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Letter

[*n*]Dendralenes as a Platform for Selective Catalysis: Ligand-Controlled Cu-Catalyzed Chemo-, Regio-, and Enantioselective Borylations

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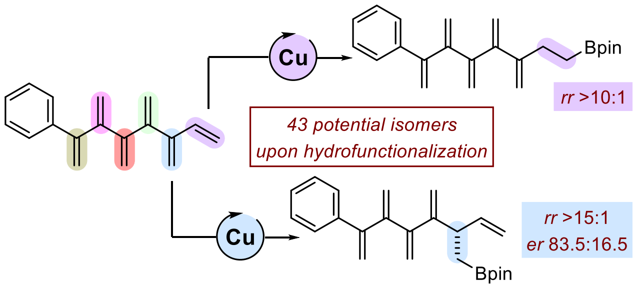
ABSTRACT: We report the development of two complementary methods for the Cu-catalyzed *anti*-Markovnikov borylation of one specific olefin in 2-substituted [*n*]dendralenes (*n* = 3−6). The first protocol operates with a bisphosphine ligand and occurs with high regio- and chemoselectivity for the terminal double bond, independently of the number of cross-conjugated alkenes. We show that the use of a chiral phosphanamine ligand enables the highly chemo-, regio-, and enantioselective borylation of the alkene cross-conjugated with the terminal olefin in [*n*]dendralenes.



Among the various classes of polyunsaturated hydrocarbons containing exclusively sp^2-hybridized carbon atoms, dendralenes occupy a singular position. Dendralenes are acyclic cross-conjugated polyenes which have been much less investigated than linear polyenes or annulenes, for instance (Figure 1A).[1,2] For a long time, these structures were difficult to prepare and were believed to be unstable entities. Owing to 20 years of remarkable synthetic efforts, the Sherburn laboratory has streamlined access to a great variety of dendralenes on a practical scale, with derivatives containing up to 12 olefinic units.[3,4] The same group has investigated the specific physicochemical properties of dendralenes as well as their ability to engage into diene-transmissive Diels−Alder cycloadditions (DTDA) (Figure 1B).[3,5−7] Selective functionalization of dendralenes is challenging. Ru-catalyzed cross-metathesis of [3]dendralenes was realized by resorting to a protection/deprotection strategy.[3h,8] Lipshutz showed that only judiciously designed [3]dendralenic Michael acceptors undergo selective Cu-catalyzed 1,4- or 1,6-conjugate addition (Figure 1B).[9] The development of general catalytic and selective protocols for the functionalization of one specific alkene in minimally biased [*n*]dendralenes remains elusive.

The metal-catalyzed selective intermolecular hydrofunctionalization of conjugated 1,3-dienes has emerged as an enthralling approach to elaborate complex multifunctional small molecules from readily available starting materials. It represents a formidable challenge for fundamental study in selective catalysis because the number of theoretical isomers depends on the substitution pattern of the diene.[10] For acyclic 2-substituted dienes, up to 11 chemo-, regio-, and stereoisomers can be obtained. In recent years, several groups have disclosed complementary selective processes for the hydrofunctionalization of branched dienes using C-, Si-, B-, N-, P-, S-, or O-based reagents.[11,12] In addition to excellent regio- and chemoselectivity, in some cases high enantioselectivity has been achieved. As a continuation of our interest in this area,[13] we wondered whether 2-substituted [*n*]dendralenes could be used as a platform for the development of chemo-, regio-, and ultimately enantioselective hydrofunctionalizations. For the simplest [3]dendralene derivatives, this would require the identification of a catalytic system able to discriminate among the 19 isomers that can be theoretically generated upon monohydro-functionalization. This number follows the linear equation displayed on Figure 1C and increases to 27, 35, and 43 for [4]-, [5]-, and [6]dendralenes, respectively. Realization of this objective would undoubtedly expand knowledge in the field of selective transition-metal catalysis where—by contrast to enzymes—site-specific modification of complex structures remains a persistent challenge.[10,14] Herein, we report our progress in this endeavor with the identification of two complementary Cu-catalyzed processes for the highly chemo-, regio-, and enantioselective borylation of 2-subsituted [*n*]-dendralenes (*n* = 3−6) (Figure 1D).

We began our investigations by evaluating several ligands under prototypical reaction conditions for the Cu-catalyzed borylation of dienes using the known 2-phenyl[3]dendralene **1a** as the model substrate (Table 1).[12e,13a,15] Whereas no

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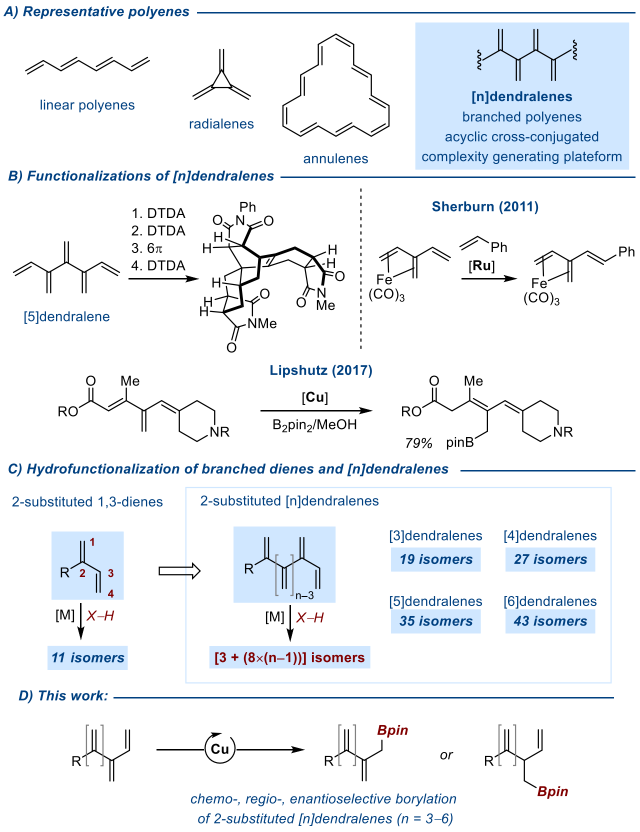
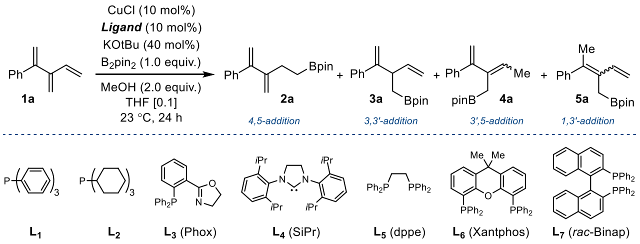


Figure 1. (A) Prototypical classes of polyenes. (B) Functionalization of [*n*]dendralenes and selective functionalizations. (C) Selectivity challenges in the hydrofunctionalization of 2-substituted 1,3-dienes and 2-substituted [*n*]dendralenes (*n* = 3−6).

Table 1. Reaction Optimization[a]



entry	ligand	conv[b] (%)	2a:3a:4a:5a[b]
1	none	nr[c]	
2	L$_1$	>99	1:5.3:8.7:10
3	L$_2$	>99	1:1.8:3.2:3.1
4	L$_3$	96	2.2:1: 1.9:1.8
5[d]	L$_4$	63	7.8:17.5:1:3.2
6	L$_5$	88	11:1.8:—:1
7	L$_6$	76	5.3:1:—:—
8	L$_7$	99	>20:1:—:—
9[e]	L$_7$	97 (81)[f]	>20:1:—:—

[a] Reaction conditions: **1a** (0.15 mmol). [b] Determined by ^{1}H NMR using an internal standard. [c] No reaction. [d] Using 50 mol % of KO*t*Bu. [e] Using 5 mol % of CuCl, 5 mol % of L$_7$, and 5 mol % of KO*t*Bu. [f] The yield after purification is shown in parentheses.

reaction occurred in the absence of ligand, complete conversion into a mixture of four distinguishable regioisomers was obtained using triphenylphosphine (L$_1$) (entries 1 and 2).[16]

Analysis of the crude reaction mixture revealed a 1:5.3:8.7:10 ratio between the products of formal 4,5-, 3,3′-, 3′,5-, and 1,3′-addition denoted as **2a**, **3a**, **4a**, and **5a**, respectively. Although **4a** and **5a** appeared to be generated as single stereoisomers, the geometry of the C═C bond could not be unequivocally determined. The use of tricyclohexyl phosphine (L$_2$) or of a (P,N) ligand (L$_3$) led to complex mixtures of inseparable isomers (entries 3 and 4). With the imidazolium salt L$_4$, **3a** was obtained as major product, and with bisphophine L$_5$, **2a** was the most abundant isomer (entries 5 and 6). The substantial amount of remaining substrate and of other chemo- and regioisomers present in these experiments hampered efficient purification in both cases. With L$_6$, **2a**, the product of formal 4,5-addition with *anti*-Markovnikov selectivity, was obtained as major isomer together with reduced amount of **3a**. No traces of **4a** and **5a** were detected (entry 7). This result was significantly improved using L$_7$, and **2a** was obtained as a single chemo- and regioisomer (rr > 20:1) in 81% yield. The catalyst loading could be reduced to 5 mol % (entries 8 and 9). Of note, the influence of the supporting ligand associated with copper on selectivity appears clearly from the results disclosed in Table 1 (entries 1−9). Formation of **5a** (entries 2−5) highlights the fact that even the less exposed internal diene units in **1a** is reactive.

We next set out to develop a modular synthetic route to readily access related 2-substituted [*n*]dendralenes; a task which remains challenging despite the development of several successful strategies. Our approach takes inspiration from previous tactics developed by the Sherburn group and builds upon our Ni-catalyzed Kumada cross-coupling protocol for the synthesis of 2-substituted 1,3-dienes (Figure 2).[3,17] Dienol phosphate **7a** was prepared in high yield by treatment of 3-phenylbut-3-en-2-one **6a** with LDA at −78 °C, followed by addition of 1.5 equiv of diethyl chlorophosphate.

With [(dmpe)NiCl$_2$] as catalyst, **7a** was cross-coupled with vinyl magnesium bromide **Mg-1**, affording **1a** in 78% yield. 2-

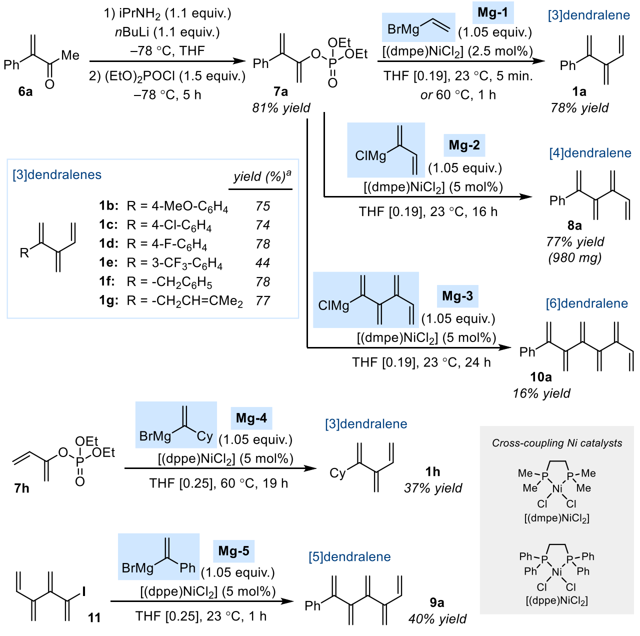


Figure 2. Syntheses of 2-aryl- and 2-alkyl[*n*]dendralenes (*n* = 3−6). [a] Yield after purification.

Phenyl[4]dendralene **8a** and 2-phenyl[6]dendralene **10a** were prepared similarly using **Mg-2** and **Mg-3**. While **8a** was isolated in 77% yield on a 7 mmol scale, **10a** was obtained in only 16% yield. Variation of the starting α,β-unsaturated methyl ketone provided expedient access to a collection of 2-substituted [3]dendralenes (**1b–g**) in usually high yields (average: 72%). The cyclohexyl derivative **1h** was prepared in 37% yield from diethylphosphate **7b** and 1-cyclohexylvinylmagnesium bromide **Mg-4** using [(dppe)NiCl$_2$] as catalyst. A similar protocol was employed for the synthesis of 2-phenyl[5]dendralene **9a** using **11** and **Mg-5** as cross-coupling partners (40% yield).

The scope of the Cu-catalyzed 4,5-borylation of 2-substituted [3]dendralenes was investigated next (Figure 3).

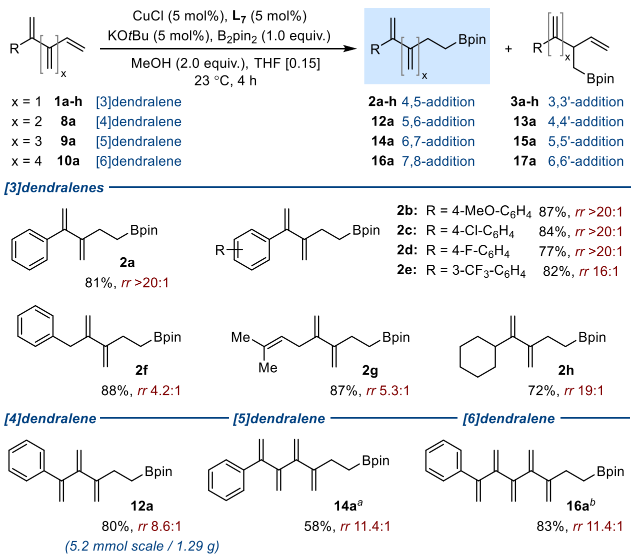


Figure 3. Cu-catalyzed borylation of the remote alkene unit in [*n*]dendralenes (*n* = 3–6) (0.15–5.2 mmol). Selectivity determined by ^{1}H NMR of the crude reaction mixture. The regioisomeric ratio rr is expressed as the major isomer over the sum of all other detectable isomers. Yield after purification. ^{a}20 h. ^{b}42 h.

Preferential borylation of the terminal alkene with perfect anti-Markovnikov selectivity occurred in all cases. The 3,3′-addition products **3a–h** were the only other detectable borylated isomers. Consistently high yield and excellent chemo- and regioselectivity were achieved with 2-aryl[3]dendralenes **2a–e**. Although a slightly diminished selectivity was noticed for [3]dendralenes with a primary alkyl substituent (**1f–g**), the cyclohexyl derivative **1h** led to results comparable to those obtained with the aryl-containing substrates. A methoxy (**2b**), a chloro (**2c**), a fluoro (**2d**), a trifluoromethyl (**2e**), and an isolated alkene (**2g**) were found to be compatible. No traces of overborylated product were detected. Quite remarkably, the anti-Markovnikov borylation could be extended to [4]-, [5]-, and [6]dendralenes, leading to products of 5,6-, 6,7-, and 7,8-addition with excellent chemo- and regioselectivity (58–83% yield). To demonstrate the robustness of the protocol, the borylation of [4]dendralene **8a** was conducted on a gram scale to afford **12a** in 80% yield and 8.6:1 rr. Our current hypothesis for the observed selectivity relies on the formation of a sterically less demanding σ-allyl copper species resulting from the addition of the putative [Cu-Bpin] intermediate to the most reactive terminal alkene.[11c,18]

[3]Dendralene **12a** was cross-coupled with 4-bromoanisole using conditions for a Pd-catalyzed Suzuki reaction to afford **18a** in 87% yield.[19] The nonsymmetrically substituted [3]dendralene **12a** was treated with an excess of *N*-methylmaleimide at 50 °C and yielded products of monocycloaddition **19a** and **20a** exclusively. The reaction occurred with a marked preference for the electron-rich alkyl substituted diene unit over the aryl substituted diene fragment (rr 7:1) (Figure 4). This results complements observations made by the Sherburn group on cycloadditions with 2-substituted [3]dendralenes, which typically generate mixtures of diastereomeric bisadducts.[3c]

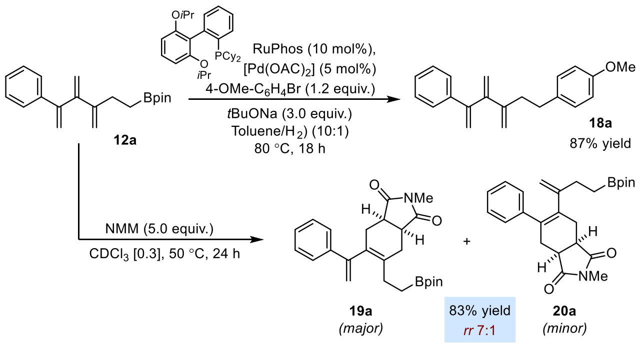
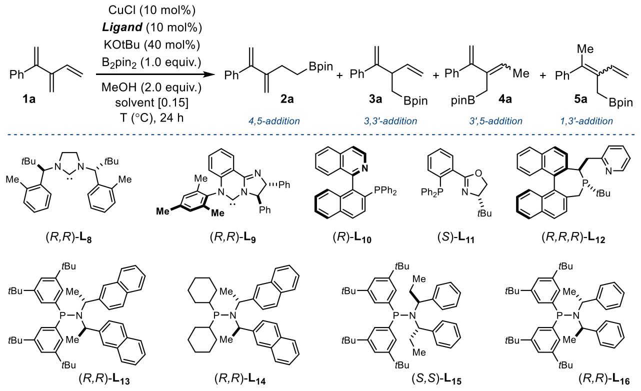


Figure 4. Postcatalytic functionalizations.

Encouraged by results obtained during our first optimization campaign (Table 1), we questioned whether a complementary catalytic system that would target isomer **3a** could be developed. Two chiral *N*-heterocyclic carbene ligands were evaluated initially (Table 2, entries 1 and 2).[20] With **L$_8$**, the reactivity was moderate, and only **2a**, **4a**, and **5a** were formed. With **L$_9$**, **2a** and **3a** were generated as major isomers in nearly equimolar amounts. A low but measurable er was obtained for the latter. The three chiral (P,N) ligands surveyed produced preferentially **3a** in low enantiomeric ratio and together with hardly tractable mixtures of isomers (entries 3–5). Phosphanamine **L$_{13}$** developed by Alexakis and which gave excellent results in the Cu-catalyzed enantioselective *anti*-Markovnikov 1,2-borylation of 2-aryl-1,3-dienes, was tested next (entry 6).[13a,21] The increased er prompted us to vary additional reaction parameters and to evaluate other structures of the same family. When the reaction was performed in pentane, **2a** and **3a** were the only detectable borylation products, and we found that the regioisomeric ratio and enantiomeric ratio were improved by conducting the reaction at low temperature (entries 7–9). Evaluation of other members of this ligand class led to the identification of **L$_{16}$** as the best candidate (entries 10–12). Finally, when 2 equiv of B$_2$pin$_2$ was employed, **3a** was generated in a 10.7:1 ratio and could be isolated in 80% yield and 93:7 er (entry 13).

The scope of this second Cu-catalyzed borylation reaction was evaluated using the same set of 2-substituted [*n*]-dendralenes (Figure 5). Electron-rich, electron-neutral, and electron-deficient 2-aryl[3]dendralenes delivered the 3,3′-addition products **3a–e** in high yield, excellent regioselectivity, and high enantiomeric ratio (average: 91:9). Lower levels of enantiocontrol were obtained for 2-aliphatic[3]dendralenes, but the chemo- and regioselectivity remained very high both for primary and secondary alkyl derivatives (**3f–h**). This borylation protocol could be applied to [4]-, [5]-, and even [6]dendralenes affording the products of 4,4′-, 5,5′-, and 6,6′-addition with anti-Markovnikov selectivity as major isomers

Table 2. Reaction Optimization[a]



entry	L	T (°C)	conv[b] (%)	solvent	**2a:3a:4a:5a**[b]	er of **3a**
1[c]	$\mathbf{L_8}$	23	53	THF	2.1:−:1:1.4	*nd*[d]
2[e]	$\mathbf{L_9}$	23	89	THF	6.4:7:1:1	64.5:35.5
3	$\mathbf{L_{10}}$	23	30	THF	1:2.9:1.3:2.6	58:42
4	$\mathbf{L_{11}}$	23	80	THF	2.1:4.5:−:1	60.5:39.5
5	$\mathbf{L_{12}}$	23	75	THF	1.1:3.2:−:1.1	54:46
6	$\mathbf{L_{13}}$	23	51	THF	2.8:4.4:1.4:1	73:27
7	$\mathbf{L_{13}}$	23	89	pentane	1:6.5:−:−	85.5:14.5
8	$\mathbf{L_{13}}$	0	98	pentane	1:5.3:−:−	88.5:11.5
9	$\mathbf{L_{13}}$	−40	93	pentane	1:7.7:−:−	92:8
10	$\mathbf{L_{14}}$	−40	85	pentane	6.6:2.4:1.4:1	78:22
11	$\mathbf{L_{15}}$	−40	88	pentane	1:9.9:−:−	85:15
12	$\mathbf{L_{16}}$	−40	90	pentane	1:10.2:−:−	91.5:8.5
13[f]	$\mathbf{L_{16}}$	−40	(80)[g]	pentane	1:10.7:−:−	93:7

[a] Reaction conditions: **1a** (0.1−0.3 mmol). [b] Determined by ^{1}H NMR using an internal standard. [c] The imidazolium iodide was employed with 50 mol % of KO*t*Bu. [d] Not determined. [e] The CuCl complex was used. [f] 3 h. [g] In parentheses, yield after purification.

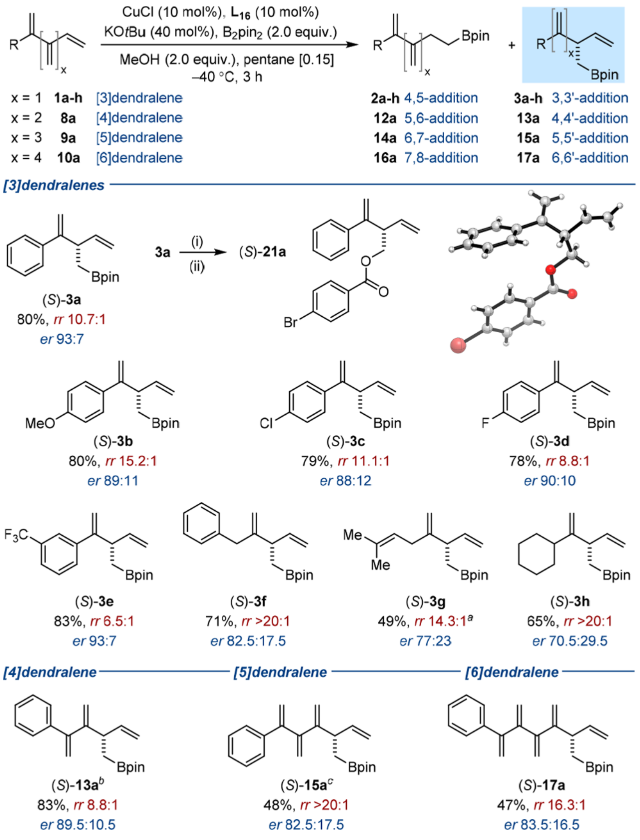


Figure 5. Scope of the enantioselective borylation of [n]dendralenes (n = 3−6) (0.14−0.3 mmol scale). rr determined by ^{1}H NMR. er determined by HPLC or SFC after oxidation to the alcohol. (i) H_2O_2 (30% aq), NaOH (4.0 M), THF, 23 °C, 30 min. (ii) 4-bromobenzoyl chloride (1.2 equiv), DMAP (0.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 23 °C, 12 h. [a] The minor isomer is **5g**. [b] 17 h. [c] 6 h. The stereochemistry of **3b**−**h**, **13a**, **15a**, and **17a** was assigned by analogy with **3a** based on the X-ray crystallographic analysis of its benzoyl derivative (*S*)-**21a**.[22]

(**13a**, **15a**, **17a**). In contrast to the first catalytic system, inspection of the crude reaction mixture revealed the formation of other borylated products, most of them being present in negligible amounts. Therefore, the values expressed as rr in Figure 5 reflect the ratio of the major isomer over the sum of all other detectable isomers. To appreciate the effectiveness of the catalytic system, these results must be analyzed in light of the theoretical number of structures that can be generated upon hydrofunctionalization. Indeed, the regioisomeric ratio (rr) indicates that, for [3]−[6]dendralenes, the catalytic system is able to generate predominantly 2 isomers out of 19, 27, 35, and 43 isomers, respectively, while the enantiomeric ratio (er) underscores the ability of the chiral catalyst to further impart appreciable levels of stereodifferentiation between the two main isomers remaining (∼90:10).

To summarize, we developed two complementary methods for the Cu-catalyzed selective borylation of 2-substituted [*n*]dendralenes. Using a bisphosphine ligand, the first protocol enables precise functionalization of the terminal olefin with excellent anti-Markovnikov selectivity. The system is applicable to various [*n*]dendralenes (n = 3−6). When $n > 3$, the possibility to engage the new dendralenes generated into postcatalytic cross-coupling and cycloaddition reactions has been established. With the second protocol, the alkene cross-conjugated with the terminal olefin is borylated preferentially with excellent anti-Markovnikov selectivity. Selectivity was modulated by changing the nature of the supporting ligand from a bisphosphine to a monosphosphine. Identification of a chiral phosphanamine afforded the borylated polyolefins with high levels of enantiocontrol for various lengths of [*n*]-dendralenes (n = 3−6). Our efforts are currently directed toward understanding the origin of the high levels of chemo-, regio-, and enantioselectivity obtained and at developing other catalytic transformations for the site-specific functionalization of [*n*]dendralenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01892.

General procedures, experimental details, and characterization and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1993603 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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