Communication

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Asymmetric Hydroarylation of Vinylarenes Using a Synergistic Combination of CuH and Pd Catalysis

Stig D. Friis, Michael T. Pirnot and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

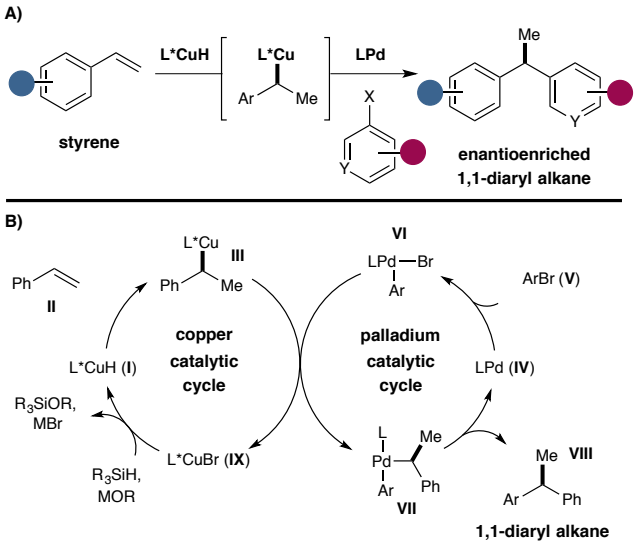
Supporting Information Placeholder

ABSTRACT: Detailed in this report is the enantioselective synthesis of 1,1-diarylalkanes, a structure found in a range of pharmaceutical drug agents and natural products, through the employment of copper(I) hydride (CuH) and palladium (Pd) catalysis. Judicious choice of ligand for both copper and palladium enabled this hydroarylation protocol to work for an extensive array of aryl bromides and styrenes, including β-substituted vinylarenes and six-membered heterocycles, under relatively mild conditions.

Palladium-catalyzed cross coupling has proven to be a successful and reliable method for carbon−carbon bond construction. Among the many substrate classes employed in this field, stoichiometric organometallic reagents (e.g., Mg, Zn, Sn reagents) are traditionally used as coupling partners in palladium chemistry due to their propensity for facile transmetalation, and much successful work has been realized with the use of these reagents to generate functionalized arenes.[1] Drawbacks associated with the use of stoichiometric organometallic reagents, including their possible sensitivity toward air/water, promiscuity towards undesired pathways of reactivity, and necessity to preform them before their use in cross coupling, has inspired methods avoiding their intermediacy.[2]

Recent advances in copper chemistry have demonstrated that nucleophilic alkylcopper(I) species can be generated catalytically via olefin insertion and successfully intercepted with a range of electrophiles.[3,4] As an alternative to stoichiometric organometallic reagents, we questioned whether an copper(I) alkyl intermediate of this nature could be generated catalytically and exploited in a palladium-catalyzed cross-coupling process to yield the corresponding sp^2−sp^3 cross-coupled product (Scheme 1). Importantly, we sought a chiral CuH catalyst that would effect an enantioselective olefin hydrocupration to form a stereodefined copper(I) intermediate, which would undergo transmetalation with palladium with high stereospecificity, ultimately leading to an enantioenriched coupling product. Using this approach, we anticipated that a suitable combination of Cu and Pd catalysts would allow for the enantioselective coupling of styrenes with aryl bromides to form 1,1-diarylalkanes, a biologically active structure

Scheme 1. A) Enantioselective access to 1,1-diarylalkanes via Pd and Cu catalysis; B) Proposed catalytic cycle for enantioselective hydroarylation of styrenes.



common in both pharmaceuticals and natural products.[5]

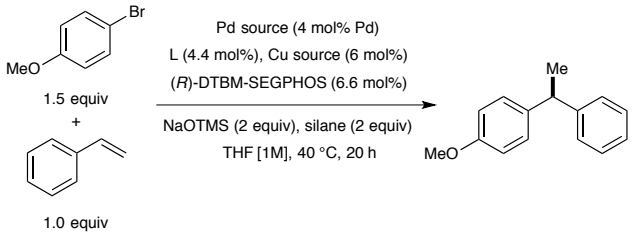
Enantioenriched 1,1-diarylalkanes have previously been prepared through the stereospecific cross coupling of enantioenriched benzylic electrophiles.[6,7] A nickel-catalyzed stereoconvergent coupling of racemic benzylic alcohols with arylzinc reagents has also been reported.[8] Methods that employ prochiral substrates include asymmetric hydrogenation of 1,1-diarylalkenes[9] and conjugate addition of arylmetal nucleophiles to cinnamaldehyde derivatives.[10] Our approach represents a highly modular alternative for the enantioselective synthesis of this class of compounds. Moreover, aryl bro-

mides and vinylarenes are widely available reagents or feedstock chemicals and are therefore nearly ideal coupling partners.[11]

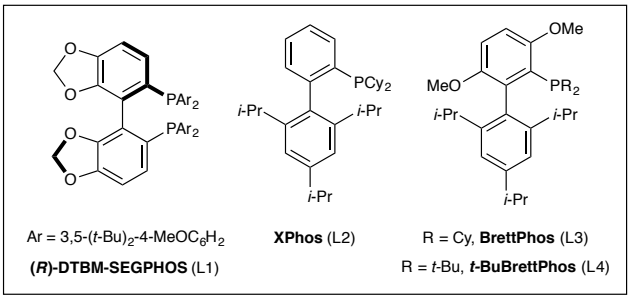
Pioneering efforts by several researchers have demonstrated the synergistic potential of Cu and Pd catalysis.[12] More recently, Nakao[13] and Brown[14] have both reported the diastereoselective borylarylation of styrene derivatives using both Cu and Pd in catalytic quantities, while Liao[15] demonstrated the enantioselective boroallylation of vinylarenes using a similar system. At the outset of this project, the use of CuH and Pd catalysis in a cooperative manner for hydrofunctionalization was unknown. However, a report detailing the Pd/Cu-catalyzed hydroarylation of styrenes to furnish racemic 1,1-diaryl alkanes was recently published.[16]

Scheme 1.B details our proposed dual catalytic cycle for enabling the described transformation. Formation of active CuH catalyst **I** would occur through the use of a Cu(I) or Cu(II) salt, chiral ligand, and silane. Enantioselective hydrocupration of olefin **II** would form stereodefined Cu(I) benzylic intermediate **III**.[17,18] In the second catalytic cycle, ligated palladium(0)

Table 1. Optimization of the Pd/Cu-catalyzed enantioselective hydroarylation of styrene.[a]



entry	silane	Pd source	L	% yield	ee
1[b]	Et_3SiH	$Pd(OAc)_2$	**L2**	14	88
2[b]	$i\text{-}Pr_3SiH$	$Pd(OAc)_2$	**L2**	2	ND
3[b]	Me_2PhSiH	$Pd(OAc)_2$	**L2**	19	85
4[b]	$MePh_2SiH$	$Pd(OAc)_2$	**L2**	58	83
5[b]	Ph_2SiH_2	$Pd(OAc)_2$	**L2**	0	--
6[b]	$MePh_2SiH$	$Pd(OAc)_2$	**L3**	66	85
7[b]	$MePh_2SiH$	$Pd(OAc)_2$	**L4**	61	85
8[b]	$MePh_2SiH$	$Pd_2(dba)_3$	**L3**	45	ND
9[b]	$MePh_2SiH$	$Pd(COD)Cl_2$	**L3**	63	86
10[b]	$MePh_2SiH$	$[Pd(cinnamyl)Cl]_2$	**L3**	75	88
11[c]	$MePh_2SiH$	$[Pd(cinnamyl)Cl]_2$	**L3**	84	90



[a]Yields determined by GC analysis of the crude reaction mixture using tetradecane as an internal standard; enantioselectivity of the purified product was determined by chiral HPLC; ND = not determined; [b]$Cu(OAc)_2$ used as the Cu source; [c] CuOAc used as the Cu source.

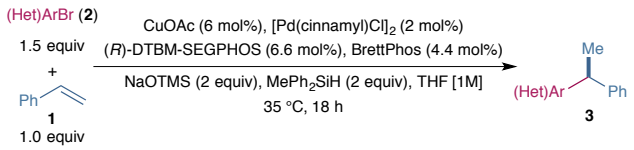
IV would oxidatively add to the aryl bromide **V** to form complex **VI**. As the key step in this process, the dual catalytic cycle converges via a stereospecific transmetalation of organocopper **III** with palladium species **VI** to form chiral palladium(II) alkyl complex **VII**.[19] Stereoretentive reductive elimination furnishes enantioenriched 1,1-diarylalkane **VIII** and regenerates palladium(0) species **IV**. Considering previous reports with CuH catalysis, we reasoned that salt metathesis of Cu(I) halide **IX** with base would be required to regenerate CuH catalyst **I**.[20] We believed that the success of our strategy was predicated on three issues: i) competitive reduction of aryl halide **V** via a metal hydride species would need to be suppressed; ii) choice in ligand would enable productive reactivity of each metal species while not deactivating the other; iii) the rate of each metal cycle would need to be matched so as to avoid unproductive side reactions.

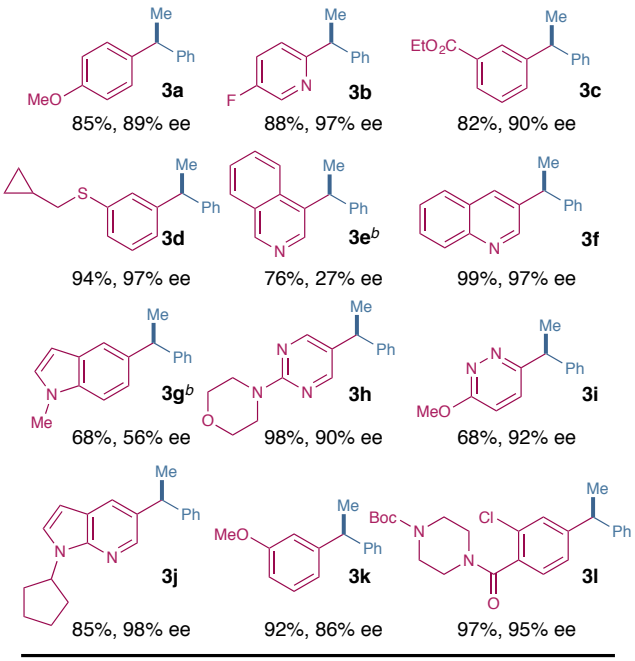
The optimization of an enantioselective hydroarylation process for styrene and 4-bromoanisole is detailed in Table 1. Examination of several silanes (entries 1−5) indicated that methyldiphenylsilane ($MePh_2SiH$) was the optimal silane tested when combined with sodium trimethylsilanolate (NaOTMS), providing a moderate yield and high level of enantioselectivity for the desired product (entry 4, 58% yield, 83% ee). NaOTMS was a uniquely effective base for this chemistry and little to no product was observed with LiOTMS and KOTMS.[21] Testing several biarylphosphine ligands (entries 4, 6, and 7) showed that a modest increase in yield was observed when using BrettPhos as a secondary ligand (entry 6, 66% yield, 85% ee). Employing $[Pd(cinnamyl)Cl]_2$ as the source of palladium for this reaction resulted in improved reactivity while not significantly affecting the enantioselectivity of the process (entry 10, 75% yield, 88% ee). A range of Cu(I) and Cu(II) salts were examined, and a slight improvement was observed using CuOAc as the source of copper (entry 11, 84% yield, 90% ee). Evaluation of a variety of chiral bisphosphines demonstrated that DTBM-SEGPHOS was an excellent ligand for this transformation with many other ligands giving significantly lower yield and enantioselectivity of the desired product.[22]

With the optimized conditions in hand, we turned toward examining the substrate scope of the aryl bromide coupling partner (Table 2 and Table 3).[23] Electron-rich aryl bromides (**2a** and **2n)** worked well in this reaction, while 4-bromobenzonitrile and aryl bromides with acidic protons were not compatible with the reactions conditions. A range of functional groups, including ethers (such as **2a**, **2i**, **2h**, **2k**, and **2n**), an ester (**2c**), a thioether (**2d**), an amine (**2h**), a carbamate (**2l**), an aryl chloride (**2l**), and an amide (**2l**), were all tolerated in this protocol. Employing *ortho*-substituted aryl bromides as viable substrates required a slightly higher reaction tem-

perature and longer reaction times to provide the product (**3n**) in good yield and high enantiopurity. Importantly, a variety of brominated heterocycles, such as pyridines (e.g., **2b** and **2m**), quinolines (**2f** and **2t**), a pyrimidine (**2h**), a pyridazine (**2i**), and an azaindole (**2j**), were competent coupling partners. In addition, a five-membered brominated heterocycle was effective (**2o**). Certain aryl bromides, such as 4-bromoisoquinoline (**2e**) and 5-bromo-1-methylindole (**2g**), resulted in moderate yields but poor to modest enantioselectivities (76% yield, 27% ee and 68% yield, 56% ee, respectively).[24] Characterization of **3i** via X-ray crystallography revealed the absolute configuration of the stereocenter. This data, combined with the sense of stereoinduction observed with our method for CuH-catalyzed hydroamination of styrenes,[3d] suggests that the proposed Cu-to-Pd transmetalation step occurs with retention of configuration (see Supporting Information for details).[25,26]

Table 2. Scope of the aryl bromide coupling partner.[a]

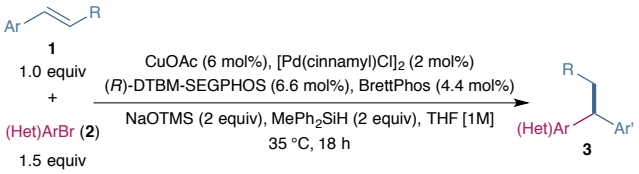


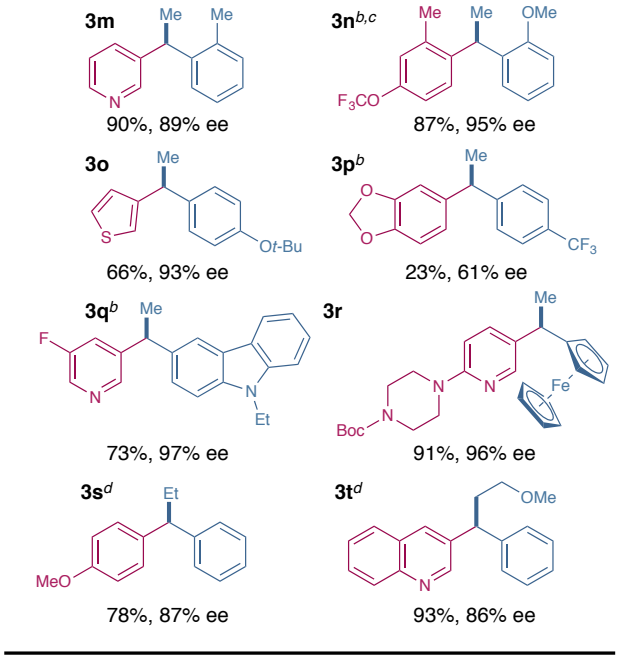


[a]All yields represent the average of isolated yields from two runs performed with 1 mmol of styrene, enantioselectivity determined by chiral SFC; [b]Average of isolated yields from three runs.

The scope of arylalkene coupling partner was then evaluated with a selection of aryl bromides (Table 3). *Ortho*-substituted styrenes were well tolerated in this chemistry (**1m** and **1n**). Electron-rich arylalkenes productively coupled with good levels of yield and enantioselectivity (for example entry **1o**, 66% yield, 93% ee), while an electron-deficient styrene (entry **1p**) produced a much lower level of yield and stereoselectivity (23% yield, 61% ee). This might be indicative of the configurational stability of the RCu intermediate. Finally, β-substituted styrenes can be utilized in this transformation, affording good yields and reasonable levels of enantioselectivity (**1s** and **1t**). Due to a more challenging hydrocupration step, a lower palladium catalyst loading (1 mol% Pd) was required for β-substituted styrenes, presumably to slow down competitive reduction of the aryl bromide and match the rate of the two productive catalytic cycles. In addition, a slightly elevated reaction temperature and use of dimethylphenylsilane (Me_2PhSiH) as the reductant was required to achieve good results with this class of olefins.

Table 3. Scope of the styrene coupling partner with various heteroaryl and aryl bromides.[a]





[a]All yields represent the average of isolated yields from two runs performed with 1 mmol of alkene, enantioselectivity determined by chiral SFC; [b]2 equiv of Me_2PhSiH used as the silane, and the reaction was run at 45 °C; [c]Reaction was run for 40 h; [d]0.5 mol% of $[Pd(cinnamyl)Cl]_2$ used with 1.1 mol% BrettPhos **L3**, 2 equiv of Me_2PhSiH used as the silane, and the reaction was run at 45 °C.

In conclusion, we report the enantioselective Pd/Cu-catalyzed hydroarylation of styrenes to form 1,1-diarylalkanes, a valuable structure in medicinal chemistry. This procedure performs well for a variety of aryl bromides, including six-membered heterocycles, to form

the respective products in generally good yields and with high levels of enantioselectivity. A range of vinylarenes, including *ortho*- and β-substituted styrenes, were also productively coupled in this hydroarylation reaction. Extending this chemistry to other substrates classes is currently being explored in our laboratory.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.
Crystallographic data for **3i** (CIF)
Experimental procedures and characterization data for all compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*sbuchwal@mit.edu

Notes

The authors declare the following competing financial interest(s): MIT has obtained patents for some of the ligands that are described in this Communication from which S.L.B. and former/current co-workers receive royalty payments.

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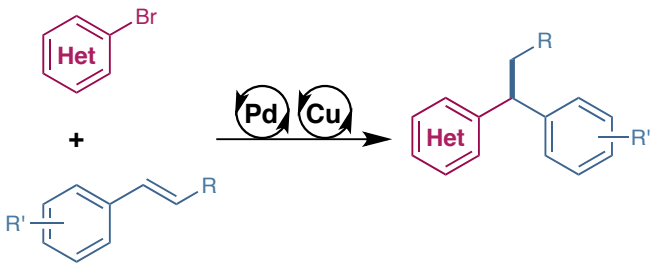
(22) Refer to the Supporting Information for an extensive list of ligands, bases, and copper sources examined.

(23) Running the reaction in an oil bath heated to 35 °C appeared to give a slight increase in enantioselectivity and yield and was used for subsequent hydroarylation reactions reported in this paper.

(24) These two entries gave variable yield and enantioselectivity, **3e**: 69-81% yield, 19-34% ee, **3g**: 52-82%, 49-65% ee. Studies with 4-bromoisoquinoline (**1e**) have indicated that increasing the palladium catalyst loading increases the enantioselectivity of product **3e**, a phenomenon we generally observed with other substrates and that is consistent with a unimolecular epimerization event competing with bimolecular transmetalation. The hydroarylation of 4-bromoisoquinoline (**1e**) and 3-bromoquinoline (**1f**) with styrene in one reaction vessel also resulted in diminished enantioselectivity of quinoline product **3f** (see Supporting Information for details and additional experiments).

(25) Recent reports on the Pd/Cu-catalyzed boryl- and hydroarylation of styrene derivatives have indicated that retention or inversion of configuration can occur during the purported transmetalation step see: (a) ref. 14. (b) ref. 16.

(26) Deuterium-labeling and computational studies for the CuH-catalyzed hydroboration of styrene derivatives indicate that hydrocupration occurs through *cis*-addition, and boryl transmetalation is stereoretentive. The sense of stereoinduction with (*R*)-DTBM-SEGPHOS for CuH-catalyzed hydroboration, hydroamination, and hydroarylation is the same see: Noh, D.; Yoon, S. K.; Won, J.; Lee, J. Y.; Yun, J. *Chem. Asian J.* **2011**, *6*, 1967 and red. 3d.


Br
Het
+
R
R'
Pd
Cu
R
Het
R'