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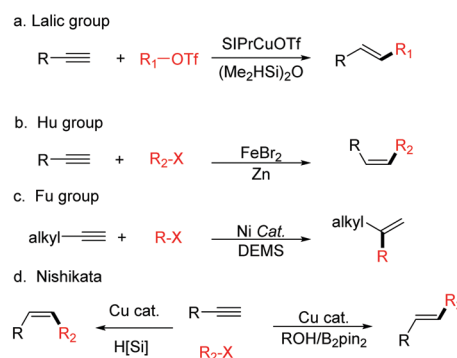
Trisubstituted olefin synthesis via Ni-catalyzed hydroalkylation of internal alkynes with non-activated alkyl halides†

Xiao-Yu Lu,^{ab} Mei-Lan Hong,^a Hai-Pin Zhou,^a Yue Wang,^a
Jin-Yu Wang^a and Xiu-Tao Ge^a

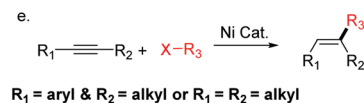
The stereoselective synthesis of tri-substituted alkenes is challenging. Herein, we report a Ni-catalyzed regio- and stereo-selective hydroalkylation of internal alkynes with non-activated alkyl halides. This method does not use any sensitive organometallic reagents and shows good functional group compatibility, 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



This work



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

^a School of Materials and Chemical Engineering, ChuZhou University, Chuzhou, 239000, China. E-mail: xiaoyulu@mail.ustc.edu.cn

^b School of Chemistry and Chemical Engineering, AnHui University, Hefei, 230601, China

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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

| <p>1a, 0.4 mmol 2a, 0.2 mmol only, 3a</p> | | | | | |
|--|---------------------------------|------------------|------------------------------------|------------------|---------------------------|
| <p>L1 R=H, L2 R=Ph L3 R=ⁱPr, L4 R=Ph L5 R=ⁱpr, L6 R=^tBu</p> | | | | | |
| <p>L7 L8 L9</p> | | | | | |
| 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

| | | |
|---------|---------|----------------|
| | | |
| 3a, 81% | 3b, 72% | 3c, 72% |
| 3d, 73% | 3e, 66% | 3f, 43% |
| 3g, 77% | 3h, 61% | 3i, 75% |
| 3j, 63% | 3k, 65% | 3l, 40% |
| 3m, 56% | 3n, 67% | 3o, 74% |
| 3p, 44% | 3q, 58% | 3r, X = Br 68% |
| 3s, 69% | 3t, 55% | 3u, 61% |
| 3v, 62% | 3w, 36% | 3x, 51% |

^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.

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