Article

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Computationally Assisted Mechanistic Investigation and Development of Pd-Catalyzed Asymmetric Suzuki-Miyaura and Negishi Cross-Coupling Reactions for Tetra-*ortho*-Substituted Biaryl Synthesis

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Abstract: Metal-catalyzed cross-coupling reactions are extensively employed in both academia and industry for the synthesis of biaryl derivatives for applications to both medicine and material science. Application of these methods to prepare tetra-*ortho*-substituted biaryls leads to chiral atropisomeric products that introduces the opportunity to use catalyst-control to develop asymmetric cross-coupling procedures to access these important compounds. Asymmetric Pd-catalyzed Suzuki-Miyaura and Negishi cross-coupling reactions to form tetra-*ortho*-substituted

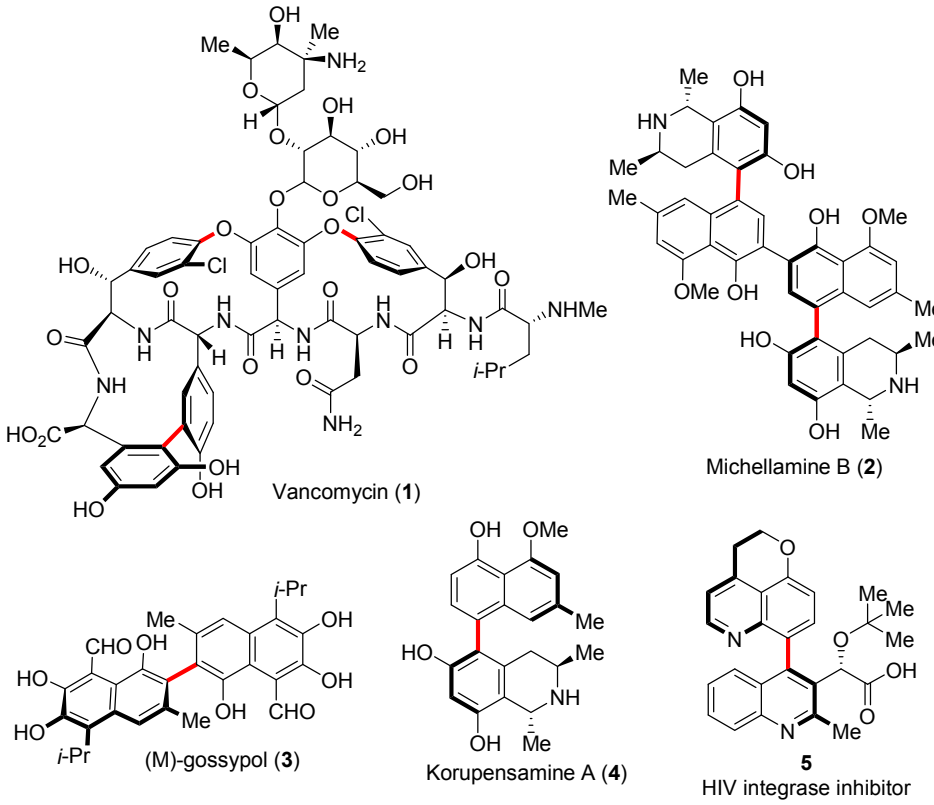
biaryls were studied employing a collection of *P*-chiral dihydrobenzooxaphosphole (BOP) and dihydrobenzoazaphosphole (BAP) ligands. Enantioselectivities of up to 95:5 and 85:15 er were identified for the Suzuki-Miyaura and Negishi cross-coupling reactions, respectively. Unique ligands for the Suzuki-Miyaura reaction *vs* the Negishi reaction were identified. A computational study on these Suzuki-Miyaura and Negishi cross-coupling reactions enabled an understanding in the differences between the enantiodiscriminating events between these two cross-coupling reactions. These results support that enantioselectivity in the Negishi reaction results from the reductive elimination step, whereas all steps in the Suzuki-Miyaura catalytic cycle contribute to the overall enantioselection with transmetalation and reductive elimination providing the most contribution to the observed selectivities.

Keywords: cross-coupling, Palladium, catalysis, asymmetric, phosphines

INTRODUCTION

Transition metal catalyzed sp^2-sp^2 cross-coupling is one of the most powerful and extensively utilized reactions in organic synthesis and materials science to access biaryl compounds.[1] Of these methods, the Pd-catalyzed Suzuki-Miyaura[2] and Negishi[3] cross-coupling have received considerable development over the past 40 years.[1,4] Significant advances in the development of highly active Pd-catalysts[5] to achieve efficient processes have even allowed for these reactions to be employed on industrial scale.[6] In general, bulky electron-rich phosphines[7] and *N*-heterocyclic carbenes[8,9] have been the ligands of choice to enable these cross-coupling reactions. Despite these advances, cross-coupling catalysts for the formation of sterically demanding biaryls, such as tetra-*ortho*-substituted systems, remains limited.[9] Additionally, because appropriately substituted tri- and tetra-*ortho*-substituted biaryls exist as chiral

atropisomers about the biaryl axis, methods to forge this bond in an enantioselective fashion are important since many biologically active natural products[10] and potential pharmaceuticals[11] contain single atropisomeric biaryl groups within their structure (Scheme 1). Therefore, one desirable strategy to access the biaryl functionality in these compounds is to utilize a catalyst-controlled asymmetric Suzuki-Miyaura or Negishi sp^2 – sp^2 cross-coupling.[12] While transition metal catalyzed asymmetric Suzuki-Miyaura[13] and Negishi[14] sp^2 – sp^2 cross-coupling reactions have been developed, significantly fewer methods are available for the asymmetric construction of tetra-*ortho*-substituted biaryls.[13c,d,p-t,14,15]

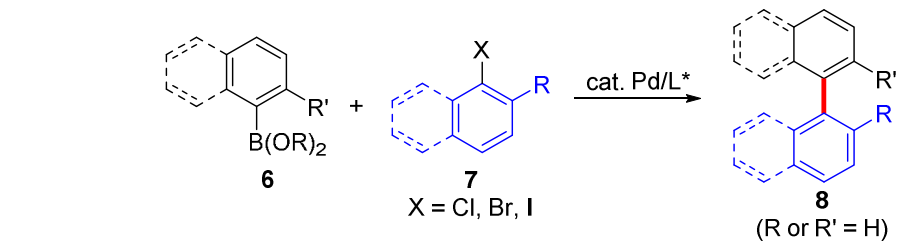


Scheme 1: Natural Products and Bioactive Atropisomeric Compounds

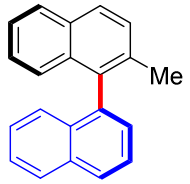
The first highly selective sp^2 – sp^2 cross-coupling reaction was reported in 1988 by Hayashi and coworkers[15] to afford atopisomeric binaphthalenes in up to 95% ee using a

Kumada-Corriu[16] coupling. It was not until the year 2000 that the first reports of Pd-catalyzed asymmetric Suzuki-Miyaura cross-coupling reactions were disclosed by the groups of Cammidge[13c,d] and Buchwald.[13a,b] Cammidge applied Hayashi's[15] chiral ferrocene ligand (PFNMe) to access tri-*ortho*-substituted biaryl **8a** with modest enantioselection (82:18 er, Scheme 2). At the same time, Buchwald discovered that KenPhos could be employed as the chiral ligand affording high enantioselectivities in the cross-coupling if the R-substituent of the aryl halide coupling partner contained a Lewis basic donating group at the *ortho*-position (**8b-d**). Mechanistic studies on this class of cross-coupling by Buchwald[13b] and others[11b,13n,x] typically consider reductive elimination as the enantiodetermining event in the catalytic cycle and have shown that these Lewis basic *ortho*-substituents aid in the stabilization of the dominating transition state. However, restricted rotation of the intermediate Pd-complexes as a function of the *ortho*-substitution pattern of the aryl halide coupling partner can lead to scenarios where oxidative addition[13f] and transmetalation[13d,f] may be involved in enantioselection.[17] After these initial reports, intense research into the area of catalyst-controlled asymmetric biaryl synthesis by a variety of groups has led to the introduction of multiple chiral ligands that affect this transformation (Scheme 2).[11,13] The majority of these studies have focused on the investigation of the formation of tri-*ortho*-substituted binapthalene derivatives.[11,13a,b,e-o,u-bb] Of these, asymmetric synthesis of the aryl phosphonate products (**8b** – **8d**) by asymmetric cross-coupling have been one of the more common systems studied between different chiral catalysts with variable results.[13a,b,j,n,u-y] For example, our group[11,13n,o] introduced the *P*-chiral dihydrobenzooxaphosphole (BOP) class of ligands (BIDIME, **9**, **10**) that are effective in asymmetric cross-coupling reactions and are highly tunable to enable ligand modification for enhancement of stereoselectivities. Suzuki-Miyaura cross-coupling to afford **8b** employing BOP

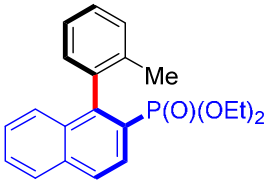
ligand **9b**[13n] gave improved enantioselectivity to that of KenPhos;[13a] however, in the coupling to produce **8b**, KenPhos resulted in improved selectivity over ligand **9b**. These results highlight the fact that asymmetric cross-coupling reactions are typically very substrate dependent. Synthesis of **8b** – **8d** has also been acheived by asymmetric cross-coupling employing the atropisomeric, hemi-labile ligands Cy-MOP,[13w] **11**,[13u,x] and **12**,[13v] and using a helically-chiral polymeric phosphine ligand (PQXPhos).[13i] Other ligand classes including chiral dienes (**13**),[13h] bis(hydrazones) (**14**),[13f] and a resin-supported chiral ligand (**15**)[13p] have all been shown to afford high enantioselectivities in certain asymmetric Suzuki-Miyaura cross-coupling reactions. Despite these significant advances in asymmetric cross-coupling methodologies, a general catalyst for a wide-array of substitution patterns is still and unsolved problem. However, these technologies have found utility in natural product[13k,o] and API synthesis (*e.g.* **5** *via* **8**).[11]



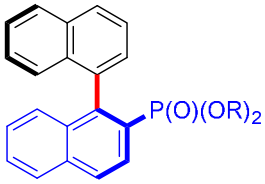
tri-*ortho*-substituted biaryls



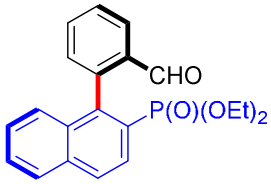
8a
(*S,R*)-PFNMe: 82:18 er
13: 5:95 er
14: 5:95 er



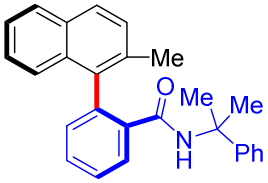
8b
(*R*)-KenPhos: 94:6 er
9b: 90:10 er
PQXPhos: 97:3 er
12a: 90:10 er



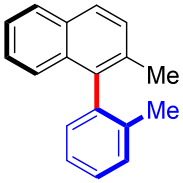
8c
(*R*)-KenPhos: 79:21 er
9b: 95:5 er
PQXPhos: 95:5 er
11: 94:6 er
12b: 84:16 er



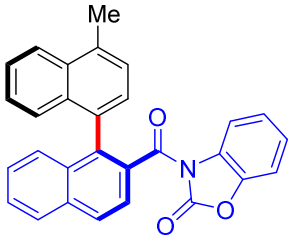
8d
(*R*)-Cy-MOP: 98:2 er



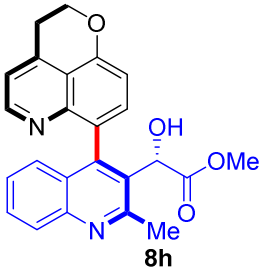
8e
(*S*)-KenPhos: 97:3 er



8f
13: 92:8 er
15: 96:4 er

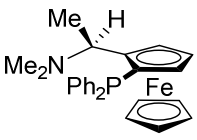


8g
9a: 98:2 er

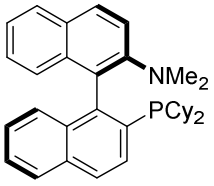


8h
(*S*)-BIDIME: 83:17 dr
(*R*)-BIDIME: 17:83 dr
(*S*)-**10**: 94:6 dr

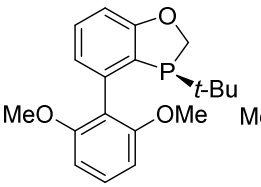
Ligands:



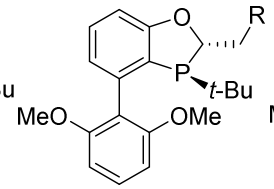
(*S,R*)-PFNMe



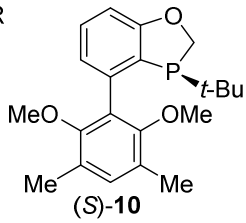
(*R*)-KenPhos



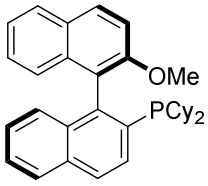
(*S*)-BIDIME



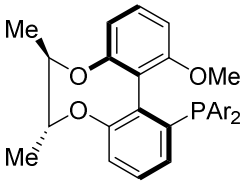
9a, R = H
9b, R = 1-napthyl



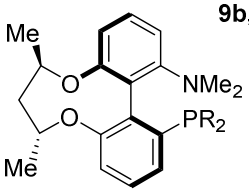
(*S*)-**10**



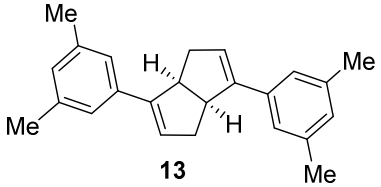
(*R*)-Cy-MOP



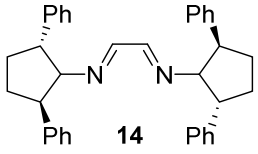
11
Ar = 3,5-di-*t*-BuPh



R = Cy: **12a**
R = Ph: **12b**

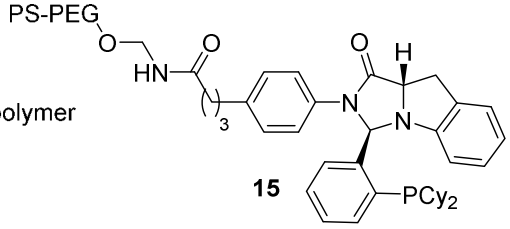


13



14

PQXPhos: helical chiral polymer

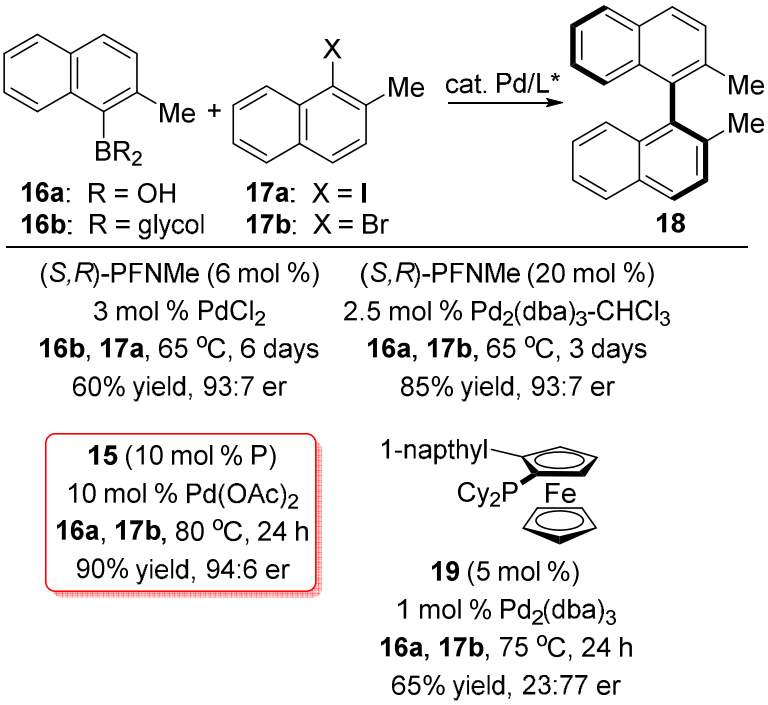


15

Scheme 2: Asymmetric Suzuki-Miyaura Cross-Coupling Reactions to Prepare Tri-*ortho*-Substituted Biaryls

While asymmetric Suzuki-Miyaura cross-coupling to generate tri-*ortho*-substituted biaryls (Scheme 2) has been successful with a variety of chiral ligand types,[13a,b,e-o,u-bb] the synthesis of tetra-*ortho*-substituted biaryls by the same means has proven more difficult.[13c,d,p-t] Tetra-*ortho*-substituted biaryl product **16** (Scheme 3)[13c,d,p-q] has typically been the standard cross-coupling reaction analyzed when developing new catalysts for this challenging coupling.[12c] While the Ni-catalyzed Kumada-Corriu[16] coupling to prepare **16** was reported by Hayashi[15] with good enantioselectivity, the analogous Suzuki-Miyaura coupling has proven more challenging.[13c,d,p-t] Cammidge's initial report[13c,d] demonstrated that the PFNMe ligand gave good enantioselectivity (93:7 er) in this reaction; however, long reaction time (6 days) was required affording only modest yield (Scheme 3). Espinet[13r] was able to optimize this result to reduce the reaction time to 3 days at 5 mol % Pd loading by using $Pd_2(dba)_3$•$CHCl_3$ as the Pd-source in the presence of excess ligand (20 mol %) to improve the yield to 85%. The catalyst loading could be reduced to employ 3 mol % Pd and 12 mol % ligand by utilizing $Pd(MeCN)_4(BF_4)_2$ in place of $Pd_2(dba)_3$•$CHCl_3$ as the precatalyst with an improvement in enantioselectivity of up to 95:5 er. However, only 55% yield was obtained after 4 day reaction time. While these conditions can be applied to the synthesis of **16**, reaction times are still quite long (days), and the scope of the reaction to other substrates is limited or has not been further investigated. Of the catalytic systems reported for the synthesis of **16** by Suzuki-Miyaura cross-coupling, Uozumi's[13p] conditions employing resin-supported phosphine ligand **15** are performed in water under heterogeneous conditions that allow for recycling of the catalyst and show the most generality in terms of reaction scope and enantioselectivity; however, only simple substituted naphthalenes

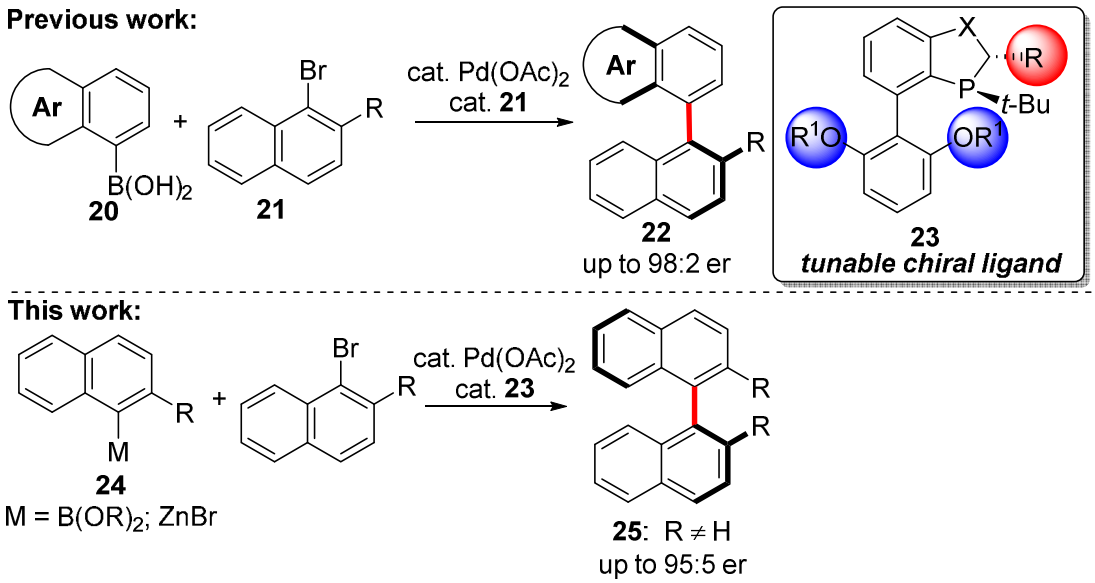
have been disclosed in the coupling. Recently there has been increased focus on the development of Suzuki-Miyaura cross-coupling reactions performed using water[18,19] as the solvent due to the potential "greenness" of replacing typical organic solvents by water.[20,21] However, none of these methods have been extended to enantioselective cross-coupling. Uozumi's[13p] report represents the only known catalytic asymmetric cross-coupling carried out in neat water.[22] Future studies are needed in this area to determine if improvements in catalytic asymmetric coupling reactions can be achieved using water as solvent.



Scheme 3. Asymmetric Suzuki-Miyaura Cross-Coupling Reactions to Prepare Tetra-*ortho*-Substituted Biaryls

As noted above (Scheme 2), previous work in our laboratories identified the *P*-chiral dihydrobenzooxaphosphole (BOP) ligand class (BIDIME, **9**, **10**) as a highly tunable scaffold for applications in many different types of asymmetric transformations by modulating the

substituents of ligand structure **23** (Scheme 4). By variation of the oxaphosphole C-2 R-substituent and the bis(alkoxy)phenyl aryl-group of ligand **23**, catalysts for Suzuki-Miyaura[7p-t,9a,19a,23] and asymmetric Suzuki-Miyaura[11,13n-o] cross-coupling, Buchwald-Hartwig amination,[24] borylation,[25] asymmetric propargylation of aldehydes[26] and imines,[27] asymmetric conjugate addition,[28] asymmetric addition of boronic acids to imines,[29] asymmetric allenylation of imines,[30] asymmetric hydrogenation of polar[31] and unfunctionalized[32] alkenes, asymmetric hydrogenation of heterocycles,[33] asymmetric hydroformylation,[34] and asymmetric hydrogenation of ketones[35] have all been developed. Due to the lack of a general solution for the asymmetric synthesis of tetra-*ortho*-substituted biaryls using the Suzuki-Miyaura cross-coupling reaction, we sought to investigate application of ligand family **23** as a potential solution to this problem because of the modular nature of **23** and because of its good activity in the asymmetric cross-coupling to furnish tri-*ortho*-substituted biaryls.[11,13n,o] In this article, we disclose our studies towards the application of the dihydrobenzooxaphosphole (**23**, X = O, BOP) and dihydrobenzoazaphosphole (**23**, X = NR, BAP) ligand scaffold for both the asymmetric Pd-catalyzed Suzuki-Miyaura and Negishi cross-coupling reaction to form tetra-*ortho*-substituted biaryls (Scheme 4). The differences in the enantiodiscrimination mechanism between these two processes was probed computationally and is also disclosed herein.



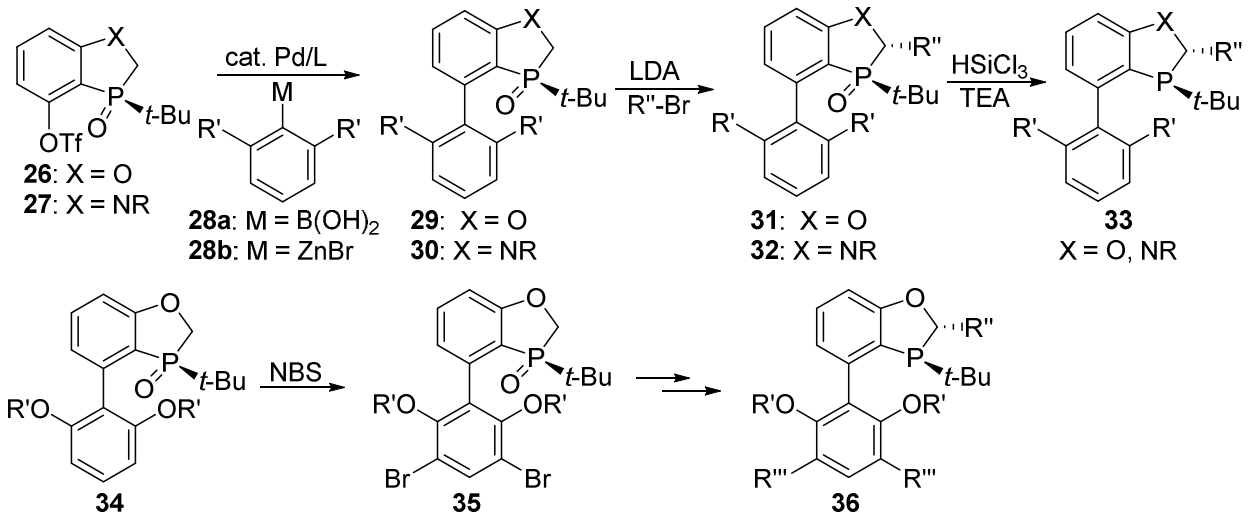
Scheme 4. Tunable *P*-Chiral Phosphine Ligands for Asymmetric Pd-Catalyzed Cross-Coupling.

RESULTS AND DISCUSSION

Ligand Synthesis.

The ligands employed in the current study were prepared by the general strategy outlined in Scheme 5. Starting from the known *P*-chiral triflates (**26**, **27**),[13n,35b] Negishi[7t] or Suzuki-Miyaura cross-coupling was used to install the lower aryl ring of the ligand biaryl axis affording oxides **29** or **30**. Deprotonation of **29** or **30** with LDA followed by electrophilic trapping allowed for substitution of the C-2 position of the oxaphosphole or azaphosphole ring providing **31** or **32**, respectively. Oxide reduction then provided the final BOP (X = O) or BAP (X = NR) ligands (**33**). Additionally, the 3,5-positions of the lower aryl ring of the biaryl group of **34** can be functionalized by bromination[11b] to afford **35** followed by cross-coupling and alkylation to afford

ligand family **36**. These procedures have enabled the synthesis of a tunable family of *P*-chiral phosphine ligands. The ligands prepared and used in this study are shown in Chart 1.



Scheme 5. Ligand Synthesis.

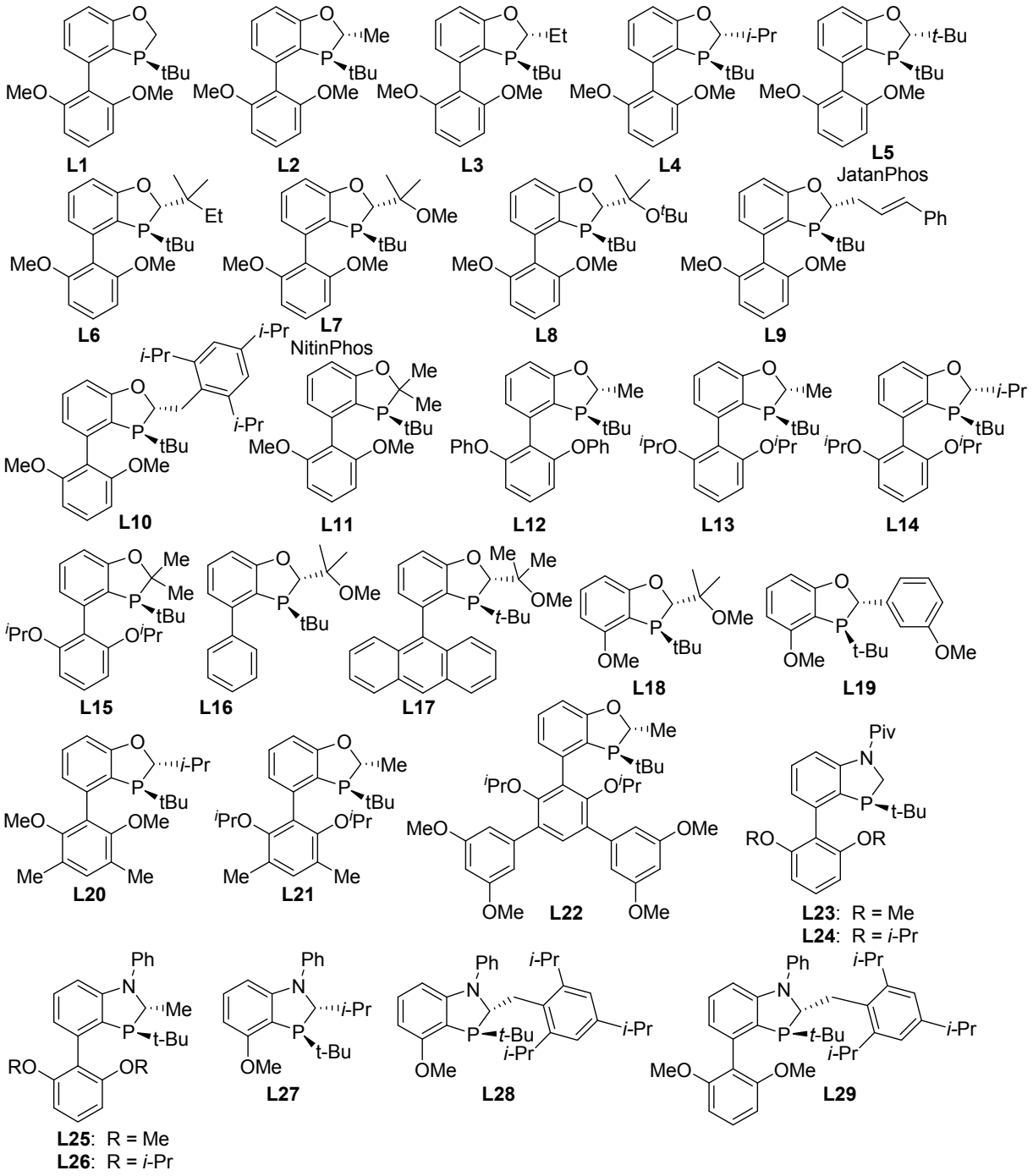
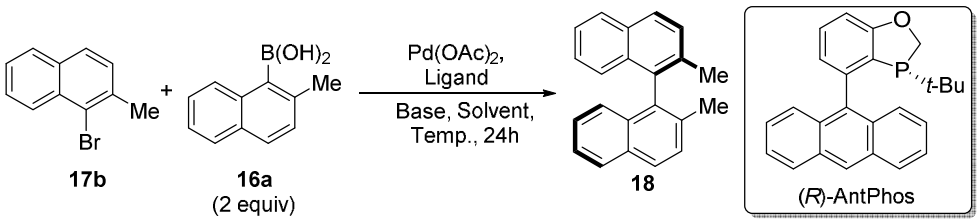


Chart 1. Ligands Used in This Study.

Asymmetric Suzuki-Miyaura cross-coupling.

To investigate the Suzuki-Miyaura cross-coupling to prepare tetra-*ortho*-substituted biaryls, we initially examined the "benchmark[12c]" cross-coupling reaction to form tetra-*ortho*-substituted biaryl compound **18** (Table 1) employing 1-bromo-2-methylnaphthalene (**17b**) and (2-methylnaphthalen-1-yl)boronic acid (**16a**) as the coupling partners. Initial experiments probed conditions that previously were shown to be suitable for hindered cross-coupling reactions (Entries 1 – 3). These consisted of the use of K_3PO_4 as base and employing BIDIME (**L1**), AntPhos, or C2-*i*-Pr-BIDIME (**L4**) as the ligand. Gratifyingly, under these conditions, product **18** was observed. While almost no enantioinduction was observed using BIDIME (**L1**) or AntPhos, which lack substitution at the C-2 position of the oxaphosphole ring (entries 1 and 2), C2-*i*-Pr-BIDIME (**L4**) afforded modest enantioselectivity and yield in the reaction (entry 3). As has been previously noted for reactions forming tetra-*ortho*-substituted biaryls,[13d,r] protodeboronation was a significant side-reaction that prevented the coupling from proceeding to full conversion. To circumvent this issue, alternate bases were examined in an effort to reduce protodeboronation; however, no improvements over the use of K_3PO_4 were identified (entries 3 – 8). Additionally, solvents such as toluene and 1,4-dioxane were found to be equally effective in the coupling and did not improve enantioselectivity or yield (entries 9 and 10). Finally, to achieve full reaction conversion, the effect of catalyst loading was examined (entries 11 – 14). Use of 5 mol % Pd was needed to achieve full conversion and allowed for high yield in the desired reaction (entry 13). Addition of water as a co-solvent to these reactions when employing THF or *n*-BuOH as solvent afforded < 10% yield of product due to significant amounts of protodeboronation (data not shown) that is not uncommon considering that the addition of excess water is often avoided in sterically demanding and asymmetric cross-coupling reactions.[9,13]

Table 1. Asymmetric Suzuki-Miyaura Cross-Coupling Towards Tetra-*ortho*-Substituted Biaryls: Base and Solvent Survey.



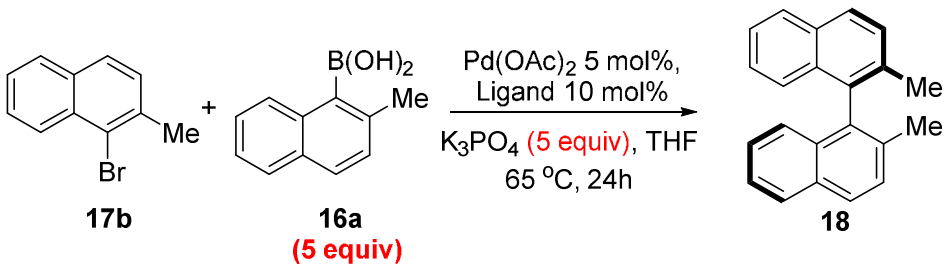
Entry	Mol % Pd	Ligand (mol%)	Base (3 equiv)	Solvent	%Yield[a]	er[b]
1	1	**L1** (2)	K_3PO_4	THF	40	55:44
2	1	(*R*)-AntPhos (2)	K_3PO_4	THF	30	50:50
3	1	**L4** (2)	K_3PO_4	THF	50	86:14
4	1	**L4** (2)	CsF	THF	18	ND
5	1	**L4** (2)	KF	THF	< 5	ND
6	1	**L4** (2)	K_2CO_3	THF	9	ND
7	1	**L4** (2)	Na_2CO_3	THF	< 2	ND
8	1	**L4** (2)	NaOtBu	THF	< 3	ND
9	1	**L4** (2)	K_3PO_4	Toluene	48	85:15
10	1	**L4** (2)	K_3PO_4	1,4-dioxane	50	85.5: 14.5
11	3	**L4** (6)	K_3PO_4	THF	64	86:14
12	3	**L4** (6)	K_3PO_4	Toluene	56	85:15
13	**5**	**L4 (10)**	**K_3PO_4**	**THF**	**90**	**86:14**
14	5	**L4** (10)	K_3PO_4	Toluene	85	85:15

[a]Isolated yield. [b]Determined by chiral HPLC analysis with Chiralpak OD-H column.

With moderate conditions in hand for the Suzuki-Miyaura cross-coupling reaction (Table 1, entry 13), we next attempted to modify the ligand structure to improve enantioselection (Table 2). The substitution at the C-2 position of the oxaphosphole ring of the ligand was first examined (entries 1 – 6). This enabled the identification of a ligand that provided enantioselectivities of up to 95:5 er when a dimethylmethoxy (DMM) substituent was at the C-2 position of the oxaphosphole ring (**L7**, NitinPhos, entry 4). Furthermore, it was critical that the ligand contained a dimethoxyphenyl ring as part of the biaryl axis of the ligand. When this group was replaced

with phenyl, anthracene, or methoxy, inferior yields and selectivities were obtained (entry 4 *vs* entries 9 – 11). The importance of the lower dimethoxyphenyl ring in enhancing enantioselectivities through an interaction between one methoxy-group and Pd has been postulated previously,[11b,13n] and is further supported by DFT modeling of this system (*vide infra*). Replacement of the methoxy-groups on this lower aryl ring with *iso*-propoxy groups afforded no improvement (entry 1 *vs* entries 7 – 8).

Table 2. Ligand Survey in the Asymmetric Suzuki-Miyaura Cross-Coupling Towards Tetra-*ortho*-Substituted Biaryls.



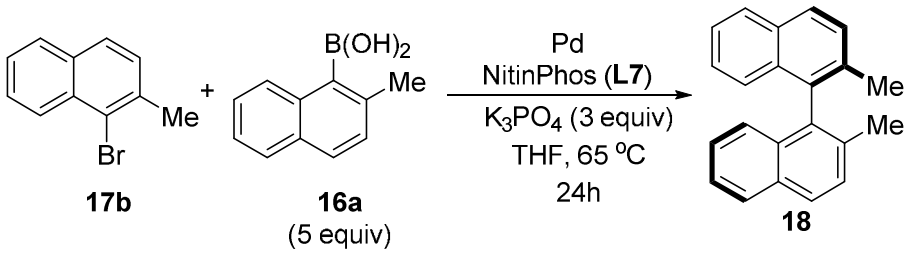
Entry	Ligand	% yield[a]	er[b]
1	**L4**	92	86:14
2	**L5**	80	90:10
3	**L6**	75	86:14
4	**L7**	**97**	**94.5:5.5**
5	**L8**	45	81.5:18.5
6	**L10**	91	83:17
7	**L13**	73	84.5:15.5
8	**L14**	75	83:17
9	**L16**	75	73:27
10	**L17**	35	88:12
11	**L18**	50	64:36
12	**L20**	89	78:22

[a]Isolated yield. [b]Determined by chiral HPLC analysis with Chiralpak OD-H column.

The effect of Pd-precatalyst and Pd:ligand loading was next examined (Table 3). The use of excess ligand enabled the highest reaction yield (entry 1 *vs* 2). Additionally, $Pd(OAc)_2$ gave

less side-product formation than compared to the use of $Pd_2(dba)_3$ or $[PdCl(allyl)]_2$ (entry 2 *vs* entries 3 – 4).

Table 3 Effect of Pd-Precatalyst and Pd:Ligand Loading.



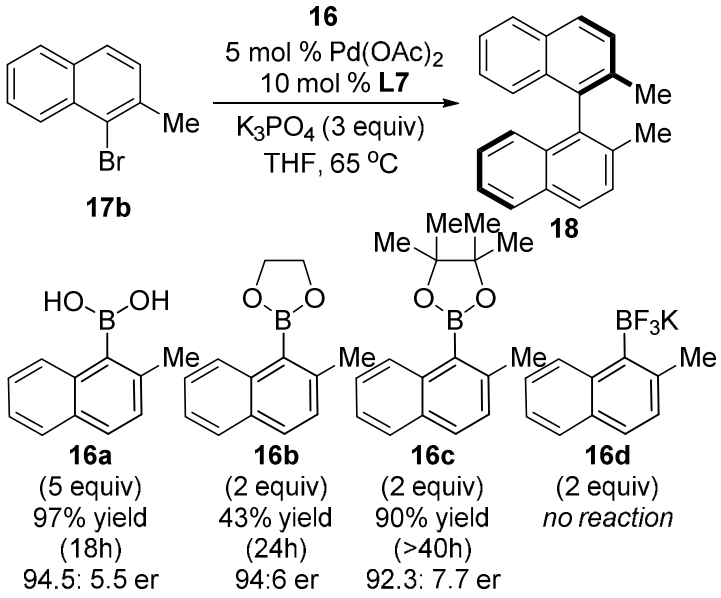
17b **16a** (5 equiv) **18**

Entry	Pd Source (mol %)	Mol % **L7**	% yield[a]	Er[b]
1	$Pd(OAc)_2$ (5)	10	97%	94.5:5.5
2	$Pd(OAc)_2$ (5)	5	75%[c]	94.5:5.5
3	$Pd_2(dba)_3$ (2.5)	5	64%[d]	94:6
4	$[PdCl(allyl)]_2$ (5)	5	55%[e]	93.7:6.3

[a]Isolated yield. [b]Determined by chiral HPLC analysis with Chiralpak OD-H column. [c]1-2% side products were observed with 23 % of bromide substrate remaining, [d]5-7% side products were observed with 29% of bromide substrate, [e]8-9% side products were observed with 35% of bromide substrate.

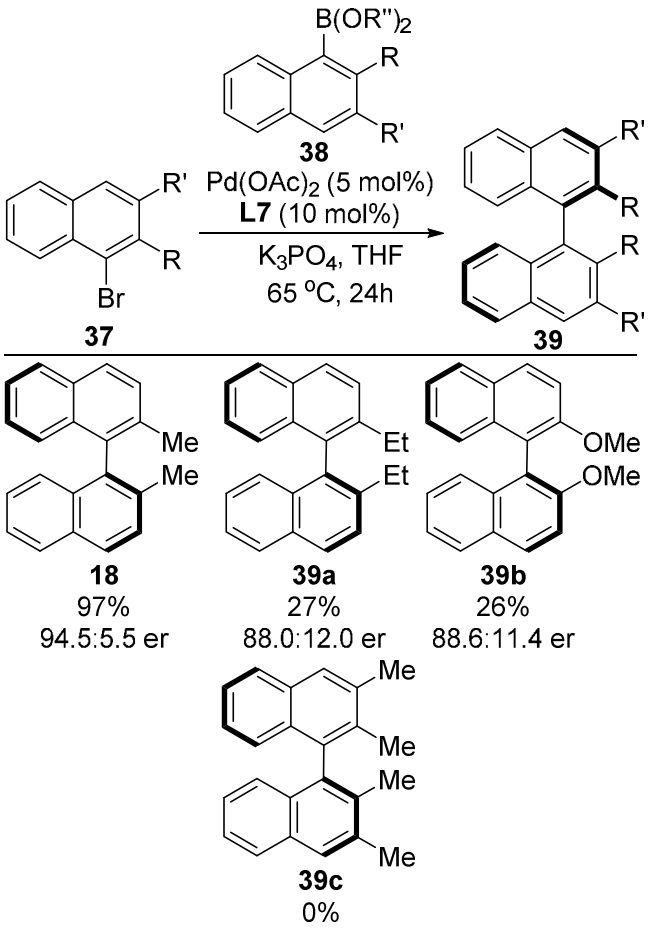
In an effort to further reduce the loading of the boron coupling partner, we next examined other boron derivatives in the coupling reaction in an effort to reduce protodeboronation side-reactions (Scheme 6). Use of the glycol ester (**16b**) that was optimal in Cammidge's system[13d] and has been recently shown to give improved transmetalation rates in Suzuki-Miyaura cross-coupling reactions[30] gave similar enantioselectivities as that observed with boronic acid **16a** but did not afford full conversion in the reaction, even at prolonged reaction times. Use of the pinacol ester **16c** allowed for reduction of the boron coupling partner to 2 equiv; however, long reaction times were required and a slight loss in enantiopurity was obtained. The change in enantioselectivity based off of the nature of the boronate employed has been observed previously[13d] and hints that the transmetalation step in the catalytic cycle for this reaction may be

involved in the enantiodeterming event (*vide infra*). Finally, use of the potassium trifluoroborate salt (**16d**), which are known for their resistance to protodeboronation,[37] was not effective in the cross-coupling reaction.



Scheme 6 Effect of Boronate Coupling Partner.

With identification of a reactive catalytic system to form tetra-*ortho*-substituted biaryl product **18** with good enantioselectivities, the scope of this catalytic system was then briefly examined (Scheme 7). Unfortunately, it was quickly determined that the present system did not show good generality, as has been a common problem in asymmetric Pd-catalyzed Suzuki-Miyaura reactions providing tetra-*ortho*-substituted biaryls. Only subtle modification to the coupling partners led to decreased reaction efficiency due to increased amounts of protodeboronation.



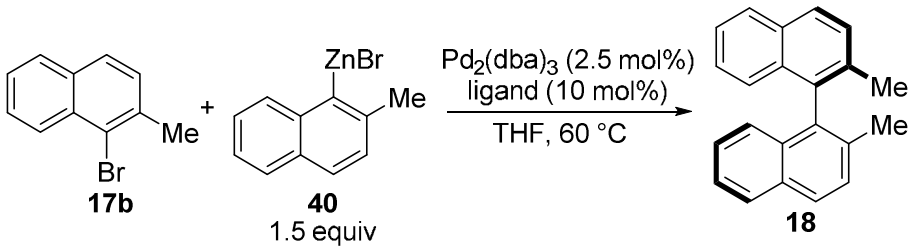
Scheme 7. Asymmetric Suzuki-Miyaura Cross-Coupling Reaction Scope.

Asymmetric Negishi cross-coupling.

Because of the issues identified with the Suzuki-Miyaura cross-coupling reaction (poor generality, high boronate loading), we decided to investigate the analogous reaction employing Negishi cross-coupling with aryl-zinc reagent **40** prepared by lithium-halogen exchange of **17b** with *t*-BuLi followed by addition of a THF solution of anhydrous $ZnBr_2$. $ZnBr_2$ was our preferred choice over $ZnCl_2$ due to its higher solubility in THF. Towards this end, we surveyed our family of *P*-chiral oxaphosphole and azaphosphole ligands in the Negishi cross-coupling reaction (Table 4). The highest yield and selectivity was obtained with **L13** having *iso*-propoxy

groups on the lower aryl-ring of the ligand biaryl axis (entry 10). Surprisingly, the optimal ligand for the asymmetric Suzuki-Miyaura reaction (NitinPhos, **L7**, entry 5) gave poor yield and selectivity in the Negishi coupling considering that the presumed enantiodetermining step of reductive elimination should be identical for the Negishi and Suzuki-Miyaura reactions. This difference in selectivity was something we wanted to understand further (*vide infra*). In general, C2-substituion on the oxaphosphole or azaphosphole ring of the ligand was required for good selectivity (entry 1 *vs* entries 2 – 10, and entries 15 – 16 *vs* entries 17 – 21). Further increasing the steric bulk at this C2-position by introducing a second methyl group enabled similar selectivities but led to a reduction in yield (entries 8 & 12). Additionally, a trend was observed where increasing the electron-donating ability of the lower aryl-ring bearing the alkoxy-substituents led to improved enantioselection (compare entries 2, 9, and 10). Lastly, the azaphosphole series of ligands were extremely efficient in terms of reaction yield; however, enantioselectivities were lower with this series (entries 15, 17, 18, 19).

Table 4. Ligand Survey in the Asymmetric Negishi Cross-Coupling Towards Tetra-*ortho*-Substituted Biaryls.



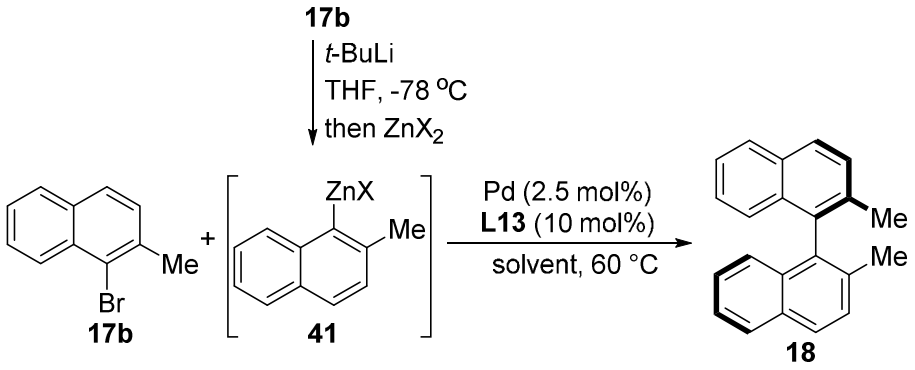
Entry	**Ligand**	% yield[a]	er[b]
1	**L1**	69	52.5:47.5
2	**L2**	49	78.5:21.5
3	**L3**	ND	81.5:18.5
4	**L4**	38	82.5:17.5
5	**L7**	10	80.5:19.5

6	**L9**	82	76.5:23.5
7	**L10**	89	83.0:17.0
8	**L11**	69	85.5:14.5
9	**L12**	81	71.3:28.7
10	**L13**	**93**	**85.0:15.0**
11	**L14**	45	82.0:18.0
12	**L15**	24	83.0:17.0
13	**L21**	67	77.0:23.0
14	**L22**	36	65.0:35.0
15	**L23**	91	60.5:39.5
16	**L24**	68	61.0:39.0
17	**L25**	96	82.5:17.5
18	**L26**	89	79.0:21.0
19	**L27**	99	53.0:47.0
20	**L28**	76	60.0:40.0
21	**L29**	82	78.0:22.0

[a]Isolated yield. [b]Determined by chiral HPLC analysis with Chiralpak OD-H column.

With identification of **L13** as the best ligand out of the ligand survey in Table 4, we further optimized parameters for the Negishi coupling reaction with ligand **L13** in an effort to improve enantioselection (Table 5). The Pd-precatalyst, metal-ligand ratio, Zn-source, and solvent were examined in the reaction (Table 5). The choice of Pd-precatalyst had little impact on the reaction enantioselectivity, but the yield varied from 70 – 80 % (entries 1, 4, 5, 7). The metal-ligand ratio also had no impact on selectivity; however, the yield improved if a 1:1.5 Pd:**L13** ratio was employed (entries 8 – 10). Finally, use of other Zn-salt precursors or other solvents did not lead to improvements in reaction efficiency (entries 2, 3, 6, 7).

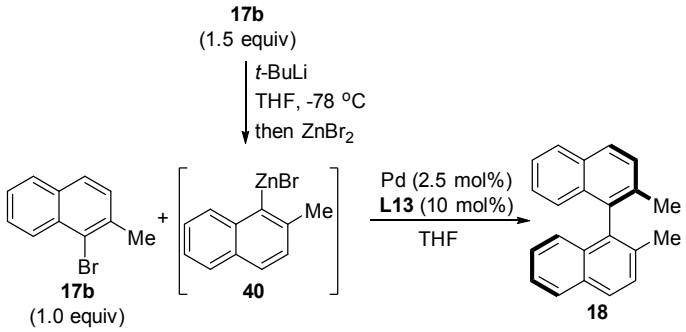
Table 5. Survey of Pd-precatalyst, Pd:L13 ratio, Zn-source, and solvent in the Negishi Cross-Coupling Reaction.



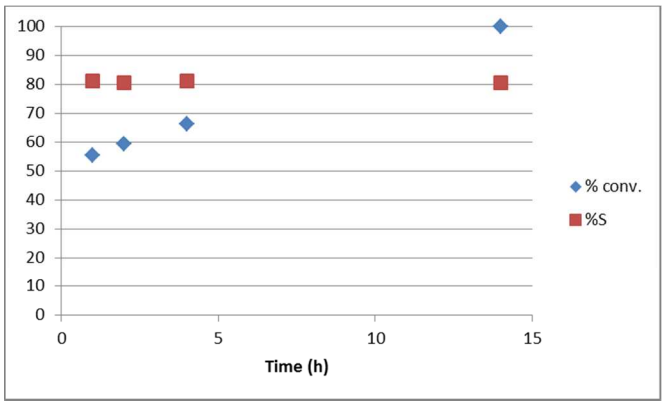
Entry	Pd	Metal:**L13** ratio	ZnX_2	Solvent	Yield %[a]	Er[b]
1	$Pd(OAc)_2$	1:2	$ZnBr_2$	THF	81	85.0:15.0
2	$Pd_2(dba)_3$	1:2	$ZnBr_2$	Toluene	80	85.0:15.0
3	$Pd_2(dba)_3$	1:2	$ZnBr_2$	Dioxane	90	85.0:15.0
4	$PdCl_2(PhCN)_2$	1:2	$ZnBr_2$	THF	71	82.0:18.0
5	$[crotylPdCl]_2$	1:2	$ZnBr_2$	THF	73	83.0:17.0
6	$Pd_2(dba)_3$	1:2	$Zn(OAc)_2$	THF	56	78.0:22.0
7[c]	$Pd_2(dba)_3$	1:2	$Zn(OPiv)_2$	THF	77	84.0:16.0
8	$Pd_2(dba)_3$	1:2	$ZnBr_2$	THF	80	85.0:15.0
9	**$Pd_2(dba)_3$**	**1:1.5**	**$ZnBr_2$**	**THF**	**93**	**85.0:15.0**
10	$Pd_2(dba)_3$	1:1	$ZnBr_2$	THF	76	85.0:15.0

[a]Isolated yield. [b]Determined by chiral HPLC. [c]The zinc reagent was prepared from the Grignard according to Knochel's protocol (ref 38a).

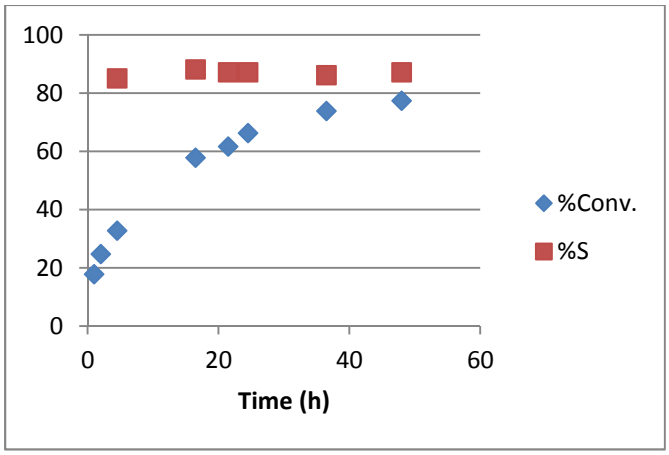
To determine if enantioselection in the reaction was variable with reaction progress, the enantioselectivity was monitored over time at both 40 and 60 °C (Scheme 8). Enantioselection was independent of conversion implying that the active catalyst was not changing over time. Reduction of the reaction temperature led to slight improvements in enantioselectivity, but incomplete conversion was obtained at 40 °C.



(a) 60 °C:



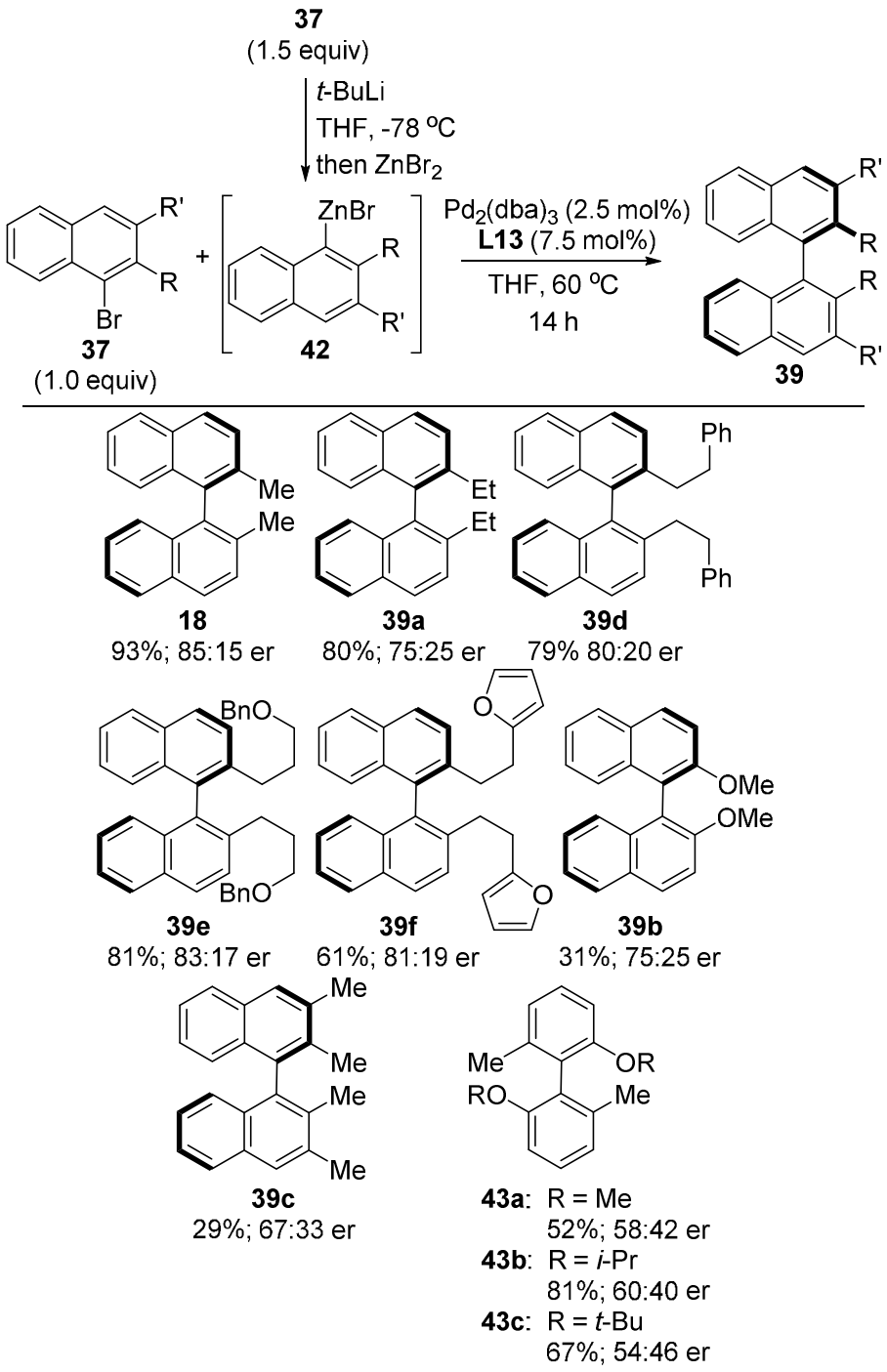
(b) 40 °C:



Scheme 8. Enantioselectivity vs Time at 40 and 60 °C.

The most efficient catalyst conditions identified in our studies (Table 5, entry 9) were next utilized to examine the scope of the Negishi cross-coupling to afford other tetra-*ortho*-

substitued biaryls (Scheme 9). Notably, the Negishi reaction showed much better scope in terms of reaction yield relative to the Suzuki-Miyaura reaction albeit with lower enantioselection. For the first time, a variety of R-alkyl substituents other than R = Me or OMe have been analyzed in an asymmetric cross-coupling reaction to provide tetra-*ortho*-substituted products (**39d-f**). In general, the cross-coupling employing **35** with R = *n*-alkyl afforded comparable results (**18**, **39a,c-f**). Methoxy-substitution (**39b**) was not well tolerated and afforded reduced yield due to significant amounts of reduction of the aryl bromide as a byproduct. Adding an additional methyl-substituent on the naphthalene ring also led to decreased reaction efficiency and enantioselectivity (**39c**); however, product formation was observed whereas the corresponding Suzuki-Miyaura coupling afforded no reaction with this substrate class (Scheme 7). Finally, the present system was specific to coupling naphthalene derivatives. Cross-coupling to afford **43** proceeded in moderate to good yields, but almost no enantioselection was observed despite the nature of the alkoxy-substituent.



Scheme 9. Asymmetric Negishi Cross-Coupling Reaction Scope.

Mechanistic Modeling by DFT Analysis.

The results of our combined studies of the asymmetric Suzuki-Miyaura and Negishi cross-coupling reactions employing ligand series **33** and **36** prompted us to investigate the mechanistic differences between these two reactions in terms of the enantiodiscrimination steps. Specifically, these ligands gave very different results in the coupling reaction when employed in a Suzuki-Miyaura *vs* a Negishi type protocol, yet mechanistically, the final step in the catalytic cycle for both processes would presumably proceed through the same reductive elimination intermediate (*vide supra*). To help understand these differences and to aid in the development of new ligand structures to improve enantioselectivity, we modeled the cross-coupling process using density functional theory (DFT) calculations.[39]

Negishi Cross-Coupling

Most analyses of the stereoselectivity in cross-couplings regard the final step as stereodetermining.[11b,13b,n,x] Such an approach assumes equal accessibility to all of the different conformers of the transition state precursors. The percentage of product that forms via each of the possible reductive elimination transitions states can then be determined by Boltzmann analysis of their relative energies.

For the system in question here, a defining feature of the Pd biaryl intermediates preceding reductive elimination is the hindered rotation along the aryl-Pd bonds due to the large size of the aryl groups employed. As such, direct interconversion[13f,15a] of the different conformations of these intermediates does not occur. However, we hypothesize that all the conformers will be equally accessible due to the reversibility of transmetalation and oxidative addition in the Negishi coupling.[40] In such a scenario, a classical analysis of just the reductive elimination transition states pertains. Thus, all four of the possible biaryl palladium isomers need

to be considered, each giving rise to two reductive elimination transition states, pro-*S* and pro-*R* (Figure 1).

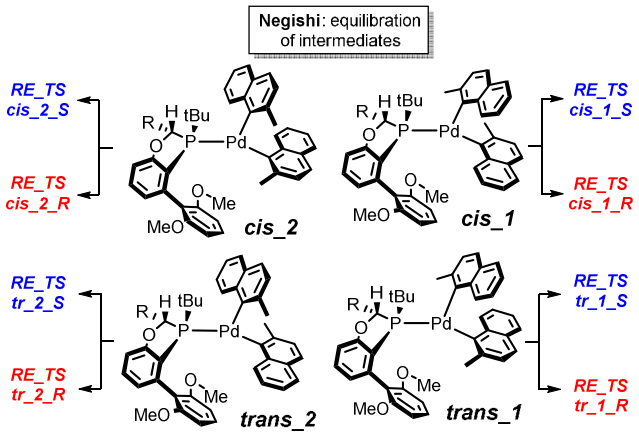


Figure 1. Stereoselection in Negishi Coupling

Analyzing reductive eliminations for the Me-BOP ligand **L2** in such a fashion, we found that there is one dominant transition state for each of pro-*S* and pro-*R* sets, controlling the overall selectivity (Figure 2).

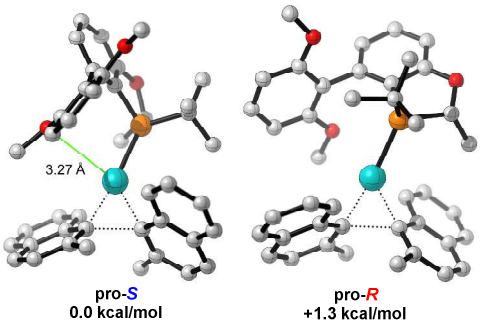


Figure 2. Lowest energy pro-*S* and pro-*R* reductive elimination transition states for Me-BOP ligand **L2**. Total of 8 transition states were located and analyzed. Free energies were computed using M06/6-311+G(d,p)-LANL2DZ(Pd)-SMD-THF//B3LYP/6-31G(d)-LANL2DZ(Pd); values are in kcal/mol.

Coordination of Pd to the methoxy-group of the lower aryl ring of the Me-BOP ligand provides extra stabilization for the pro-*S* transition state, resulting in highly *S*-selective reaction. For the pro-*R* transition state, such an arrangement is not favorable due to the steric interactions with the ligand. A correlation between the electron-donating properties of the lower ring substituent (σ_p) and the experimental *er* of the product supports the contribution of this specific substituent to the enantioselection mechanism (Figure 3).

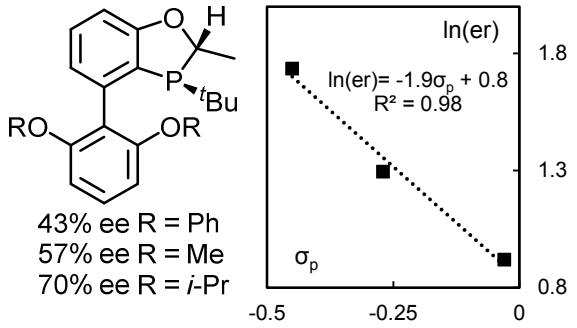


Figure 3. Efficiency of the chiral Me-BOP ligand vs electron donating property of the lower aryl-ring substituent.

When the Negishi coupling is performed with the alternate DMM-substituted BOP ligand (NitinPhos, **L7**), enantioselectivity drops. This result can be rationalized using the same approach. Analysis of the selectivity-determining transition states revealed that the additional coordinating group of the DMM-substituent of NitinPhos ligand **L7** allows selective stabilization of the higher energy pro-*R* transition state (Figure 4), which diminishes the pro-*R* – pro-*S* energy gap and hence the selectivity of the overall process.

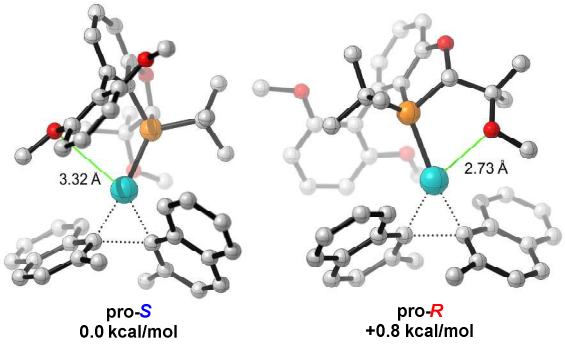


Figure 4. Lowest energy pro-*S* and pro-*R* reductive elimination transition states for the DMM-BOP ligand (NitinPhos, **L7**). Total of 32 transition states were located and analyzed. Free energies were computed using M06/6-311+G(d,p)-LANL2DZ(Pd)-SMD-THF//B3LYP/6-31G(d)-LANL2DZ(Pd); values are in kcal/mol.

This analysis of the reductive elimination transition states for the Negishi reaction rationalizes the experimentally observed enantioselectivities and highlights the key interactions (Figure 5).

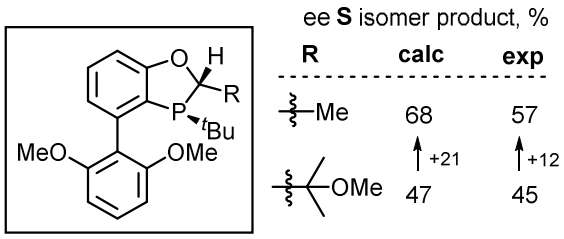


Figure 5. Comparison of the experimental and calculated efficiencies of the ligands in Negishi coupling.

Suzuki-Miyaura Coupling

The different performance of the DMM-BOP ligand (NitinPhos, **L7**) in the Suzuki-Miyaura coupling requires a different enantioselection mechanism. Irreversible transmetalation[41] in Suzuki-Miyaura coupling would prevent pre-equilibration of pre-reductive elimination Pd(II) species. As such, enantioselectivity of the overall process would be determined not only by the

energetics of reductive elimination, but also by the relative population of the pre-reductive elimination Pd(II) intermediates. Thus, it is necessary to consider the relative rates of formation of corresponding species by modeling the transmetalation step. Based on the proposed structures of the pre-transmetalation intermediates,[42] the same hindered rotation issues are expected as for the pre-reductive elimination intermediates. Therefore, pre-transmetalation intermediates partition into two groups that react via independent pathways. In turn, the population of the pre-transmetalation intermediates is controlled by the energetics of oxidative addition. Therefore, all three major steps of the cross-coupling mechanism contribute to the overall selectivity of the reaction (Figure 6). Earlier computational studies of the stereoselectivity in Suzuki-Miyaura cross-coupling suggest that oxidative addition is the stereodetermining step.[43] We further develop this idea of early enantioinduction by employing the experimental findings of Denmark,[42a,b] Hartwig,[42c] and others[42d,e] that point to the mechanism of the transmetalation step proceeding through a Pd-OH complex.[17] The exact mechanism for the transmetalation step in Suzuki-Miyaura cross-coupling is still somewhat controversial[39] as there are some reports[44] that support the alternate "boronate"-transmetalation pathway.[45] The studies reported herein are calculated using the Pd-OH transmetalation pathway;[42] however, we would like to stress that the model proposed herein is also compatible with the "boronate"-transmetalation[44,45] mechanism: both possibilities ultimately lead to the same transmetalation transition states. The nature of the incoming boron species (boronate *vs* boronic acid) is not crucial for the selection of the productive oxidative addition step (discussed later) as the same steric interactions are present.

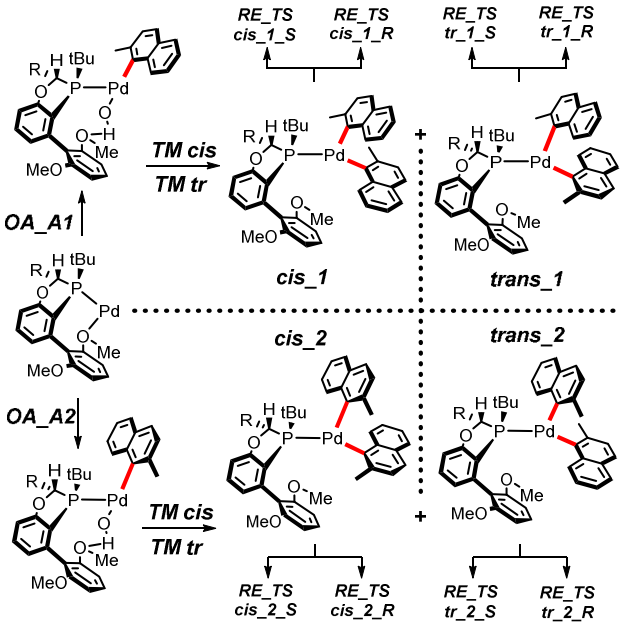


Figure 6. Proposed stereoselection mechanism in Suzuki coupling. Species separated by dashed lines cannot equilibrate. Rotation around the bonds marked in red is hindered.

Hence, detailed computational analysis of all the steps of the coupling is required. The resultant three-layer selectivity mechanism is shown on Figure 6. This important difference between the Suzuki-Miyaura and Negishi couplings is the result of the irreversible nature of transmetalation in Suzuki-Miyaura coupling. As such, the difference in the energetics of transmetalation significantly complicates the stereoselection process, which explains the well-known challenges in the design of stereoselective Suzuki-Miyaura couplings.

This analysis of the Suzuki-Miyaura coupling focuses two very similar ligands, DMM- and DME-BOP (**L7** *vs* **L6**, respectively). Despite minor differences in structure, these ligands provide substantially different selectivity levels. The following study rationalizes these selectivity differences within the proposed multi-level selectivity framework. To begin, a detailed analysis of the DME-BOP (**L6**) ligand is outlined.

Oxidative addition

Oxidative addition to Pd(0) can occur via two pathways, A and B (Figure 7). Exchange of the bromide ultimately leads to several isomers of the PdOH species (Figure 8).

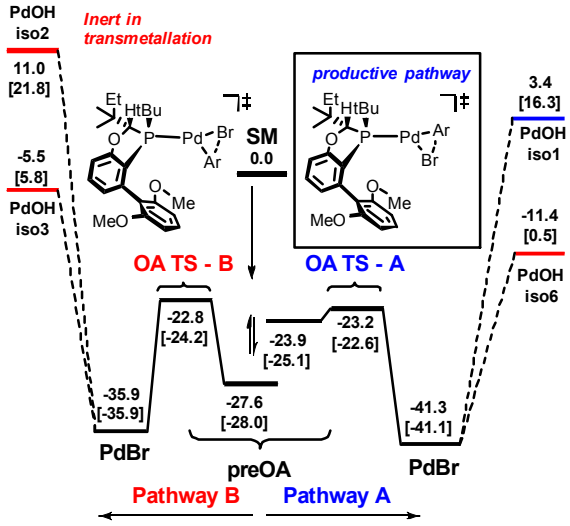


Figure 7. Oxidative addition pathways in Suzuki coupling. Intermediates marked in red are inert in transmetallation step. Enthalpies and free energies (in brackets) were computed using B3LYP-d3/6-31G(d)-lanl2dz(Pd, Br); values are in kcal/mol. Reactions are balanced using water as the OH source and HBr as the by-product of the exchange.

In considering the PdOH isomers (Figure 8), only **iso1** is ultimately relevant to the next step, transmetalation. For transmetalation to take place, the hydroxyl group and the vacant orbital in PdOH species must be positioned *cis* on the metal center, which rules out **iso2** and **iso3**. Isomers **iso4** and **iso5** have severe destabilizing steric interaction between ligand and the naphthyl group, making them unlikely to be formed. Furthermore, **iso6** is not active in transmetalation as the vacant orbital is blocked by the ligand, so the approach of incoming boronic acid is problematic. As a consequence, only **iso1**, which arises from oxidative addition pathway A, needs to be analyzed. Given the activity of **iso1** PdOH in transmetalation, we theorize that the other species may eventually convert to **iso1**.

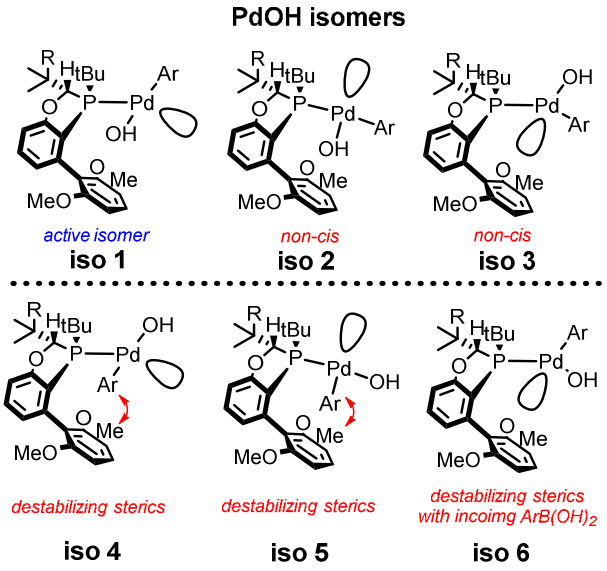


Figure 8. Isomeric PdOH intermediates.

Pathway A oxidative addition can occur via two conformations, corresponding to different orientations of the aryl group ('up' and 'down', see Figure 9). The relative energies of these conformations ultimately translate to the ratio of the PdOH species after exchange of the bromide. Based on the energies of oxidative addition transition states, 85% of the formed PdOH arises from **OA A1** where the methyl of the naphthyl unit is pointing 'away'. This selectivity is attributed to an unfavorable methyl-ligand interaction in the transition state **OA A2** (red arrow, Figure 9 insert). This differentiation sets up the first layer in the enantioselection mechanism.

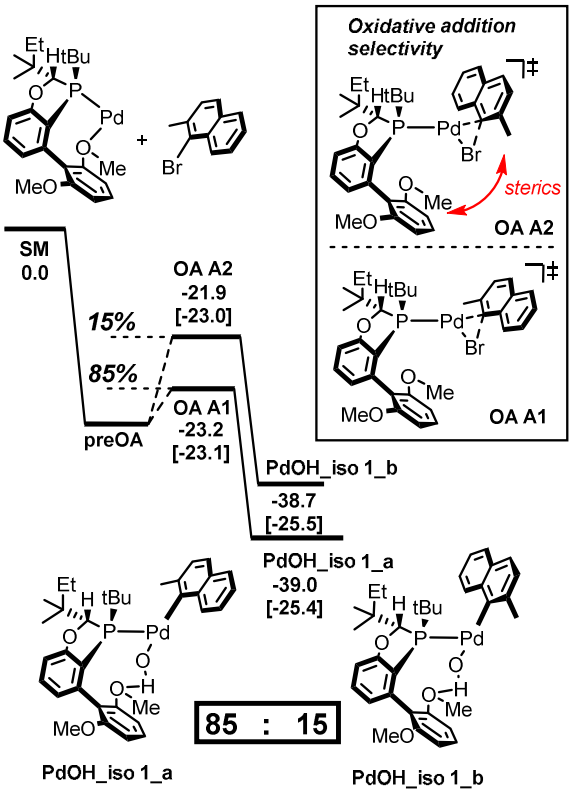


Figure 9. Energetics and selectivity of the productive oxidative addition pathway in Suzuki coupling. Total of 8 oxidative addition transition states were located and analyzed. Enthalpies and free energies (in brackets) were computed using B3LYP-d3/6-31G(d)-LANL2DZ (Pd, Br); values are in kcal/mol. From here on the reactions are balanced using KOH as the OH source and KBr as the by-product of PdOH formation.

Transmetalation

The resultant PdOH intermediates form a pre-transmetalation complex with the boronic acid (preTM, insert in Figure 10). The incoming boronic acid can coordinate such that the methyl substituents on the naphthyl rings are *cis* or *trans*. Starting from the major PdOH adduct (**PdOH_iso 1_a**, Figure 9), the *trans* adduct is more favorable due to the lack of Me-Me repulsion. This interaction also controls the energies of the concomitant transmetalation transition states (**TM TS** *cis* and *trans*, figure 10). The energy gap between transition states

results in 85% of the **pre-RE-*trans*** product vs 15% of the **pre-RE-*cis*** product. For the minor PdOH adduct (**PdOH_iso 1_b**, Figure 9), these trends are reversed (see Figure 11) due to the greater spacing between the naphthyl units. As a result, the *cis* adduct (**pre-RE-*cis***, figure 11) predomominates over the *trans* (**pre-RE-*trans***, figure 11) adduct (76% vs 24%). During the transmetalation process, an equivalent of boronic acid is released that exists as the borate under the basic reaction conditions.[46]

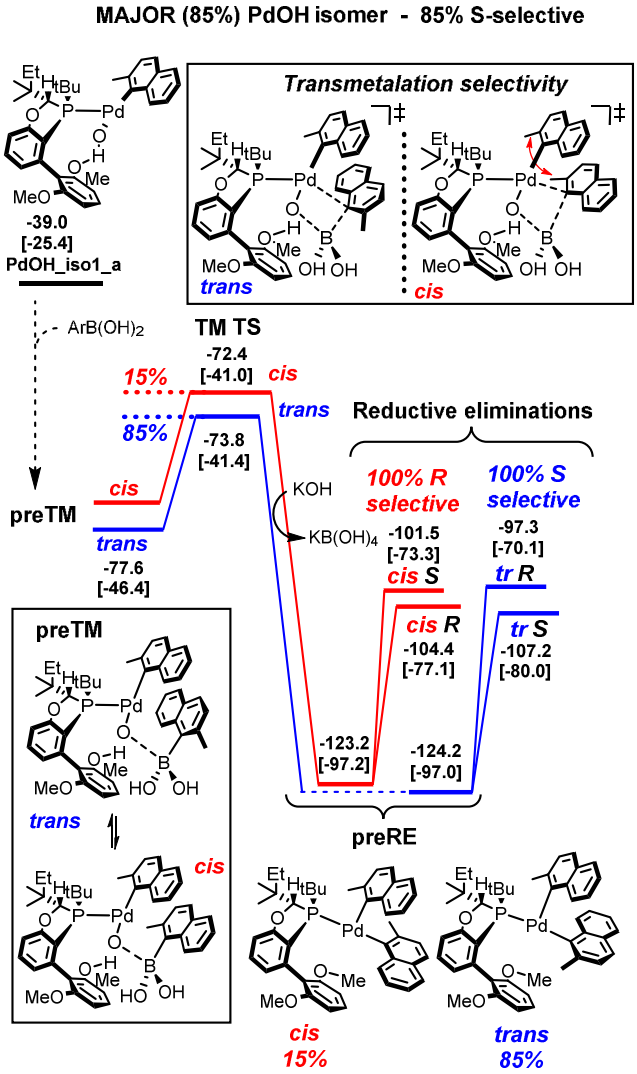


Figure 10. Energetics and selectivities of the transmetalation and reductive eliminations arising from the major PdOH isomer. Total of 8 transmetalation transition states and 16 reductive

elimination transition states were located and analyzed. Enthalpies and free energies (in brackets) were computed using B3LYP-d3/6-31G(d)-LANL2DZ (Pd, Br); values are in kcal/mol.

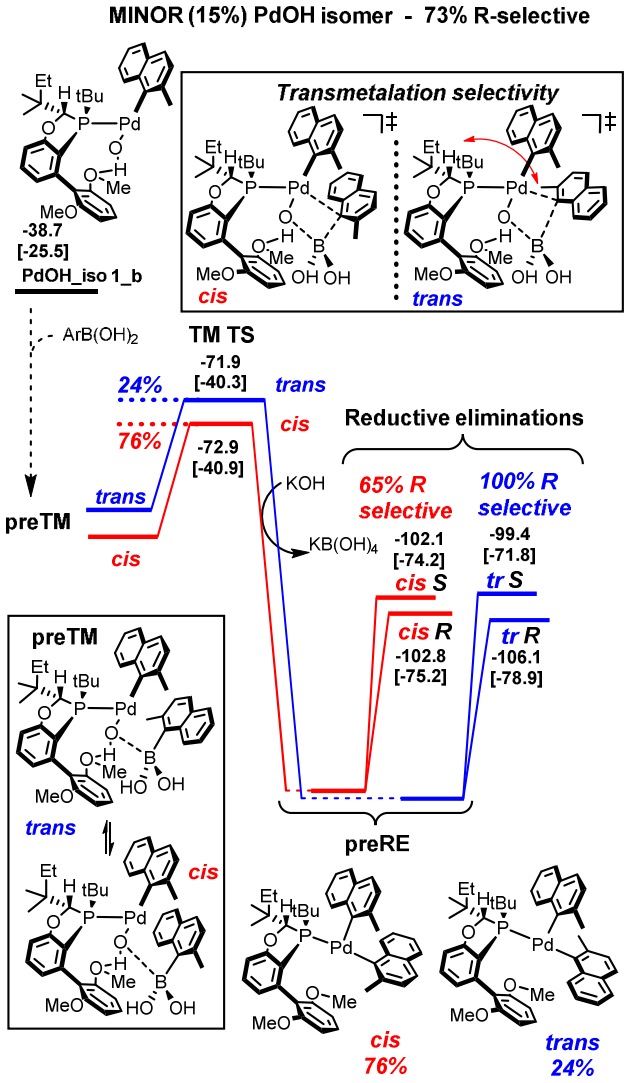


Figure 11. Energetics and selectivities of the transmetalation and reductive eliminations arising from the minor PdOH isomer. Total of 10 transmetalation transition states and 16 reductive elimination transition states were located and analyzed. Enthalpies and free energies (in brackets) were computed using B3LYP-d3/6-31G(d)-lanl2dz (Pd, Br); values are in kcal/mol.

Reductive Elimination

Both the *cis* and *trans* isomers of the diaryl Pd species (**preRE** intermediates in Figures 10 and 11) can reductively eliminate to form either the *S* or *R* binaphthyl. Analyzing the energetics of reductive eliminations resulting from the major PdOH isomer, we found that *cis* pre-reductive elimination intermediate affords the *R*-isomer with excellent selectivity, while the *trans* isomer furnishes exclusively the *S*-product (reductive eliminations, Figure 10).

The extremely high selectivity of the individual reductive eliminations is due to the compact nature of the transition states. Even minor deviations from the optimal arrangement result in significant energetic penalties. For example, the reductive elimination transition states from the major PdOH isomer depicted in Figure 10, illustrate these phenomena (Figure 12). For the pre-RE-*trans* isomer, ***tr S*** transition state (100%) is much more favorable than ***tr R***, in which interactions of the methyl of the upper naphthyl unit (arising from the aryl bromide) and the back side of the ligand destabilize the structure. Similarly, ***cis R*** (100%) is more stable than ***cis S*** for the pre-RE-*cis* isomer.

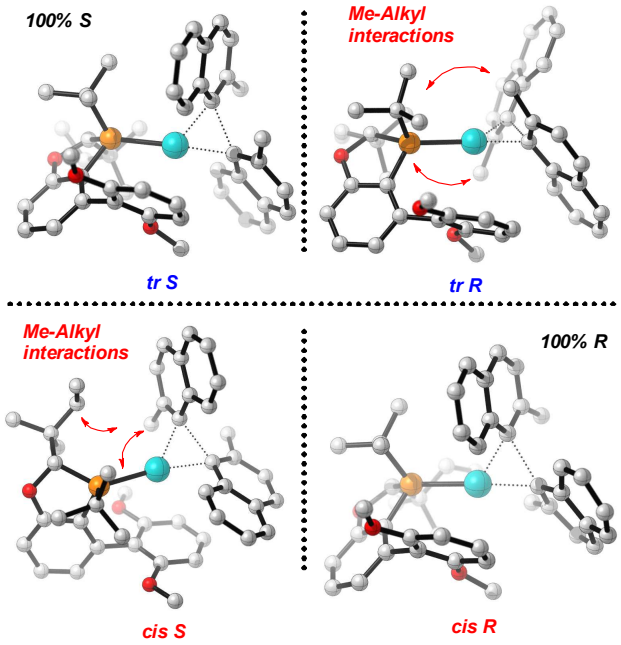


Figure 12. Lowest energy pro-*S* and pro-*R* reductive elimination transition states from the major *trans* and *cis* isomers of diaryl Pd.

As the orientation of the naphthyl fragment is important for the high stereoselectivity of reductive elimination, one might expect lower selectivities for the case of reductive elimination from the minor PdOH isomer (Figure 11), where the upper naphthyl unit is rotated in the opposite direction. Indeed, the pre-RE-*cis* is only moderately selective towards reductive elimination *vs* ***cis R*** (65%). Reductive elimination from **pre-RE-*trans*** remains highly selective (100% ***tr R***) because the methyl group on the lower ring is pointing toward a sterically crowded portion of the transition state.

However, the relative energies of the reductive elimination transition states do not tell the whole story as the intermediates needed for this step form at different rates with both oxidative addition and transmetalation contributing to the partitioning. Figure 13 illustrates a simplified version where different conformational isomers are not shown for each of the branches. Oxidative addition leads to two branches (left = minor, right = major), which again bifurcate at transmetalation and reductive elimination. The pathway highlighted with blue arrows is the only *S*-selective channel on the diagram. Even though there are more pathways to the *R*-enantiomer, the *S*-selective channel is lower in energy and is the main route responsible for formation of the product.

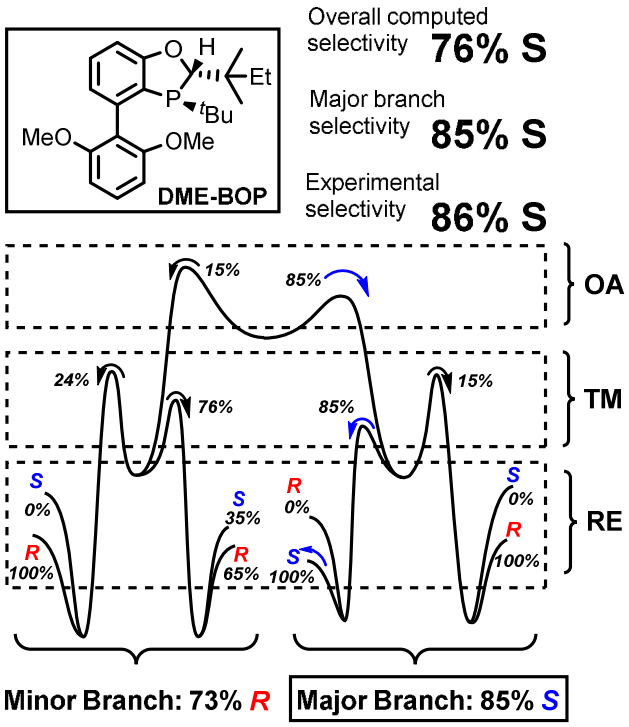


Figure 13. Simplified energy diagram for Suzuki coupling with DME-BOP (**L6**) ligand. Selectivities of each step were calculated based on the Boltzmann distribution of the energies of corresponding transition states. (Alternatively, such multi-level processes can be analyzed using a system of rate equations, *i.e.* microkinetic modeling.[47])

Analysis of the DMM-BOP (NitinPhos, **L7**) ligand generates a similar outcome (Figure 14). The entire transformation is still *S*-selective and just like in a previous case, there is only one pathway responsible for the production of the major product. However, this pathway is more favorable than it is in the DME-BOP (**L6**) case. For the DMM ligand (NitinPhos, **L7**) transmetalation selectivity in the 'major branch' (Figure 14) is 90:10, whereas for the DME ligand it is at a slightly smaller 85:15. This difference causes selectivity levels to be higher for DMM (NitinPhos, **L7**).

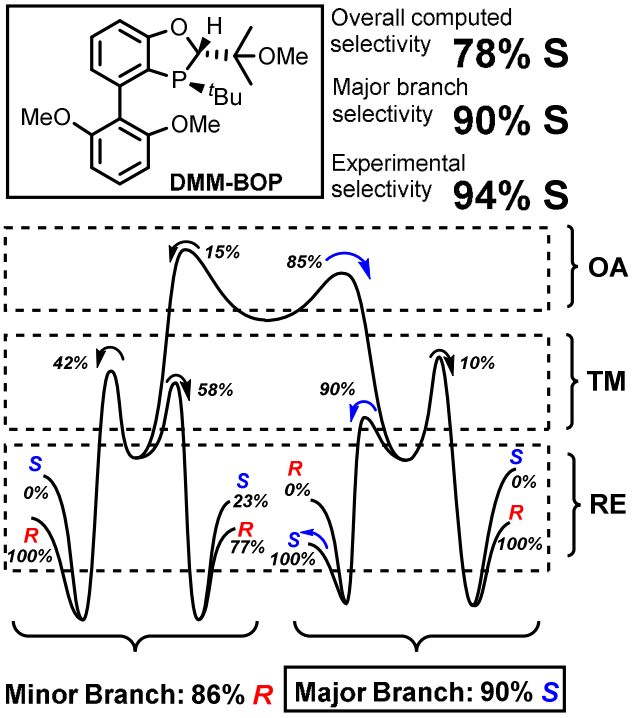


Figure 14. Simplified energy diagram for Suzuki coupling with DMM-BOP (NitinPhos, **L7**) ligand.

If one assumes that the entire reaction is controlled only by the selectivity of the major branch, then the difference in the transmetalation energetics would predict the experimentally observed selectivities with improved accuracy (see 'major branch' selectivities on each of the diagrams). Thus, our model would predict 85% *S* selectivity for DME-BOP (**L6**) ligand vs 86% experimental and 90% *S* selectivity for DMM-BOP (NitinPhos, **L7**) ligand vs 94% experimental. Given the complex nature of the selectivity mechanism and the large number of transition states that contribute to the finalized percentages (26 transition states conformers were analyzed and utilized in Boltzmann distributions), this result may indicate that the major branch is indeed the only controlling channel. Such a situation would occur if our estimates of the pre-transmetalation intermediates are not entirely accurate. In our work we tested five computational methods (different combinations of various optimization and single-point calculations) with 36-56

transition state conformations depending on the method. These analyses did not improve the quality of the predictions. This high sensitivity of the selectivity estimates to the type of method used may indicate that our method of choice is not optimal and leads to incorrect estimates of the energetics of major/minor branch splitting. It might also point to the existence of other selectivity-contributing steps (for example, Br exchange) that were not considered.

Since the transmetalation selectivity in the major branch seems to account for the observed difference in the performance of the ligands, we undertook further study of the transmetalation step. As discussed earlier, each of the energy levels shown on the diagrams represents only the lowest energy structure out of a set of calculated conformational isomers. Importantly, molecules traversing the reaction coordinate proceed through a distribution of available conformational transition states rather than through the single lowest energy pathway;[48] therefore, the calculated selectivities given in this study were determined using the energies of all the available conformations identified by calculation. This consideration accounts for the computationally observed different transmetalation selectivities of the DMM-BOP (NitinPhos, **L7**) and DME-BOP (**L6**) ligands (Figure 15). For the DMM-BOP (NitinPhos, **L7**) ligand, the transmetalation pathways leading to *S*-selective reductive elimination are more populated than that for the DME (**L6**) ligand (90% vs 85%), while the other pathways are less populated (10% vs 15%). This result arises from the greater partitioning to the *S*-selective transition states for the DMM-BOP ligand which are clustered close together relative to those for the DME-BOP ligand which cover a larger range and are less populated overall relative to the R-selective transition state. This phenomenon accounts for the improved transmetalation selectivity obtained with the DMM-BOP ligand (**L7**) *vs* the DME-BOP ligand (**L6**), and can be explained structurally by the presence of hydrogen bonding interactions between weak C–H hydrogen bond donors of the

methylnaphthalene coupling partners with the methoxy-group of the DMM-BOP ligand that is not possible in the DME-BOP ligand case (*i.e.* **42** *vs* **45**). Hydrogen bond contacts between the methoxy-group of NitinPhos (**L7**) and C–H bonds of the methylnaphthalene coupling partners are present in transmetalation transition states (**42**, **43**). The bond distances for these O–H interactions are within the distance and angles typical of weak C–H–O hydrogen bonds (2.2 – 2.8 A; **42**: C_{sp2}–H–O = 119°, C_{sp3}–H–O = 157°; **43**: C_{sp3}–H–O = 158°, 135°).[13b,49] These stabilizing interactions cause fewer accessible low-energy transmetalation transition state conformations to be available in the DMM-BOP ligand case because rotation of the DMM-group results in loss of these interactions which creates a higher energy gap between these conformations such that they cannot contribute to product formation. In contrast, the DME-BOP ligand does not have these interactions, and therefore, the energy splitting between conformers is less severe and leads to several accessible pathways of various energy levels with slight differences in steric interactions due to the orientation of the ethyl-group of the DME-substituent. Finally, it is worth noting that direct coordination of the methoxy-substituent of the DMM-BOP ligand (**L7**) to the metal center was not found in any of the relevant transition states.

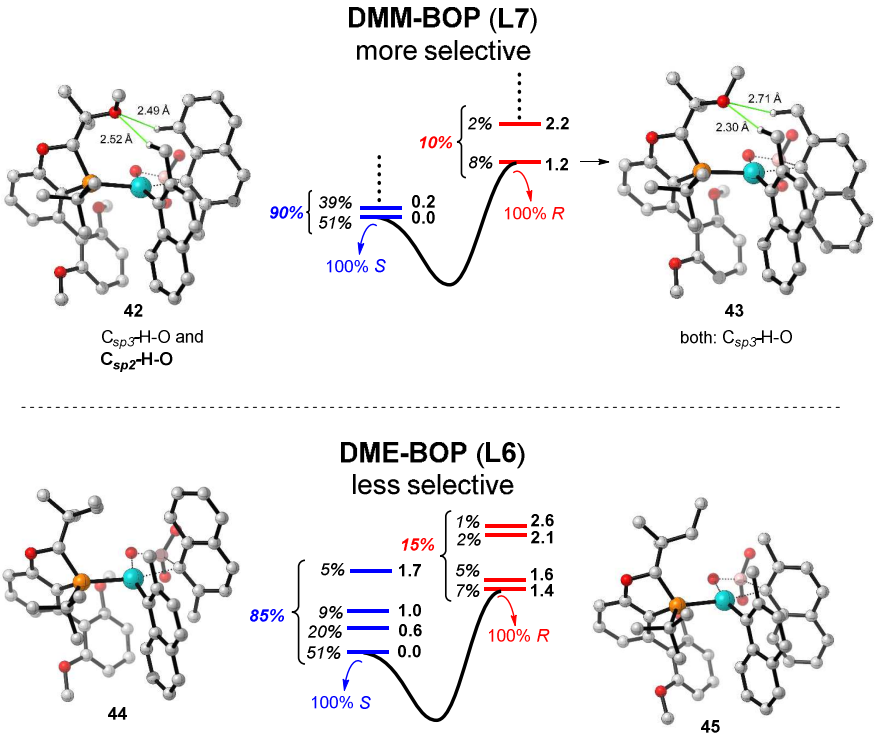


Figure 15. Relative energies (in bold), and relative populations of the major branch transmetalation transition states for DMM-BOP (NitinPhos, **L7**) and DME-BOP (**L6**) ligands. Green lines represent C–H---O hydrogen bonding interactions. Dashed lines indicate additional high-energy conformations that do not significantly contribute to the population distribution.

This DFT study of the stereoselectivity of Suzuki-Miyaura coupling allowed us to propose a multi-step stereoselection framework. This mechanism is likely to operate in the coupling of sterically hindered substrates, where isomeric organometallic intermediates do not readily interconvert.

CONCLUSION

In conclusion, Pd-catalyzed asymmetric Suzuki-Miyaura and Negishi cross-coupling reactions to form tetra-*ortho*-substituted biaryls were developed. Higher enantioselectivities were

obtained for the Suzuki-Miyaura reaction; however, better substrate generality was obtained for the Negishi coupling. For each coupling reaction, a unique ligand was identified to be optimal for the Suzuki-Miyaura *vs* the Negishi reaction in terms of providing maximum enantioselection. Detailed DFT calculations of these two processes offered an explanation for the differences in the enantiodiscrimination mechanism between the Suzuki-Miyaura and Negishi cross-coupling reactions that likely proceed through the same Pd-intermediate for reductive elimination.

Analysis of only the reductive elimination step in the Negishi cross-coupling reaction by DFT provided good correlation with the experimental enantioselectivity, implying that reductive elimination was enantiodetermining. In contrast, this same analysis for the Suzuki-Miyaura coupling did not accurately predict the observed experimental selectivities. A complete analysis of the oxidative addition, transmetalation, and reductive elimination steps in the Suzuki-Miyaura reaction using DFT revealed that the selectivity in the Suzuki-Miyaura reaction was influenced by all three steps in the catalytic cycle. The delicate interplay of oxidative addition, transmetalation, and reductive elimination calculated for stereocontrol in the Suzuki-Miyaura cross-coupling reaction for the formation of tetra-*ortho*-substituted biaryls may be the reason why the Suzuki-Miyaura reaction was less tolerant to substrate modifications relative to the analogous Negishi reaction. These findings may aid in the design and development of new catalysts to improve reactivity and selectivity in asymmetric cross-coupling reactions to furnish tetra-*ortho*-substituted biaryls

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publication website at DOI: Experimental procedures, characterization data for new compounds, DFT methods, intermediate and transition state coordinates, and copies of ^{1}H, ^{13}C , and ^{31}P NMR spectra of all new compounds.

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Notes

The authors declare the following competing financial interest(s): Some of the ligands used in this work are covered by the following patents: US 9096626, US 20130137902, US 20180155377, WO 2011126917.

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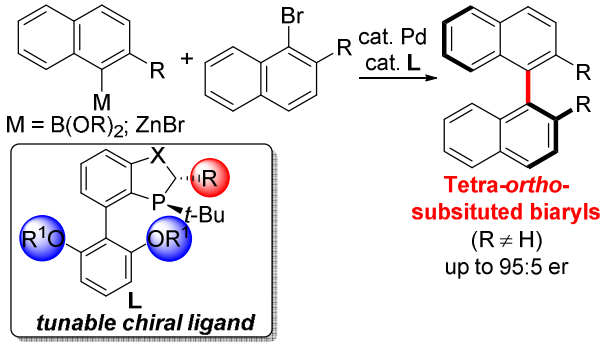
R
M
M = B(OR)2; ZnBr
Br
R
cat. Pd
cat. L
R
R
Tetra-ortho-
subsituted biaryls
(R ≠ H)
up to 95:5 er
X
R
P
t-Bu
R1O
OR1
L
tunable chiral ligand