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Asymmetric Catalysis

Phospholane-Phosphite Ligands for Rh Catalyzed Enantioselective Conjugate Addition: Unusually Reactive Catalysts for Challenging Couplings

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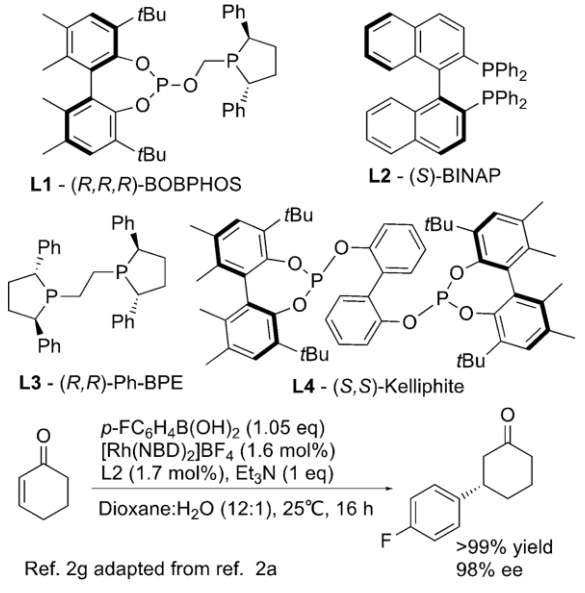
Abstract: The use of Rh catalysts derived from a phospholane-phosphite ligand were found to be more productive than the classic rhodium/BINAP system in enantioselective conjugate additions. These catalysts enable the use of lower amounts of aryl boronic acid in an asymmetric arylation reaction that required an impractical excess of nucleophile. This catalyst was also found to enable the coupling of a poorly reactive Michael acceptor, *N*-CBz-2-3-dehydro-4-piperidone, or the coupling of poorly reactive 2-furyl boronic acids at ambient or near temperatures.

Introduction

The last two decades have seen great advances in enantioselective conjugate additions of aryl (or alkenyl) boronic acids. These reactions have received significant attention, and are a useful tool for the asymmetric synthesis of quite a wide variety of target molecules.[1] There are also quite a range of different catalysts that have been developed and shown to be effective from the perspective of promoting highly enantioselective coupling reactions (Scheme 1). Rh/BINAP catalysts are especially widely used catalysts since they deliver high *ee* for quite a range of couplings, and because the BINAP ligand is commercially available.[2] The protocols using the Rh/BINAP system have been improved and modified to improve reactivity,[2f,2g] with the protocols used as control reactions in this work being based on reference 2g. Since this is now quite an important catalytic reaction, there are many other catalysts that have been designed and tested.[1b] Fluorinated BINAP analogues have been shown to allow lower catalyst loadings to be used than the Rh/BINAP system, and more practical conditions for one substrate studied here.[3] Non-C_2-symmetric Phosphine-alkene ligands,[5] phosphine-amide ligands,[6] phosphine-sulfoxide[7] and phosphine-NHC ligands[8] have all been examined in Rh catalyzed conjugate additions of important but generally unproblematic substrates and also for novel target synthesis.[1c] The diversity of ligands studied in these reactions is large, but no phosphine-phosphite ligands seem to have been studied in this reaction thus far.[4] We felt it would be of interest to know how this type of ligand fared in Rh catalyzed conjugate additions, since we were encouraged by the successful examples using bidentate ligands with electronic asymmetry in references 5–8.



Scheme 1. Ligands used in this study, and a typical modified protocol using Rh/BINAP catalysts.

We were aware of some problematic examples of Rh catalyzed conjugate addition, and felt attempting these with a new catalyst would be a good test for any genuine advance. For example, in the course of developing an assisted tandem catalysis protocol involving an asymmetric Rh catalyzed conjugate addition,[9] we became aware that certain combinations of aryl boronic acids and Michael acceptors did not deliver acceptable

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product yields. There were additional cases that required impractical amounts of boronic acid (e.g. > 4 equivalents) in order to deal with the issue of competing proto-deborylation.[3b,10] In this paper we show how the commercially available phospholane-phosphite, **L1**, known as BOBPHOS,[11] gives enhanced reactivity relative to the use of BINAP as the ligand and enabled the preparation of some of the compounds that couldn't be easily be made following standard Rh/BINAP promoted protocols.

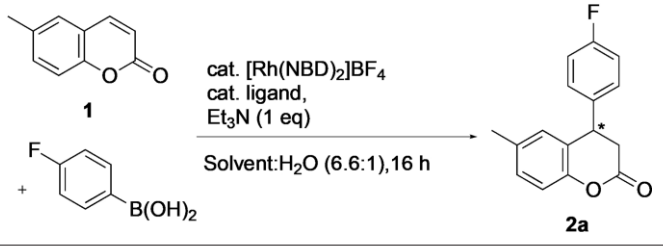
Results and Discussion

The reaction of *para*-fluorophenylboronic acid with 6-methyl coumarin was used as an assay for catalyst performance. The literature describes successful coupling of this Michael acceptor using an Rh/Segphos catalyst.[10a] Catalyst loadings of 3 mol-% and 10 equivalents of boronic acid were required for high yields. In this case, there was a subsequent publication describing a bespoke fluorinated ligand that makes this reaction more practical with lowered amounts of aryl boronic acid.[3c] However, this seemed a good model example of a challenging coupling, and was amenable to measuring conversion and protodeboration using $^{19}F\{^1H\}$ NMR spectroscopy.

The results described in Table 1 compare catalysts derived from phospholane-phosphite, **L1** with other relevant ligands. As expected, the use of just 3 equivalents of aryl boronic acid delivers almost no product for the Rh/BINAP catalyst (Table 1, Entry 2). Pleasingly, changing to phospholane-phosphite, BOBPHOS, (*R*,*R*,*R*)-**L1** as ligand, but keeping the smaller excess of aryl boronic acid led to essentially quantitative conversion to product. BOBPHOS is a hybrid of ligands **L3**[12] and **L4**.[13] However, surprisingly, neither of the ligands from which BOBPHOS is derived show any competence in this reaction, even if you increase the aryl boronic acid loading to ten equivalents. Given the good results previously obtained with electron-deficient fluorinated BINAP analogues, the bis-phospholane might be too electron-donating to be an effective catalyst. Consistent with this, quite a large amount of aryl boronic acid (not fully quantified due to solubility issues) remains in this reaction, in contrast to both successful reactions using Rh/(*R*,*R*,*R*)-**L1** and an unsuccessful reaction using Rh/Kelliphite. It is possible the phosphite hydrolytically degrades or is too sterically hindered to form a good catalyst for this transformation. In any case, despite the parent diphosphite or bis-phospholane being unsuccessful, the results represent a new example where a ligand with two phosphorus donors with quite different steric and electronic environments is beneficial to some part of a catalytic process.

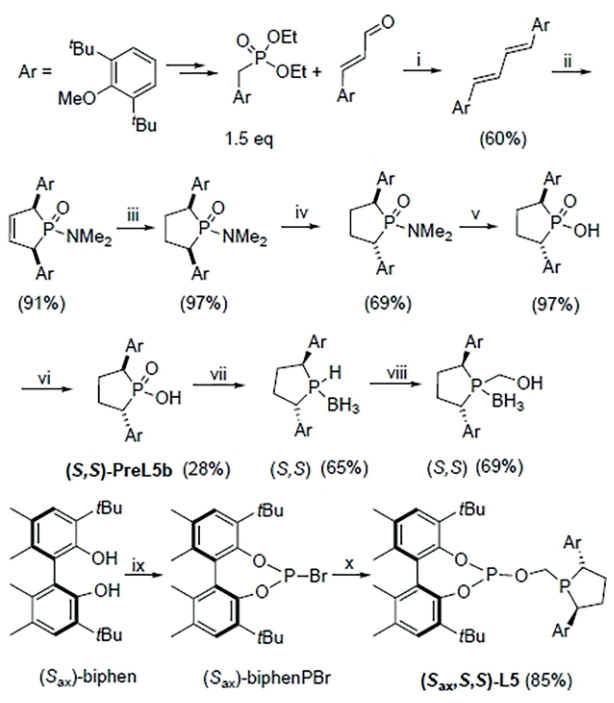
We also report here the synthesis of a new derivative of the BOBPHOS ligand, (*S*,*S*,*S*)-**L5**. This ligand was studied here since we felt it could shed light on how the alkene coordinates in these reactions. Models built using extensive data with previous conjugate addition catalysts strongly suggest that the enantioface selective binding of the alkene leads to the enantioselectivity. Our working hypothesis was that a bulkier phospholane would only significantly alter the enantioselectivity if the alkene was binding *cis* to it. The synthesis of this new ligand proved quite long, resulting in only small batches of ligand being easily available. So far, attempts at more streamlined routes have proven unworkable. The synthesis of the new ligand is shown in Scheme 2. The absolute configuration was determined by X-ray crystal structure determination on the resolved phospholanic acid (also represented in Scheme 2).

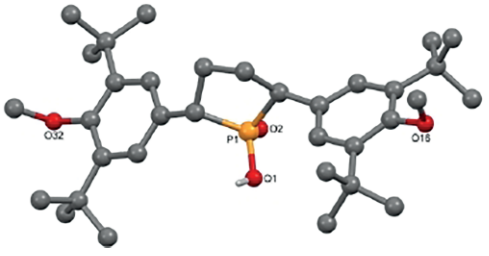
Table 1. Effect of ligand structure on catalyst performance in a challenging conjugate addition.



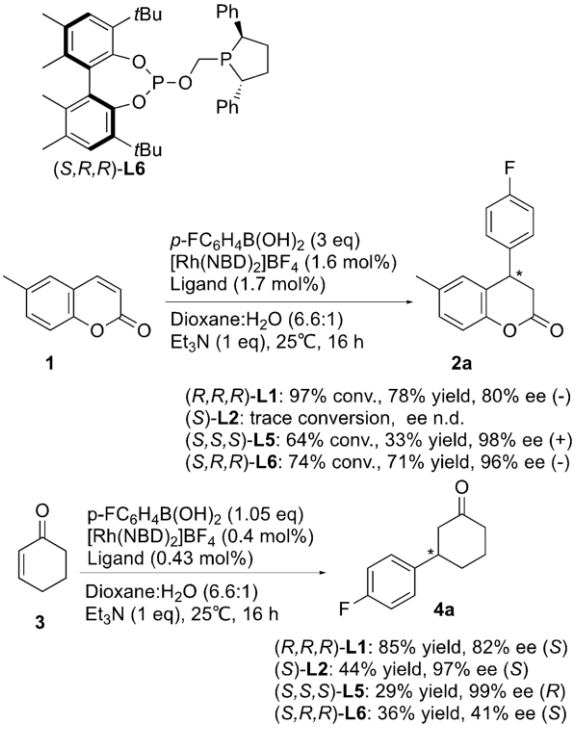
Entry	Ligand [mol-%]	Rh[a] [mol-%]	Nuc. [equiv.][a]	Conv. [%][b,e]	PhF[b] [equiv.]	Yield [%][c]	*ee*[d][%]
1	**L1** (1.7)	1.6	3	97	1.3	78	80 (–)
2	**L2** (1.7)	1.6	3	trace	0.7	ND[f]	ND
3[f,g]	**L2** (1.7)	3.0	10	ND	10	17[f]	98 (–)
4	**L3** (1.7)	1.6	3	trace	0	ND	ND
5[f]	**L3** (1.7)	3.0	10	trace	2.5	ND[f]	ND
6	**L4** (1.7)	1.6	3	0	0	–	–
7[f]	**L4** (1.7)	3.0	10	0	7	–	–
8	**L1** (0.6)	0.4	4.5	57	1.0	47	80 (–)
9[h]	**L1** (0.6)	0.4	4.5	66	3.3	60	75 (–)
10[h,i]	**L1** (0.6)	0.4	4.5	75	3.8	73	75 (–)
10[i]	**L1** (1.7)	1.6	3	99	n.d.	78	81 (–)

[a] General conditions: The given amounts of $[Rh(NBD)_2]BF_4$ are pre-mixed with a slight excess of ligand w.r.t Rh for 2 h (using the enantiomer of ligand shown in Scheme 1); 0.75 mmol of **1**, Nuc. = 4-fluorophenylboronic acid, 0.75 mmol Et_3N,1 mL of dioxane, 25 °C, 16 hours. [b] Determined by $^{19}F\{^1H\}$ NMR relative to 1-fluoronaphthalene. [c] Isolated yield. [d] *ee* determined by chiral HPLC (see ESI for details). [e] $^{19}F\{^1H\}$ NMR integration shows approximate amounts of the partially soluble 4-fluorophenylboronic acid at the end of the reaction, with experiments (entries) 2 and 3 showing around two equivalents boronic acid, and expt. 5 around seven equivalents. [f] Catalyst is [Rh(acac)(COD)] (3.0 mol-%), ligand (3.3 mol-%), with no base added as per ref. 10a. [g] Heated to 60 °C. [h] Heated to 70 °C. [i] MeTHF as solvent.





Scheme 2. Reactions and conditions: i) K*t*BuO (2.5 equiv.), DMF, r.t, 2 h. ii) (a) $AlCl_3$ (1.15 equiv.), Me_2NPCl_2 (1.15 equiv.), DCM, 0 °C, 16 h, (b) $NaHCO_3$ (aq), EDTA, 0 °C, 4 h. iii) H_2 (50 bar), Pd/C (10 %), EtOAc, 60 °C, 17 h. iv) K*t*BuO (3 equiv.), MeOH, 50 °C, 24 h. v) HCl (6 N)/dioxane 1:2, 85 °C, 22 h. vi) (a) quinine, MeOH, 80 °C, 30 min. (28 % is out of 50 % max theoretical yield. (b) acetone, (c) NaOH (2 M), DCM. vii) (a) $PhSiH_3$ (2 equiv.), toluene, 110 °C, 4 h, (b) $BH_3.SMe_2$ (1 equiv.), r.t, 19 h. viii) $(CH_2O)_n$, KOH, MeOH, r.t, overnight. ix) PBr_3 (1.5 equiv.), Et_3N (3 equiv.), toluene, 0 °C to r.t, overnight. x) Alcohol from step (viii) (1 equiv.), DABCO (5 equiv.), toluene, r.t, 17 h. Scheme 2 (bottom). Representation of the X-ray crystal structure of the new phospholanic acid, (*S,S*)-PreL5b, after resolution with quinine.



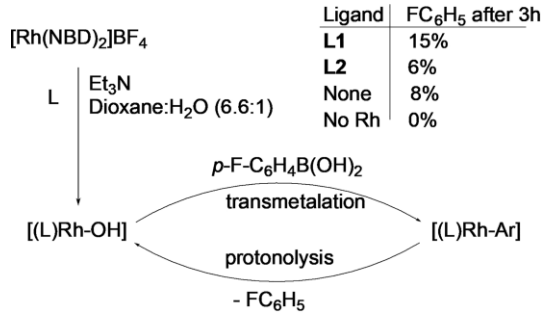
Scheme 3. Improved enantioselectivity using a phospholane-phosphite with larger phospholane substituents, and the same sense of stereoselectivity is observed using the mis-matched diastereomer of BOBPHOS.

The key finding here is that the new phospholane-phosphite, **L5** with a larger phospholane unit delivers higher enantioselectivity in the two model reactions tested (Scheme 3). However, this is accompanied by conversions more typical to Rh/BINAP catalysts under these conditions, removing the reactivity advantage that catalysts derived from **L1** exhibit. This rather inaccessible catalyst was therefore not pursued further in terms of scope. The selectivity observed is consistent with the alkene binding *cis* to the phospholane, although it is not absolute proof of this, since it is just about possible subtle conformation changes could lead to an unexpected influence of chiral substituents *trans* to the alkene.

To add further support, or refute this mechanistic hypothesis, we also tested the mis-matched diastereomer of ligand, (*R,R,R*)-**L1** in which the opposite enantiomer of chiral biphenol is used, (*S,R,R*)-**L6**.[14] In the Michael additions promoted by Rh/(*S,R,R*)-**L6**, one might expect a *switch* in enantiopreference if the alkene was binding *cis* to this phosphite group, since the opposite enantiomer of phosphite component is used. In contrast, if the phosphite is remote from the enantio-face binding of the alkene, it would give the same configuration of product as Rh/(*R,R,R*)-**L1** catalyst, and significant enantioselectivity. The Rh/(*S,R,R*)-**L6** catalyst not only gives the same configuration of product, but the *ee* of **2a** is actually slightly greater using this catalyst (Scheme 3). This is fully consistent with the alkene binding *cis* to the phospholane. The picture is a little more complicated however, and when the Rh/(*S,R,R*)-**L6** catalyst was tested in the conjugate addition of cyclohexanone, while the same enantiomer was formed, the *ee* of **4** is significantly lower.

The Rh/(*R,R,R*)-**L1** catalyst is more productive, and also enables lower amounts of the aryl boronic acid to be used. The rate-determining step of Rh catalyzed arylation of an activated Michael acceptor has been determined to be transmetalation.[2f] However, since less activated Michael acceptors of the type studied here show much lower rates, the C-C bond-forming process can also clearly impact on the rate, so it is likely the two stages are quite finely balanced for less activated Michael acceptors. A partial solution to get high yields for less activated Michael acceptors is to use a very large excess of the aryl boronic acid; this suggests it is important to maintain a large enough concentration of the Rh-aryl species that must undergo the more challenging C-C bond forming reaction. Thus, the efficient formation of the Rh-aryl intermediate is important in Rh catalyzed arylations, regardless of which step has the largest energy barrier.

We therefore wanted to investigate if Rh/**L1** showed an enhanced rate of transmetalation relative to Rh/BINAP. To study this, we reacted *para*-fluorophenylboronic acid with water in the presence of various catalysts to study the overall rate of the process of transmetalation and protonolysis that makes up a Rh catalyzed proto-deboronation (Scheme 4, and for full data, see ESI). Since we have already established that the Rh/**L1** catalysts are more productive than the Rh/BINAP catalyst, it is a reasonable assumption that the former must either enhance the rate of transmetalation, or deliver a Rh-aryl species that is more stable to protonolysis, and in this way delivers a greater proportion of the desired product in catalytic arylations. Our assumption is to consider it impossibly unlikely that the Rh/**L1** catalysts could be similar or worse than Rh BINAP at transmetalation, and more prone to unproductive Rh-aryl protonolysis, yet somehow deliver more product in the catalytic arylation reactions.

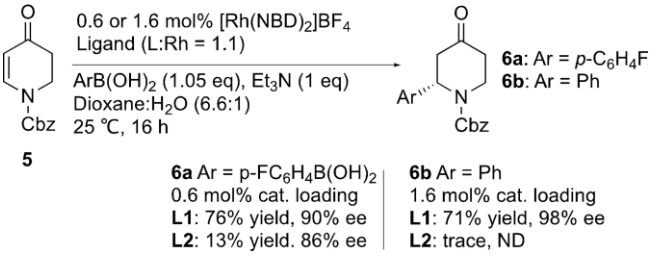


Scheme 4. Transmetalation-protodeboration reactions are faster for Rh/**L1** catalysts.

Control reactions without any Rh catalyst present did not undergo any proto-deboronation, meaning the transmetalation/protonation mechanism produces all the fluorobenzene detected. If the Rh/(*R*,*R*,*R*)-**L1** catalysts were better Michael addition catalysts because they give a more hydrolytically stable Rh-aryl species, less fluorobenzene would be formed in this experiment, since the catalysts would not readily turnover. The fact that we observed significantly faster fluorobenzene formation when catalyzed by Rh/(*R*,*R*,*R*)-**L1**, when considered alongside the higher yields at lower aryl boronic acid concentrations for Rh/(*R*,*R*,*R*)-**L1** is consistent with faster transmetalation than Rh/BINAP.

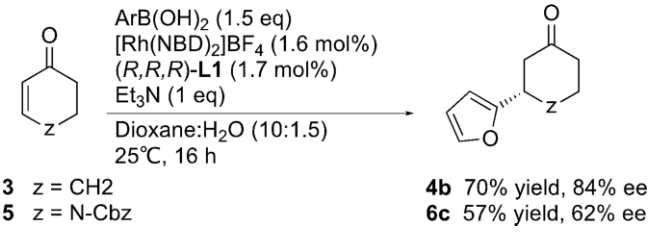
The results obtained reveal Rh/BOBPHOS catalysts to be especially promising from the point of view of reactivity, and we next studied some challenging couplings that did not proceed well using Rh/BINAP catalysts during our previous study.[9] The synthesis of chiral piperidones is also a desirable, yet challenging conjugate addition. Most approaches focus on alternative air sensitive and expensive nucleophiles such as arylzinc reagents,[15] alkenyl alanes,[16] or organostannane reagents.[17] Jagt et al. developed a method of coupling arylboroxines with *N*-Substituted-2–3-dehydro-4-piperidones using a Rh-Phosphoramidite ligand, but this required high loadings of arylboroxines and the slow addition of water.[18a,18b] It should be noted that there is an example using 3 mol-% of a Pd chiral NHC complex to give very high *ee* for this difficult substrate.[18c]

We decided to test our Rh/BOBPHOS catalyst with this challenging conjugate addition substrate. We found that the Rh/(*R*,*R*,*R*)-**L1** catalyst gave us good yields, clearly surpassing Rh/(*S*)-**L2** catalysts. For the synthesis of **6a**, the Rh/(*R*,*R*,*R*)-**L1** catalyst gave higher enantioselectivity than the Rh/BINAP one using 0.6 mol-% catalyst (Scheme 5).



Scheme 5. Improved protocol for arylation of CbZ-dehydropiperidone using Rh/BOBPHOS catalyst.

In our previous study we also found the use of heteroarylboronic acids, in particular 2-furylboronic acid were challenging substrates for conjugate addition reactions.[9] This is because heteroarylboronic acids are prone to protodeborylation.[19] There are studies aiming to overcome this using alternative boronate substrates such as MIDA, trifluoroborates or triol-borates,[20] but the use of the boronic acid would be desirable. The coupling of the two enone substrates in a conjugate addition with 2-furylboronic acid was compared using Rh/(*R*,*R*,*R*)-**L1** and Rh/(*S*)-**L2** catalysts. These results show that Rh/BOBPHOS catalysts are more reactive than Rh/BINAP again; in the formation of **4b** and **6c**, Rh/BINAP catalysts gave 15 % and 0 % yields respectively, while moderate to good yields can be achieved using the Rh/(*R*,*R*,*R*)-**L1** combination (Scheme 6).



Scheme 6. Challenging couplings of 2-furyl boronic acids are possible.

Conclusion

This project spun out of a desire to prepare multigram amounts of some of the products here using commercially available rhodium catalyst systems. Fully exploring the scope of the previously unused Rh/**L1** catalysts is outside of this study, but we would predict advantageous productivity in other difficult Rh catalyzed arylations. The results present clear evidence that catalysts derived from ligand **L1** are more efficient at the transmetalation step in Rh catalyzed conjugate addition. It is likely that other phosphine-phosphites are unusually reactive ligands for Rh catalyzed conjugate additions, and are worthy of investigation for challenging couplings. Transmetalation could be rate-determining in itself, or part of the rate determining states

that lead to a challenging C-C bond-forming event, with the efficient generation of a reasonable concentration of Rh-aryl species being critical to the success of the reaction. If C-C bond formation is slow, more significant amounts of proto-deboronation can occur when using challenging Michael acceptors. It is hoped this new catalyst, or as yet undiscovered phosphine-phosphite derived catalysts could be used in the future to extend the scope of Rh catalyzed conjugate additions.

Experimental Section

General: Commercially available starting materials were purchased from Sigma Aldrich, Alfa Aesar, Acros, STREM or Apollo Scientific and were used without further purification. (*R*,*R*,*R*)-BOBPHOS,[11b] (*S*)-Kelliphite,[13] benzyl 4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate[9,21] were synthesized in house according to published procedures.

All catalytic reactions and all air sensitive procedures were carried out under inert conditions or under hydrogen pressure using standard Schlenk techniques. All solvents used for these systems were dry and degassed; taken from solvent purification systems, or commercially supplied anhydrous bottles. Removal of solvent was assisted by a rotary evaporator. Analytical thin layer chromatography (TLC) was performed on pre-coated alumina plates (Kieselgel 60 F254 silica), before analyzing under ultraviolet light (254 nm). All SiO_2 column chromatography was performed with Kieselgel 60 silica. The research data underpinning this publication can be accessed at https://doi.org/10.17630/bf27a028-7eb7-472b-8891-c3558bbcae8a[22]

Synthesis of 6a: The pre-dried vial was filled with 4-fluorophenylboronic acid (73.5 mg, 0.525 mmol), $[Rh(NBD)_2]BF_4$ (1.1 mg, 0.6 mol-%), (*R*,*R*,*R*)-BOBPHOS (2.1 mg, 0.64 mol-%), a magnetic stirrer bar, and sealed with crimped caps. The reaction vessel was purged with N_2 3 times, before the addition of the dioxane (0.5 mL) via syringe. The reaction mixture was stirred for 2 hours before the addition of H_2O (0.15 mL), Et_3N (70 μL, 0.5 mmol) and a stock solution of benzyl 4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate in dioxane (1 M, 0.5 mmol, 0.5 mL). The reaction was then left to stir at room temperature for 16 hours. The reaction mixture was dissolved in a heptane:methyl *tert*-butyl ether (10:3, 8 mL) and washed with water (2 × 5 mL). The combined aqueous layers were then extracted with further heptane: methyl *tert*-butyl ether (2:1, 5 mL). The combined organic layers were dried ($MgSO_4$) and solvent was removed in vacuo. Purification was carried out by column chromatography (SiO_2 9:1, hexane/ethyl acetate) to yield a yellow oil as the isolated product (125 mg, 76 %, 90 % *ee*). Enantiomeric excess was determined by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.41–7.36 (m, 5H, 9-*H*, 10-*H*, 11-*H*), 7.25–7.21 (m, 2H, 13-*H*), 7.03 ("t", $^3J_{HH} = {}^3J_{HF}$ = 8.7, 2H, 14-*H*), 5.84 (br s, 1H, 5-*H*), 5.28–5.20 (m, 2H, 7-*H*), 4.36–4.27 (m, 1H, 1-*H*), 3.18 (t, $^3J_{HH}$ = 12.0, 1H, 1-*H*), 2.97 (dd, J_{HH} = 15.4, 2.1, 1H, 4-*H*), 2.89 (dd, J_{HH} = 15.4, 6.9, 1H, 4-*H*), 2.60–2.53 (m, 1H, 2-*H*), 2.39 (d, J_{HH} = 15.4, 1H, 2-*H*) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ = 207.2 (s, 3-*C*), 162.2 (d, $^1J_{CF}$ = 247.6 Hz 15-*C*), 155.4 (s, 6-*C*), 136.1 (s, 8-*C*), 135.5 (s, 12-*C*), 128.6 (s, Ar-*C*H), 128.5 (d, $^3J_{CF}$ = 5.1 Hz 13-*C*), 128.4 (s, Ar-*C*H), 128.1 (s, Ar-*C*H), 115.7 (d, $^2J_{CF}$ = 21.5 Hz 14-*C*), 67.9 (s, 7-*C*), 54.1 (s, 5-*C*), 44.3 (s, 4-*C*), 40.6 (s, 2-*C*), 38.9 (s, 1-*C*) ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = –114.4 (s, 15-*F*) ppm. HRMS (ES$^+$) *m*/*z*: 350.1155 $[M + Na]^+$, $[C_{19}H_{18}O_3NF + Na]$ requires 350.1163. HPLC (Chiralpack OD-H, hexane/2-propanol 80:20, 0.5 mL/min, RT): t_R = 35.5 min (*S*), 43.3 min (*R*). Optical rotation: $[\alpha]_{20}^{D}$ = –70.3 (*c* = 1.0, $CHCl_3$).

Supporting Information (see footnote on the first page of this article): For full experimental details available.

Acknowledgments

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Keywords: Asymmetric arylation · Michael addition · Aryl boronic acids · Phospholane ligands · Asymmetric catalysis

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