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Regioselective Cu-Catalyzed Hydroboration of 1,3-Disubstituted-1,3-Dienes: Functionalization of Conjugated Dienes Readily Accessible through Ene–Yne Metathesis

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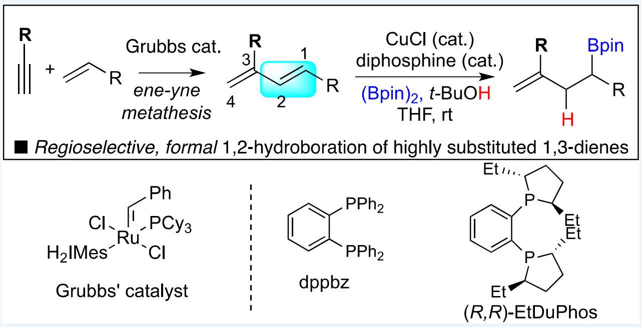

ABSTRACT: A regioselective Cu-catalyzed formal hydroboration of 1,3-disubstituted-1,3-dienes is reported. Highly substituted 1,3-dienes produced through catalytic ene–yne metathesis provided substrates for the regioselective hydroboration with variable substituents conveniently introduced from a 1-alkene and a terminal alkyne. For the achiral reaction, the diphosphine 1,2-bis(diphenylphosphino)benzene (dppbz) was used as the ligand. For the enantioselective reaction, EtDuPhos was used as the diphosphine ligand, and good enantioselectivites were obtained in most cases. Control studies showed that the stereoisomeric purity of the 1,3-diene and the Cu(I) source were key variables that led to the highest regioselectivity. In situ NMR experiments and deuterium quenching confirmed the presence of an allyl copper intermediate, which did not exchange with other 1,3-dienes. A proposed model for the regioselectivity is based on the addition of Cu-B to the 1,3-diene where steric effects in the 3,4-addition are more severe than those in the favored 1,2-addition mode. The products were further functionalized and were employed in a dual-catalytic cross-coupling reaction.

KEYWORDS: *hydroboration, 1,3-dienes, ene–yne metathesis, copper catalysis, borylation, homoallylic alcohols*

With the ready availability of 1,3-dienes from ene–yne metathesis, functionalization of the conjugated diene would greatly increase the synthetic utility of these readily accessible materials. In recent years, 1,3-diene functionalization reactions have been developed with a wide variety of catalytic and asymmetric catalytic addition reactions now possible.[1] Still, despite the intense activity in this area, the substitution patterns of the diene substrates tend to be monosubstituted or in some cases 1,1- or 1,2-disubstituted.[1] There are few examples of diene functionalization using 1,4-difunctionalized or 1,3-disubstituted dienes.[2] The lack of these other substitution patterns might be explained by the weak regiocontrol of diene addition reactions, which can be dramatically affected by substitution along the diene subunit (Scheme 1c). When each double bond possesses two substituents, similar reactivity tends to give mixtures of products. In the past, our group[3] and others[4] have developed ene–yne cross metathesis reactions and catalytic carbon–carbon coupling reactions. In some cases, equal molar equivalents of alkene and alkyne may be used, making this a highly efficient, atom-economical reaction with no by-products.[5] Based on our motivation to use the 1,3-diene substitution patterns accessed through ene–yne metathesis, we sought to develop regioselective (also called position-selective) hydroboration of the 1,3-diene subunit, typically bearing substitution at the 1- and 3-positions (Scheme 1d).

Copper-catalyzed hydroboration reactions are powerful because they provide valuable organoboron intermediates that are useful in organic synthesis. In the formal hydroboration chemistry, we were inspired by early work of Ito et al.[6] who demonstrated chemo- and enantioselectivity using mostly cyclic 1,3-dienes (Scheme 1a). A study by Mazet and co-workers[7] showed site- and enantioselectivity in acyclic, monosubstituted dienes (Scheme 1b). If the regioselectivity in Mazet's system is mapped onto the 1-alkyl-substituted diene in Scheme 1c, this amounts to 4,3-hydroboration where the higher number is assigned to the heavier boron atom.[8] In Mazet's Cu work,[7] 1,3-disubstituted-1,3-dienes were not used; in Mazet's related Ir work,[9] a 1,3-disubstituted-1,3-diene was tried and found not to react. Most recently, Fañanás-Mastral et al. reported a selective hydroboration of dendralenes.[10] Other

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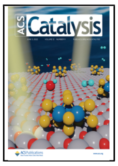


https://doi.org/10.1021/acscatal.2c01190

Scheme 1. Copper-Catalyzed Hydroboration of Conjugated Dienes

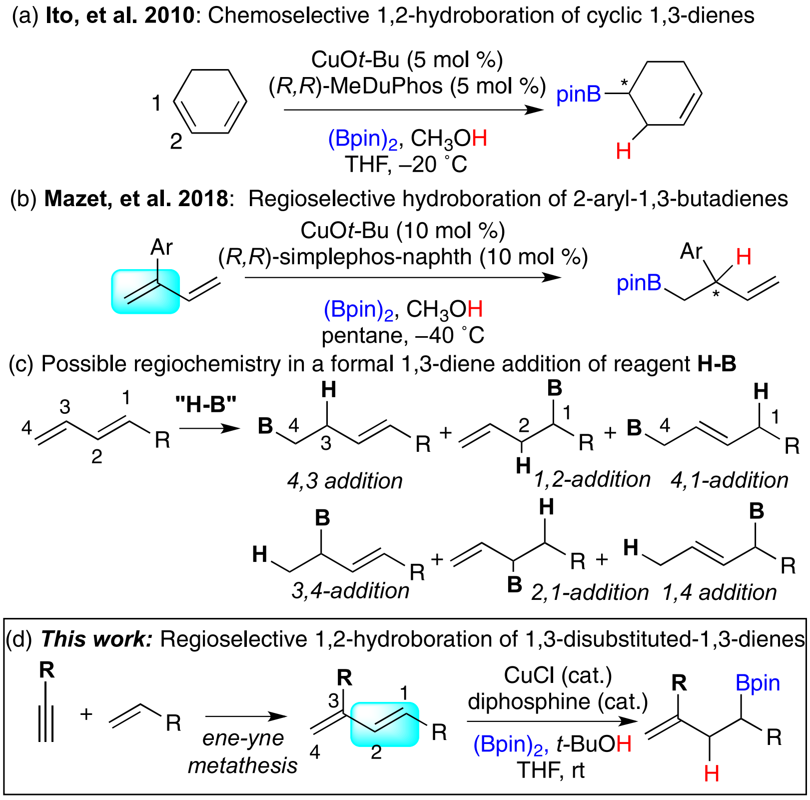
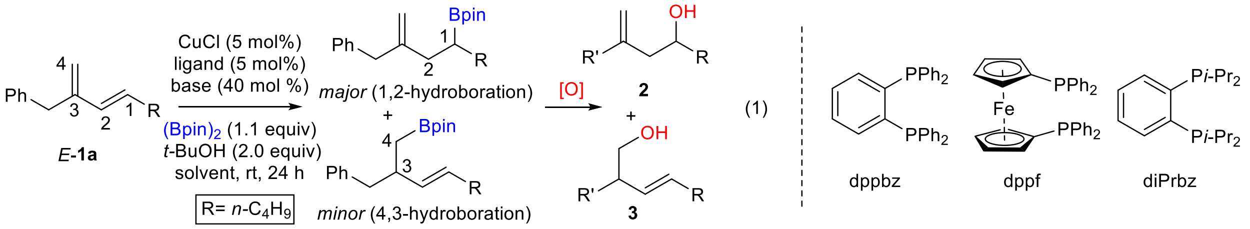


Table 1. Optimization of Regioselective Hydroboration of a Disubstituted 1,3-Diene



entry	ligand	solvent	base	2a:3a[a]	yield of 2a[b]
1	dppbz	hexanes	KO*t*-Bu	3.2:1	70%
2	dppbz	toluene	KO*t*-Bu	1.3:1	40%[c]
3	dppbz	THF	KO*t*-Bu	5:1	81%
4	dppf	THF	KO*t*-Bu	1:1	22%[c]
5	dppbz	THF	LiO*t*-Bu	11:1	78%[c]
6	dppbz	THF	NaO*t*-Bu	9:1	88%
7	diPrbz	THF	NaO*t*-Bu	5:1	71%[d]

[a] **2a**:**3a** regioisomer ratio was determined by proton NMR of the crude product. [b] Isolated yield of major regioisomer **2a** (R' = CH_2Ph) after oxidation. [c] Did not reach full conversion. [d] NMR yield of major regioisomer **2a** (R' = CH_2Ph) after oxidation. Oxidation conditions [O] = H_2O_2, NaOH, THF/H_2O, rt, 4 h.

groups have developed LCu-Bpin addition reactions to 1,3-dienes as a first step in additional bond forming reactions such as Hoveyda's multicomponent reactions,[11] Cao and Liao's imine addition,[12] ketone additions,[13] and Brown's dual-Cu/Pd catalytic diene arylation reactions,[2b,14] among others.[1]

The highly substituted 1,3-dienes can provide access to more highly substituted organoboronates, which are among the most versatile building blocks in catalysis and organic synthesis. Organoboronates can be employed in catalytic cross-coupling reactions and are readily converted to a variety of other functional groups such as C−O or C−N bonds.[15] With the unique regioselectivity possible in Scheme 1d, the formal hydroboration is more versatile because the higher degree of substitution in the 1,3-diene gives more highly substituted boronates. The unique 1,2-addition also creates a chiral center, raising the possibility of enantioselectivity. The unique regiocontrol might be further applied in dual catalysis or multicomponent applications. Since the 1,3-dienes are readily obtained from ene−yne metathesis, this net hydroboration reaction should increase the utility of these dienes in organic synthesis.

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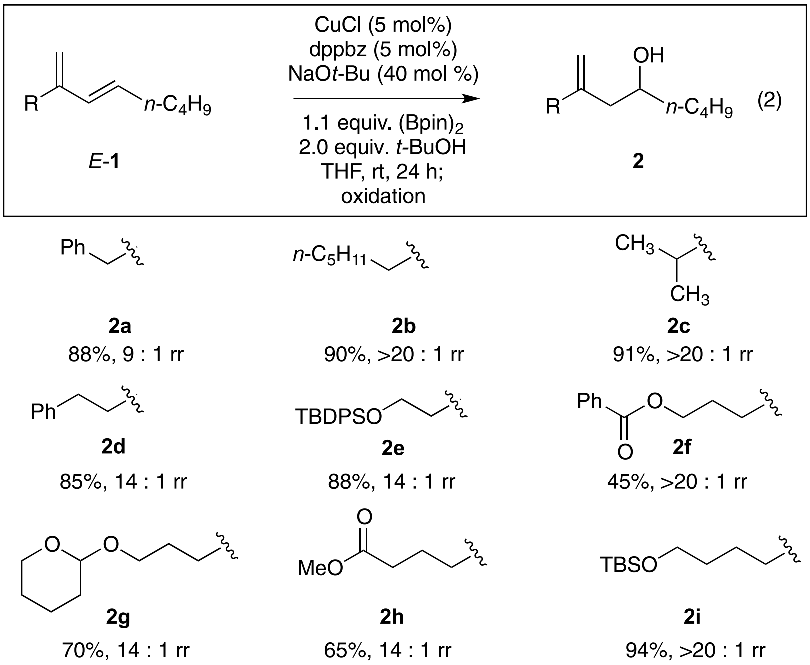
Scheme 2. Variation of the R Substituent at the 3-Position



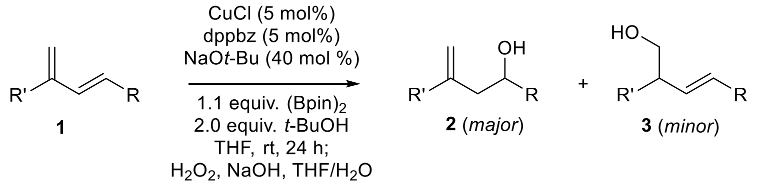
First, different achiral diphosphines were investigated to identify conditions for the regioselective hydroboration of acyclic 1,3-dienes obtained from ene−yne metathesis (Table 1). As a representative example, we chose 1-butyl-3-benzyl-1,3-butadiene E-**1a**, the ene−yne cross metathesis (EYM) product from 3-phenyl-1-propyne and 1-hexene. The data are presented in Table 1. We chose 1,2-bis(diphenylphosphino)-benzene (dppbz) as the chelating diphosphine ligand. Different solvents were investigated at a standard reaction time of 24 h. Hexanes gave a good yield and produced a 3.2:1 regioisomer ratio (rr, entry 1). The major regioisomer was the 1,2-hydroboration product, and the minor product arose from competing 4,3-hydroboration. The use of toluene reduced both the yield and regioselectivity (entry 2). Tetrahydrofuran (THF) gave a 5:1 regioisomer ratio (rr) of intermediate boronates, which matched that of the isolated alcohols (entry 3). The use of dppf as a diphosphine ligand had a deleterious effect on both the yield and the selectivity (entry 4). Other alkoxides resulted in higher regioselectivities (entries 5 and 6), but NaO*t*-Bu was found to give complete conversion and the highest yield.[16] A related diphosphine bis-(diisopropylphosphino)benzene (diPrbz) was synthesized as a slightly more electron-rich analogue of dppbz.[17] With diPrbz, full conversion was observed, but a diminished regioisomer ratio was found with a 5:1:1 mixture of 1,2-, 4,3-, and 1,4-isomers. We adopted the conditions of entry 6 as our standard conditions.

Next, with the optimized conditions, we began to investigate the scope of the Cu-catalyzed hydroboration with respect to the substituent at the 3-position of the 1,3-diene. In terms of the EYM preparation of these disubstituted 1,3-dienes, the R substituent in eq 2 arises from the terminal alkyne. For the formal hydroboration described in Scheme 2, a two-step procedure was applied: the optimized hydroboration was followed by oxidation to afford the homoallylic alcohol. Isolated yields are for the major regioisomer, obtained over the two steps. Unless otherwise stated, the other regioisomer is the 4,3-addition product **3** shown above in eq 1. Hydrocarbon sidechains, protected alcohols, and ester functionality all underwent the hydroboration giving high yields and high regioselectivity. Branching in the sidechain was also tolerated as found in product **2c**.

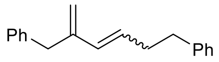
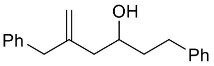
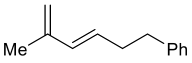
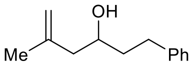
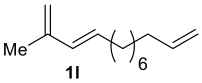
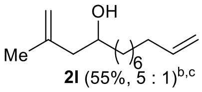
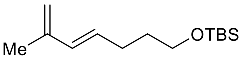
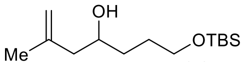
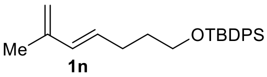
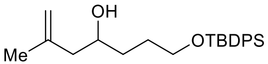
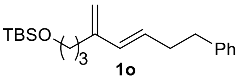
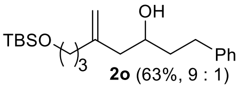
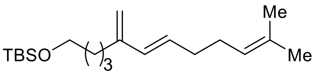
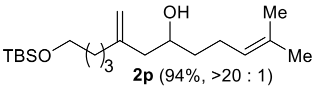
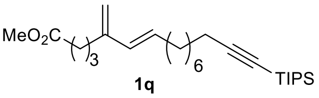
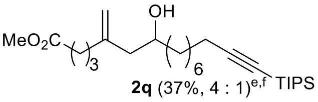
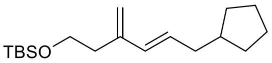
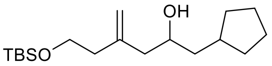
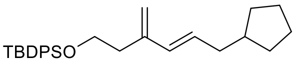
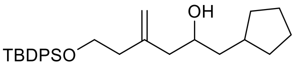
Various combinations of the substituents at both the 1- and 3-positions were explored next to gauge the scope and chemoselectivity of the reaction (Table 2). Some of the dienes were prepared by EYM between an R'-substituted alkyne and an R-substituted alkene (entries 1, 7−10), whereas others were made using the Wittig reaction (entries 2−6). In Table 2, the diene substrate is shown along with the final product obtained after oxidation. Yields in entries 3−6 and 9−10 are the average of at least two runs. Remote phenyl substituents were tolerated (entries 1 and 2). A terminal alkene survived the reaction, showing that the Cu-Bpin addition step is chemoselective for the 1,3-diene moiety (entry 3). Remote silyl ethers were well-behaved (entries 4−10). A trisubstituted alkene or substituted alkyne could be carried in the substrate without undergoing addition (entries 7 and 8). Lastly, branching in the sidechain gave a diminished yield in one case due to poor conversion (entry 9). When the TBS ether was replaced with the TBDPS group, complete conversion was observed giving a higher yield but a lower regioselectivity (entry 10). These last two examples show that there is a subtle interplay of steric effects that can decrease either the yield or regioselectivity.

The reactivity and regioselectivity of the individual E and Z dienes were investigated. Because the major product of the formal hydroboration arises by addition to the 1,2-disubstituted alkene, we expected there to be a difference in the reactivity profile depending on the alkene geometry. This question is also relevant in the context of the diene substrates: ene−yne cross metathesis usually affords E/Z mixtures of 1,3-dienes. We were curious if the E/Z mixtures could be used as reactants and whether they would give a different reaction outcome. First, regioselectivity was probed in substrate **1a**: in Table 1, pure E-**1a** was found to give a 9:1 mixture of regioisomers and an 81% yield of the 1,2-hydroboration product. In Scheme 3, Z-**1a** was prepared by the Wittig

Table 2. Additional Examples of the Regioselective Cu-Catalyzed Hydroboration

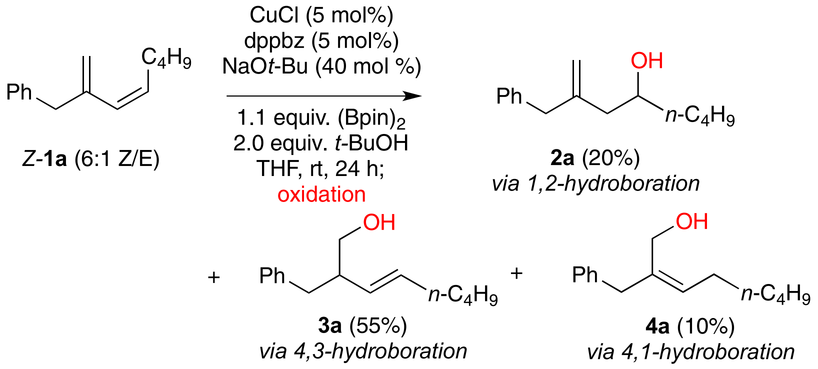


(3)

entry	diene reactant	major product (yield, rr)[a]
1	 **1j** (1:1 E/Z, 2 equiv.)	 **2j** (74%, >20 : 1)
2	 **1k**	 **2k** (82%, 8 : 1)
3	 **1l**	 **2l** (55%, 5 : 1)[b,c]
4	 **1m**	 **2m** (55%, 5 : 1)[b,d]
5	 **1n**	 **2n** (63%, 6 : 1)
6	 **1o**	 **2o** (63%, 9 : 1)
7	 **1p** (4:1 E/Z, 1.2 equiv.)	 **2p** (94%, >20 : 1)
8	 **1q**	 **2q** (37%, 4 : 1)[e,f]
9	 **1r**	 **2r** (27%, 5 : 1)[g]
10	 **1s**	 **2s** (67%, 3 : 1)

[a] Isolated yields. Entries 3−6, 9,10 are the average of two runs. [b] Using 1.5 equiv $(Bpin)_2$. [c] Reaction time 3 h. [d] Reaction time 1 h. [e] CuCl (20 mol %), dppbz (20 mol %) used. [f] Nonbasic oxidation conditions: $NaBO_3$, THF/H_2O. [g] Incomplete conversion; 80% yield based on recovered SM.

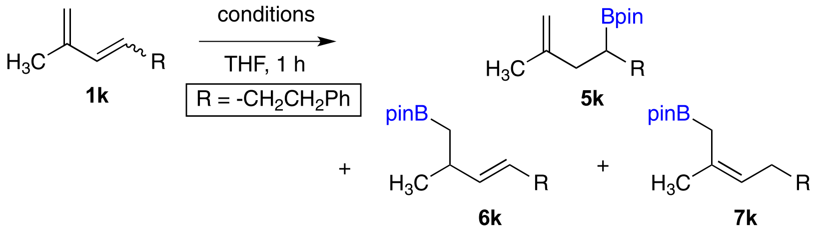
Scheme 3. Z-Stereoisomer Gives Altered Regioselectivity



reaction and subjected to the same reaction conditions, carried out in an inert atmosphere glovebox, followed by oxidation.

The products in Scheme 3 are the products of the formal hydroboration−oxidation sequence. Full conversion of *Z*-**1a**

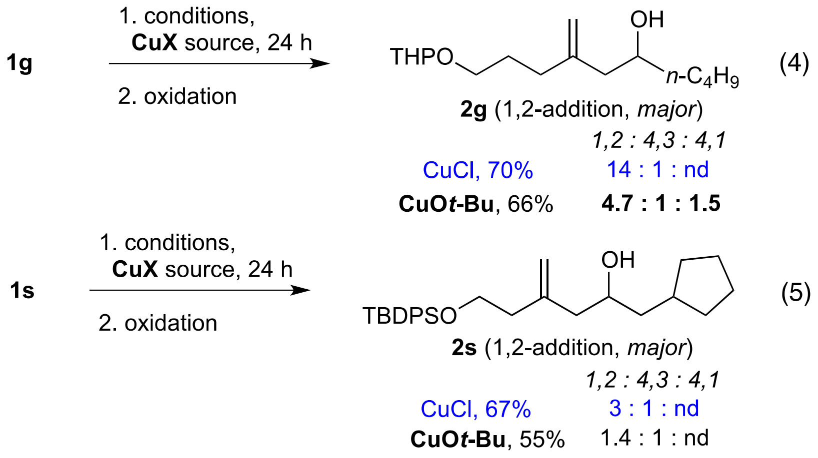
Table 3. E/Z Mixtures Give Diminished Regioselectivity[a]



entry	E/Z ratio of **1k**	$(Bpin)_2$ (equiv)	**5k**:**6k**:**7k**	E/Z of recovered **1k**
1	E only	1.1	8:1:nd[b]	
2	1.1/1.0 E/Z	1.0	3.2:1:0.5	
3	1.1/1.0 E/Z	0.5	3:1:nd[c]	1:1.1 E/Z

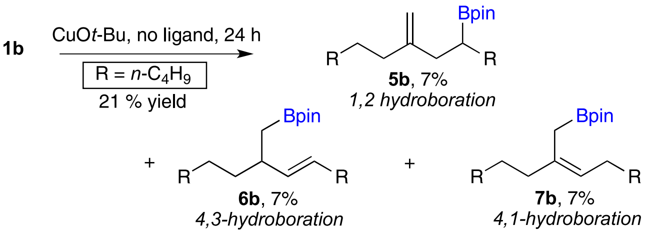
[a]Conditions: CuCl (5 mol %), dppbz (5 mol %), NaO*t*-Bu (40 mol %), 1.1 equiv $(Bpin)_2$, 2.0 equiv *t*-BuOH, THF, rt, 1 h. [b]nd = not detected. [c]50% conversion due to limiting $(Bpin)_2$.

Scheme 4. Regioselectivity Based on the Cu Source[a]



[a]Conditions: CuX (5 mol %), dppbz (5 mol %), NaO*t*-Bu (40 mol %), 1.1 equiv $(Bpin)_2$, 2.0 equiv *t*-BuOH, THF, rt, 24 h. NMR yields after the oxidation step.

Scheme 5. Nonselective Background Reaction by CuO*t*-Bu[a]



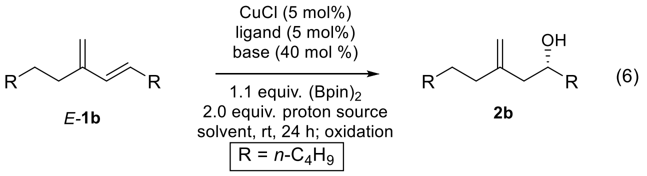
[a]Conditions: CuO*t*-Bu (5 mol %), NaO*t*-Bu (40 mol %), 1.1 equiv $(Bpin)_2$, 2.0 equiv *t*-BuOH, THF, rt, 24 h.

was observed, yet the ratio of regioisomers was reversed in favor of 4,3-hydroboration: a 2:5.5:1 ratio of **2a**:**3a**:**4a** was found. The conversion of the Z-alkene into E-**3a** is interesting; similar observations have been obtained by others, consistent with isomerization via an allylic Cu intermediate.[2b,18] Despite the changed regioselectivity, the Z-isomer was fully converted to products under the standard reaction conditions.

The reaction of E/Z mixtures showed diminished selectivity, as observed in the intermediate boranes (Table 3). In Table 3, the regioselectivity obtained with E-**1k** was compared to that obtained from the mixture E/Z-**1k**. For pure E-**1k**, full conversion was observed after 1 h in d_8-THF, giving an 8:1 rr of **5k** and **6k** (entry 1). The E/Z mixture produced a lower regioselectivity of 3.2:1:0.5 **5k**:**6k**:**7k**. In this case, the 1,4-hydroboration product **7k** also appeared. Both E and Z stereoisomers fully reacted over a 1 h time interval. Finally, we probed whether one stereoisomer of **1k** reacted faster. Limiting (0.5 equiv) $(Bpin)_2$, a 50% conversion was observed with an eroded regioselectivity, similar to that found when using 1 equiv of the diboronate. Interestingly, the unreacted 1,3-diene **1k** in entry 3 was found to have a 1:1.1 E/Z ratio, validating that the stereoisomers of **1k** had similar reactivity under the reaction conditions. These data show that the Z-isomer gives lower regioselectivity than that of pure E-isomer and also that each stereoisomer has similar reactivity. Thus, it can be inferred that substrates **1** used in Scheme 2 and Table 2 would give diminished regioselectivity if E/Z mixtures of 1,3-dienes were employed.

Interestingly, different regioselectivity values were observed for the 1,3-disubstitution pattern when CuO*t*-Bu was used as the copper source. Because some of the substrates mentioned above required a full 24 h to undergo complete conversion, we reasoned that this might be due to slow formation of the active catalyst. This prompted us to further investigate CuO*t*-Bu, a highly air-sensitive, soluble Cu(I) species.[6] Three substrates were examined, and each showed diminished regioselectivity using CuO*t*-Bu (Scheme 4). First, diene **1g** from Scheme 2 was subjected to hydroboration using CuO*t*-Bu and gave diminished regioselectivity but had a similar yield as obtained

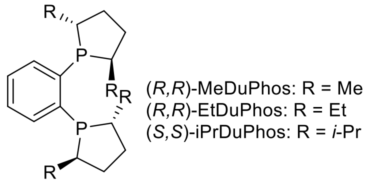
Table 4. Optimization of the Enantioselective Hydroboration of Disubstituted 1,3-Dienes



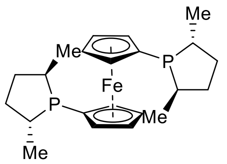
E-**1b** **2b**

entry	ligand	base	solvent, proton source	yield,[a] (%ee)[b]
1	(*R*,*R*)-MeDuPhos	LiO*t*-Bu	hexanes, *t*-BuOH	55% (77%)
2	(*R*,*R*)-MeFerrocelane	LiO*t*-Bu	hexanes, *t*-BuOH	nr, (--)
3	(*R*,*R*)-MeDuPhos	KO*t*-Bu	THF, *t*-BuOH	75% (75%)
4	(*R*,*R*)-MeDuPhos	KO*t*-Bu	THF, *t*-BuOH	92%, (74%)
5	(*R*,*R*)-MeDuPhos	NaO*t*-Bu	THF, *t*-BuOH	93%, (76%)
6[c]	(*R*,*R*)-MeDuPhos	NaO*t*-Bu	THF, *t*-BuOH	92%, (75%)
7	(*R*,*R*)-MeFerrocelane	NaO*t*-Bu	THF, *t*-BuOH	94%, (8%)
8	(*R*,*R*)-EtDuPhos	NaO*t*-Bu	THF, *t*-BuOH	94%, (79%)
9	(*R*,*R*)-EtDuPhos	NaO*t*-Bu	THF, CH_3OH	94%, (75%)
10	(*R*,*R*)-EtDuPhos	NaO*t*-Bu	hexanes, CH_3OH	93%, (67%)
11[d]	(*R*,*R*)-EtDuPhos	NaO*t*-Bu	THF, *t*-BuOH	65%, (80%)
12	(*S*,*S*)-iPrDuPhos	NaO*t*-Bu	THF, *t*-BuOH	11%, (--)
13	(*R*,*R*)-QuinoxP*	NaO*t*-Bu	THF, *t*-BuOH	21%, (--)
14	(*R*,*R*)-Ph-BPE	NaO*t*-Bu	THF, *t*-BuOH	nr, (--)

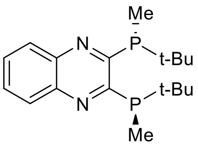
[a] Yield of the desired product was determined based on the isolated yield of the alcohol product after oxidation. [b] Enantiomeric excess was determined by the HPLC method after oxidation and benzoylation of alcohol; the absolute configuration was determined by Mosher ester analysis. [c] Diene **1b** (1.8 equiv) was added as a 5:4 E/Z mixture. [d] The reaction was carried out at 0 °C.



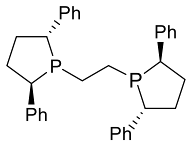
DuPhos



(*R*,*R*)-MeFerrocelane

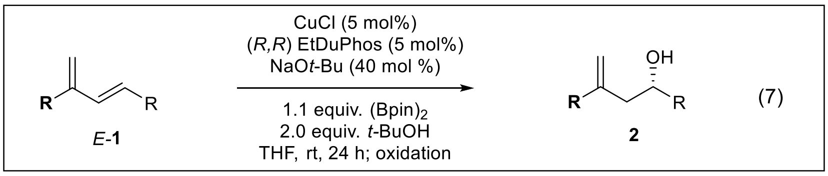


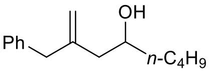
(*R*,*R*)-QuinoxP*



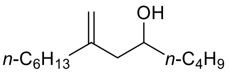
(*R*,*R*) Ph-BPE

Scheme 6. Enantioselective Examples

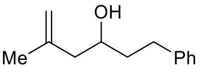




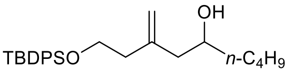
ent-**2a**, 95%, 65% ee[a]



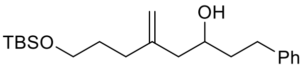
ent-**2b**, 94%, 79% ee



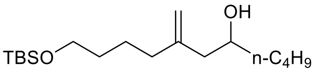
ent-**2k**, 95%, 64% ee



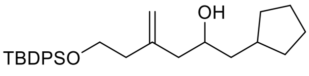
ent-**2e**, 88%, 74% ee



ent-**2o**, 80%, 74% ee[b]



ent-**2i**, 87%, 75% ee



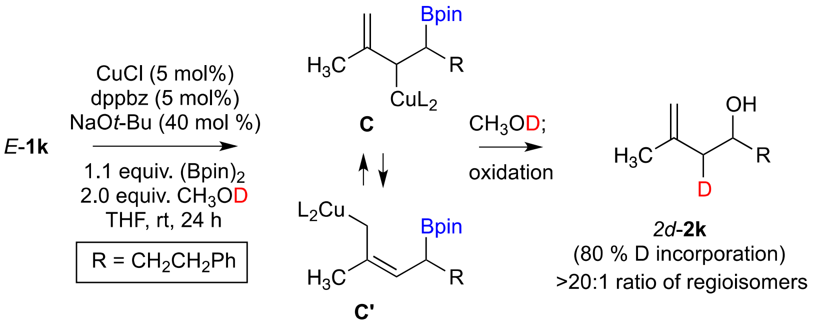
ent-**2s**, 75%, 85% ee[c]

[a] Mosher study was used to assign absolute configuration. [b] Used 2 equiv of the 1,3-diene. [c] Using CuO*t*-Bu as a catalyst. Oxidation conditions: H_2O_2, NaOH, and THF/H_2O.

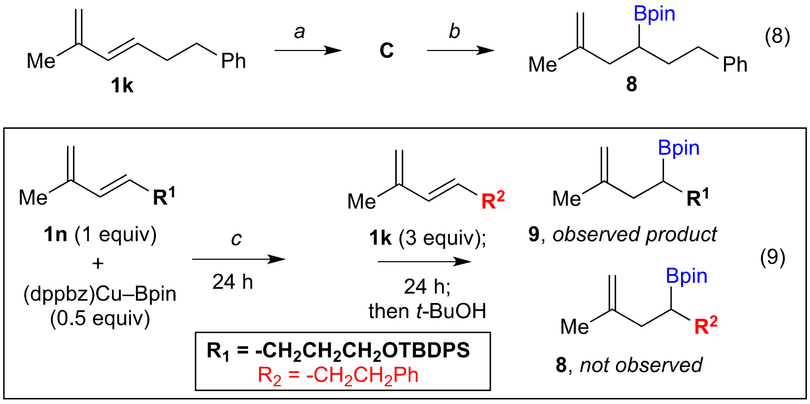
with CuCl. With CuO*t*-Bu as the copper source, the 14:1 ratio eroded to 4.7:1, and the 1,4-addition product was also observed (eq 4). The regioselectivity observed with **1s** was reduced from 3:1 using CuCl to 1.4:1 using CuO*t*-Bu (eq 5). The yields were comparable, but better with CuCl (67 vs 55%). Lastly, triene **1l** gave a 5:1 selectivity of 1,2- and 4,3-hydroboration using the CuCl precatalyst (entry 3 in Table 2), but this diminished to a 1.4:1 mixture of intermediate boranes using CuO*t*-Bu (NMR vs an internal standard, after 2 h of reaction; see the Supporting Information for details). Although diphosphine ligation to insoluble CuCl and soluble CuO*t*-Bu may be relevant,[19] the change in selectivity was surprising since the active catalyst is expected to be the same, LCuB(pin), in both reactions.

The eroded regioisomer ratio was found to arise from a nonselective background reaction. Diene **1b** was subjected to CuO*t*-Bu in the absence of the diphosphine ligand, where a 21% yield of three regioisomers had formed (Scheme 5). In

Scheme 7. Deuterium Labeling Study

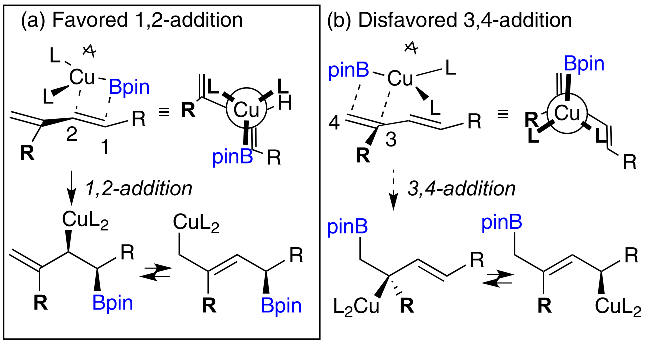


Scheme 8. Mechanism Studies



[a]1 equiv CuO*t*-Bu, 1 equiv dppbz, 1 equiv $(Bpin)_2$, d_8-THF, rt, 24 h. [b]2 equiv *t*-BuOH. Dppbz = 1,2-bis(diphenylphosphino)benzene. [c]Conditions: **1n** (1 equiv), 0.5 equiv CuO*t*-Bu, 0.5 equiv dppbz, 0.5 equiv NaO*t*-Bu, 0.5 equiv $(Bpin)_2$, d_8-THF, rt, 24 h; then **1k** (3 equiv), 24 h; and then *t*-BuOH (2 equiv).

Scheme 9. Model for Regioselectivity



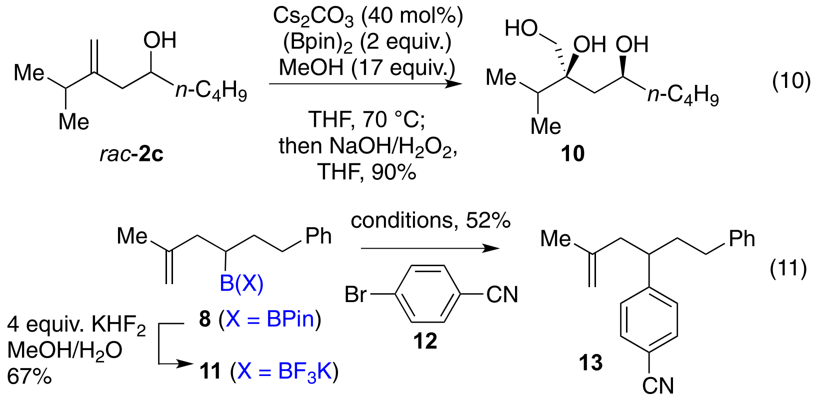
this background process, there was no regioselectivity. The lower selectivity observed using the soluble active form of the catalyst is likely due to a competitive background reaction by soluble CuO*t*-Bu.

Next, we turned our attention to developing an enantioselective reaction using different commercially available chiral diphosphines (Table 4). MeDuPhos in hexanes with LiO*t*-Bu gave a moderate yield but good enantioselectivity (Table 4, entry 1), whereas the analogous reaction with the ferrocelane ligand did not work (entry 2). In THF solvent, variation of the *t*-butoxide salt slightly affected the enantioselectivity with NaO*t*-Bu and KO*t*-Bu giving similar results (entries 3−5). Diene **1b** could be used as an E/Z mixture if supplied in molar excess (entry 6). In THF, the ferrocelane ligand gave a high yield but low %ee (entry 7). The greater steric demand of EtDuPhos resulted in a slight improvement in enantioselectivity as compared with MeDuPhos (entries 8, 9 vs entry 6). A slightly lower %ee was registered in hexanes (entry 10). Reducing the temperature to 0 °C with the EtDuPhos ligand gave a slight improvement in %ee but at the expense of yield (entry 11). The higher steric demand of iPrDuPhos resulted in low conversion, which precluded an enantiomeric excess determination (entry 12). Under the optimized conditions, QuinoxP gave a low yield, and Ph-BPE gave no reaction (entries 13,14). The conditions of entry 8 were adopted as the standard conditions. Notably, under the optimum conditions of entry 8, a single regioisomer was formed with no trace of the 4,3-hydroboration product.[20]

For two products, the determination of absolute stereochemistry was made by comparison of the diastereomeric Mosher esters. In two separate reactions, the scalemic homoallylic alcohol was reacted with *R*- and *S*-MTPA acid chloride to provide the corresponding diastereomeric esters. Comparison of the chemical shift of the protons in the vicinity of the chiral center, especially the methine proton at C5, was possible based on the Hoye model.[21] This analysis indicated that the absolute stereochemistry was the *R*-configuration obtained from reaction employing (*R*,*R*)-EtDuPhos as the chiral diphosphine ligand. For a detailed discussion and additional examples, see the Supporting Information.

Using the (*R*,*R*) EtDuPhos ligand, the enantioselective reaction was extended to other substrates, which all gave good to very good enantioselectivities (eq 7). Because both E and Z isomers were found to be reactive using the achiral diphosphine, we were worried about the possibility of different

Scheme 10. Functionalization of the Products[a]



[a]Conditions: **11** (3 equiv), **12** (1 equiv), [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (2.5 mol %), Ni(dme)Cl$_2$ (5 mol %), dtbbpy (5 mol %), Cs$_2$CO$_3$ (1.5 equiv), 1,4-dioxane, rt, 24 h, and 26W CFL white light.

enantioselectivities with E and Z isomers. As a result, we used pure E-isomers as starting materials. The range of substrates is shown in Scheme 6. The major enantiomer was tentatively assigned by analogy with two cases that were determined by application of the Mosher method. Seven substituted 1,3-dienes were found to give good to very good enantioselectivities (65−85% ee). In one case, use of 2 equiv of diene **1o** gave a slight improvement of yield and enantioselectivity. In all cases, no minor regioisomers could be detected.

Deuterium labeling studies were consistent with an intermediate organocopper species in the major regiochemical pathway (Scheme 7). Based on the literature precedent, the intermediacy of allyl copper (I) species **C** and **C'** was expected. In this labeling experiment, CH$_3$OD was used as the deuterium source. In the ^{1}H NMR spectrum, the product **2k** was found to have 80% deuterium incorporation by integration of the allylic resonance at δ 2.3 ppm. In addition, in the ^{13}C NMR spectrum, the allylic carbon showed the expected 1:1:1 triplet, indicating direct coupling to the deuterium atom.

The allyl copper intermediate was observed by NMR tube experiments, and once formed, it did not exchange with another 1,3-diene. First, the intermediate allylic copper(I) species was detected in a ^{1}H NMR experiment where a stoichiometric copper reagent (with the dppbz ligand) was formed and allowed to react with diene **1k** (Scheme 8). At 0.05 M concentration, complete conversion of the 1,3-diene resulted in a new species, assigned as intermediate σ-allyl species **C**. Key to the assignment was the appearance of the two terminal vinyl protons due to the $\Delta^{3,4}$ methylene group. After a 24 h period, quenching by the addition of *t*-BuOH resulted in the disappearance of the Cu intermediate and isolation of the expected 1,2-hydroboration product **8** (eq 8). Second, reversibility was probed in a crossover experiment (eq 9). In the absence of a proton donor, diene **1n** reacted with 0.5 equiv of a (dppbz) CuBpin reagent formed in situ. After 24 h, a second diene **1k** was introduced. After another 24 h of reaction, quenching by *t*-BuOH resulted in solely the formation of **9** and none of the possible crossover product **8**, which had been previously observed and isolated. This experiment shows that the Cu-Bpin addition step is not reversible and possibly rate-determining.

A working model for the favored addition mode is based on steric strain in the addition step (Scheme 9). The addition step has two substituted atoms adding to alkene carbons, which have different degrees of alkyl substitution (1,2-addition vs 3,4-addition). We propose that the regioselectivity is guided by the bulk at L$_2$Cu, where L$_2$ is a chelating diphosphine ligand. In the favored 1,2-addition, the Cu atom is added to carbon C2, which has a small hydrogen and one carbon substituent, the vinyl group (Scheme 9, panel a). The Newman projection viewing down the forming Cu−C2 bond shows the eclipsing interactions. In the less-favored 3,4-addition (Scheme 9, panel b), the Cu ligands are compressed against two substituents at C3, inducing greater strain. The sterically hindered pinacolatoboron (Bpin) plays a lesser role and has a preference that runs counter to that predicted for the CuL$_2$ group. With respect to Bpin, its addition to C1 bearing an R group occurs in the favored pathway, which is slightly destabilizing. As the boron atom adds to an unsubstituted terminal alkene carbon C4 in the disfavored addition, it experiences less strain since the alkene C4 carbon is unsubstituted. These considerations assume that the addition step is irreversible, which was observed in Scheme 8 and is similar to observations made by Brown using a Cu catalyst bearing an N-heterocyclic carbene ligand.[14b] For Z-isomers, $A^{1,3}$ strain between R groups causes the 1,3-diene to adopt a nonplanar conformation, which results in greater steric strain in the 1,2-addition (due to the branched vinyl group). This results in lower regioselectivity observed for the Z-isomers and E/Z mixtures.

Synthetic utility of the products was demonstrated in product functionalization and a photoredox cross-coupling (Scheme 10). First, the homoallylic alcohol **2c** was functionalized through a net dihydroxylation using Morken's hydroxyl-directed 1,2-diboration, followed by oxidation of the C−B bonds.[22] In this way, the geminal alkene was functionalized to give the corresponding triol **10** in 90% overall yield (eq 10). Second, inspired by Molander's photoredox cross-coupling of secondary trifluoroborates with aryl bromides,[23] we were able to bring about cross-coupling of the secondary homoallylic boronate **11** and *p*-bromobenzonitrile, giving **13** (eq 11). This reaction is a net coupling of a homoallyl fragment with an aromatic electrophile; viewed from the 1,3-diene precursor, **13** is the product of a formal, regioselective 1,2-hydroarylation. Further applications utilizing the homoallylic boron compounds as nucleophiles for conventional cross-coupling[24] are also foreseeable.[25]

In conclusion, a regioselective and enantioselective Cu-catalyzed hydroboration of 1,3-disubstituted-1,3-dienes was developed. Previously, this 1,3-diene substitution pattern was seldom utilized despite the ready accessibility of 1,3-disubstituted-1,3-dienes from catalytic ene-yne metathesis (EYM). A chelating diphosphine ligand gave the highest regioselectivity. It was found that both the Cu source and the E/Z purity of the 1,3-dienes had an impact on the regioselectivity. Using the analogous chiral diphosphine DuPhos, an enantioselective reaction was observed. Similar to previous literature studies, an allylic copper species is an intermediate, as determined from mechanistic studies and by deuterium incorporation. A steric model for the selective addition to the 1,2-disubstitued alkene of the conjugated diene is proposed. Both the intermediate homoallylboronates and the products of oxidation, the homoallylic alcohols, are useful synthetic intermediates. Further transformations such as a directed diboration to form highly oxygenated products and a photoredox cross-coupling show a high degree of synthetic utility of the products of the regioselective hydroboration. Overall, the regioselective hydroboration of the 1,3-dienes obtained through EYM extends the utility of the dienes for the synthesis of functionalized molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c01190.

> Experimental procedures for the synthesis of 1,3-dienes and for the formal Cu-catalyzed hydroboration, mechanistic experiments, and characterization data for new compounds (PDF)

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Author Contributions

The article was written through contributions of all authors. All authors have given approval to the final version of the article.

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Notes

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■ ABBREVIATIONS

$(Bpin)_2$, bis(pinacolato)diboron; dppbz, 1,2-bis(diphenylphosphino)benzene; EtDuPhos, 1,2-bis(2,5-diethylphospholano)benzene; EYM, ene−yne metathesis; MTPA, α-methoxy-α-(trifluoromethyl)phenylacetate; Ph-BPE, 1,2-bis(2,5-diphenylphospholano)benzene

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