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The Enantioselective Preparation of Arenes with β-Stereogenic Centers: Confronting the 1,1-Disubstituted Olefin Problem Using CuH/Pd Cooperative Catalysis

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Abstract: Arenes with β-stereogenic centers are important substructures in pharmaceuticals and natural products. Their synthesis traditionally involves two separate and individually challenging steps: enantioselective synthesis of a chiral main-group organometallic complex and subsequent cross-coupling with an aryl electrophile. We describe the development of asymmetric anti-Markovnikov hydroarylation of 1,1-disubstituted olefins by dual palladium and copper hydride catalysis as a convenient and significantly more general alternative. This reaction is an efficient one-step process that addresses several limitations of the stepwise approaches. The use of cesium benzoate as a base and a common phosphine ligand for both the Cu- and Pd-catalyzed processes were important discoveries that allowed these challenging olefin substrates to be efficiently transformed to products. A variety of aryl bromide coupling partners, including numerous heterocycles, were coupled with 1,1-disubstituted alkenes to generate arenes with β-stereogenic centers. Finally, the effect of the level of olefin substitution on reaction yield and enantioselectivity has been investigated.

Introduction

Arenes with β-stereogenic centers are widely found in biologically active drugs and natural products (Figure 1A)[1]. A straightforward and convergent strategy for their synthesis involves the cross-coupling of β-chiral main-group organometallics with aryl halides.[2] These β-chiral nucleophiles are typically made in one of two ways. First, an alkyl halide can be metallated by a strongly reducing metal or by lithium-halogen exchange, followed by further transmetallation (e.g., to Sn, B, or Zn, Figure 1B)[2c,2d]. In such methods, the synthesis of the chiral alkyl halide precursor is an additional challenge. A second approach is the asymmetric hydrometallation of 1,1-disubstituted olefins, which are relatively available starting materials (Figure 1B)[3,4]. However, the stereoselective functionalization of 1,1-disubstituted olefins has been a major challenge[5], and only three enantioselective methods for the hydroboration of 1,1-disubstituted olefins have been reported.[4] Most notably, Yun has accomplished the only highly enantioselective catalytic hydroboration of 1,1-disubstituted olefins, also demonstrating the further transformation of an isolated β-chiral boronic ester product by Suzuki-Miyaura coupling with bromobenzene.[4c] Thus, there have been no general methods reported for the anti-Markovnikov asymmetric hydrometallation of 1,1-disubsituted olefins with subsequent cross-coupling of the resulting organometallic intermediate.

We wondered whether a single-step, dual-catalytic approach that combines asymmetric hydrometallation and cross-coupling into one process might provide expanded access to arenes with β-stereogenic centers. Such a process would improve on Yun's important report in several ways (Figure 1C).[6] Besides operational efficiency, one clear potential advantage is that, by transmetallating directly from the metal involved in hydrometallation (Cu) to the catalyst involved in cross-coupling (Pd), the need to prepare, isolate and purify an organoboron intermediate can be avoided. Further, since transmetallation from branched alkyl pinacol boronates is often slow[2d,7] or requires harsh reaction conditions including the use of a strong base[8], avoiding the intermediacy of an aryl boronate ester might also provide a method with improved functional-group compatibility.

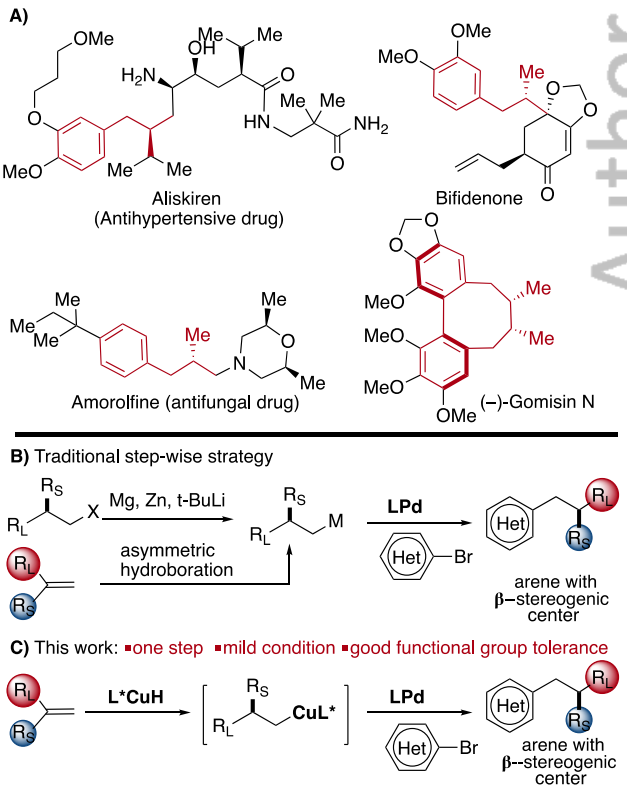


Figure 1. A) Representative bioactive molecules or natural product-containing β-stereogenic arene motifs. B) Traditional stepwise strategy to access β-stereogenic arenes. C) Our one-step transformation process to access β-stereogenic arenes.

Recently, hydroarylation processes that involve the reaction of olefins with metal hydride catalysts have attracted attention from the synthetic chemistry community due to the mild reaction conditions, high functional group tolerance, and broad substrate scope.[9] In 2014, we reported an enantioselective anti-Markovnikov hydroamination of 1,1-disubstituted alkenes catalyzed by CuH, which enabled the preparation of β-chiral amines.[10] In this process, the stereocenter was set through an asymmetric hydrocupration of the alkene, a process which generated a chiral alkylcopper intermediate. We considered whether the same type of intermediate could also participate in Pd-catalyzed cross-coupling. If successful, the net reaction would be CuH/Pd-dual catalyzed asymmetric hydroarylation of 1,1-disubstituted alkenes, a transformation which has yet to be realized in a single-step fashion.

The proposed dual catalytic cycle is depicted in Figure 2. A CuH catalyst **I** is the starting point for the mechanism and could be generated *in situ* from an appropriate Cu salt, chiral ligand, and silane. The enantioselective hydrocupration of 1,1-disubstituted alkene **II** would be expected to proceed through the transition state **III** with anti-Markovnikov regioselectivity, forming a Cu(I) alkyl intermediate **IV** with the desired β-stereogenic center.[4c,10] At the same time, in the Pd catalytic cycle, the oxidative addition of ligated Pd(0) complex **V** to an aryl bromide would form the arylpalladium species **VII**. The transmetallation of the Cu(I) alkyl intermediate **IV** with the palladium species **VII** would generate the β-chiral palladium alkyl complex **VIII** and L*CuBr (**X**). Reductive elimination from **VIII** would furnish enantioenriched β-chiral arene **IX**, while regenerating the Pd(0) species **V** and closing the Pd-catalyzed cycle. Meanwhile, in the presence of base and silane the reactive CuH catalyst **I** could be regenerated from **X** by a ligand substitution/σ-bond metathesis sequence.[11] In order for a successful cross-coupling reaction, the rates of the two catalytic processes would need to be carefully matched. This is particularly important in order to prevent undesired pathways such as the direct reduction of the aryl bromide (**VI**), as depicted by the red arrow in Figure 2.[12]

Compared to our previous work on CuH/Pd dual catalysis, the challenges of rate-matching and preventing undesired reduction were expected to be particularly prominent in the current context. Although we have reported CuH/Pd dual catalyst process for the enantioselective hydroarylation from styrenes or terminal terminal alkenes [6j,6k], the rate of hydrocupration of 1,1-disubstituted alkenes is much slower in comparison[13]. Thus, we expected that, under previously developed conditions, the reduction of the aryl bromide might be the major pathway. Further, due to the relatively hindered and unactivated nature of branched alkylcopper species, it was unclear whether the transmetallation to Pd would be as efficient as in our earlier work. Below, we report the discovery of optimized reaction conditions (different silane, ligand for Pd, base, Pd source) that overcome these obstacles and accomplish the anti-Markovnikov enantioselective hydroarylation of 1,1-disubstituted alkenes (Figure 1C), thus allowing for the direct synthesis of arenes with β-stereogenic centers under mild reaction conditions.

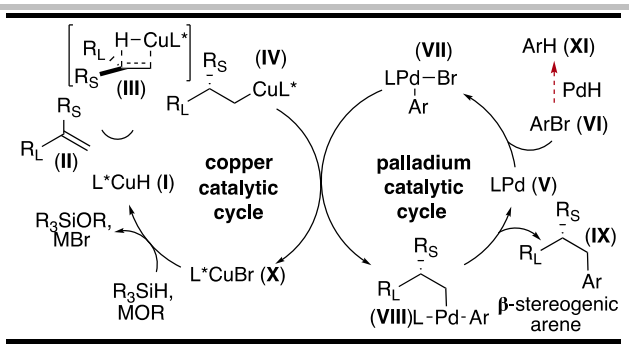
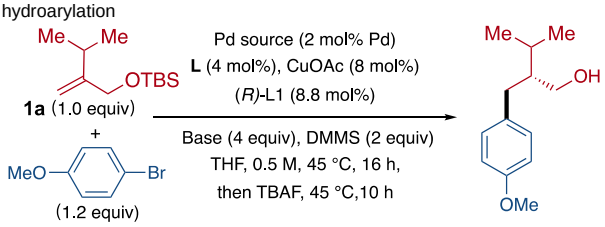


Figure 2. Proposed catalytic cycles

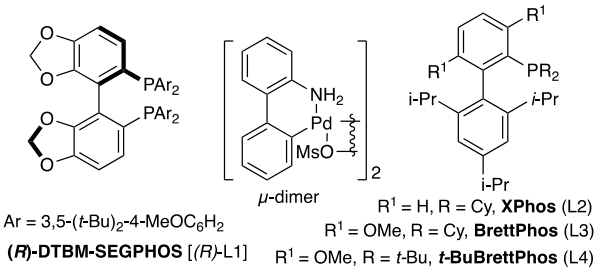
Results and Discussion

We began our investigation by examining of the hydroarylation of tert-butyldimethyl(3-methyl-2-methylenebutoxy)silane as a model 1,1-disubstituted alkene. As expected, following previously reported procedures optimized for terminal alkenes, the desired coupling product was produced in low yield (Table 1, entry 1, 13% yield, 95:5 er).[6k] A significant quantity of anisole was observed, resulting from the reduction of 4-bromoanisole. This was consistent with our hypothesis that the rate of reduction might greatly exceed the rate of hydrocupration or transmetallation under previous conditions.Replacement of MePh2SiH with the more reactive silane Me(OMe)2SiH (DMMS) or the use of several other commonly employed weak bases (NaOPh, LiOMe, KOAc) failed to improve the outcome (entries 2–4). However, employing CsOAc as the base significantly improved the yield and gave product with high enantioselectivity (50% yield, 95:5 er). We hypothesize that this effect might be due to the improved solubility of the salt, as well as the low coordinating ability of the cesium cation, which might accelerate salt metathesis of CsOAc with L*CuBr (**X**).[14,15] Faster regeneration of LCuH might promote the formation of a higher steady-state quantity of the alkylcopper nucleophile. In turn, this should allow for more of the productive cross-coupling reaction to occur rather than competing reduction of the arylpalladium(II) species. The use of CsOBz, an even more soluble Cs carboxylate, provided a slight further improvement in yield (entry 6, 59%). The μ-dimer shown in Table 1 was more effective than $[Pd(cinnamyl)Cl]_2$ and $Pd(OAc)_2$ as the Pd source (entries 6–8). Evaluation of a variety of phosphine ligands for Pd indicated that using DTBM-SEGPHOS (**L1**) as the ligand for both the Pd- and Cu-catalyzed transformations, gave the best yield (entry 11, 81% yield). We found that CuOAc is a better copper source than the Cu(II) salt $Cu(OAc)_2$ (entry 12). Finally, the addition of PPh_3 was not beneficial for this transformation (entry 13).[10]

Table 1. Optimization of the Pd/CuH-catalyzed enantioselective hydroarylation

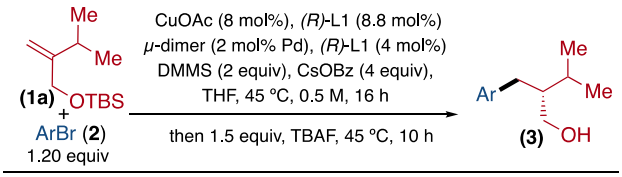


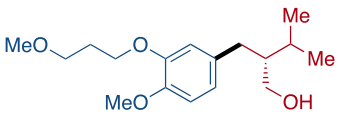
entry	base	Pd source	L	% yield[a]	er[a]
1[b]	NaOTMS	$[Pd(cinnamyl)Cl]_2$	**L3**	13	95:5
2	NaOPh	$[Pd(cinnamyl)Cl]_2$	**L3**	2	ND
3	LiOMe	$[Pd(cinnamyl)Cl]_2$	**L3**	19	95:5
4	KOAc	$[Pd(cinnamyl)Cl]_2$	**L3**	0	ND
5	CsOAc	$[Pd(cinnamyl)Cl]_2$	**L3**	50	95:5
6	CsOBz	$[Pd(cinnamyl)Cl]_2$	**L3**	59	95:5
7	CsOBz	$Pd(OAc)_2$	**L3**	38	95:5
8	CsOBz	μ-dimer	**L3**	61	95:5
9	CsOBz	μ-dimer	**L2**	63	95:5
10	CsOBz	μ-dimer	**L4**	63	95:5
11	CsOBz	μ-dimer	**L1**	81	95:5
12[c]	CsOBz	μ-dimer	**L1**	71	95:5
13[d]	CsOBz	μ-dimer	**L1**	52	95:5



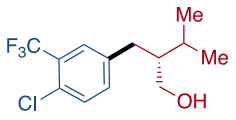
[a]Yields determined by ^{1}H NMR of the crude reaction mixture using mesitylene as an internal standard; enantioselectivity of the purified product was determined by HPLC analysis on commercially available chiral stationary phases (see Supporting Information for details); ND = not determined; [b]$MePh_2SiH$ used as the silane; [c]$Cu(OAc)_2$ used as the Cu source.[d]8 mol% PPh_3 was used

Table 2. Scope of the aryl bromides[a]

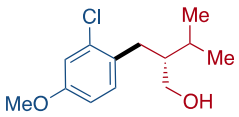




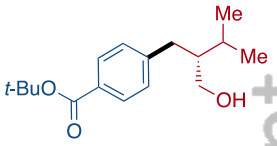
3a 61% yield, 95:5 er



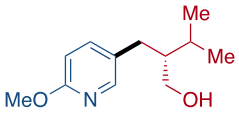
3b 72% yield, 94:6 er



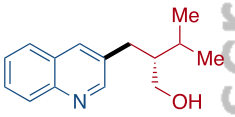
3c 68% yield, 95:5 er



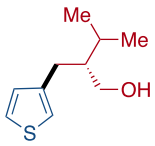
3d 67% yield, 94:6 er



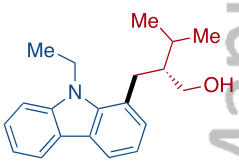
3e 73% yield, 95:5 er



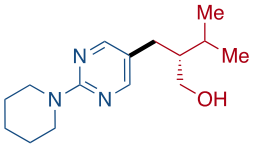
3f 38% yield, 95: 5 er



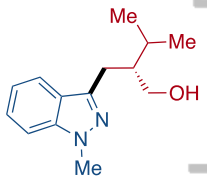
3g 70% yield, 95:5 er



3h 56% yield, 95:5 er



3i 51% yield, 95:5 er



3j 76% yield, 95:5 er

[a]All yields represent the average of isolated yields from two runs performed with 1.0 mmol of alkene; enantioselectivity determined by chiral SFC.

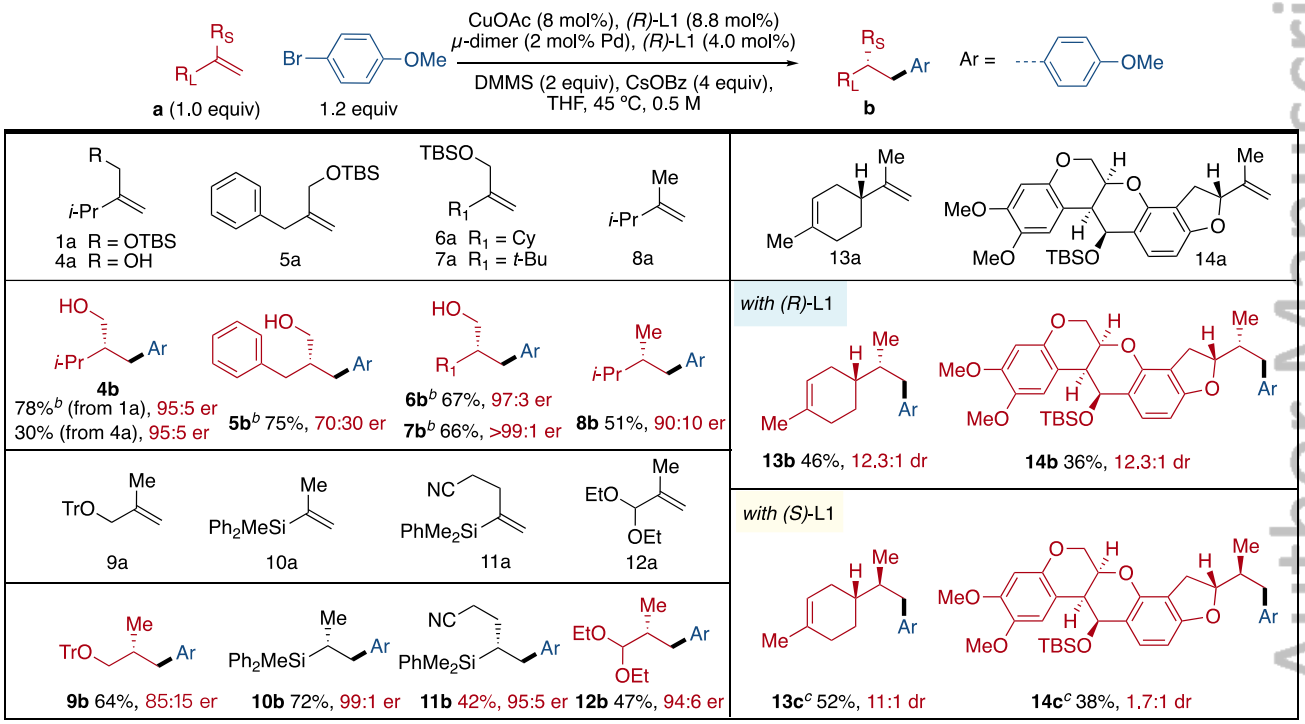
Using the optimized olefin hydroarylation conditions, we examined the scope of this reaction. As shown in Table 2, a broad range of aryl bromides were effective coupling partners in this protocol. Deprotection of the coupling products was performed for ease of purification and determination of the enantiomeric ratio. An advanced synthetic intermediate for the synthesis of Aliskiren, which is used for the treatment for high blood pressure,[16] could be prepared using this method in good yield and high enantioselectivity (3a, 61% yield, 95:5 er). Compared to a previous synthesis of this advanced intermediate based on Evans' auxiliary (7 steps, 38% overall yield, 99% ee), our catalytic approach is a viable alternative. Chemoselective coupling with bromochlorobenzenes provided products containing aryl chlorides, which could serve as a handle for further functionalization (**3b**, **3c**). An electron-deficient aryl bromide proved to be effective in this transformation, and an ester was also tolerated (**3d**, 67% yield, 94:6 er). A variety of heterocycles, including a pyridine (**3e**), a quinoline (**3f**), a thiophene (**3g**), a carbazole (**3h**), a pyrimidine (**3i**), and an indazole (**3j**), were suitable heteroaryl bromide

coupling partners. For 3-bromoquinoline (**2f**), the low yield was due to incomplete conversion of alkene, which was recovered in 50% yield. Presumably, deactivation of the catalyst(s) through coordination of the unhindered basic nitrogen present in the quinoline is responsible.

To study the effects of olefin substitution on stereoselectivity and yield, a series of alkenes were coupled with 4-bromoanisole following the optimized procedure. A free alcohol (**4a**) was tolerated, but a significantly lower yield was obtained. An increase in the difference in steric hindrance (**5a**, **1a**, **6a**, **7a** sequentially) between the two olefin substituents correlated with an increase in enantioselectivity and with a slight decrease in yield. For example, alkene **5a** afforded hydroarylation product in 70:30 er, while substrate **7a** provided the coupling product with >99:1 er. A trityl-protected 2-methylprop-2-en-1-ol was arylated with moderate enantioselectivity (**9b**). Substrate **10a**, a vinylsilane, produced a highly enantioenriched hydroarylation product (**10b**) containing a silicon-substituted stereogenic center. Another sterically encumbered vinylsilane (**11a**) bearing a nitrile group can also be compatible with these conditions. Using an acetal-containing substrate (**12a**), the hydroarylation product was formed with good enantioselectivity (**12b**, 47%, 94:6 er).

Finally, to explore the possibility of catalyst-controlled diastereoselectivity, we examined the use of opposite enantiomers of **L1** in reactions of each of two enantiopure chiral alkenes (Table 3). Indeed, the olefin hydroarylation of (*R*)-limonene provided the opposite major diastereomers when using (*R*)-**L1** vs. (*S*)-**L1** giving the hydroarylation product in 12.3:1 dr (**13b**) and 1:11 dr (**13c**), respectively. However, hydroarylation of Rotenone derivative proceeded with good diastereoselectivity in the presence of (*R*)-**L1** (**14b**, 12.3:1) but poor diastereoselectivity in the presence of (*S*)-**L1** (**14c**, 1:1.7). Thus, while facial selection in the hydrocupration is primarily dictated by the catalyst, substrate bias can still have a significant effect in some cases.

Table 3. Scope of 1,1-disubstituted alkenes[a]



[a]All yields represent the average of isolated yields from two runs performed with 1.0 mmol of alkene; enantioselectivity determined by chiral SFC or chiral GC. [b]workup with TBAF (1.5 equiv) to deprotect (see supporting information Procedure B) [c](*S*)-**L1** was used instead of (*R*)-**L1** for copper and palladium.

Conclusion

In summary, we described the CuH/Pd-catalyzed asymmetric hydroarylation of 1,1-disubstituted alkenes with anti-Markovnikov regioselectivity under mild conditions. Notably, this method is single-step process and uses the same ligand, DTBM-SEGPHOS, as the ligand for both the Pd- and Cu-catalyzed processes. This protocol provides a convenient and efficient way to access β-chiral arenes, which are found in many drugs and natural products. A wide range of aryl bromides, including several heterocycle-containing substrates, can be used with good efficiency and enantioselectivity. Various 1,1-disubstituted alkenes have also been examined. Efforts toward expanding the scope of Cu/Pd dual catalysis toward other classes of alkenes are currently underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: enantioselective • hydroarylation • Cu/Pd dual catalysis • single ligand

[1] (a) D. Lednicer, *The Organic Chemistry of Drug Synthesis: Lednicer/Organic Chem Synthesis V7*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2007**. (b) J. Chang, J. Reiner, J. Xie, *Chem. Rev.* **2005**, *105*, 4581–4609. (c) R. Wang, D. Liu, X. Li, J. Zhang, D. Cui, X. Wan, *Macromolecules* **2016**, *49*, 2502–2510.

[2] (a) N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Sato, A. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 314–321. (b) Norio. Miyaura, Akira. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483. (c) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568. (d) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492.

[3] (a) F.-M. Zhang, L. Peng, H. Li, A.-J. Ma, J.-B. Peng, J.-J. Guo, D. Yang, S.-H. Hou, Y.-Q. Tu, W. Kitching, *Angew. Chem. Int. Ed.* **2012**, *51*, 10846–10850; Angew. Chem. 2012, 124, 11004 –11008. (b) M. M. Midland, Y. C. Kwon, *J. Org. Chem.* **1981**, *46*, 229–230.

[4] (a) S. Masamune, B. M. Kim, J. S. Petersen, T. Sato, S. J. Veenstra, T. Imai, *J. Am. Chem. Soc.* **1985**, *107*, 4549–4551. (b) A. Z. Gonzalez, J. G. Román, E. Gonzalez, J. Martinez, J. R. Medina, K. Matos, J. A. Soderquist, *J. Am. Chem. Soc.* **2008**, *130*, 9218–9219. (c) W. J. Jang, S. M. Song, J. H. Moon, J. Y. Lee, J. Yun, *J. Am. Chem. Soc.* **2017**, *139*, 13660–13663.

[5] (a) S. McIntyre, E. Hörmann, F. Menges, S. P. Smidt, A. Pfaltz, *Advanced Synthesis & Catalysis* **2005**, *347*, 282–288. (b) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402–1411. (c) Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, K.-X. Su, *Chem. Rev.* **2005**, *105*, 1603–1662. (d) R. Corberán, N. W. Mszar, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2011**, *50*, 7079–7082; Angew. Chem. 2011, 123, 7217 – 7220.

[6] (a) J. Huang, J. Chan, Y. Chen, C. J. Borths, K. D. Baucom, R. D. Larsen, M. M. Faul, *J. Am. Chem. Soc.* **2010**, *132*, 3674–3675. (b) F. Nahra, Y. Macé, D. Lambin, O. Riant, *Angew. Chem. Int. Ed.* **2013**, *52*, 3208–3212; *Angew. Chem*. **2013**, *125*, 3290–3294. (c) S. Vercruysse, L. Cornelissen, F. Nahra, L. Collard, O. Riant, *Chem. Eur. J.* **2014**, *20*, 1834–1838. (d) F. Nahra, Y. Macé, A. Boreux, F. Billard, O. Riant, *Chem. Eur. J.* **2014**, *20*, 10970–10981. (e) K. Semba, Y. Nakao, *J. Am. Chem. Soc.* **2014**, *136*, 7567–7570. (f) K. B. Smith, K. M. Logan, W. You, M. K. Brown, *Chem. Eur. J.* **2014**, *20*, 12032–12036. (g) K. M. Logan, K. B. Smith, M. K. Brown, *Angew. Chem. Int. Ed.* **2015**, *54*, 5228–5231; *Angew. Chem.* **2015**, *127*, 5317–5320. (h) T. Jia, P. Cao, B. Wang, Y. Lou, X. Yin, M. Wang, J. Liao, *J. Am. Chem. Soc.* **2015**, *137*, 13760–13763. (i) K. Semba, K. Ariyama, H. Zheng, R. Kameyama, S. Sakaki, Y. Nakao, *Angew. Chem. Int. Ed.* **2016**, *55*, 6275–6279; *Angew. Chem.* **2016**, *128, 6383*–6387. (j) S. D. Friis, M. T. Pirnot, S. L. Buchwald, *J. Am. Chem. Soc.* **2016**, *138*, 8372–8375. (k) S. D. Friis, M. T. Pirnot, L. N. Dupuis, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2017**, *56*, 7242–7246; *Angew. Chem.* **2017**, *129*, 7348–7352..

[7] (a) S. N. Mlynarski, C. H. Schuster, J. P. Morken, *Nature* **2014**, *505*, 386–390. (b) M. Sato, N. Miyaura, A. Suzuki, *Chem. Lett.* **1989**, *18*, 1405–1408.

[8] (a) C.-T. Yang, Z.-Q. Zhang, H. Tajuddin, C.-C. Wu, J. Liang, J.-H. Liu, Y. Fu, M. Czyzewska, P. G. Steel, T. B. Marder, et al., *Angew. Chem. Int. Ed.* **2012**, *51*, 528–532; Angew. Chem. 2012, 124, 543 –547. (b) K. Yang, Q. Song, *Green Chem.* **2016**, *18*, 932–936.

[9] (a) S. W. M. Crossley, C. Obradors, R. M. Martinez, R. A. Shenvi, *Chem. Rev.* **2016**, *116*, 8912–9000. (b) X. Ma, S. B. Herzon, *J. Am. Chem. Soc.* **2016**, *138*, 8718–8721. (c) X. Ma, H. Dang, J. A. Rose, P. Rablen, S. B. Herzon, *J. Am. Chem. Soc.* **2017**, *139*, 5998–6007. (d) S. L. Shevick, C. Obradors, R. A. Shenvi, *J. Am. Chem. Soc.* **2018**, *140*, 12056–12068.(e) S. A. Green, S. Vásquez-Céspedes, R. A. Shenvi, *J. Am. Chem. Soc.* **2018**, *140*, 11317–11324. (f) S. D. Friis, M. T. Pirnot, S. L. Buchwald, *J. Am. Chem. Soc.* **2016**, *138*, 8372–8375. (g) S. D. Friis, M. T. Pirnot, L. N. Dupuis, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2017**, *56*, 7242–7246; Angew. Chem. 2017, 129, 7348 –7352. (h) Y. He, Y. Cai, S. Zhu, *J. Am. Chem. Soc.* **2017**, *139*, 1061–1064. (i) F. Chen, K. Chen, Y. Zhang, Y. He, Y.-M. Wang, S. Zhu, *J. Am. Chem. Soc.* **2017**, *139*, 13929–13935. (j) J. Nguyen, A. Chong, G. Lalic, *Chem. Sci.* **2019**, *10*, 3231–3236. (k) L.-J. Xiao, L. Cheng, W.-M. Feng, M.-L. Li, J.-H. Xie, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2018**, *57*, 461–464; Angew. Chem. 2018, 130, 470 –473.

[10] S. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2014**, *136*, 15913–15916.

[11] Y.-M. Wang, N. C. Bruno, Á. L. Placeres, S. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 10524–10527.

[12] H. Kotsuki, P. K. Datta, H. Hayakawa, H. Suenaga, *Synthesis* **1995**, 1348–1350.

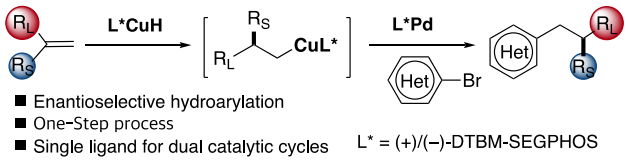
[13] G. Lu, R. Y. Liu, Y. Yang, C. Fang, D. S. Lambrecht, S. L. Buchwald, P. Liu, *J. Am. Chem. Soc.* **2017**, *139*, 16548–16555.

[14] G. Dijkstra, W. H. Kruizinga, R. M. Kellogg, *J. Org. Chem.* **1987**, *52*, 4230–4234.

[15] R. N. Salvatore, A. S. Nagle, K. W. Jung, *J. Org. Chem.* **2002**, *67*, 674–683.

[16] E. Cini, L. Banfi, G. Barreca, L. Carcone, L. Malpezzi, F. Manetti, G. Marras, M. Rasparini, R. Riva, S. Roseblade, *et al. Org. Process Res. Dev*. **2016**, *20*, 270–283.

Entry for the Table of Contents



We described the CuH/Pd-catalyzed enantioselective hydroarylation of 1,1-disubstituted alkenes with anti-Markovnikov regioselectivity under mild conditions. Notably, the single ligand, DTBM-SEGPHOS, was used for both the Pd- and Cu-catalyzed processes. β-Stereogenic arenes were accessed by this convenient and efficient single-step protocol. A wide range of aryl bromides, including several heterocycle-containing substrates, can be used with good efficiency and enantioselectivity. Various 1,1-disubstituted alkenes have also been examined.