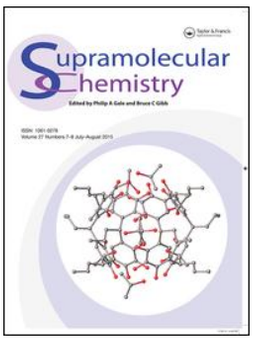

Supramolecular Chemistry

ISSN: 1061-0278 (Print) 1029-0478 (Online) Journal homepage: http://www.tandfonline.com/loi/gsch20

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To cite this article: Hsin Y. Su, Daniel Gorelik & Mark S. Taylor (2019): Chiral phosphine ligand libraries based on the Bull–James three-component supramolecular assembly, Supramolecular Chemistry, DOI: 10.1080/10610278.2018.1564829

To link to this article: https://doi.org/10.1080/10610278.2018.1564829

SUPRAMOLECULAR CHEMISTRY
https://doi.org/10.1080/10610278.2018.1564829

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ARTICLE

Chiral phosphine ligand libraries based on the Bull–James three-component supramolecular assembly

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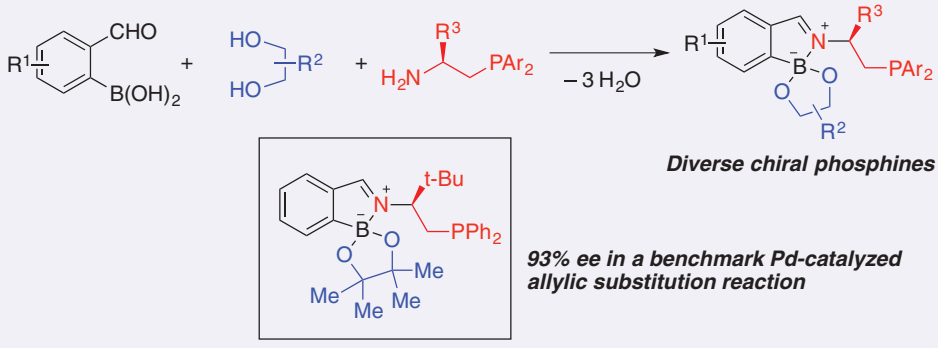
ABSTRACT

An approach to the synthesis of libraries of chiral phosphine ligands is described, using condensations of 2-formylarylboronic acids, diols or related compounds, and aminophosphines. The three-component nature of this condensation, along with the ready availability of the building blocks, enables the rapid generation of diverse structures. From a library of iminoboronate-derived phosphines, three ligands that gave 90% ee or greater in a benchmark palladium-catalyzed allylic substitution reaction were identified. Significant variation of selectivity as a function of the structure of each component was observed. ^{11}B NMR spectroscopy was used to evaluate the existence of B–N interactions in the free ligands as well as their Pd-derived complexes. A bidentate *P,N*-coordination mode was inferred for ligands that gave high enantioselectivity in the allylic substitution reaction.

Abbreviation: BINOL: 1,1'-bi-2-naphthol; BSA: N,O-bis(trimethylsilyl)acetamide; DIOP: (2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane; HPLC: high-performance liquid chromatography; NMR: nuclear magnetic resonance; THF: tetrahydrofuran



Diverse chiral phosphines

93% ee in a benchmark Pd-catalyzed allylic substitution reaction

ARTICLE HISTORY
Received 26 September 2018
Accepted 27 December 2018

KEYWORDS
Boronic acids; combinatorial chemistry; enantioselective catalysis; phosphine ligands

1. Introduction

Methods that enable the rapid discovery of new chiral ligand structures have an important role to play in the discovery and optimization of enantioselective, transition metal-catalyzed reactions. Modular ligands that can be assembled by high-yielding coupling reactions of readily available, chiral components such as diols or amino acids have been useful in this regard (1–5). More recently, an alternative approach that relies on supramolecular chemistry and self-assembly has emerged: ligands are constructed by simple mixing of two or more building blocks that interact through non-covalent or reversible covalent interactions. A range of supramolecular interactions – including metal-ligand coordination (6–9), hydrogen bonding (10–14), ion-pairing (15, 16) and the formation of interlocked structures (17) – have been employed to build new chiral phosphorus-centered ligands (18–20).

Reversible covalent interactions of boronic acids have been applied extensively in chemical sensing and molecular recognition (21, 22). Their advantages include favourable thermodynamics (which can be varied substantially by changing the structure of the boronic acid and diol or related partner), equilibration under relatively mild conditions, and compatibility with a range of functional groups and reaction media. As part of a research program aimed at developing new applications of such interactions in catalysis

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Supplemental data for this article can be accessed here.

(23), we considered whether condensations of boronic acids could be employed as the basis for self-assembly of libraries of phosphine ligands. Precedent for this idea dates back to 1993, when the groups of Kagan (24) and Jacobsen (25) reported the synthesis, complexation behaviour and catalytic applications of boronic ester-bearing analogs of the chiral bis(phosphine) DIOP (**1**, Figure 1). More recently, the group of Gudat has explored the assembly of bis(phosphines) through complexation of main group Lewis acids to catechol-bearing phosphine subunits (26, 27). Condensation with boric acid was employed to generate a zwitterionic Ag(I) complex (**2**, Figure 1). Self-assembly of chiral organocatalysts through boronic ester formation has also been studied. In these systems, the boronic ester group is often proposed to play a functional role, either by direct complexation to the substrate or by intramolecular coordination to a catalyst-derived functional group such as a Brønsted acid moiety (28–31).

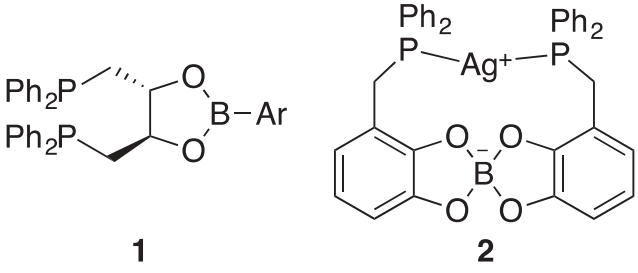


Figure 1. Previously reported examples of boronic ester-containing phosphine derivatives.

The design concept for the self-assembled chiral phosphine ligands explored in this study is based on the Bull–James three-component condensation of formylphenylboronic acids, diols and primary amines (32, 33). This process, in which the three components are linked by Schiff base and boronic ester formation (Figure 2), has been employed in the development of NMR- and fluorescence-based methods for determination of enantiomeric excess (34–37), and in the self-assembly of complex architectures such as macrocycles and cages (38, 39). Applications in asymmetric synthesis or catalysis are less well explored, with the use of a chiral iminoboronate as a chiral auxiliary for an enantioselective azide-alkyne cycloaddition being a notable recent example (40). Several features of the Bull–James assembly appeared to offer unique advantages in the context of using self-assembly to generate libraries of chiral phosphines. Firstly, it is a relatively rare example of a supramolecular interaction that engages three different components: the ability to efficiently generate condensation product from an equimolar mixture of the three components stems, at least to some extent, from the positive cooperativity between imine and boronic ester formation (41). The three-component nature of the assembly offers the prospect of particularly rapid generation of structural variants, as demonstrated by the utility

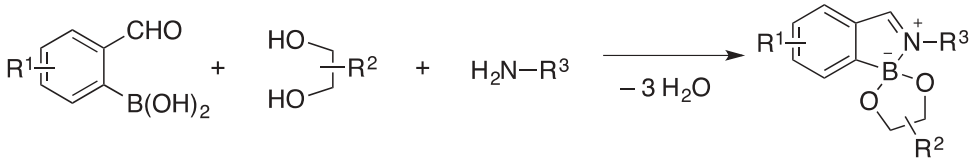


Figure 2. The Bull–James three-component condensation.

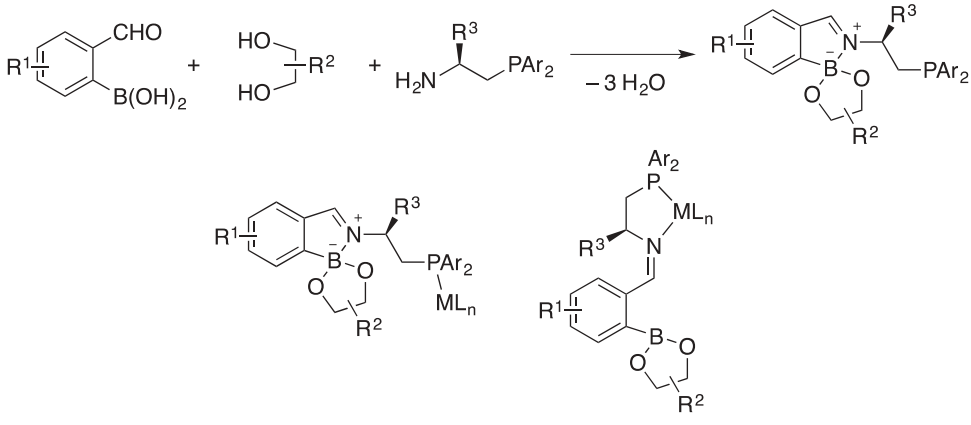


Figure 3. Design for a library of chiral phosphines based on the Bull-James assembly. Potential coordination modes to a metal ML_n are shown below the reaction.

of multicomponent reactions in diversity-oriented synthesis (42). Secondly, it is clear that the Bull-James assembly is well suited to applications of chiral components, as demonstrated by the numerous reported applications involving enantioenriched amines and/or diols. Thirdly, and related to this previous point, chiral phosphines having free diol (24–26) or primary amine groups (43) are readily accessible building blocks that could be employed in such an application.

The assembly process employed to construct libraries of chiral phosphine ligands in this study is shown in Figure 3. It combines a chiral aminophosphine, a formylarylboronic acid derivative, and a (chiral) diol or related compound capable of two-point covalent interaction with a boronic acid. Both monodentate and bidentate (*P,N*-) coordination modes – the latter being possible only at the expense of the B–N interaction – can be envisioned for this type of ligand framework. We show that this three-component condensation can be employed to generate a library of 100 chiral phosphine ligands, differing both in structure and in enantioselectivity for a representative palladium-catalyzed allylic substitution reaction. With the optimal combination of aminophosphine, diol and formylarylboronic acid, the allylic substitution product can be obtained in greater than 90% enantiomeric excess (ee).

2. Results and discussion

2.1. Iminoboronate ligand building blocks

The components employed in the construction of chiral iminoboronate-based phosphines explored in this study are depicted in Figure 4. Formylarylboronic acids **3a**–**3c**, diols **4a**–**4i'** and β-aminophosphine **5d** were purchased from chemical suppliers. Aminophosphines **5a** (44), **5b** (45) and **5c** (46) were synthesized according to previously reported protocols.

2.2. Ligand assembly by three-component condensation, and preliminary evaluation in an enantioselective allylic substitution reaction

The assembly protocol developed for the determination of enantiopurity of diols or amines by ^{1}H NMR spectroscopy (22) was adapted for condensation of **3a, 4b** and **5a**. A solution of equimolar quantities of the three components in degassed chloroform was heated to 50°C and stirred for 30 minutes (Figure 5). The assembly reaction proceeded to completion, as judged by the disappearance of the signal in the ^{1}H NMR spectrum corresponding to the formyl hydrogen of **3a** (9.93 ppm in $CDCl_3$) and the appearance of a new signal corresponding to the imine hydrogen of **6aba** (8.31 ppm). (The letters in the notation **6aba**

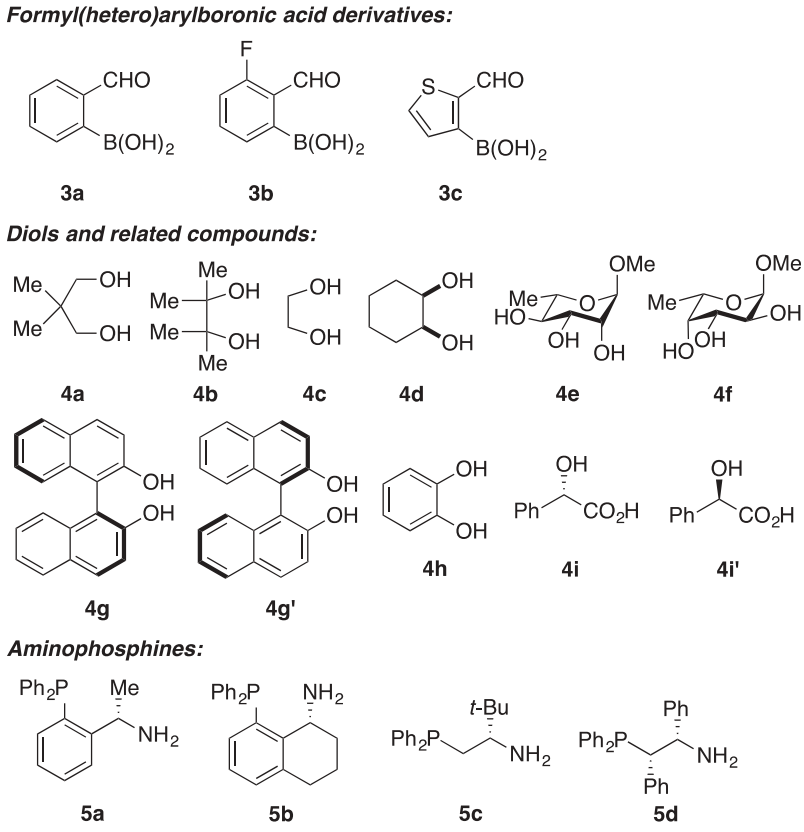


Figure 4. Components of chiral iminoboronate-based phosphine library.

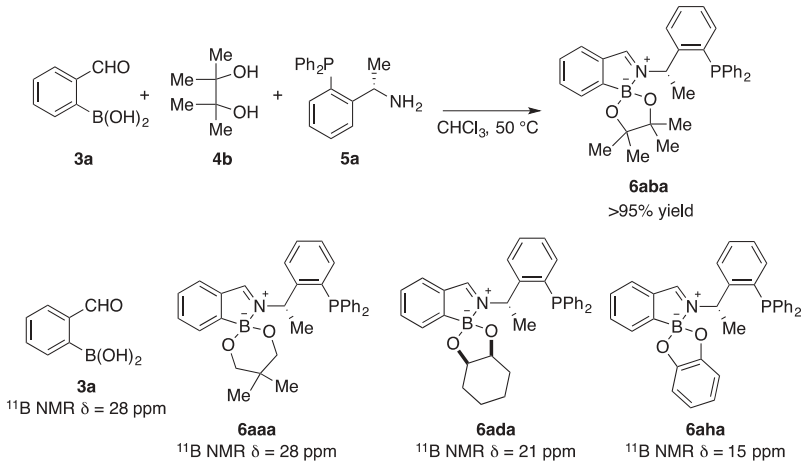
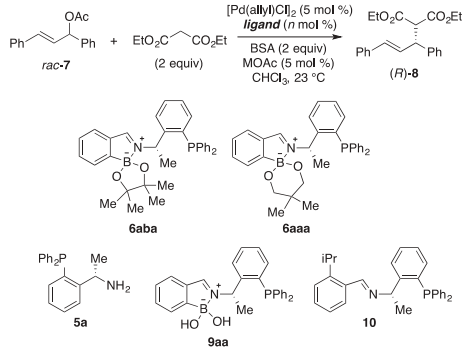


Figure 5. Protocol for ligand assembly by three-component condensation. ^{11}B NMR chemical shifts of **3a, 6aaa, 6ada** and **6aha** are reported ($CDCl_3$ solvent, with BF_3•OEt_2 (δ = 0 ppm), as an external reference standard).

correspond to those of the individual components **3a, 4b** and **5a** from which it was constructed.) The condensation took place more rapidly in the presence of molecular sieves (data not shown), but it was more convenient to omit this component when carrying out multiple, small-scale ligand preparations in parallel. ^{11}B NMR spectroscopy was used to assess the coordination mode of the boron center in constructs **6aaa, 6ada** and **6aha**. The ^{11}B NMR chemical shifts for **6ada** and **6aha** (21 ppm and 15 ppm, respectively, relative to BF_3•OEt_2 (δ = 0 ppm)) were in keeping with reported data for uncharged, tetracoordinate boronic esters having a B–N interaction (41, 47, 48). The lower chemical shift of **6aha** is consistent with a stronger B–N interaction due to the increased Lewis acidity of the boron center upon coordination to catechol (38, 47). In contrast, the ^{11}B NMR chemical shift of neopentyl glycol-derived **6aaa** (28 ppm) was identical to that of formylphenylboronic acid **3a**, suggesting that a B–N interaction was absent in this case. It should be noted that the structures of all iminoboronates **6** were drawn in a consistent format (having a B–N bond), even in cases such as **6aaa** where the ^{11}B NMR chemical shift was not consistent with such an interaction being present.

The utility of the iminoboronate ligand design in a benchmark enantioselective transformation was assessed using the palladium-catalyzed allylic substitution of substrate **7** with diethyl malonate (Table 1) (49). Under standard conditions for this type of transformation ([Pd(allyl)Cl]$_2$

Table 1. Evaluation of chiral iminoboronates as ligands for enantioselective, palladium-catalyzed allylic alkylation.[a]



Entry	Ligand (mol %)	MOAc	Conversion (%)[b]	ee (%)[b]
1	**6aba** (20)	KOAc	>97	88
2	**6aba** (20)	NaOAc	86	83
3	**5a** (20)	KOAc	>97	67
4	**9aa** (20)	KOAc	51	65
5	**10** (20)	KOAc	66	61
6	**6aaa** (20)	KOAc	>97	91
7	**6aaa** (10)	KOAc	>97	83

[a]BSA denotes *N,O*-bis(trimethylsilyl)acetamide.
[b]Conversion and ee were determined by HPLC analysis using a chiral stationary phase.

pre-catalyst, *N,O*-bis(trimethylsilyl)acetamide (BSA), potassium acetate, chloroform, 23°C) (50, 51), ligand **6aba** led to the formation of product (*R*)-**8** in 88% enantiomeric excess (ee) (>97% conversion of **7**, as judged by high-performance liquid chromatography (HPLC) analysis prior to purification: entry 1). The ligand employed in this experiment was generated by assembly of the three components in $CHCl_3$ at 50° C for 30 minutes as described above, followed by removal of the solvent *in vacuo*. The reagents needed for the Pd-catalyzed allylic substitution were added to the resulting material without further purification of the iminoboronate ligand. A similar protocol was followed for all evaluations of the iminoboronate ligands described below. Under preparative conditions on 0.25 mmol scale, product (*R*)-**8** was isolated in 94% yield and 90% enantiomeric excess. Using NaOAc in place of KOAc led to diminished conversion and enantioselectivity (entry 2). To assess whether the Bull–James assembly remained intact under the conditions of palladium-catalyzed allylic substitution, aminophosphine component **5a** was evaluated as a chiral ligand for the reaction (entry 3). The enantiomeric excess of **8** was significantly lower than that obtained using the ligand construct **6aba**. The iminoboronic acid ligand **9aa** obtained in the absence of a diol component gave rise to lower catalytic activity and enantioselectivity than **6aba** (entry 4). The same was true of iminophosphine **10** lacking a boronic acid group (entry 5). Taken together, these control experiments indicated that the three-component iminoboronate assembly was indeed responsible for enantioselectivity under the conditions of Table 1, entry 1. Furthermore, the observation of lower enantioselectivity and reactivity using iminophosphine **10** suggests that the boronate group does not simply act as a sterically hindered substituent. The effect of ligand:Pd ratio was evaluated using construct **6aaa** (entries 6 and 7). The enantioselectivity was appreciably lower using a 1:1 phosphine:Pd ratio rather than the 2:1 ratio employed for the remaining entries in Table 1.

2.3. Effects of variation of diol and aminophosphine component for ligands constructed from 2-formylphenylboronic acid

Prior to generating a full library by variation of all three components of the phosphine-functionalized Bull–James assembly, we sought to determine whether changing the structure of the diol and aminophosphine components would have an appreciable effect on the enantioselectivity of the benchmark reaction. Eight diols were employed in condensations with **3a** and **5a**, and the resulting ligands were tested in the palladium-catalyzed allylic substitution reaction (Figure 6). Iminoboronates having coordinated phenol ligands (BINOL derivatives **6aga, 6aga'** and catechol ester **6aha**) gave lower enantioselectivities than those derived from aliphatic diols. Among the aliphatic diols, those having substituents capable of steric shielding of the boron center upon condensation gave rise to the most enantioselective catalysts (compare **6aaa** and **6aba** to **6aca, 6aea** and **6afa**). The overall trend appears to be that the most selective ligands are derived from diol components that would result in a less Lewis acid boron center, and thus a weaker B–N interaction. This observation may represent indirect evidence for a *P,N*-coordination mode, since chelation to palladium in this way would require the loss of the B–N bond.

To probe the issue of monodentate versus bidentate *P,N*-coordination further, ligands **6aaa** and **6aha** were treated with allylpalladium(II) chloride dimer in $CDCl_3$ and the resulting solutions were analyzed by ^{1}H, ^{11}B and ^{31}P NMR spectroscopy (see the Supplemental Material). In the case of neopentyl glycol-derived ligand **6aaa**, a single major complex having a ^{31}P NMR chemical shift of 16.6 ppm (relative to 85% phosphoric acid in H_2O, $\delta = 0.0$ ppm) was observed. As anticipated, no appreciable change in the ^{11}B NMR chemical shift ($\delta = 28$ ppm, characteristic of a boronic ester without B–N coordination – see Section 2.2 above) was observed upon formation of this complex. These observations suggested a *P,N*-coordination mode for ligand **6aaa**, consistent with the numerous successful applications of this general class of ligands for Pd-catalyzed allylic substitutions (43), and in particular the results obtained using chiral β-iminophosphines (52, 53). For catechol-derived adduct **6aha**, addition of $[Pd(allyl)Cl]_2$ resulted in two predominant signals ($\delta = 20.0$ and 19.4 ppm, 2.4:1 ratio) in the ^{31}P NMR spectrum. The ^{11}B NMR chemical shift ($\delta = 15$ ppm) did not change to an appreciable extent from that of free **6aha**, suggesting that the B–N bond was maintained upon complexation. The ^{1}H NMR spectra were consistent with the conclusion of a *P,N*-coordination mode for **6aaa** but not for **6aha**: the signal corresponding to the azomethine hydrogen of **6aaa** underwent a significant downfield shift upon complexation with Pd(II) ($\delta = 9.52$ ppm for the complex versus 8.32 ppm for the free ligand), whereas a smaller change in the corresponding signal for **6aha** was observed upon complexation.

Returning to the data from Figure 6, an appreciable difference in selectivity between methyl L-rhamnopyranoside-derived ligand **6aea** and methyl L-fucopyranoside-derived **6afa** was observed. At this stage, it is not clear whether this difference reflects a difference in the steric environments of the *cis*-diol groups of **4e** and **4f** (the latter being more hindered due to the *cis* relationship between the 3-OH and 4-methyl groups), or a matching/mismatching effect

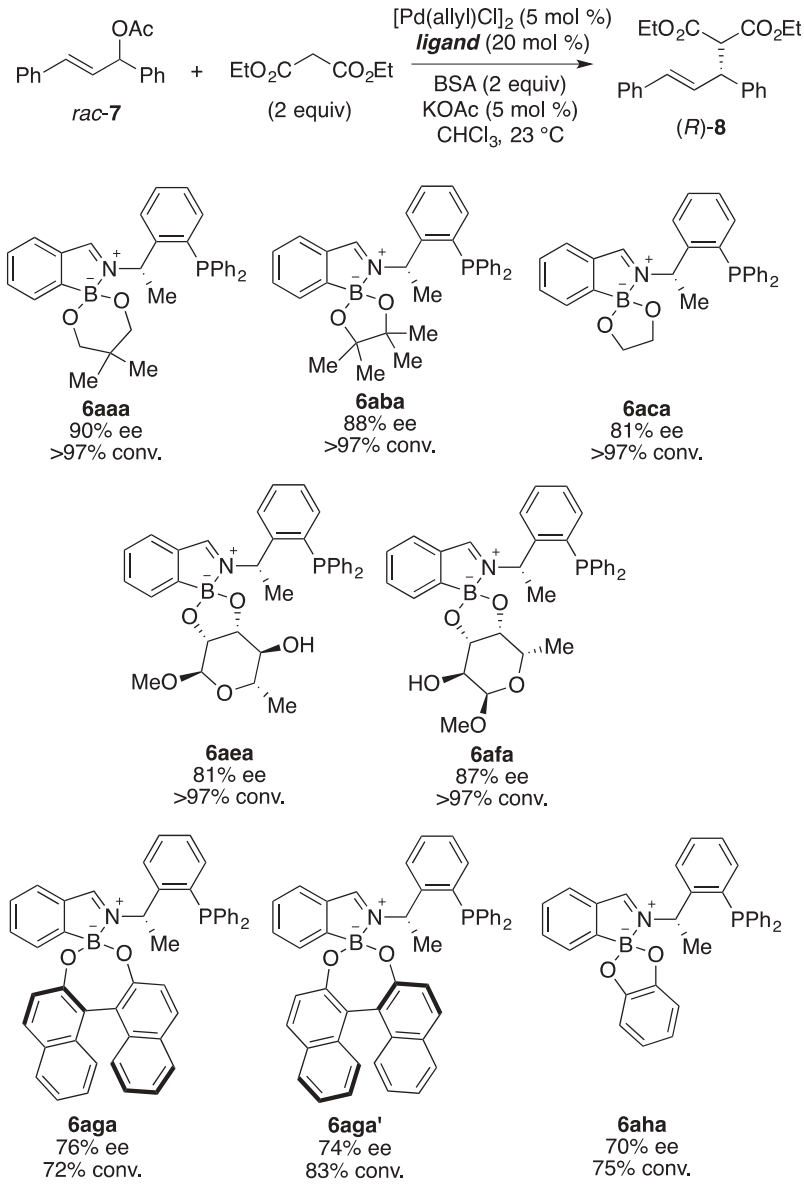


Figure 6. Effect of diol structure on enantioselectivity obtained with ligands derived from arylboronic acid **3a** and aminophosphine **5a**. BSA denotes *N,O*-bis(trimethylsilyl)acetamide. Conversion and ee were determined by HPLC analysis using a chiral stationary phase.

with the chirality of the aminophosphine ligand (the *cis*-diol groups have a pseudo-enantiomeric relationship in **4e** and **4f**). This type of matching/mismatching effect was not evident in the enantioselectivities of ligands **6aga** and **6aga'**, which differ in the configuration of the BINOL component.

In a similar way, a sub-library was constructed by keeping the boronic acid and diol components constant (**3a** and **4a**) while varying the identity of the aminophosphine (Figure 7). Whereas the assemblies derived from benzylic aminophosphine **5a** and *tert*-leucinol-derived **5c** gave high enantioselectivities (with the latter favouring the formation of the *S*-configured product), inferior results were obtained for ligands derived from **5b** and **5d**. For each assembly that gave appreciable enantioselectivity (>10% ee), the enantiomeric excess obtained with the corresponding free aminophosphine is provided for comparison. The results provide strong evidence that the intact iminoboronates are responsible for the enantioselectivities observed using the ligand self-assembly protocol.

2.4. Assembly and evaluation of a library of 100 iminoboronate-based chiral phosphines

Having demonstrated that variations of the structures of the diol and aminophosphine components gave rise to significant changes in the enantioselectivity

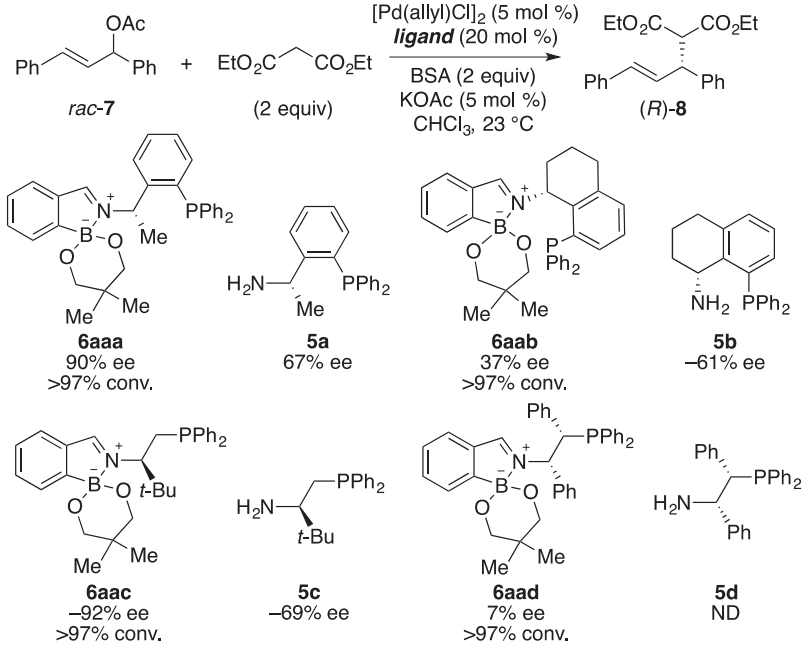


Figure 7. Effect of aminophosphine structure on enantioselectivity obtained with ligands derived from arylboronic acid **3a** and diol **4a**. BSA denotes *N,O*-bis(trimethylsilyl)acetamide. The ee values obtained using aminophosphines **5a**–**5c** as ligands are provided for comparison. Conversion and ee were determined by HPLC analysis using a chiral stationary phase.

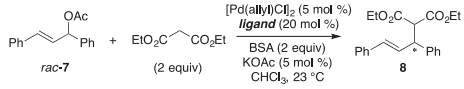
of the test reaction, we undertook the synthesis of a 100-ligand library. Forty ligands derived from 2-formylphenylboronic acid **3a** were generated, using ten OH-containing compounds (**4a**–**4c, 4e**–**4i**) and four aminophosphines (**5a**–**5d**). Because ligands based on **5d** generally showed relatively low levels of enantioselectivity, this component was omitted from the sublibraries generated from boronic acids **3b** and **3c**. Enantioselectivity data for all of the ligands are provided in Table 2, and are summarized in graphical form in Figure 8. Some variations in catalyst activity were also evident across the ligand library: assemblies derived from catechol, BINOL and mandelic acid generally gave rise to lower substrate conversions than those derived from aliphatic alcohols. The data provided in Figure 6 are representative of this effect, and conversions for the 100-ligand library are not included in the Table

Several overall trends can be inferred from Table 2 and Figure 8. Ligands derived from 2-formylphenylboronic acid **3a** were generally more selective than those derived from thiopheneboronic acid **3c** or 3-fluoro-substituted **3b**, with the latter giving particularly poor enantioselectivities (ee < 60% in all cases). Of the aminophosphine components tested, **5a** and **5c** gave rise to higher enantioselectivities than **5b** and **5d**. Interplay between the components is also evident from the data. In particular, the trend of aliphatic, sterically hindered diol components leading to higher enantioselectivities than electron-deficient and/or sterically unhindered ligands for boron is clear in several cases, including for the assemblies derived from **3a** and **5a** or **5c, 3b** and **5a**, and **3c** and **5a**. However, this trend did not hold for the series derived from boronic acid **3c** and aminophosphine **5c**, or from boronic acid **3a** and aminophosphine **5d**. In these cases, ligands derived from catechol and mandelic acid were more selective than those derived from the aliphatic alcohols. Ligands based on aminophosphine **5c** appeared to be more sensitive to variations of the diol component than those derived from **5a**. Overall, of the 100 ligands tested, three gave enantioselectivities of 90% ee or higher, and another ten gave >80% ee. Limits to the scope of application of these newly discovered ligands were encountered upon attempted allylic substitutions of (*E*)-4-phenylbut-3-en-2-ol and cyclohex-2-en-1-ol derivatives, both of which resulted in lower reactivity and enantioselectivity than substrate **7** (data not shown).

2.5. Extension to decarboxylative allylic substitutions: a cautionary tale

With the aim of applying this ligand library design to a more challenging enantioselective transformation, the palladium-catalyzed decarboxylative allylic

Table 2. Enantioselectivity data for evaluation of a library of 100 chiral phosphine ligands in the Pd-catalyzed allylic substitution of *rac*-**7**.[a]



Aminophosphine **5a**		Aminophosphine **5b**		Aminophosphine **5c**		Aminophosphine **5d**	
Ligand	% ee	Ligand	% ee	Ligand	% ee	Ligand	% ee
Ligands derived from boronic acid **3a**							
6aaa	90 (*R*)	**6aab**	37 (*R*)	**6aac**	92 (*S*)	**6aad**	7 (*R*)
6aba	88 (*R*)	**6abb**	60 (*R*)	**6abc**	93 (*S*)	**6abd**	4 (*R*)
6aca	81 (*R*)	**6acb**	14 (*S*)	**6acc**	81 (*S*)	**6acd**	9 (*R*)
6aea	81 (*R*)	**6aeb**	22 (*R*)	**6aec**	83 (*S*)	**6aed**	13 (*R*)
6afa	87 (*R*)	**6afb**	34 (*R*)	**6afc**	88 (*S*)	**6afd**	33 (*R*)
6aga	76 (*R*)	**6agb**	8 (*R*)	**6agc**	83 (*S*)	**6agd**	43 (*R*)
6aga′	74 (*R*)	**6abg′**	14 (*S*)	**6agc′**	51 (*S*)	**6agd′**	23 (*R*)
6aha′	70 (*R*)	**6ahb**	7 (*R*)	**6ahc**	75 (*S*)	**6ahd**	69 (*R*)
6aia	66 (*R*)	**6aib**	13 (*R*)	**6aic**	73 (*S*)	**6aid**	67 (*R*)
6aia′	69 (*R*)	**6aib′**	27 (*R*)	**6aic′**	0	**6aid′**	52 (*R*)
Ligands derived from boronic acid **3b**							
6baa	52 (*R*)	**6ab**	35 (*S*)	**6bac**	4 (*S*)		
6bba	57 (*R*)	**6bbb**	51 (*S*)	**6bbc**	46 (*S*)		
6bca	58 (*R*)	**6bcb**	21 (*S*)	**6bcc**	26 (*S*)		
6bea	51 (*R*)	**6beb**	39 (*S*)	**6bec**	30 (*S*)		
6bfa	65 (*R*)	**6bfb**	45 (*S*)	**6bfc**	29 (*S*)		
6bga	27 (*R*)	**6bgb**	21 (*S*)	**6bgc**	47 (*S*)		
6bga′	23 (*R*)	**6bgb′**	20 (*S*)	**6bgc′**	14 (*S*)		
6bha	21 (*R*)	**6bhb**	11 (*S*)	**6bhc**	52 (*S*)		
6bia	41 (*R*)	**6bib**	2 (*S*)	**6bic**	33 (*S*)		
6bia′	30 (*R*)	**6bib′**	0	**6bic′**	41 (*S*)		
Ligands derived from boronic acid **3c**							
6caa	83 (*R*)	**6cab**	24 (*S*)	**6cac**	72 (*S*)		
6cba	82 (*R*)	**6cbb**	2 (*R*)	**6cbc**	67 (*S*)		
6cca	72 (*R*)	**6ccb**	1 (*S*)	**6ccc**	74 (*S*)		
6cea	61 (*R*)	**6ceb**	36 (*R*)	**6cec**	65 (*S*)		
6cfa	66 (*R*)	**6cfb**	15 (*R*)	**6cfc**	64 (*S*)		
6cga	26 (*R*)	**6cgb**	8 (*S*)	**6cgc**	67 (*S*)		
6cga′	43 (*R*)	**6cgb′**	5 (*S*)	**6cgc′**	75 (*S*)		
6cha	34 (*R*)	**6chb**	13 (*R*)	**6chc**	74 (*S*)		
6cia	36 (*R*)	**6cib**	5 (*R*)	**6cic**	75 (*S*)		
6cia′	38 (*R*)	**6cib′**	3 (*R*)	**6cic′**	77 (*S*)		

[a] BSA denotes *N,O*-bis(trimethylsilyl)acetamide. ee was determined by HPLC analysis using a chiral stationary phase.

alkylation of enol carbonate **11** (54–56) was investigated (Figure 9). The stereochemical issues involved with this transformation are distinct from those of the benchmark allylic substitution described above, and relatively few chiral ligands capable of delivering product **12** in high enantiomeric excess – either by decarboxylative allylic alkylation or by direct allylation of the β-ketoester – have been identified (57–59). In light of previous work by Stoltz and co-workers showing that phosphinooxazolines bearing electron-deficient aryl groups at phosphorus provided highest selectivity in such decarboxylative allylic alkylations of enol carbonates (58, 59), we evaluated ligand **13**. The requisite bis(trifluoromethyl)phenyl-substituted β-aminophosphine **5e** was synthesized according to a protocol developed in our laboratory (60). While not synthetically useful, the 48% ee obtained with ligand **13** was somewhat encouraging, given that an extensive screen of ligands and conditions was needed before a catalyst system that gave product **12** in 70% ee was identified (58). However, repeating this reaction using aminophosphine component **5e** gave an identical result to that obtained using the ligand assembly, suggesting that cleavage of the Bull–James assembly took place under the conditions of catalysis, and that the aminophosphine component was the active ligand. At this stage, it is not clear whether a difference in the reaction conditions or the relative activities of the iminophosphine versus aminophosphine-based complexes was responsible for this unsuccessful application. In any case, the construction of a library of electron-deficient phosphine iminoboronates for decarboxylative allylic alkylation of **11** was not pursued further in light of this result.

Another observation highlighting the potential for disassembly of the iminoboronates under conditions relevant to transition metal catalysis emerged from our

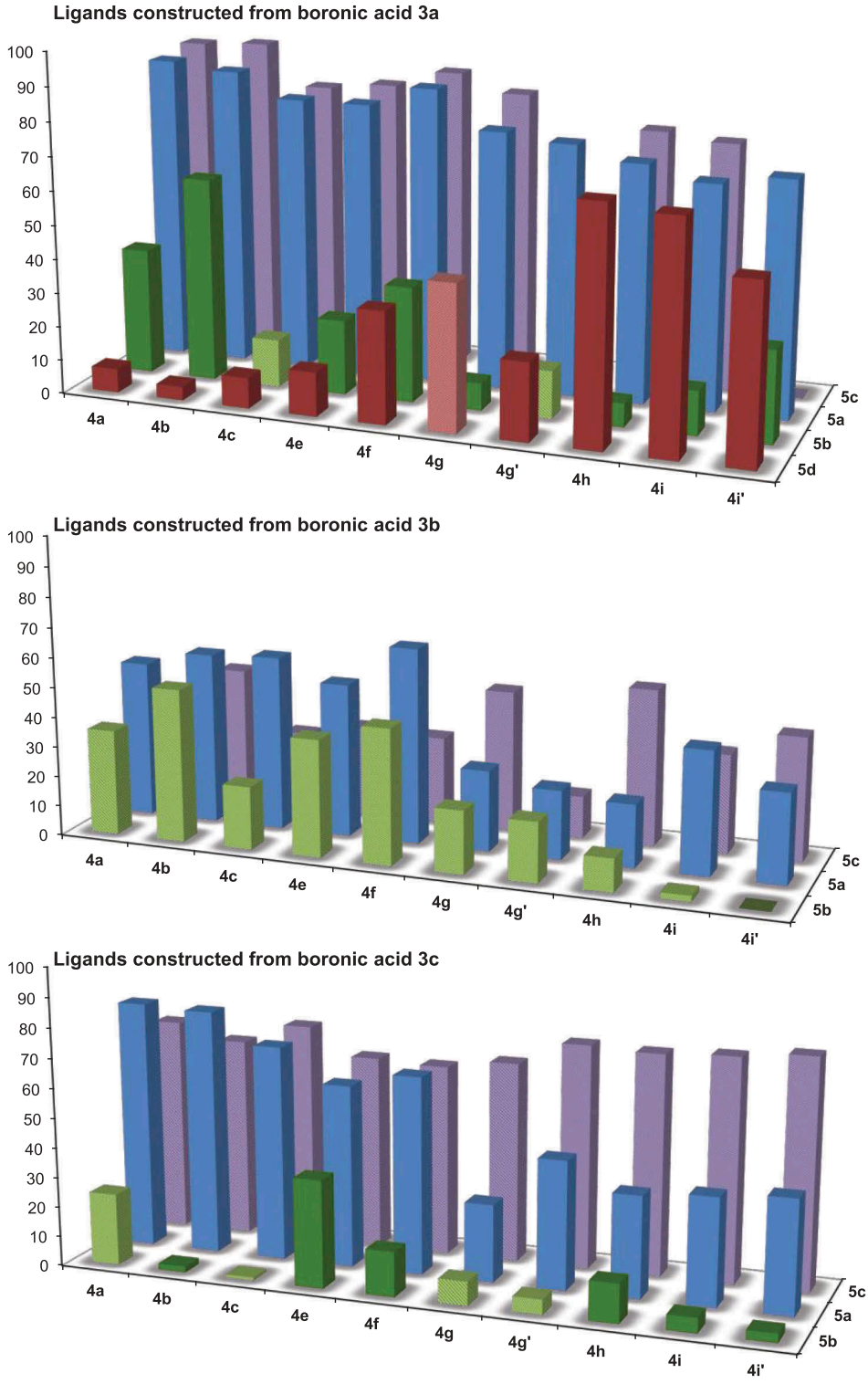


Figure 8. (colour online) Graphs of enantioselectivity data for the library of iminoboronate-based chiral phosphines. The lighter shading of the bars is used to denote congeners that gave (*S*)-**8** as the major enantiomer in the allylic substitution reaction.

attempts to generate and structurally characterize a nickel(II) complex (2, 61) of ligand **13** (Figure 10). After treatment with nickel(II) tetrafluoroborate hexahydrate in ethanol, a crystal suitable for X-ray diffraction analysis was obtained by slow diffusion of diethyl ether into a solution of the complex in acetonitrile. The crystalline material was found to be the 2:1 complex of free aminophosphine **5e** and nickel(II), indicating that ligand disassembly occurred under the conditions of complexation. In an attempt to reduce the likelihood of solvolysis

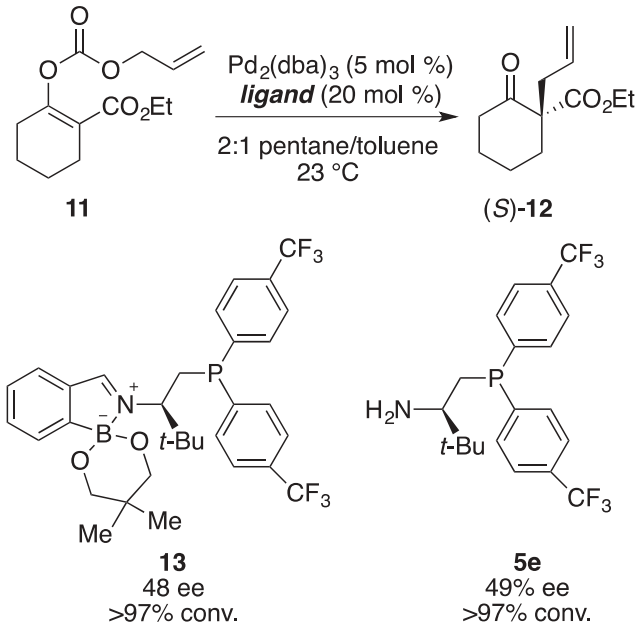


Figure 9. Enantioselective, decarboxylative allylic alkylation of enol carbonate **11** using assembly **13** and component **5e**. Conversion and ee were determined by HPLC analysis using a chiral stationary phase.

of the iminoboronate, the complexation experiment was repeated using acetonitrile as the solvent. Under these conditions, an iminophosphine oxide resulting from protodeboronation of **13** was obtained (results not depicted). In any case, both the complexation experiment as well as the results depicted in Figure 9 indicate that disassembly of the phosphine-bearing iminoboronates can occur in the presence of certain metal complexes or under particular reaction conditions. The relative activities of the complexes generated from the aminophosphine and iminophosphine ligands will also be important in catalytic applications. These results highlight the importance of control experiments to assess the activity and selectivity of complexes generated from the free aminophosphine when using self-assembled ligands of the type described here.

3. Conclusion

In conclusion, we have shown that the use of aminophosphines as components in the Bull–James supramolecular assembly permits the rapid construction of chiral phosphine ligands. This three-component condensation offers several unique advantages for such applications, including the ability to rapidly generate structural diversity, the ready availability of each of the three components, and the relatively high stability of the obtained assemblies. The structure of each of the three components was found to have a significant influence of the enantiomeric excess obtained using the resulting ligands in a palladium-catalyzed allylic substitution reaction. This approach was used to synthesize a library of 100 chiral phosphine ligands that ranged in performance from <10% to >90% ee in the benchmark reaction. Although some general trends could be inferred – for example, assemblies derived from aliphatic diols gave higher enantioselectivities than those derived from phenols or hydroxy acids – the data also revealed examples of 'interplay' between the components that might not have been evident from a conventional ligand optimization process. Control experiments showed that the iminoboronate assemblies, and not the free aminophosphines, were responsible for the observed enantioselectivities. However, an attempted extension to palladium-catalyzed decarboxylative allylic alkylation illustrated the potential for disassembly of the constructs under catalytically relevant conditions. Further opportunities exist to apply this approach to the synthesis of chiral ligands or organocatalysts.

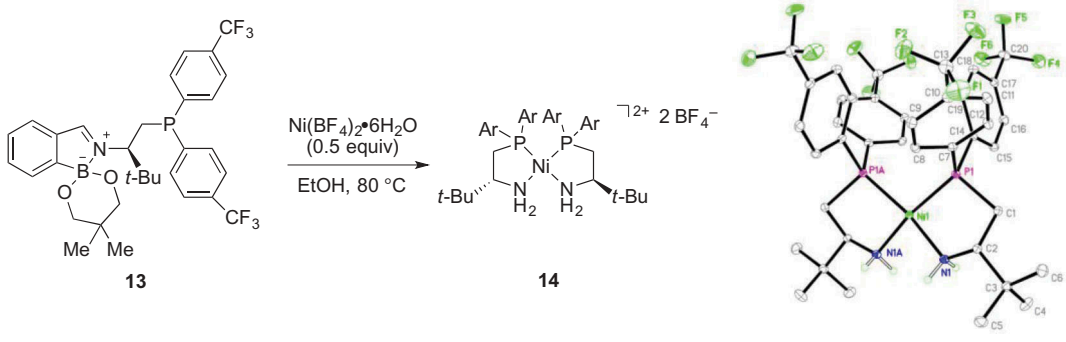


Figure 10. (colour online) Attempted preparation of a Ni(II) complex of ligand **13**. The structure of **14** determined by single crystal X-ray diffraction analysis, with displacement ellipsoids drawn at the 30% probability level, is depicted on the right (tetrafluoroborate counterions omitted for clarity).

3.1. Experimental section

Unless otherwise stated, all reactions and purifications were carried out under argon atmosphere using Schlenk, vacuum line, or glovebox techniques in dry, oxygen-free solvents. Flash column chromatography was carried out using 35–75 μm particle size silica gel. Tetrahydrofuran (THF), diethyl ether, dichloromethane, toluene and hexanes were dried using a solvent purification system and degassed through three freeze-pump-thaw cycles. Deuterated solvents were degassed through three freeze-pump-thaw cycles. All commercially available reagents and chemicals were used as received without purification unless noted otherwise. Allylic acetate *rac*-**7** (62), enol carbonate **11** (63) and aminophosphines **5a** (44), **5b** (45), **5c** (46), and **5e** (60) were synthesized according to published protocols.

A 400 MHz spectrometer was employed for recording ^{1}H (400 MHz), ^{11}B (128 MHz) and ^{31}P (162 MHz) NMR spectra at ambient temperature. ^{1}H chemical shifts are reported in ppm relative to tetramethylsilane, and were measured by referencing the spectra to residual protium in the solvent. ^{11}B NMR spectra were referenced to BF_3•OEt_2 (δ = 0 ppm), and ^{31}P NMR spectra were referenced to 85% H_3PO_4 in H_2O (δ = 0 ppm).

3.1.1. General procedure for assembly of ligands and evaluation in the allylic substitution of rac-7

A 0.5-dram vial equipped with a magnetic stirring bar was charged with stock solutions of 2-formylphenylboronic acid (0.10 M, 200 μL, 0.02 mmol), pinacol (0.10 M, 200 μL, 0.02 mmol) and **5c** (0.25 M, 80 μL, 0.02 mmol). The solvents were removed *in vacuo*. $CHCl_3$ (50 μL) was added under a positive pressure of argon. The reaction was stirred at 50°C for 30 min. The volatiles were then removed under high vacuum. $[Pd(allyl)Cl]_2$ (0.13 M in $CHCl_3$, 40 μL, 5.0 μmol) was added under a positive pressure of argon and the reaction stirred at 23°C for 15 min. Allyl acetate *rac*-**7** (0.01 M in $CHCl_3$, 10 μL, 0.10 mmol), bis(trimethylsilyl) acetamide (49 μL, 0.20 mmol), diethyl malonate (30 μL, 0.20 mmol) and potassium acetate (0.50 mg, 5.0 μmol) were added sequentially. The reaction was stirred at 23°C for 24 hours. The crude reaction mixture was then filtered through a short plug of Celite and rinsed three times with CH_2Cl_2. An aliquot of the reaction mixture (5.0 μL) was used for conversion and ee analyses using HPLC. **HPLC conditions:** Chiralpak IA column, 2.0% isopropanol/hexanes, 0.5 mL/min, 254 nm, t_r: 22.9 and 29.2 min.

3.1.2. Diethyl (R)-2-(1,3-diphenylallyl)malonate ((R)-8)

The protocol described above was carried out on 0.25 mmol scale of *rac*-**7**, using ligand **6aba**. Purification by flash chromatography on silica gel (4% EtOAc/hexanes) gave the product as a colorless oil in 94% yield and 90% ee. Characterization data were consistent with reported values (64). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.31–7.12 (m, 10H), 6.44 (d, *J* = 15.7 Hz, 1H), 6.30 (dd, *J* = 15.7, 8.5 Hz, 1H), 4.23 (ddd, *J* = 11.0, 8.5, 0.8 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.97–3.90 (m, 2H), 3.88 (d, *J* = 11.0 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 168.0, 167.5, 140.4, 137.0, 131.8, 129.5, 128.8, 128.6, 128.1, 127.6, 127.2, 126.5, 61.7, 61.5, 57.9, 49.4, 14.3, 13.9. **Optical rotation:** $[\alpha]_D$ = +10.7 (*c* = 0.13 g/mL, $CHCl_3$).

3.1.3. Procedure for decarboxylative allylic alkylation of 11

A 0.5-dram vial equipped with a magnetic stirring bar was charged with stock solutions of 2-formylphenylboronic acid (0.10 M, 200 μL, 0.02 mmol), pinacol (0.10 M, 200 μL, 0.02 mmol) and **5e** (0.25 M, 80 μL, 0.02 mmol). The solvents were removed *in vacuo*. $CHCl_3$ (50 μL) was added under a positive pressure of argon. The reaction was stirred at 50°C for 30 min. The volatiles were then removed under high vacuum. $Pd_2(dba)_3$ (4.6 mg, 5.0 μmol) was added in a nitrogen-filled glovebox. 2:1 Pentane/toluene (50 μL) was added, and the reaction stirred at 23°C for 30 min. Allylic carbonate **11** (25.0 mg, 0.1 mmol) was added under a positive pressure of argon. The reaction was stirred at 23°C for 24 hours. The crude reaction mixture was then filtered through a short plug of Celite and rinsed three times with CH_2Cl_2. An aliquot of the reaction mixture (5.0 μL) was used for conversion and ee analyses using HPLC. **HPLC conditions**: Chiralpak IA, AD-H and IB (three columns in series), 0.5% isopropanol/hexanes, 210 nm, 0.5 mL/min, t_r: 38.7 and 40.6 min.

(*S*)-**12**: Purification by flash chromatography on silica gel (5% Et_2O/hexanes) gave the product in 48% ee as a colorless oil. Characterization data were consistent with reported values (57). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.83–5.65 (m, 1H), 5.11–4.98 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.60 (ddt, *J* = 14.0, 7.0, 1.2 Hz, 1H), 2.55–2.40 (m, 3H), 2.33 (ddt, *J* = 13.9, 7.8, 1.1 Hz, 1H), 2.08–1.93 (m, 1H), 1.82–1.57 (m, 3H), 1.45 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 207.6, 171.5, 133.3, 118.3, 61.2, 60.9, 41.1, 39.3, 35.8, 27.5, 22.5, 14.2. **Optical rotation**: $[\alpha]_D$ = – 75.1 (*c* = 0.20 g/mL, $CHCl_3$).

3.1.4. Synthesis and recrystallization of complex 14

A 2-dram vial equipped with a magnetic stirring bar was charged with 2-formylphenylboronic acid (30.0 mg, 0.2 mmol), **5e** (84.0 mg, 0.2 mmol) and neopentyl glycol (21.0 mg, 0.2 mmol). $CHCl_3$ (50 μL) was added under a positive pressure of argon. The reaction was stirred at 50°C for 30 min. The volatiles were then removed under

high vacuum. $Ni(BF_4)_2$•$6H_2O$ (34.0 mg, 0.1 mmol) was added in a nitrogen-filled glovebox. EtOH (2.5 mL) was added under an inert atmosphere. The reaction was sealed and stirred at 80°C for 30 min. The volatiles were removed under high vacuum. A crystal suitable for X-ray diffractometry (m.p. 143–147°C) was obtained by diffusion of diethyl ether vapor into a solution of **14** in acetonitrile.

Single-crystal X-ray diffraction data were collected at 147 K with a Bruker Apex-II CCD diffractometer with Mo-Kα radiation (λ = 0.71073 Å). The structure was solved and refined using SHELXL2013 (65). Refinement was by full-matrix least-squares on F^2 using all data. The structure has been deposited to the Cambridge Crystallographic Database (CCDC 1869791).

Acknowledgments

Dr. Alan J. Lough (University of Toronto) is gratefully acknowledged for carrying out the single crystal X-ray diffraction experiment and solving the structure of **14**.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

Acknowledgment is made to the donors of the American Chemical Society Petroleum Research Fund for partial support of this research. Funding was also provided by NSERC (Discovery Grants and Canada Research Chairs Programs) and the Canada Foundation for Innovation (Project nos. 17545 and 19119).

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