

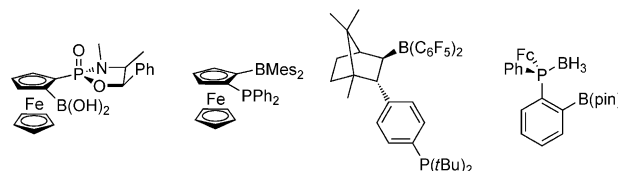
Catalytic Asymmetric Synthesis of Phosphine Boronates**

Valentín Hornillos,* Carlos Vila, Edwin Otten, and Ben L. Feringa*

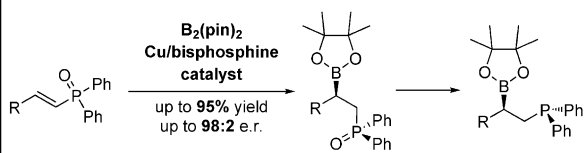
Abstract: The first catalytic enantioselective synthesis of ambiphilic phosphine boronate esters is presented. The asymmetric boration of α,β -unsaturated phosphine oxides catalyzed by a copper bisphosphine complex affords optically active organoboronate esters that bear a vicinal phosphine oxide group in good yields and high enantiomeric excess. The synthetic utility of the products is demonstrated through stereospecific transformations into multifunctional optically active compounds.

Chiral organophosphorus compounds play a prominent role in many areas, including organometallic chemistry, chemical biology, and the production of pharmaceuticals or agrochemicals.^[1] In homogeneous catalysis, chiral phosphines are essential in the field of asymmetric catalysis as we take advantage of their ability to serve as ancillary ligands with tunable steric and electronic properties.^[2] More recent applications in the rapidly emerging field of frustrated Lewis pair (FLP) chemistry have led to new catalytic systems for small-molecule activation.^[3] In particular, phosphine-substituted borane and boronate esters have gained increasing interest for their applications in intramolecular FLP chemistry^[4] and as organocatalysts or ligands in metal-catalyzed transformations.^[5] In these systems, the boron atom also has the ability to bind transition metals by acting as a σ -acceptor ligand, offering new fascinating possibilities in terms of controlling reactivity.^[6] Furthermore, the boronate group enables a variety of transformations by virtue of its ability to undergo stereospecific transformations to form C–O, C–N, or C–C bonds.^[7] Despite the promising reactivity of these compounds, a catalytic asymmetric method to readily access phosphine-substituted chiral boronates has not been described, and to the best of our knowledge, only a limited range of these chiral structures have been explored because of a lack of methods for their synthesis (Scheme 1 a).^[8]

a) Chiral phosphine boronates obtained by diastereoselective methods^[8a–d]



b) This work: Catalytic asymmetric synthesis of phosphine boronates



Scheme 1. Methods for the synthesis of chiral phosphine boronates.

Important procedures for the asymmetric synthesis of chiral organoboranes are transition-metal- and organocatalyzed additions of diboron reagents, such as bis(pinacolato)-diboron, to electron-deficient alkenes.^[9] In particular, the use of copper catalysts^[10] has been highly successful, and a variety of cyclic or acyclic chiral β -boron-substituted carbonyl derivatives can now be obtained with excellent levels of enantiopurity. We questioned whether a related process involving the copper-catalyzed conjugate boration of alkenyl phosphine oxides could be developed despite the fact that the use of these substrates in catalytic asymmetric conjugate additions (ACAs) with organometallic reagents has remained a major challenge to date.^[11] The corresponding enantiomerically enriched vicinal phosphine oxide boronates could then also be derivatized through stepwise stereospecific transformations at both the boron and phosphorus functional groups. Herein, we report an efficient catalytic method using a chiral copper(I) complex to produce optically active vicinal ambiphilic phosphine oxide boronates with excellent enantioselectivity (up to 98:2 e.r., Scheme 1 b).

We started our study with the evaluation of various common chiral bisphosphine ligands (**L1–L7**) in the reaction of (*E*)-oct-1-enyldiphenylphosphine oxide **1a** (readily obtained by hydrophosphinylation of 1-octyne)^[12] with $B_2(\text{pin})_2$ in the presence of catalytic amounts of $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ and LiOtBu at room temperature. Under these conditions, the use of **L1**, which has previously been shown to be effective for the enantioselective boration of cyclic β,β -disubstituted enones,^[10a] led to 74 % conversion with 90:10 e.r. (Table 1, entry 1). Using other bisphosphines with different steric and electronic properties, we found that the conversion and e.r. values were highly dependent on the nature of the ligand. To our delight, the use of (*R,S*)-Josiphos **L4** led to chiral phosphine oxide boronate ester **2a** with excellent conversion and enantioselectivity (96:4 e.r.,

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Table 1: Optimization of the reaction conditions.

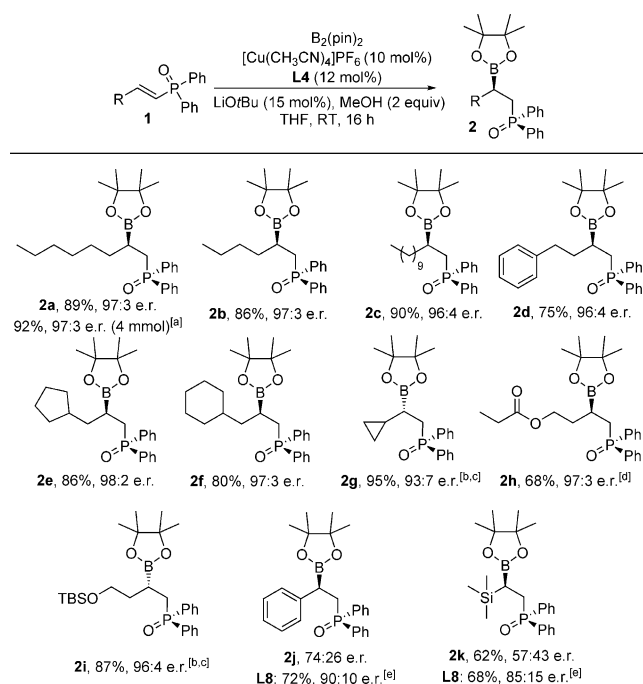
Entry ^[a]	Ligand	Variations in the reaction conditions	Conv. ^[b] [%]	e.r. ^[c]
1	L1	—	74	90:10
2	L2	—	20	50:50
3	L3	—	> 95	66:34
4 ^[d]	L4	—	> 95	96:4
5	L5	—	> 95	66:34
6	L6	—	> 95	72:28
7	L7	—	90	78:22
8 ^[d]	L4	NaOtBu	95	96:4
9	L4	CuBr·SMe ₂	78	68:32
10	L4	in DMSO	> 95	78:22
11	L4	in CH ₂ Cl ₂	5	58:42
12	L4	in toluene	> 95	89:11
13 ^[d]	L4	in dioxane	> 95	92:8
14	L4	[CuL] (10 mol%)	99	96:4
15	L4	[CuL] (10 mol%) and MeOH (2 equiv)	99 (89) ^[e]	97:3 ^[f]

[a] Reaction conditions: **1a** (0.2 mmol), B₂(pin)₂ (0.3 mmol), THF (500 μ L). [b] Determined by ³¹P NMR spectroscopy and GC analysis. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Conversion and e.r. values were poorly reproducible, varying inconsistently from 66 to 97% conversion and 82:18 to 96:4 e.r. [e] Full conversion was reached in 3 h. [f] The absolute configuration was determined to be *R* by X-ray crystallographic analysis.

entry 4). The use of other ferrocenyl-type ligands (entries 2, 3, and 5), BINAP- or BIPHEP-derived ligands (entries 6 and 7) as well as variations in the copper salt, base, or solvents did not improve these results (entries 8–13). Despite the excellent selectivity achieved with **L4**, using 5 mol% of catalyst (entry 4), we observed a lack of reproducibility of both the enantiomeric ratio (varying from 82:18 to 96:4 e.r.) and conversion (from 66 to 97%). However, we could consistently obtain the desired product with excellent selectivity by increasing the catalyst loading (entry 14). Furthermore, in

accordance with previous findings,^[9c,d,10d,k] the addition of two equivalents of MeOH markedly improved the rate of the reaction, providing full conversion in three hours, and the desired product was isolated in 89% yield (entry 15). The absolute configuration of the stereogenic center was determined to be *R* by X-ray crystallographic analysis of compound **2a**.^[13]

We next investigated the substrate scope under the optimized reaction conditions. As shown in Scheme 2, substrates bearing different linear aliphatic substituents provided the desired products in high yields and enantiomeric ratios (compounds **2b** and **2c**). An important feature is that the reaction may also be performed on a larger scale. The reaction of **1a** on a 4.0 mmol scale provided 1.62 g (92% yield) of **2a** with similar enantioselectivity.^[13]



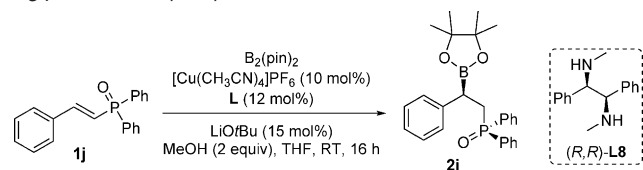
Scheme 2. Catalytic enantioselective boration of β -substituted α,β -unsaturated phosphine oxides. Conditions: **1** (0.2 mmol), B₂(pin)₂ (0.3 mmol), THF (500 μ L). The e.r. ratios were determined by HPLC analysis on a chiral stationary phase. Yields refer to the isolated materials after purification. [a] On a 4 mmol (1.25 g) scale. [b] Reaction time: 48 h. [c] (*S,R*)-Josiphos was used instead. [d] Reaction time: 30 h. [e] In DME. TBS = *tert*-butyldimethylsilyl.

α,β -Unsaturated phosphine oxides with aromatic or saturated carbocycles in the alkyl chain (compounds **2d–2f**) as well as branching at the γ -position (**2g**) also displayed high reactivity and enantioselectivity regardless of the nature of the cyclic structure. Importantly, it was found that the reaction tolerates the presence of ester and silyl ether functional groups, although longer reaction times were needed to reach full conversion (**2h** and **2i**).

A limitation for the Josiphos-based catalytic system is that more sterically demanding electrophiles, such as β -aryl- and trimethylsilyl-substituted substrates, suffered from lower reactivity and diminished selectivity as seen for compounds

2j (74:26 e.r.) and **2k** (57:43 e.r.). To solve this problem, we examined various chiral phosphine ligands but the enantioselectivity remained unsatisfactory (Table 2, entries 1 and 2 and results not shown). When exploring other chiral ligands,

Table 2: Optimization of the reaction conditions for sterically demanding β -substituted phosphine oxides.



Entry ^[a]	Ligand	Variations in the reaction conditions	Conv. ^[b] [%]	e.r. ^[c]
1	L4	—	85	74:26
2	L1	—	15	76:24
3	L8	—	ca. 80	81:19
4	L8	in DME	ca. 80	90:10
5	L8	substrate 1a	ca. 80	91:9

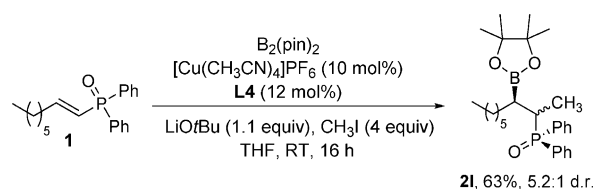
[a] Conditions: **1a** (0.2 mmol), $B_2(\text{pin})_2$ (0.3 mmol), THF (500 μL).

[b] Determined by ^{31}P NMR spectroscopy and GC analysis. [c] Determined by HPLC analysis on a chiral stationary phase.

we found that the use of **L8**, which contains a 1,2-diphenylethylenediamine scaffold, enhanced the enantioselectivity (entry 3). Solvent effects were also examined, and the use of 1,2-dimethoxyethane (DME), which has been shown to be effective for the enantioselective boration of linear β,β -disubstituted enones,^[10b] improved the e.r. to 90:10 without affecting the reactivity. Under these conditions, the more sterically demanding substrate **1k** was converted into β -boryltrimethylsilyl phosphine oxide **2k** in good yield and high selectivity (Scheme 2). The use of ligand **L8** in the boration reaction of phosphine oxide **1a** afforded the desired compound **2a** (entry 5), but with decreased conversion and enantioselectivity in comparison with the use of **L4**.

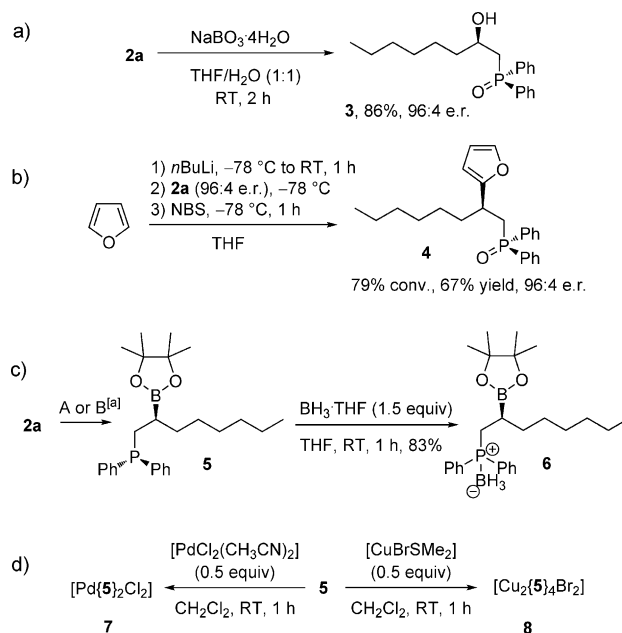
It has been proposed that in the copper(I)-catalyzed boration of α,β -unsaturated acceptors, following the initial conjugate addition of a copper boryl complex, the resulting enolate reacts with MeOH to yield the protonated product and regenerate the catalytically active copper alkoxide.^[9c,d,f-h] Based on this mechanistic proposal, we wondered if the boration reaction in the presence of CH_3I as an electrophile (instead of MeOH) would allow for a catalytic three-component reaction in which a C–B and a C–C bond are created in a single catalytic process.^[14] The use of stoichiometric amounts of base would in this case be required to transform the CuI formed by reaction of the copper ylide with CH_3I into the catalytically active CuOtBu.^[14] To our delight, the use of CH_3I (4 equiv) and LiOtBu (1.1 equiv) at room temperature gave product **2l**, which features a boron and a methyl moiety, in 5.2:1 d.r., along with a minor amount of the hydroborated product **2a** (Scheme 3).

To further demonstrate the synthetic potential of this new method, compound **2a** was used as a platform for the synthesis of various new chiral building blocks that are otherwise difficult to access. Oxidation with sodium perbo-



Scheme 3. Methylboration of α,β -unsaturated phosphine oxide **1**. Conditions: **1a** (0.5 mmol), $B_2(\text{pin})_2$ (0.75 mmol), THF (1.5 mL). Full conversion; **2l/2a** = 71:29 as determined by ^{31}P NMR spectroscopy and GC analysis.

rate^[9d] led to chiral β -hydroxyphosphine oxide **3** in high yield without racemization (Scheme 4a). By exploiting the propensity of organoboronates to undergo stereospecific 1,2-metal-late rearrangements, the chiral secondary boronic ester^[15] in **2a** was subjected to an oxidative $\text{C}(\text{sp}^2)\text{--}\text{C}(\text{sp}^3)$ cross-coupling



Scheme 4. Stereospecific transformations at the boron and phosphorus functional groups. [a] Conditions A: HSiCl_3 , Et_3N , toluene, 90 °C, 16 h, 66% yield; conditions B: bis(4-nitrophenyl) hydrogen phosphate (7.5 mol%), $(\text{EtO})_2\text{MeSiH}$ (4 equiv), toluene, 110 °C, 16 h, 77% conversion, 58% yield.

with furyllithium, under conditions recently described by the group of Aggarwal,^[16] delivering the cross-coupled product **4** with preserved stereochemical integrity (Scheme 4b). It should be noted that this transformation would be difficult to achieve in the corresponding β -boron-substituted carbonyl derivatives owing to the reactivity of a carbonyl group towards organolithium reagents.

Finally, **2a** was reduced to the corresponding chiral phosphine **5** without affecting the boronate group by using either classical conditions ($\text{HSiCl}_3/\text{Et}_3\text{N}$) or with $(\text{EtO})_2\text{MeSiH}$ in the presence of catalytic amounts of a Brønsted acid, as recently described by the group of Beller^[17] (Scheme 4c). A phosphine borane complex was

prepared in 83% yield by treating **5** with one equivalent of $\text{BH}_3\cdot\text{THF}$. Furthermore, the copper and palladium complexes **7** and **8** were also prepared by mixing two equivalents of **5** with the corresponding copper or palladium salts at room temperature (Scheme 4d).^[13]

In conclusion, we have developed the first catalytic asymmetric β -borylation of α,β -unsaturated phosphine oxides that provides ready access to chiral ambiphilic phosphine oxide and phosphine boronates in good yields under mild conditions. Broad structural scope, functional group tolerance, and high enantiomeric excess were obtained using a chiral catalytic system based on copper(I) and **L4** or **L8** at room temperature. Stereospecific transformations to new optically active products and metal complexes demonstrate the synthetic versatility of these compounds. Novel applications and extensions of this process are currently under investigation in our laboratory.

Keywords: asymmetric catalysis · borylation · copper catalysis · phosphine boronates · organophosphorus compounds

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