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Stereospecific Synthesis of E-Alkenes through Anti-Markovnikov Hydroalkylation of Terminal Alkynes

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Supporting Information

ABSTRACT: We have developed a method for stereospecific synthesis of E-alkenes from terminal alkynes and alkyl iodides. The hydroalkylation reaction is enabled by a cooperative action of copper and nickel catalysts and proceeds with excellent anti-Markovnikov selectivity. We demonstrate the broad scope of the reaction, which can be accomplished in the presence of esters, nitriles, aryl bromides, ethers, alkyl chlorides, anilines, and a wide range of nitrogen-containing heteroaromatic compounds. Mechanistic studies provide evidence that the copper catalyst activates the alkyne by hydrocupration, which controls both the regio- and diastereoselectivity of the overall reaction. The nickel catalyst activates the alkyl iodide and promotes cross coupling with the alkenyl copper intermediate.

lkenes are ubiquitous in organic chemistry. They are used Aas versatile synthetic intermediates and are common among complex organic molecules with important applications. The importance of alkenes in organic chemistry has fueled persistent efforts aimed at developing new methods for their synthesis. As a result of these efforts, the hydroalkylation of alkynes has recently emerged as a powerful new approach to alkene synthesis. The main benefit of this approach is the use of simple and readily available alkynes as precursors to a variety of alkenes.

Current methods for the hydroalkylation of alkynes provide access to several classes of alkenes (Scheme 1). Z-Substituted aryl alkenes can be prepared using a radical hydroalkylation of aryl alkynes that was reported in 2015 by Hu et al. (Scheme 1a).¹ More recently, Fu et al. developed a selective synthesis of 1,1-disubstituted alkenes through a nickel-catalyzed hydroalkylation of terminal alkynes (Scheme 1b).² A similar transformation of terminal alkynes into 1,1-disubstituted alkenes was subsequently accomplished by MacMillan et al. using a cooperative photoredox/nickel catalysis (Scheme 1b).^{3,4} This approach has also allowed the transformation of sterically differentiated internal alkynes into trisubstituted alkenes with moderate regioselectivity.³

Surprisingly, there are few hydroalkylation methods that effectively target disubstituted E-alkenes. In 2015, our group reported the copper-catalyzed hydroalkylation of terminal alkynes using alkyl triflates as electrophiles (Scheme 1c).^{5,6} This transformation demonstrates key benefits of hydroalkylation as an approach to the synthesis of E-alkenes. The reaction increases both the structural and the stereochemical

Scheme 1. Hydroalkylation of Alkynes



complexity of the starting materials. A new C-C bond is formed, and, in the process, the stereochemistry of the new alkene is established. The excellent regioselectivity and diastereospecificity of the reaction allow the exclusive formation of a single *E*-alkene.

Nevertheless, our original hydroalkylation reaction has some significant limitations. The reaction is highly sensitive to steric properties of the electrophile and only linear primary alkyl triflates with no α -branching were viable substrates.

Additionally, both alkyl triflates and reagents used in their preparation are highly reactive, further limiting the reaction scope and introducing practical problems related to the preparation, purification, and stability of the starting electrophiles.

In this Communication, we report the development of a new method for the hydroalkylation of terminal alkynes that

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addresses the key shortcomings of our original hydroalkylation reaction, while retaining its major benefits. We demonstrate that a dual Cu/Ni catalyst system allows the use of both primary and secondary alkyl iodides as coupling partners and enables the stereospecific synthesis of a wide range E-alkenes from terminal alkynes.

The hydroalkylation of alkynes that we reported in 2015 involves hydrocupration of an alkyne followed by electrophilic functionalization of alkenyl copper intermediate **3** (Scheme 2a).^{7,8} The key hydrocupration step is highly regioselective and

Scheme 2

a) Copper-catalyzed hydrofunctionalization



b) Alkylation of NHC-supported alkenyl copper complex



c) Nickel-catalyzed alkylation of alkenyl copper complex



syn-stereospecific, ultimately resulting in excellent regio- and diastereoselectivity of the overall reaction. Unfortunately, the low reactivity of alkenyl copper complexes makes their alkylation difficult. The stoichiometric reaction of alkenyl copper complex **5** with alkyl triflate **6** provides the desired product, while the less reactive alkyl iodide 7 does not react and under more forcing conditions leads to the decomposition of the starting materials (Scheme 2b).⁵ Mankad et al. have made similar observations about the reactivity of alkenyl copper complexes with alkyl halides.⁹

Inspired by the pioneering work of Nakao^{10,11} and Brown,¹²⁻¹⁴ our plan was to use a nickel co-catalyst to facilitate the cross coupling of the organocopper intermediate with alkyl iodides (Scheme 2c). The main challenge in implementing this cooperative catalysis¹⁵⁻¹⁷ approach to hydroalkylation of alkynes was a clear overlap in the reactivity of the nickel and the copper catalyst systems. The nickelcatalyzed Markovnikov hydroalkylation² (Scheme 1b) is performed under conditions that are very similar to those required for copper hydride formation. Both reactions require a combination of a silane and a base additive. In principle, the nickel co-catalyst in the hydroalkylation reaction may promote not only the desired alkylation of the alkenyl copper intermediate, it could also promote a Markovnikov hydroalkylation and compromise the regioselectivity of the overall transformation.

In our initial experiments we found that the common cross coupling catalyst (dtbpy)NiCl₂ promotes efficient cross coupling of the isolated alkenyl copper intermediate **5** and cyclohexyl iodide (Scheme 3a). However, in a catalytic hydroalkylation reaction, the same nickel catalyst provides desired *E*-alkene in only 23% yield (Scheme 3b). Equally unsuccessful, were reactions with a variety of mono and bidentate phosphine and nitrogen-based ligands.

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Scheme 3. Preliminary Results

a) Nickel-catalyzed cross coupling of alkenyl copper



Contrary to our expectations, the Markovnikov hydroalkylation product was not a significant byproduct in these reactions. Instead, the major problem was the formation of a mixture of higher molecular weight products. We reasoned that these products are likely formed through Reppe's trimerization¹⁸ and related tetramerization¹⁹ of alkynes promoted by nickel(0) complexes.^{20–24} A mechanistically distinct trimerization of alkynes is also promoted by nickel hydride complexes.²⁵

Established mechanisms of these major side reactions suggested that the desired reactivity of the nickel catalyst may be achieved using tridentate ligands. Considering the mechanism of Reppe's trimerization, tridentate ligands should suppress this side reaction by preventing simultaneous coordination of two alkyne molecules.²⁶ Additionally, the less common trimerization promoted by nickel hydride complexes requires a tricoordinate nickel hydride intermediates.²⁷ Again, strongly coordinating tridentate ligands should prevent formation of such an intermediate. We also found precedent indicating that the formation of the nickel hydride complexes is suppressed by tricoordinate nitrogen-based ligands.²⁸ This observation is consistent with Fu's recent finding that tridentate nitrogen-based ligands completely suppress the Markovnikov hydroalkylation of alkynes,² although no explanation for this effect was offered. Finally, the documented use of tridentate ligands in nickel-catalyzed cross coupling reactions of alkyl halides²⁹ indicates that these ligands should allow the desired cross coupling of alkenyl copper intermediate with alkyl iodides.

Indeed, the use of tridentate ligands was the key modification that allowed us to develop the hydroalkylation reaction shown in Table 1. The best results in a reaction of terminal alkyne **12** and cyclohexyl iodide were obtained using IPrCuCl catalyst and a nickel(I) co-catalyst supported by tridentate tpy' ligand (Table 1). Additionally, Ph₃SiH was used as a hydride source and LiO*i*-Pr as a turnover reagent for the copper catalyst (for the role of LiO*i*-Pr, see Scheme 4).

During the development of the reaction, we made several observations about reaction parameters (Table 1). Alkyl iodides were superior substrates, while alkyl bromides provided dramatically lower yields (entry 2). As in most other coppercatalyzed hydrofunctionalization reactions of alkynes, catalysts supported by IPr and the closely related SIPr ligands were the only competent catalysts (entry 3). Even IMesCuCl catalyst provided only 5% of the product (entry 4). The identity of the nickel catalyst was also key for the success of the reaction. The catalyst prepared in situ from NiI₂ performed nearly as well as the optimal catalyst, while the catalyst prepared from NiCl₂

Table 1. Reaction Development



^aDetermined by GC using internal standard.



gave a lower yield (entries 5 and 6). Nickel complexes supported by other closely related ligands were inferior (entries 7–9). With LiOt-Bu in place for LiO*i*-Pr we observed a small amount of Sonogashira product and complete recovery of the starting silane (entry 10). These results suggest that IPrCuOt-Bu does not readily react with Ph₃SiH to form IPrCuH and instead leads to the formation of copper-acetylide and Sonogashira product. Similarly, changing the alkoxide counterion from lithium to sodium led to lower yield of the product (entry 11).

Among common ethereal solvents, THF was the only solvent other than DME that afforded the desired product in a significant yield (entry 12). Finally, PMHS and silanes closely related to Ph_3SiH were all significantly inferior to Ph_3SiH (entries 13–15).

Using the standard conditions shown in Table 1 (entry 1), we explored the scope of the reaction and found that a wide range of *E*-alkenes can be prepared (Table 2). It is important to note that all products shown in Table 2 are obtained as a single regioisomer and a single diastereoisomer. Even severe steric hindrance in the propargylic position does not impede the formation of the product (17) and substitution at the propargylic (13) and homopropargylic position (27) is

tolerated. The reaction is compatible with a wide range of functional groups and can be accomplished in the presence of nitriles (19), esters (20), aryl ethers (15), silyl ethers (13, 17, 21, and 27), alkenes (15), alkyl chlorides (26), sulfonamides (31), dialkyl anilines (25), and aryl bromides (18). The synthesis of compound 16 on a 5 mmol scale demonstrates that the reaction can be used as a preparative method.³⁰

One of the limitations of our original hydroalkylation method was that nitrogen-based heteroarenes were not compatible with the reaction. The new reaction tolerates a wide range of heteroarenes including furans (23), 2-chloropyridines (24), pyridazines (30), thiazoles (28), pyrimidines (29), tetrazoles (33), and benzoxazoles (34). In general, heteroarenes less basic than pyridine are tolerated, while pyridine and more basic heterocycles are not.

We also explored the reaction with a range of secondary alkyl iodides. Cyclic substrates, such as 5- through 7-membered cyclic alkyl iodides, generally perform well (36, 40, 41). Acyclic alkyl iodides are also viable substrates, although yields tend to be lower.

Our initial attempts at using primary alkyl iodides as coupling partners were unsuccessful. Under the reaction conditions used for coupling secondary alkyl iodides, product 8 was formed in only 32% yield. The major side reactions in this case were the reduction of the alkyl iodide³¹ and the semi-reduction of the alkyne to an alkene. Eventually, we found that with subtle changes to the reaction conditions we can obtain alkene 8 in 90% yield (eq 1).



To achieve these results, we changed the catalyst from IPrCuCl to SIPrCuCl, changed the solvent from DME to DME/isooctane (1:1), adjusted the stoichiometry of the turnover reagent (from 1.5 to 2.0 equiv), and lowered the loading of the nickel catalyst (from 5 to 3 mol%).³²

The conditions developed for the synthesis of 8 proved general for a range of primary alkyl halides (Table 2). In departure from the original hydroalkylation with alkyl triflates, we could achieve hydroalkylation using α -branched (46, 49, 50, and 51) and even neopentyl-like alkyl iodide (45) in relatively high yield. Similarly, electrophiles with heteroatoms in the α position (46), which are incompatible with the previous hydroalkylation, are also tolerated.

We also noted a few limitations of the hydroalkylation reaction. Protic functional groups, such as hydroxyl and amino, are not tolerated. Reducible functional groups, such as aldehydes and activated alkene are also not compatible with reactions conditions. Finally, tertiary alkyl iodides, arylsubstituted alkynes, and disubstituted alkynes did not participate in the hydroalkylation reaction.

Considering the generally established mechanisms of copper-catalyzed hydrofunctionalization of alkynes⁸ and nickel-catalyzed cross coupling reactions,³³ we propose that the hydroalkylation reaction proceeds according to the mechanism shown in Scheme 4. Initial hydrocupration of the alkyne $(\mathbf{V} \rightarrow \mathbf{VI})$ is followed by transmetalation to nickel (VI $\rightarrow \mathbf{VIII}$). The alkyl iodide is activated by the newly formed alkenyl nickel complex (VIII). Reductive elimination results in

Table 2. Reaction Scope^a



^{*a*}Yields of isolated products are reported. Reactions performed on 0.5 mmol scale. ^{*b*}Conditions A: see Table 1, entry 1. Conditions B: see eq 1. ^{*c*}The product was isolated as a free alcohol after TBS deprotection. ^{*d*}SIPrCuCl was used as a catalyst. ^{*e*}See SI for details.

the formation of the desired product and the regeneration of the nickel(I) catalyst (VII). The copper hydride intermediate

 $\left(V\right)$ is regenerated in sequential reactions of the copper catalyst with the alkoxide and the silane.

Scheme 4. Proposed Mechanism



In preliminary experiments, we probed the proposed interaction of the two established catalytic cycles. In a nickelcatalyzed cross coupling of the presumed alkenyl copper intermediate with a secondary alkyl iodide we obtained the expected *E*-alkene in 92% yield (Scheme 5a). In the absence of

Scheme 5

a) Nickel-catalyzed cross coupling of alkenyl copper and alkyl iodides



the nickel catalyst we did not detect the formation of the *E*alkene. These experiments demonstrate the feasibility of the proposed nickel-catalyzed cross coupling of the alkenyl copper intermediate and an alkyl iodide and establish the need for the nickel catalyst.

Next, we probed the relationship between transmetalation and alkyl halide activation. We propose that the activation of the alkyl iodide happens only after the transmetalation and the formation of the alkenyl nickel intermediate **VIII**. In some nickel-catalyzed cross coupling reactions the activation of the alkyl halide occurs prior to transmetalation.^{34,35}

To probe this alternative mechanism, we exposed cyclohexyl iodide to our nickel(I) catalyst ((tpy')NiI). After 1 h at room temperature, the starting alkyl iodide was fully recovered (Scheme 5b). This result suggests that, in our reaction, transmetalation ($VI \rightarrow VIII$) likely precedes the activation of the alkyl iodide ($VIII \rightarrow IX$). Further studies of the reaction mechanism are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b04800.

Experimental procedure and product characterization (PDF)

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Notes

The authors declare no competing financial interest.

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