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Enantioselective Hydroalkenylation of Olefins with Enol Sulfonates Enabled by Dual Copper Hydride and Palladium Catalysis

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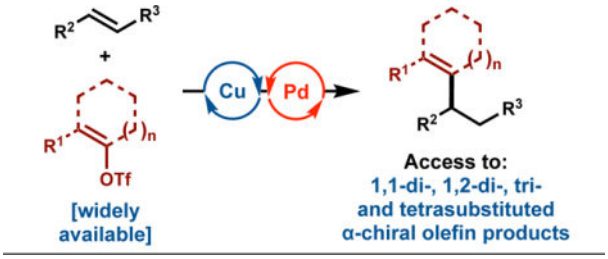
Abstract

The catalytic enantioselective synthesis of α-chiral olefins represents a valuable strategy for rapid generation of structural diversity in divergent syntheses of complex targets. Herein, we report a protocol for the dual CuH- and Pd-catalyzed asymmetric Markovnikov hydroalkenylation of vinyl arenes and the anti-Markovnikov hydroalkenylation of unactivated olefins, in which readily available enol triflates can be utilized as alkenyl coupling partners. This method allowed for the synthesis of diverse α-chiral olefins, including tri- and tetrasubstituted olefin products, which are challenging to prepare by existing approaches.

Graphical Abstract



The development of transition-metal-catalyzed methods for enantioselective Csp^3–Csp^2 cross-coupling is a vibrant area of research due to the ability of these reactions to rapidly generate structural diversity through the strategic construction of carbon–carbon bonds.[1]

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, and characterization data for all new compounds including NMR spectra, SFC and HPLC traces (PDF).

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Specifically, asymmetric arylation and alkenylation reactions with alkylmetal nucleophiles allow access to important substructures present in many pharmaceuticals and biologically active natural products. However, these approaches often necessitate the use of stoichiometric quantities of organometallic reagents.[2–6] Owing to the numerous subsequent functionalization reactions olefins can undergo, the enantioselective installation of an alkenyl fragment represents a particularly valuable synthon for divergent synthesis.[7–8] A conceptually straightforward way to access α-chiral olefin products is through hydroalkenylation of olefin precursors. Although numerous approaches for the racemic hydroalkenylation of olefins exist,[9–12] a general method for the analogous asymmetric variant of this transformation remains underdeveloped.

Pioneering work on enantioselective hydrovinylation, by RajanBabu[13,15–21] and others,[14,22–23] demonstrated an atomeconomical coupling of ethylene with vinyl arenes. However, attempts to expand this strategy to additional unactivated olefins often led to mixtures of products.[24] The prototypical approach for asymmetric olefin hydroalkenylation, which avoids these regioisomeric product mixtures, involves the coupling of a preformed stoichiometric organometallic reagent to an alkene (Figure 1A, top).[25–27] To circumvent specific limitations of these prior methods, Zhu and Gong recently reported a NiH-catalyzed enantioselective migratory olefin hydroalkenylation to prepare 1,2-disubstituted olefins from alkenyl bromides and vinyl arenes (Figure 1A, middle).[28] Complementary syntheses of enantioenriched 1,1-aryl, alkenyl alkanes, including stereospecific reductive cross-coupling of racemic benzylic halides and β-bromostyrenes,[29–32] asymmetric allylic alkylation,[33–39] and stereospecific cross-coupling of activated phenethyl derivatives,[40–42] have also been developed.

Our group's continued interest in exploring the propensity of a stereodefined organocopper intermediate to engage various electrophiles in catalytic hydrofunctionalization reactions[43–44] led us to propose a complementary approach for asymmetric olefin hydroalkenylation. As an alternative to preformed stoichiometric organometallic reagents and vinyl halides, which are generally prepared through multi-step sequences,[45–47] we sought to leverage a copper hydride (CuH) and Pd dual catalyst system (Figure 1A, bottom) to effect the enantioselective hydroalkenylation of olefins. This approach would utilize an *in situ* generated Cu(I)-alkyl species (**I**) and widely available enol triflates (**2**). Although the proposed synergistic CuH and Pd catalytic cycles involve similar elementary steps to olefin hydroarylation (Figure 1B),[48–52] we anticipated several unique challenges for the dual-catalytic olefin hydroalkenylation (Figure 1C). It was evident that the enol triflate (**2**) could undergo facile hydrolysis or reduction to the corresponding olefin (**V**), which may then be subject to further hydrofunctionalization reactions. A similar outcome, such as reduction, olefin isomerization, or oligomerization, is also conceivable for the product (**3**) of this transformation. Therefore, construction of the critical C–C bond of the α-chiral olefin would necessitate the design of a synergistic catalyst system in which the rates of key steps in both catalytic cycles, hydrocupration (**1**→**I**), oxidative addition (**2**→**II**), transmetallation (**I** + **III**→**IV**), and catalyst regeneration, are well aligned.

Accordingly, we focused on finding a suitable dual catalytic system for the asymmetric olefin hydroalkenylation, using styrene (**1a**) as a model substrate and 1-cyclohexenyl

trifluoromethanesulfonate (**2a**) as the alkenyl coupling partner (Table 1). Utilizing our previously described conditions for dual CuH/Pd-catalyzed hydroarylation of olefins in this reaction system,[48–49] we observed minimal hydroalkenylation product **3a** (see Table SI1–3 for further details on the reaction optimization). Investigation of the optimal reaction conditions identified the air-stable Pd-precatalyst, Pd(cinnamyl)(dppbz)(Cl) (**P1**), CuI, (*S*)-DTBM-SEGPHOS (**L1**), NaOTMS, and Me_2PhSiH as crucial to form **3a** in high yield and enantioselectivity (entry 1, 96% ^1H NMR yield and 96:4 er). An alternative ligand, (*S*)-DTBM-MeO-BIPHEP (**L2**), performed with similar efficiency to **L1** (entry 2). The use of a vinyl bromide (**2b**) or iodide (**2c**) furnished **3a** in moderate yield but low enantioselectivity (entries 3, 4). However, when the corresponding enol tosylate (**2d**) was employed in the olefin hydroalkenylation, **3a** was formed with increased enantioselectivity and minimal reduction of the alkenyl coupling partner (entry 5, 69% ^1H NMR yield and 92:8 er). Substituting **L1** with **L2** in conjunction with an enol tosylate further increased the enantioselectivity (entry 6). This suggested that enol tosylates may be suitable substrates for the olefin hydroalkenylation if the analogous enol triflate undergoes facile reduction or hydrolysis (see Table SI3 for additional experiments comparing the efficiency of enol triflates and tosylates). Evaluation of a series of Cu salts demonstrated a dependence on the counterion (entries 7–9), with CuBr and CuI performing similarly. Variation of the Pd ligand scaffold, from dppbz (**L4**) to other bisphosphine or biarylphosphine ligands, resulted in a substantially diminished yield of the olefin hydroalkenylation adduct **3a** (see entry 10 and **Table SI2**), further demonstrating the importance of tuning the rates of the two catalytic cycles. When the reaction was run in the absence of **P1** (entry 11) or Cu and **L1** (entry 12), minimal or no **3a** was observed, respectively.

Having established excellent reaction conditions for the asymmetric olefin hydroalkenylation, we investigated the scope of olefin products which could be prepared by this protocol (Scheme 1). Cyclic, benzofused (**3b**), and heterocyclic (**3g**, **3j, 3p,** and **3v**) α-stereogenic olefin products could be accessed in good yield and enantioselectivity. Additionally, tetrasubstituted (**3d**, **3n**), acyclic trisubstituted (**3c, 3f, 3h**, **3k**, **3l,** and **3m**), and 1,1-disubstituted olefins (**3i**), which are challenging substrates to prepare by complementary methods,[25–28] were obtained in high yield and enantiopurity. We were also able to synthesize a cyclic 1,3-butadiene (**3s**) diastereoselectively (>20:1 dr) through the use of a dienyl-triflate. When an *E/Z*-mixture (6.5:1 *E*:*Z*) of the alkenyl coupling partner was utilized, the olefin product was isolated as a single olefin isomer (**3c**). A geometrically pure *Z*-alkenyl coupling partner resulted exclusively in ***Z*-3e** in similar yield and enantioselectivity (78%, 97:3 er) to ***E*-3e**. These experiments suggest that the reaction of an *E*-alkenyl coupling partner outcompetes the corresponding *Z*-substrate. Notably, despite 1,2- and 1,1-disubstituted olefin products (**3e, 3i**) being common substrates for copper hydride-catalyzed hydrofunctionalization reactions, we detected no significant dimerization or oligomerization of the product with excess enol triflate.

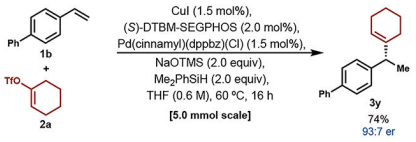
A variety of heterocycle-containing vinyl arene and enol triflates could be coupled to yield the corresponding hydroalkenylation products, including pyrimidine (**3f**), benzothiophene (**3g**), furan (**3h**), thiomorpholine (**3i**), 7-azaindole (**3k**), carbazole (**3n**), pyrazole (**3o**), pyridine (**3p**, **3t**), benzothiazole (**3q**), and quinoline (**3v**). Substrates containing an ester (**3g**),

aryl chloride (**3l**), thiomethyl (**3m**), carbamate (**3t**, **3v**), or a tertiary amine (**3u**), were well tolerated under the reaction conditions and resulted in good yields and enantioselectivities of the olefin products. However, when a substrate bearing a ketal was employed, hydrolysis of the corresponding product (**3r**) was observed, resulting in diminished yield (37%). A sterically congested vinyl arene containing an alkyl *ortho*-substitution was effectively converted to a trisubstituted olefin (**3h**) in high yield and 95:5 er. While electron deficient vinyl arenes (**3g**, **3r**) could be readily converted to the hydroalkenylation product, an electron-rich vinyl heteroarene (**3j**) necessitated a lower Pd-catalyst loading to minimize competing reduction of the enol triflate.

1,2-Disubstituted olefin substrates, which have higher barriers to hydrocupration relative to vinyl arenes,[53–54] were equally competent substrates for the hydrofunctionalization reaction (**3p**–**3r**). A cinnamyl amine substituted with a basic $-NMe_2$ group furnished **3x** with moderate enantioselectivity (81:19 er). The enantiomeric ratio could be increased (92:8 er) by employing the corresponding enol tosylate and **L2**. Moreover, when the $-NBn_2$ derivative was employed under analogous conditions **3w** was isolated with 99:1 er, suggesting that the pendant $-NMe_2$ group present in **3x** may be competing as a ligand or slowing the transmetallation step.

In cases where highly activated enol triflates were employed, such as **3d**, **3i**, and **3m**, reduction of the alkenyl coupling partner competed with the desired olefin hydroalkenylation reaction. This undesired pathway could be suppressed by utilizing the corresponding enol tosylate in conjunction with **L2**. Contrary to our observation that unactivated vinyl halides, such as **2b** (Table 1), were poor substrates for this method, we found that a β-bromostyrene provided an enantioenriched 1,2-disubstituted α-stereogenic olefin with excellent yield and selectivity (**3e**). Additionally, when cycloalkyl enol triflates were utilized, the catalyst loading could be significantly decreased (**3o**, **3q**, **3t**, and **3u**). Employing an α-substituted cyclic enol triflate resulted in an unexpected regioisomeric mixture of the Markovnikov and anti-Markovnikov hydroalkenylation products (**3n**).

To further demonstrate the utility of this enantioselective olefin hydroalkenylation method we subjected several medicinally relevant molecules to the hydroalkenylation reaction to afford derivatives of cholesterone (**3s**), loratadine (**3t**) and chlorpromazine (**3u**). Pharmaceutical intermediates, including a precursor to a Cephalon FASN inhibitor (**3v**)[55] and **3x**, could readily be synthesized with high enantioselectivity by this approach. Subsequent hydrogenation of **3x** to (*S*)-Gamfexine, an antidepressant,[56] represents a net formal enantiospecific Csp^3–Csp^3 coupling. The hydroalkenylation process could be easily conducted on 5.0 mmol scale with vinyl arene **1b** and commercially available enol triflate **2a** (eq 1). Using reduced catalyst loading, 1.5 mol% Cu and Pd catalysts, **3y** could be synthesized in 74% isolated yield with high stereoselectivity (93:7 er).



(1)

Given the general reactivity we observed while studying the hydroalkenylation of vinyl arenes, we were interested in extending the scope of this transformation to include unactivated olefins. Typically, these products are accessed using the *B*-alkyl Suzuki-Miyaura reaction, which represents a robust way to couple olefins to alkenyl (pseudo)halides in a regiospecific manner.[57] However, these reactions rely on the generation of stoichiometric quantities of alkyl-boron species from olefin precursors, limiting their step and atom economy. As an alternative, we reasoned that the catalytic generation of a terminal organocopper species would allow us to extend our protocol to the hydroalkenylation of unactivated olefins. Without significant modification of the reaction conditions, we could achieve a regioselective hydroalkenylation of terminal olefins (Scheme 2). A variety of important structural elements were tolerated in this process, including a basic quinuclidine (**6a**), indole (**6c**), amide (**6d**), morpholine (**6e**), dioxolane (**6f**), and thiopyrimidine (**6h**). This Csp^3–Csp^2 coupling facilitated the synthesis of tetrasubstituted olefins (**6b**, **6g**) and a vinyl arene (**6f**). Further, this approach to generate vinyl arenes may be a viable strategy for the synthesis of starting materials for ensuing hydrofunctionalization reactions.[43–44]

In summary, we have developed a method for asymmetric olefin hydroalkenylation that allows access to a wide variety of α-stereogenic olefins using widely available starting materials. Our dual CuH- and Pd-catalyzed approach allowed entry to olefin classes that are difficult to synthesize by complementary strategies, including tri- and tetrasubstituted olefin products. The reaction conditions tolerated a variety of medicinally relevant substructures and enabled the synthesis of several pharmaceutical intermediates. This protocol was expanded to the anti-Markovnikov hydroalkenylation of unactivated olefins.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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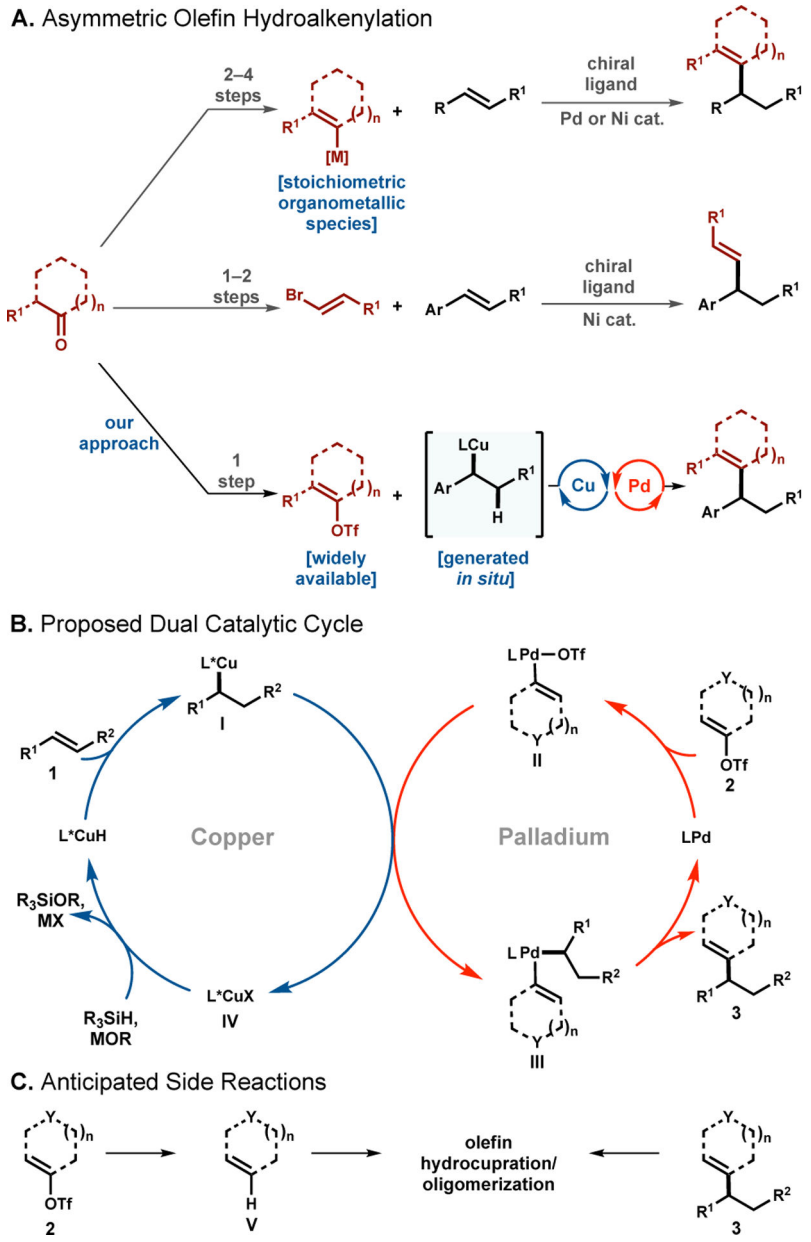
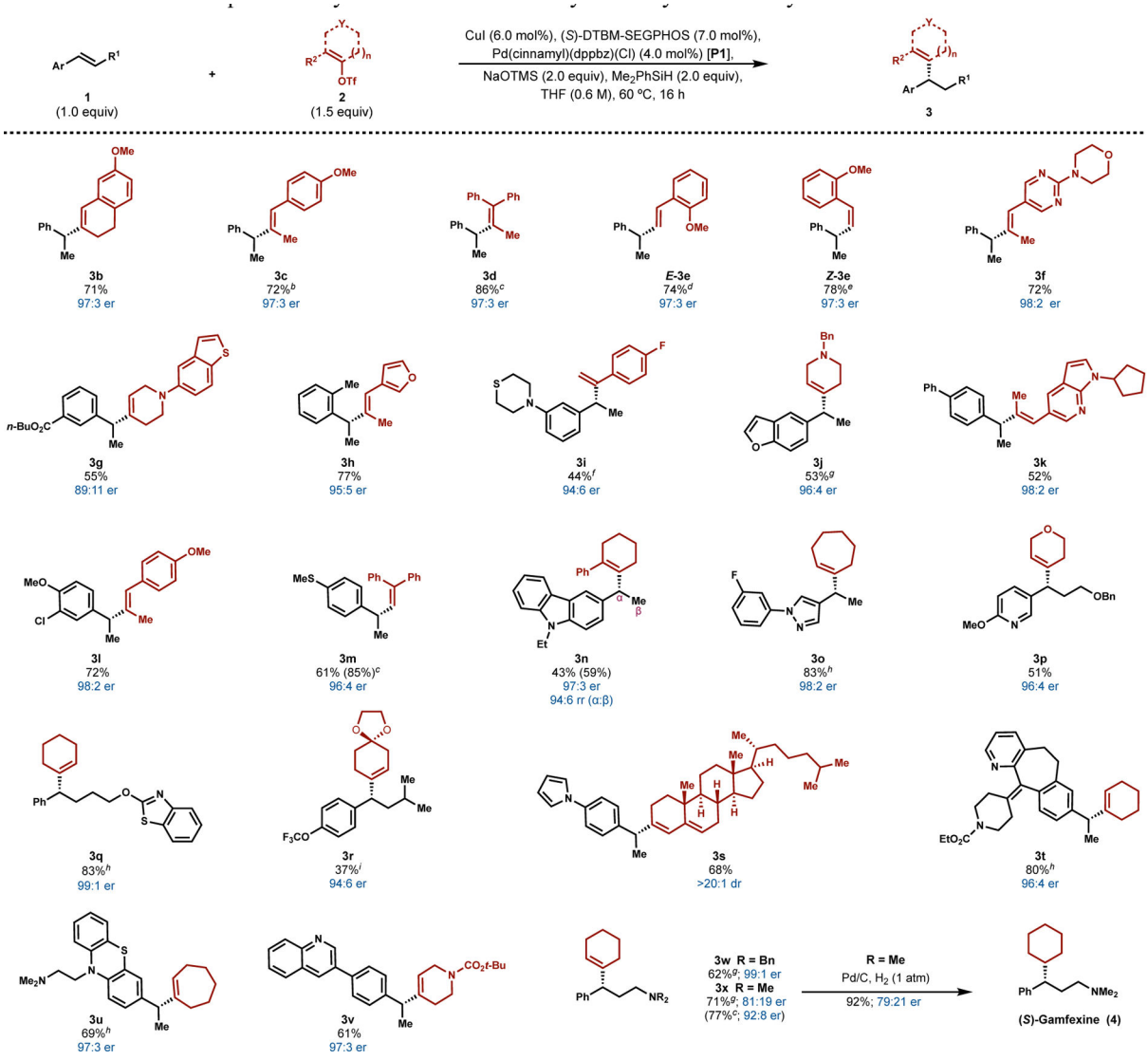


Figure 1.

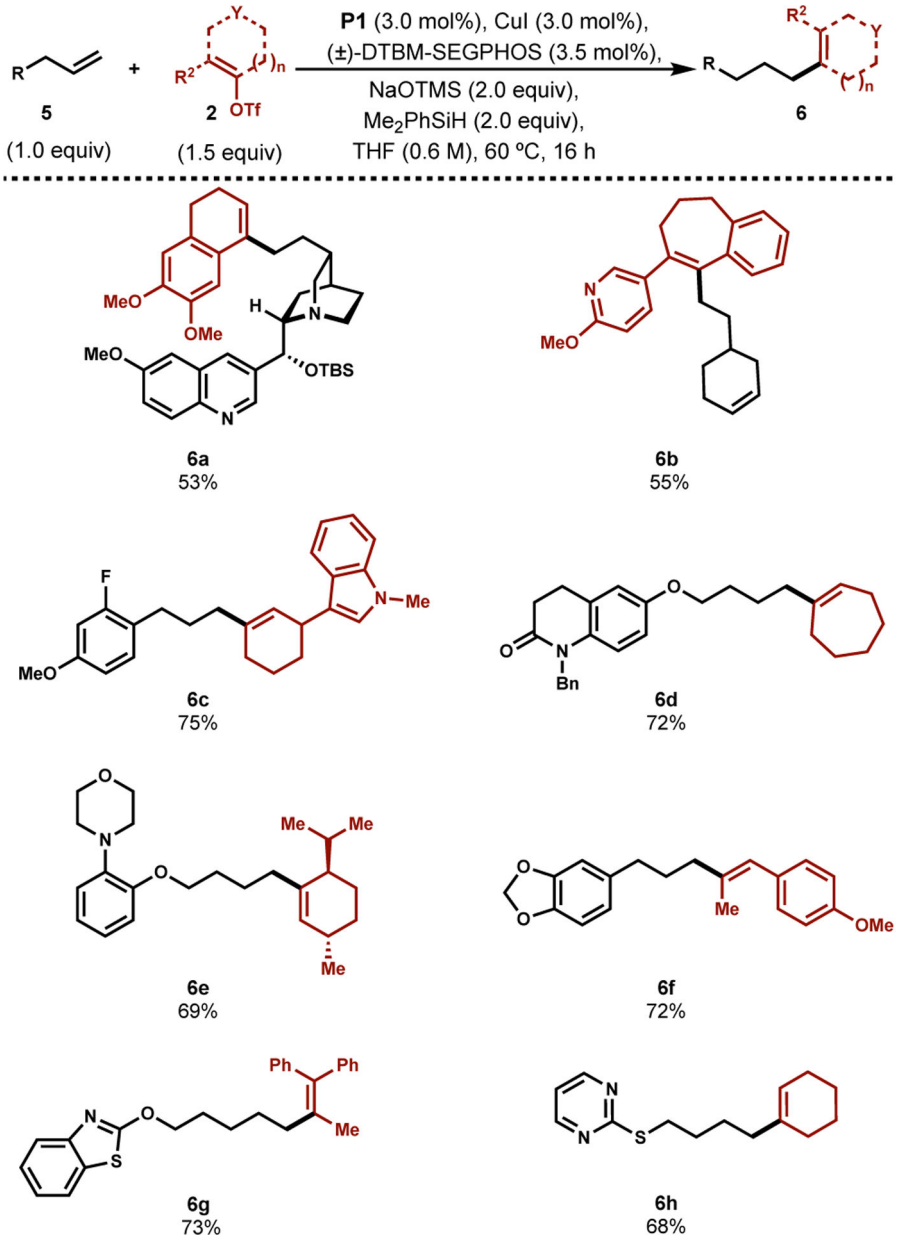
A. Previous approaches to asymmetric olefin hydroalkenylation and our approach. **B.** Proposed dual CuH/Pd catalytic cycles. **C.** Potential side reactions for the hydrofunctionalization process involving an enol triflate (**2**).



Scheme 1.

Substrate scope of the asymmetric Markovnikov hydroalkenylation of vinyl arenes.[a]

[a]All yields represent the average of at least two isolated yields with 0.5 mmol alkene (**1**); the corresponding enol triflate was used unless otherwise noted, enantioselectivity determined by chiral SFC or HPLC. Yield in parenthesis determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard. [b] An *E*:*Z* mixture (6.5:1) of the enol triflate was employed. [c] Enol tosylate was employed with 7.0 mol % **L2**. [d] *E*-Vinyl bromide was employed with 7.0 mol% **L2**. [e] *Z*-Vinyl bromide was employed with 7.0 mol% **L2** and 0.2 mmol **1**. [f] Enol tosylate was employed under standard reaction conditions. [g] 2.0 mol% **P1**. [h] 3.0 mol% CuI, 3.5 mol% **L1**, and 3.0 mol% **P1**. [i] 7.0 mol% **L2**.



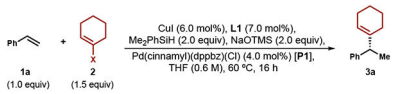
Scheme 2.

Scope of the anti-Markovnikov hydroalkenylation of unactivated olefins.[a]

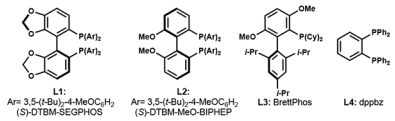
[a]All yields represent the average of at least two isolated yields with 0.5 mmol alkene. [b]6.0 mol% CuI, 7.0 mol% (±)-**L1**, and 4.0 mol% **P1** were used. [c]45 °C

Table 1.

Optimization of the enantioselective hydroalkenylation of styrene (**1a**) with alkenyl coupling partner (**2**).[a]



entry	variation from standard conditions	yield (%)	er
1	none, **2a** (X= OTf)	96	96:4
2	**2a** (X= OTf), **L2**	92	96:4
3	**2b** (X= Br)	60	67:33
4	**2c** (X= I)	34	65:35
5	**2d** (X= OTs)	69	92:8
6	**2d** (X= OTs), **L2**	55	98:2
7	CuOAc	49	95:5
8	CuCl	54	96:4
9	CuBr	93	96:4
10	BrettPhos (**L3**) and [Pd(cinnamyl)(Cl)]$_2$ (4 mol%)	6	N.D.
11	no Pd and dppbz	11	N.D.
12	no CuI and **L1**	0	–



[a]Reaction conditions: 0.2 mmol styrene (**1a**) (1.0 equiv), alkenyl coupling partner (**2**) (0.3 mmol, 1.5 equiv), yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture, using 1,1,2,2-tetrachloroethane as internal standard. Enantiomeric ratio (er) was determined by chiral SFC. N.D.: not determined.