyl substituted alkynes, but also alkyl-alkyl substituted alkynes, can be successfully transformed into the desired products. This method without using sensitive organometallic reagents and both of the starting materials are readily available, thus enabling efficient synthesis of many tri-substituted olefines. Due to the mild

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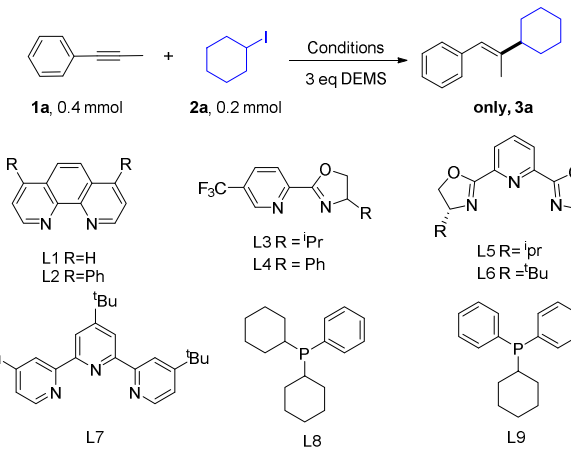
conditions, this new approach shows good functional group compatibility. Also, it provides a method to modification of complex organic molecules.

Table 1 Optimization of the reaction conditions.

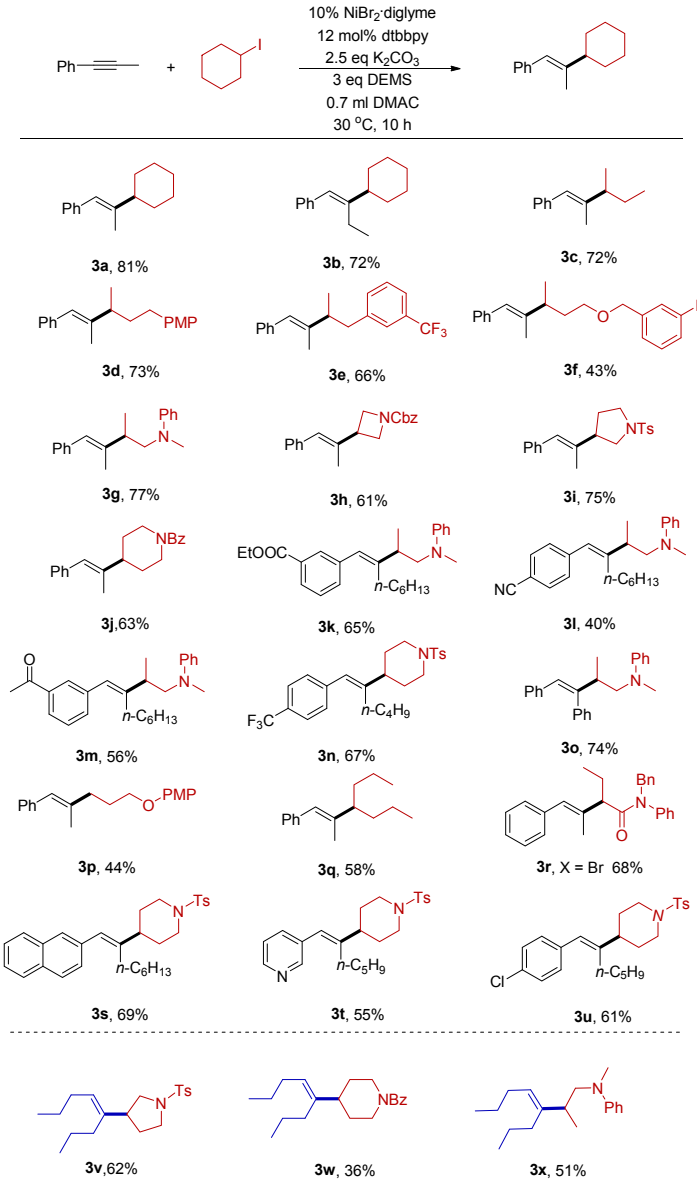


Entry	Cat. (10 %)	Ligand (12 %)	Base (2.5 eq)	Solvent (0.6 ml)	Yield% [a]3a
1	$NiBr_2$·diglyme	dtbbpy	Cs_2CO_3	DMAc	32
2	$NiBr_2$·diglyme	L1	Cs_2CO_3	DMAc	5
3	$NiBr_2$·diglyme	L2	Cs_2CO_3	DMAc	trace
4	$NiBr_2$·diglyme	L3	Cs_2CO_3	DMAc	4
5	$NiBr_2$·diglyme	L4	Cs_2CO_3	DMAc	8
6	$NiBr_2$·diglyme	L5	Cs_2CO_3	DMAc	7
7	$NiBr_2$·diglyme	L6	Cs_2CO_3	DMAc	5
8	$NiBr_2$·diglyme	L7	Cs_2CO_3	DMAc	4
9	$NiBr_2$·diglyme	L8	Cs_2CO_3	DMAc	trace
10	$NiBr_2$·diglyme	L9	Cs_2CO_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	**$NiBr_2$·diglyme**	**dtbbpy**	**K_2CO_3**	**DMAc**	**85(81)[c]**
15[b]	-	dtbbpy	K_2CO_3	DMAc	trace

[a] The reaction was carried out at 30 °C for 10 h under Ar atmosphere. 3 equiv diethoxymethylsilane as a hydride donor. Yields determined by GC analysis use biphenyl as internal standard (average of two GC runs). [b] Without $NiBr_2$·diglyme. [c] Yield of isolated product. DMAC = N,N-Dimethylacetamide.

We began our study by choosing commercially available 1-Phenyl-1-propyne (1a) and iodocyclohexane (2a) as the model substrates (Table 1). On the basis of previous work on Ni-catalyzed hydroalkylation of alkynes with alkyl halides, we first examined previously reported catalytic conditions for the reaction.[11] Gratifyingly, we observed the product in moderate yield (entry 1). The results showed that the previously conditions were not suitable. Next we examined other bidentate nitrogen ligands, such as phenanthroline family ligands (L1-L2) and pyrox family ligands (L3-L4). Disappointingly, these ligands are useless to increase the yield. Then we used tri-nitrogen ligands instead of the bidentate nitrogen ligands (L5-L7). However, the desired product remained very bad. We also tested some phosphine ligands (L8-L9). Disappointingly, it did not afford any desired product. Following, we have to screen a series of bases (entry 11-14). Gratifyingly, when use K_2CO_3 as the base, we obtained the optimal reaction conditions (85% GC yield and 81% isolated yield, entry 14, product ratio >30:1). Finally, control experiments indicated that the reaction almost shut down without using nickel source (entry 15).

Table 2 Scope of cross-couping[a,b].



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

With the optimized conditions in hand, we explored the scope of hydroalkylation reaction of internal alkynes. As shown in Table 2, our protocol exhibited an excellent regio- and stereo-selective (product ratio >25:1, determined by GC and ^{1}HNMR). The coupling partners with different functional groups can be successfully converted into the desired products with modest to excellent yields. Both cyclic and acyclic alkyl halides can be transformed. Due to the mild reaction conditions, the hydroalkylation of internal alkynes is compatible with lots of synthetically relevant functional groups, such as

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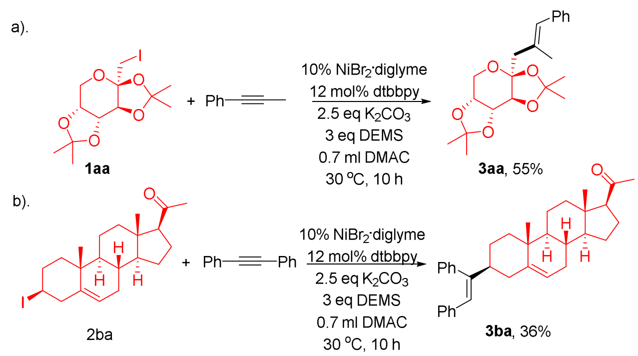
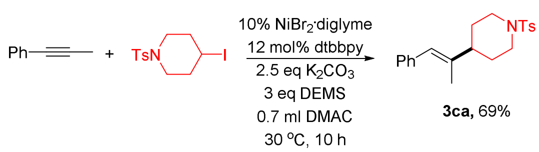
trifluoromethyl (**3e**), amine (**3g**), fluoride (**3f**), amide (**3h**, **3j**), and sulfonamide (**3i**). Some base-sensitive functional groups such as ester (**3k**) and nitrile (**3l**) groups can be well tolerated. Even more active groups, such as ketone (**3m**), were compatible in the reaction. The success of the reaction inspired us to apply them to the cross-coupling of primary alkyl halides. For example **3p**, it can straightforward use of this kind of compound. Activated secondary α-bromo amide (**3r**) war also a good substrate except alkyl iodides. Furthermore, heterocycles, for example, pyrrolidine (**3i**), piperidine (**3j**), naphthaline (**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 lower activity alkyl-alkyl substituted alkynes could involve in the reaction. Fortunately, the present conditions were applicative for these substrates. Alkyl halides bearing sulfonamide (**3v**), amide (**3w**), and amine (**3x**) groups reacted under these conditions to afford the desired products in moderate yields.

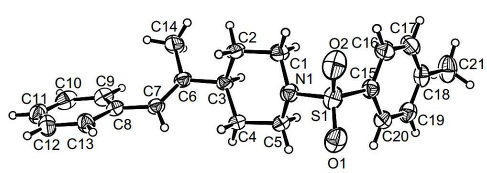


Scheme 2. Modification of complex molecules.

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

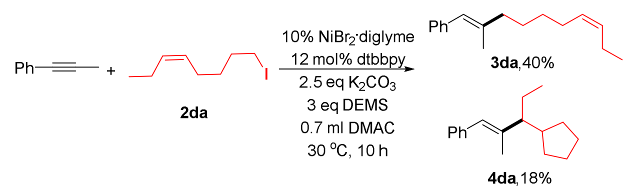


(1)



Single-crystal XRD analysis of **3ca** confirmed the regio- and stereo-selective hydroalkylation of internal alkynes (Eq (1)). So it provides an efficient method for synthesis many of the single configuration tri-substituted olefines.

In order to explore the reaction mechanism, several experiments were conducted. First, when we added 1.0 equiv. 2,2,6,6-tetramethylpiperidineoxy (TEMPO), the reaction was completely inhibited. Nest, we tested an experiment between **2da** with phenyl-1-propyne (Eq (2)). A mixture of linear coupling product (3da) and ring-cyclized product (4da) were obtained. The above results were consistent with a radical-type mechanism of the alkyl halides.[10, 16] Nonetheless, the detailed reaction process was not clear at now. Our preliminary view is that the reaction goes through the L_nNiH intermediate and then the intermediate reacts with internal alkynes by cis addition. The detailed mechanism is under study.



(2)

In summary, for the first time, we have developed a nickel-catalyzed regio- and stereo-selective hydroalkylation of non-functionalized internal alkynes with non-activated alkyl halides. This method without using sensitive organometallic reagents and both of the starting materials are readily available, thus enabling efficient synthesis of many of the single configuration tri-substituted olefines. Due to the mild 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.

Notes and references

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/.

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