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Copper-Catalyzed Hydroarylation of Internal Alkynes: Highly Regio- and Diastereoselective Synthesis of 1,1-Diaryl, Trisubstituted Olefins

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Supporting Information Placeholder

ABSTRACT: The copper-catalyzed hydroarylation of internal, unsymmeric alkynes is presented. Trisubstituted alkenes are obtained as single diastereomers in good to excellent yields and excellent regioselectivities. The scope of the reaction is presented with respect to alkyne and aryl iodide coupling partners. Initial mechanistic experiments indicate a hydrocupration event followed by a two-electron oxidative addition/reductive elimination pathway. **KEYWORDS:** Copper, C–C coupling, Alkynes, Arenes, Synthetic Methods

Olefins are a prominent functionality found in organic materials and pharmaceuticals and are versatile synthetic intermediates for further functionalization. Despite well-established methods for forming disubstituted olefins,¹ the regio- and stereospecific synthesis of trisubstituted olefins remains a challenge.² Alkyne hydroarylation represents an attractive route for the synthesis of this important functionality in an efficient manner.³ 1,1-diaryl olefins, specifically, represent a class of compounds for which hydroarylation would decrease synthetic overhead and promote rapid assembly of diverse products (Figure 1).⁴



Figure 1. Biologically Active 1,1-diaryl olefins.

Several hydroarylation methods have been reported for the assembly of 1,1-diaryl alkenes (Scheme 1a-c); however, these methods have shortcomings which preclude them from being broadly applicable. Friedel-Crafts hydroarylation (Scheme 1a) relies on a π -acidic catalyst to activate the alkyne for an electrophilic aromatic substitution. These reactions are limited to nucleophilic electron neutral and rich arenes.⁵ The use of organometallic arenes with transition metal catalysts was an important advance, providing access to broader substrate classes; however, 1,2-diaryl alkenes are formed as the major or exclusive regioisomer with aryl- or alkyl-substituted internal alkynes.⁶ Directing groups on the alkyne which employ steric, electronic, or chelation effects can control the selectivity of a metal–



Scheme 1. Alkyne hydroarylation

arene migratory insertion to afford the 1,1-diaryl alkene (Scheme 1b).7 While the scope of arenes is vastly improved compared to Friedel-Crafts methods, the alkyne partners are limited due to the requisite directing group. Arenes bearing a ligand directing group can also select for the 1,1-diaryl alkene product if C-H migratory insertion occurs prior to C-C bond formation (Scheme 1c). Unfortunately, the scope of this approach is limited to 2-pyridyl⁸ and 1-benzotriazole⁹ directing groups, as they do not undergo further intramolecular cyclization after hydroarylation.^{3b} Despite the limited scope of these C-H activation methods, we were inspired by the excellent selectivity for the 1,1-diaryl product without the need for a directing group on the alkyne. We hypothesized that an in situ generated metal-H could undergo a selective migratory insertion across an aryl alkyne. Subsequent oxidative addition into an aryl iodide and reductive elimination would furnish a 1,1-diaryl alkene (Scheme 1d). We chose to pursue a Cu-catalyzed hydroarylation reaction utilizing a silane as an in situ hydride source given the tremendous recent advances in other Cu-catalyzed hydrofunctionalization reactions.¹⁰

In 1990, Stryker reported the formal *cis*-hydrogenation of alkynes via a Cu–H intermediate wherein water served as the H^+

Table 1. Selected reaction optimization*



entry	ligand	Additive	yield of 1a $(\%)^b$
1	DTBM-segphos	CsOAc	4
2	BINAP	CsOAc	42
3	DPEphos	CsOAc	82
4	dppf	CsOAc	92
5	dppf	None	3
6	dppf	CsOAc ^c	42
7	dppf	KOAc	15
8	dppf	NaOAc	4
9 ^d	dppf	CsOAc	62
10 ^e	dppf	CsOAc	76
	PAr ₂ PAr ₂ PAr ₂	h ₂ PPh ₂	PPh ₂ Ph ₂ P
DTBM-segphos rac-BINAP DPEphos dppf Ar = 3,5-bis-tBu-4-OMe-C ₆ H ₂			

^a Reaction conditions: Cu(OAc)2 (1.0 mol %), Ligand (1.5 mol %), PMHS (1.75 equiv), Additive (1.1 equiv), diphenylacetylene (1.5 equiv), PhI (1.0 equiv), THF (0.5 M), at 80 °C for 24 h. ^b Yield determined by GC analysis of the crude reaction mixture by comparison to undecane as an internal standard. ^c 0.50 equiv of CsOAc used. ^d 1.0 equiv of diphenyl acetylene added. e 1.25 equiv of diphenyl acetylene added.

source.¹¹ Later, other electrophiles were utilized in this reaction to trap the vinyl copper intermediate to form α,β -unsaturated carboxylic acids,12 vinyl boranes,13 enamines,14 vinyl bromides,15 and alkenes;16 however, the related Cu-catalyzed C-Aryl bond forming reaction has not been described. The hydroarylation of styrene with dual Cu/Pd catalysts (the Cu catalyst generates the Cu-benzyl intermediate which then transmetallates to Pd and undergoes C-C bond forming reductive elimination) has been reported to provide the 1,1-diaryl alkanes by Nakao and Buchwald.¹⁷ Furthermore, Nakao demonstrated that alkynes can undergo hydroarylation with this Cu/Pd co-catalytic system; however, only three examples were shown and a moderate 7.3:1 regioselectivity was observed for 1-phenyl-1-butyne.^{17a} Given the recent advances in Cu-catalyzed C-C bond forming reactions by Giri¹⁸ and carboboration by Brown,¹⁹ we hypothesized that the Pd cocatalyst could be removed and the formed Cu(I)-vinyl intermediate, generated upon alkyne insertion into a Cu-H, could be directly oxidized with an aryl iodide to give the desired 1,1-diaryl alkene upon reductive elimination.

We began our studies on the coupling of diphenylacetylene with PhI with $Cu(OAc)_2$ as the precatalyst and polymethylhydrosiloxane (PMHS) as the hydride source (Table 1). Acetate salts were added to the reaction to transmetalate with CuI to form CuOAc thereby increasing the rate of transmetallation with PMHS.²⁰ Investigation of

Table 2. Scope of symmetric alkynes^{4,b}



^a Isolated yields reported as an average of two runs. ^b Reaction conditions: Cu(OAc)₂(1.0 mol %), dppf (1.5 mol %), PMHS (1.75 equiv), CsOAc (1.1 equiv), diphenylacetylene (1.5 equiv), and ArI (1.0 equiv) in THF (0.5 M) at 80 °C for 24 h. ^cReaction conducted at 120 °C for 60 h with 3-hexyne (2.5 equiv). ^dYield determined by ¹H NMR analysis of the crude reaction mixture and comparison to 1-methylnaphthalene as an internal standard.

bidentate phosphines showed that dppf afforded **1** in an excellent yield (92%) with 1.0 mol % catalyst. Reducing CsOAc to 0 or 0.5 equiv significantly reduced the yield of **1** to 3% or 42%, respectively, indicating that added acetate is required for catalyst turnover. Cesium proved to be a superior cation (Table 1, entries 4, 7, and 8), likely due to its increased solubility in THF. Finally, alkyne equivalency was reevaluated and we found that a moderate excess of alkyne is required for excellent yields (Table 1, entries 4, 9, and 10).

With the optimized conditions in hand, we explored aryl coupling partners (Table 2). Aryl iodides with varying electronic profiles were well tolerated resulting in the formation of the coupled products in excellent yields as single diastereomers. A 2-pyridyl group was also amenable to the reaction, although in slightly reduced yield.²¹ A *t*-butyl ester group was tolerated; reducing the size of the alkyl group on the ester to a methyl group lead to undesired Cu-catalyzed reduction of the carbonyl. Similarly, other reducible functional groups were not tolerated; e.g. 4-iodobenzonitrile, and 4-iodoacetophenone. Finally, under these optimized conditions, 3-hexyne provided trace quantities of **2** (< 5% yield); however, increasing the equivalents of alkyne to 2.5 and temperature to 120 °C provided **2** in a moderate 24% NMR yield.

Next the scope of differentially substituted internal alkynes was investigated (Table 3).²² Using 1-phenyl-1-propyne, under the conditions utilized in Table 2, gave 3a in 24% GC yield when coupled with PhI. Reoptimization led to the conditions shown in Table 3 which employ 50 mol % pyridine²³ as an additive and higher concentration which provided **3a** in 81% GC yield. Varying the aryl iodide results in the formation of 1,1-diaryl propenes in good yields and excellent regioisomeric ratios (r.r.) as single diastereomers (the 1,1-diaryl relationship was unambiguously confirmed by x-ray crystallography of 3d). Gratifyingly, given their readily derivatized functionalities, 4-Br-, 4-Cl-, and 4-tosyl- substituted iodobenzenes react readily affording **3d**, **3e**, and **3f** in 68%, 60%, and 79% yields. The electronic nature of the aryl iodide does not have a significant effect on the yield or selectivity of the reaction; both electron rich and electron poor arenes are incorporated in good to excellent yields. An ortho-substituent on the aryl iodide is tolerated; although, the rate of the reaction is slowed; 2-methoxyiodobenzene is coupled with 1-phenyl-1propyne to supplying **3h** in an 89% yield after 48 h. Sensitive functionalities and Lewis basic groups are incorporated into the products (3i and 3j and 3k respectively), albeit in somewhat reduced yields. Other hetercyclic aryl iodides; e.g. 2-iodothiophene, 1-methyl-2-

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^{*a*} Isolated yields reported as an average of two runs. ^{*b*} Regioisomeric ratio(**3-13:3'-13'**) determined by GC analysis of the crude reaction mixture. ^{*c*} Reaction conditions: Cu(OAc)₂ (1 mol %), dppf (1.5 mol %), PMHS (1.75 equiv) CsOAc (1.1 equiv), pyridine (0.5 equiv), alkyne (1.75 equiv), ArI (1.0 equiv) in THF (1.0 M) at 100 °C for 24 h. ^{*d*}Cu(OAc)₂ (2 mol %), dppf (3 mol %) ^{*c*} Regioselectivity determined by NMR analysis of the crude reaction mixture. ^{*f*} 48 h. ^{*s*} Reaction conducted without pyridine. ^{*h*} 120 °C. ^{*f*} Reaction conducted with conditions shown in table 2.

iodo-indole, 2-iodobenzofuran, and 2-iodobenzothiophene, did participate in the hydroarylation.²⁴ The reaction is readily scaled, as **3a**, **3c**, **3d**, and **3e** were run on 2.0 mmol scale and isolated by recrystallization with no need for chromatographic purification.²⁴ The reaction is readily scaled, as **3a**, **3c**, **3d**, and **3e** were run on 2.0 mmol scale and isolated by recrystallization with no need for chromatographic purification.

The conditions for 1-phenyl-1-propyne proved to be general for other 1-aryl-2-alkyl alkynes. Coupling alkynes of varying electronic profiles with 3-methoxyiodobenzene gave excellent yields for electron withdrawing substrates; 4-CF3- and 4- Cl- phenyl groups provided 4 and 5 in 91% and 89% yields respectively. The less electrophilic 4-Me- and 4-OMe-phenyl propynes are sluggish and require 48 h for full conversion, giving 6 and 7 in 79% and 61% yield, respectively. The extremely electron donating 4-NMe2-phenyl required elevated temperature to promote the reaction and afforded 8 in a 7.2:1 (8:8') regioisomeric ratio in a 32% combined yield. The yield and selectivity of the reaction is not sensitive to steric changes of the alkyl substituent of the alkyne as substrates with either a *n*-butyl or *t*-butyl are obtained in good yields and regioisomeric ratios (90% for 11 and 78% for 12). A propargyl amine and homopropargyl benzyl ether also couple successfully; however, at slightly reduced regioselectivities, perhaps due to a competitive Lewis base directed hydrocupration. Finally, an electronically biased diphenyl acetylene derivative was tested, yielding 15 in a 98% yield and a 3.1:1 regioisomeric ratio, demonstrating a moderate electronic bias for the hydrocupration step.

Previously reported Cu-catalyzed C–C bond forming reactions proceed through two-electron oxidative addition/reductive elimination sequences.¹⁸ To gain insight into the mechanism, competition Hammett studies and an intramolecular radical trap experiment were conducted. Alkyne competition Hammett studies show that the electron bias of the alkyne is the source of regioselectivity in the reaction while aryl iodide competition studies are consistent with a two-electron oxidative addition.^{25,26} Subjecting **16**, which has a pendant prenyl group, to standard coupling conditions, we obtained **17** in 85% yield along with an 8% NMR yield of **18** (Scheme 2); **19** was not observed. As **17** is the major product, it is likely that the reaction is proceeding though a two-electron oxidative addition/reductive elimination pathway and **18** is being formed either via an off-cycle reaction or by a migratory insertion after the oxidative addition step; however, a rapid one- electron oxidative addition pathway cannot be ruled out.^{18,27}





A catalytic cycle consistent with the mechanistic insights is proposed in Scheme 3. [Cu]–OAc (I) can undergo a transmetalation with PMHS to yield II, subsequent hydrocupration of an alkyne yields the vinyl copper intermediate III. III can then undergo oxidative addition into the aryl iodide resulting in the formation of the Cu⁺³ intermediate IV¹⁸ which undergoes rapid reductive elimination

to furnish the product and $\mathbf{V}^{.^{18}}$ Finally, a transmetalation with CsOAc regenerates $\mathbf{I}.$



Scheme 3. Proposed catalytic cycle

In conclusion, a Cu-catalyzed hydroarylation reaction has been developed. Yields ranging from 32-99% are obtained with regioisomeric ratios of 7.2-44:1 as single diastereomers in all cases. A variety of electronically and sterically differentiated alkynes and aryl iodides are competent coupling partners, and the reaction is readily scalable. Initial mechanistic studies show electronic bias of the alkyne is the source of regioselectivity in the hydrocupration step and the oxidative addition/reductive elimination sequence is likely a two-electron process.

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Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data (PDF)

Crystallographic data for **3d** (CIF)

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²¹ Reduced yield is due to protodeiodination of the starting material.

²² Terminal Alkynes lead to a complex mixture of products.

 23 The role of pyridine is not fully understood; however, it is likely that it solubilizes higher order [Cu-H] clusters.

²⁴ See supporting information for a full list of unsuccessful substrates.

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²⁶ See supporting information for more details.

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