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Nickel-Catalyzed Hydroarylation

Nickel-Catalyzed Directed Hydroarylation of Alkynes with Boronic Acids

Luke E. Hanna,[a] Mikhail O. Konev,[a] and Elizabeth R. Jarvo*[a]

Abstract: A regio- and stereoselective nickel-catalyzed hydroarylation of alkynes using propargylic carbamates as directing groups has been developed. The reaction proceeds under mild reaction conditions using arylboronic acids in the absence of base. A range of heterocycles and functional groups are tolerated under the reaction conditions, providing high yields of trisubstituted alkenes with control of olefin geometry.

Introduction

Functionalized alkenes are present in pharmaceutical agents and natural products (Figure 1) and are common building blocks in synthesis.[1,2] Hydroarylation reactions using arylboronic acids offer a simple and attractive manifold for the preparation of substituted alkenes from alkyne precursors.[3,4] Precious metal catalysts have been established for reactions employing arylboronic acids, beginning with pioneering work of Hayashi using rhodium complexes (Scheme 1a).[5,6] Control of regioselectively in reactions of internal alkynes, in the absence of strong electronic bias, has been accomplished with elegant use of directing groups, with recent focus on directing groups that serve as synthetic handles for subsequent manipulation (Scheme 1c and d).[7,8] Establishing base metal catalysts for alkyne hydroarylation is of interest, in part to provide the practical and synthetic advantages of an earth-abundant metal.[9] For example, Hartwig and co-workers reported the use of nickel catalysts (Scheme 1b), providing smooth hydroarylation of symmetrical alkynes with arylboronic acids; Reddy and co-workers developed regioselective hydroarylation of propargylic alcohols (Scheme 1e).[10,11]

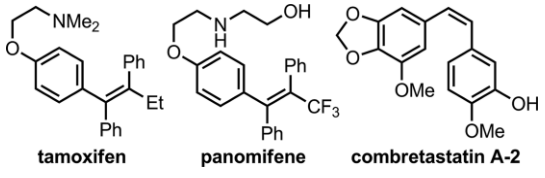
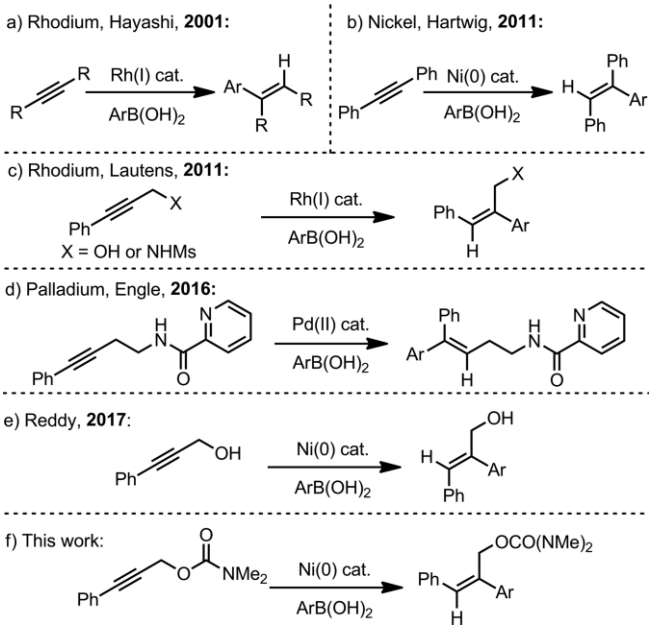


Figure 1. Examples of stilbene-containing pharmaceutical agents and natural products.

We hypothesized that carbamates could serve as directing groups for nickel-catalyzed hydroarylation. This hypothesis was based on previous work in our laboratory, where we found that carbamates serve as directing groups and could direct oxidative addition of nickel for stereospecific Suzuki reactions.[12] In this manuscript, we report a regio- and stereoselective hydroarylation of propargylic carbamates. These reactions proceed under mild conditions, at room temperature with no added base (Scheme 1f).



Scheme 1. Transition metal-catalyzed hydroarylation reactions of alkynes with boronic acids.

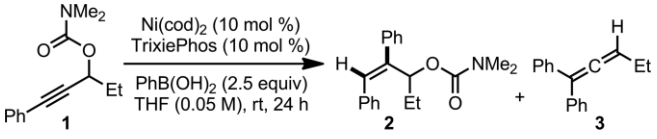
Results and Discussion

We began our investigation by interrogating a range of alkynes, including those with propargylic directing groups such as pivalates, carbonates, and carbamates. The highest yield of hydroarylated product **2** was formed when a dimethylcarbamate was employed as a directing group (Table 1, entry 1). Use of a simple alkyne (**4**) with no directing group resulted poor conversion

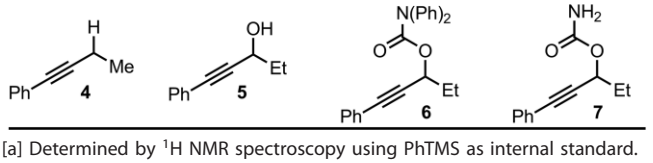
[a] *Department of Chemistry, University of California, Irvine, CA 92697, USA*
E-mail: erjarvo@uci.edu; http://sites.uci.edu/jarvogroup/
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201801494.

and recovered starting material (entry 2). A mixture of byproducts and only 20 % hydroarylated product could be observed when propargylic alcohol **5** was used (entry 3). Using pivalates and carbonates as directing groups lead to formation of allene **3** and small amounts of desired product **2**. The steric properties of the directing group also proved important, as more bulky carbamates such as diphenyl carbamate lead to a severe drop yield (entry 4). A range of ligands was evaluated during the course of reaction optimization. The reaction performs well with monodentate phosphine ligands, and bulky Buchwald-type ligands such as TrixiePhos were uniquely capable of furnishing good yields of product and suppressing the formation of allene. Notably, subsequent allylic substitution of the allylic carbamate **2** was not observed under our reaction conditions.

Table 1. Optimization of reaction conditions.



Entry	Variation from standard conditions	Recovered alkyne (%)[a]	**2** (%)[a]	**3** (%)[a]
1	none	<2	70	<2
2	**4** instead of **1**	57	19	<2
3	**5** instead of **1**	73	20	<2
4	**6** instead of **1**	57	16	14
5	**7** instead of **1**	81	8	<2
6	no nickel	100	0	0
7	no ligand	8	55	15
8	SPhos instead of TrixiePhos	16	63	2
9	BrettPhos instead of TrixiePhos	11	50	9
10	CPhos instead of TrixiePhos	12	50	12
11	1 equivalent of K_3PO_4	10	40	6
12	1 equivalent of LiCl	100	0	0
13	DMF instead of THF	86	13	7
14	PhBpin instead of $PhB(OH)_2$	78	8	4
15	$(PhBO)_3$ instead of $PhB(OH)_2$	65	19	6

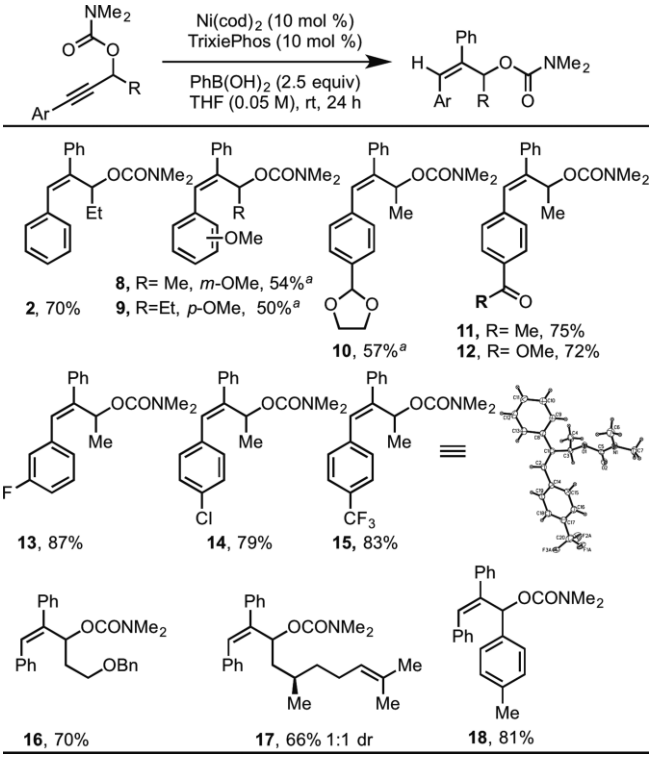


[a] Determined by ^1H NMR spectroscopy using PhTMS as internal standard.

Typical additives and reaction conditions for hydroarylation and Suzuki-type coupling reactions were evaluated as part of reaction optimization. Interestingly, the presence of bases such as *t*BuOK and K_3PO_4 that are commonly used to promote transmetallation provide lower yield (Table 1, entry 11). Furthermore, the addition of just one equivalent of LiCl to the reaction mixture lead to a complete shutdown of reactivity and recovery of starting material (entry 12). Additionally, during an investigation of suitable solvents it was found that the use of strongly coordinating solvents such as DMF also shut down reactivity (entry 13). Notably, under optimized reaction conditions, the hydroarylation reaction proceeds at room temperature for a majority of substrates; related hydroarylation reactions frequently require elevated temperatures.[13]

Having identified suitable reaction conditions for model substrate **1**, we interrogated a range of internal alkynes (Table 2). Substrates bearing electron-deficient arenes provided the highest yields of hydroarylated product at room temperature (**11–15**). Electron-rich arenes required heating (**8** and **10**). Ketone and ester substituents are well-tolerated (**11** and **12**), however, free aldehydes were not. Gratifyingly, protection of the aldehyde as an acetal restored clean hydroarylation under moderately elevated reaction temperatures (**10**). Halides were well tolerated under the reaction conditions (**13–15**). Aryl fluorides and chlorides allow for the potential for subsequent functionalization. X-ray crystallographic analysis of a single crystal of trifluoromethyl-substituted **15** established the olefin geometry and supported that the reaction provides *cis* hydroarylation.[14] Benzyl-protected alcohols on the alkyl moiety of the starting materials were carried through the reaction untouched (**16**). Citronellal-derived **17** was obtained in good yield, demonstrating that pendant alkenes do not diminish reactivity. Surprisingly, aryl-substitution at the propargylic position was also tolerated, providing hydroarylation in high yield and no subsequent allylic substitution (**18**).

Table 2. Scope of hydroarylation with respect to alkyne.

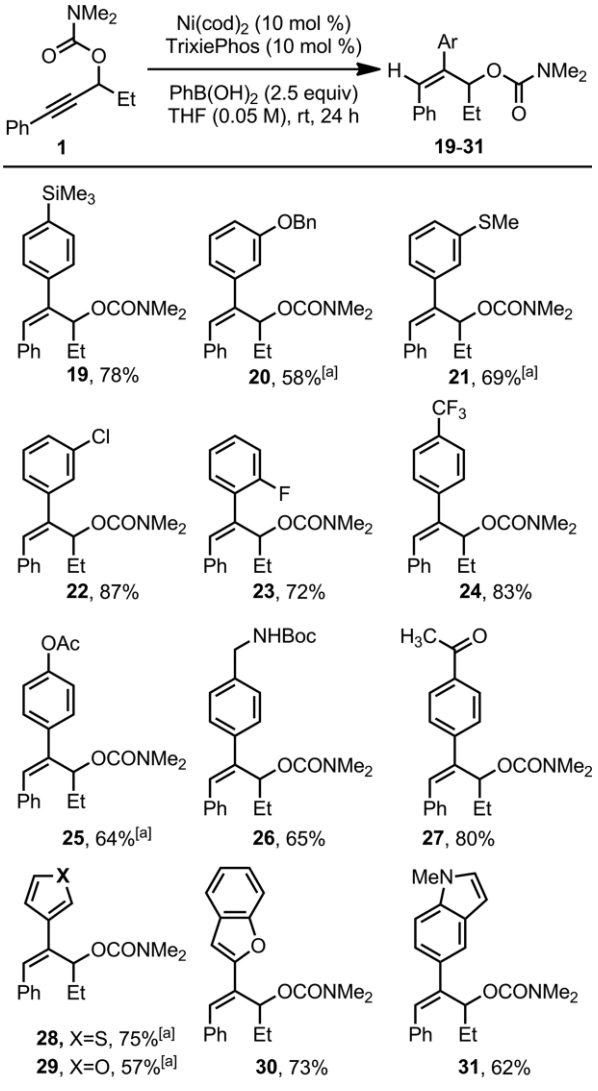


[a] Reaction was heated at 80 °C instead of 24 °C.

Next, we turned our attention to investigating the scope with respect to arylboronic acids (Table 3). A similar trend in sensitivity to electronics was observed and electron-deficient arylboronic acids provided the highest yields at room temperature while electron-rich arylboronic acids typically required heating. A variety of functional groups were well-tolerated, allowing for the incorporation of trimethylsilyl, ether, thioether, and trifluoromethyl moieties (**19–21**, **24**). Aryl chlorides and

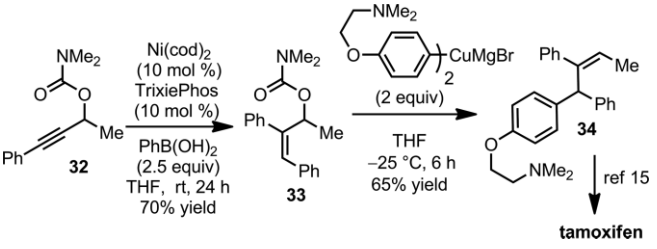
fluorides participated cleanly in hydroarylation (**22–23**), with no observed competitive hydrodehalogenation or cross-coupling. Esters, ketones and carbamates were also well-tolerated (**25–27**). Furthermore, boronic acids containing heterocycles such as indole, furan, benzofuran, and thiophene provided smooth hydroarylation (**28–31**).

Table 3. Scope of hydroarylation with respect to boronic acid.



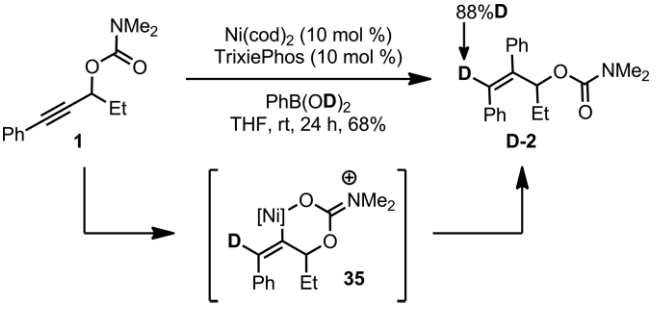
[a] Reaction was heated at 80 °C instead of 24 °C.

Allylic alcohols are excellent functional handles in synthesis. Moreover, activated allylic alcohols such as allylic carbamates have been used as electrophiles in both palladium and copper catalyzed allylic substitution reactions.[15] Thus, the directing group employed in this hydroarylation reaction is poised for subsequent metal-catalyzed transformations. To highlight the potential application of such a reaction in the preparation of medicinal agents including selective estrogen receptor modulators, we undertook synthesis of tamoxifen.[1] Sequential nickel-catalyzed hydroarylation and allylic displacement with a cuprate reagent transforms alkyne **32** into trisubstituted alkene **34** (Scheme 2). Base-mediated olefin isomerization provides tamoxifen.[16]



Scheme 2. Synthesis of Tamoxifen.

To gain insight into the mechanism of the reaction we sought to determine the origin of the hydrogen atom in our hydroarylation reaction. Employing $PhB(OD)_2$ in the reaction lead to a 68 % yield of product **D-2** with 88 % deuterium incorporation (Scheme 3). Alternatively, use of $(PhBO)_3$ and deuterium oxide resulted in 99 % deuterium incorporation, albiet in low yield of product (17–30 %), presumably by formation of $PhB(OD)_2$ in situ. One possible mechanism that is consistent with these results is one where the low-valent nickel catalyst is first protonated by the boronic acid. Carbamate-directed hydrometallation of the alkyne provides vinylnickel intermediate **35** in a regio- and stereoselective manner. This intermediate can then undergo transmetallation and reductive elimination to furnish the desired product. This mechanism is consistent with the mechanisms previously proposed for hydoarylation reactions in the absence of base.[3]



Scheme 3. Deuterium labeled boronic acid reveals the origin of hydrogen in the reaction.

Conclusions

In conclusion, we have developed a regio- and stereoselective nickel-catalyzed hydroarylation of alkynes with arylboronic acids using a propargylic carbamate as a directing group. The reaction is tolerant of a range of functional groups and heterocycles. Application in the synthesis of a representative triarylethylene, tamoxifen, is demonstrated.

Experimental Section

In a glove box, a flame dried 7 mL dram vial was charged with $Ni(cod)_2$ (5.5 mg, 0.020 mmol, 0.10 equiv.), TrixiePhos (8.0 mg, 0.020 mmol, 0.10 equiv.), arylboronic acid (0.50 mmol, 2.5 equiv.),

and the alkyne (0.20 mmol, 1.0 equiv.) and dissolved in THF (4.0 mL). The reaction was then stirred for 24 h at 24 °C or 80 °C depending on the substrate and arylboronic acid used. The reaction mixture was then filtered through a pad of silica and eluted with Et_2O to remove the catalyst and then concentrated under reduced pressure. The product was purified by flash column chromatography.

Acknowledgments

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Keywords: Directed · Hydroarylation · Nickel · Trisubstituted alkenes · Boronic acids

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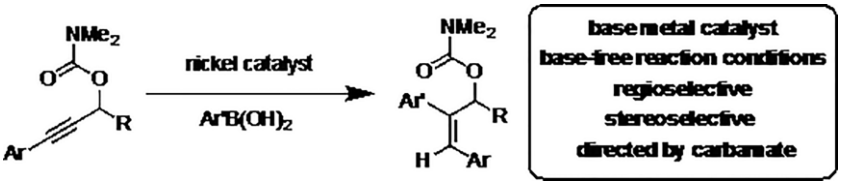

Stereoselective synthesis of trisubstituted alkenes using a nickel catalyst under mild reaction conditions is reported. A propargylic carbamate serves as a directing group. Products are allylic carbamates that can undergo further transformation, for example, by copper-mediated allylic substitution

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