JOC The Journal of Organic Chemistry

Article

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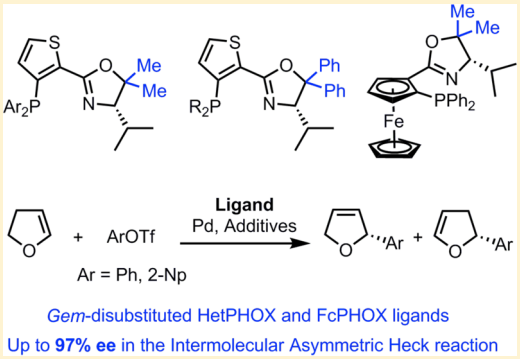
Exploiting the *gem*-Disubstitution Effect in FcPHOX and HetPHOX P,N Ligands: Synthesis and Applications in Pd-Catalyzed Intermolecular Heck Reactions

Dennis McCartney, Chris Nottingham, Helge Müller-Bunz, and Patrick J. Guiry*

Centre for Synthesis and Chemical Biology, UCD School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland

Supporting Information

ABSTRACT: The synthesis of a range of novel *gem*-disubstituted and electronically varied thiophene−oxazoline (HetPHOX) ligands and ferrocene−oxazoline (FcPHOX) ligands and their application in the Pd-catalyzed intermolecular asymmetric Heck reaction (IAH) is described. These investigations show that *gem*-disubstitution of *i*-Pr-PHOX-type ligands can lead to effective and cost-efficient alternatives to the corresponding *t*-Bu-PHOX systems. The Pd complexes of these ligands were very effective in the IAH, providing phenylated products in up to 100% conversion with up to 97% ee.



INTRODUCTION

The design and synthesis of new oxazoline-containing ligands for asymmetric catalysis is an extensive, thriving field of research.[1−3] Metal complexes of oxazoline-based ligands such as PHOX (Figure 1), bearing a *t*-Bu group at C(4), often afford high ee's for a variety of asymmetric transformations. However, the synthesis of these ligands involves starting from the prohibitively expensive, non-natural amino acids (*S*)- and (*R*)-*tert*-leucine.[4]

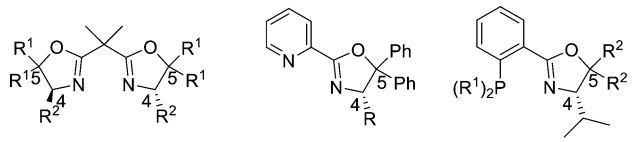


Figure 1. BOX, PyOX, and PHOX analogues with *gem*-disubstitution at C(5).

In most cases, exchanging the *t*-Bu group for an *i*-Pr group results in a significant decrease in enantioselectivity due to conformational control of the C(4)-stereodirecting group. However, when a *gem*-dimethyl group is located **α** to the *i*-Pr group at C(5) in an oxazoline ring the *i*-Pr group is forced to adopt a conformation analogous to that of a *t*-Bu group. Some early examples of oxazoline-containing ligands featuring *gem*-disubstitution in order to provide a more sterically rigid system include BOX analogues from the group of Corey,[5] PyOx analogues from the group of Brunner,[6] and PHOX analogues from the groups of Pfaltz,[7] Paquin[8,9] (Figure 1), and most recently, Stoltz.[10] Paquin's work, the synthesis and application of 5,5-dimethyl-*i*-Pr-PHOX as a practical equivalent of the expensive *t*-Bu-PHOX, was motivated by a key concept in modern ligand research, i.e., the design and application of more economical ligands.[8] Davies was the first to demonstrate the *gem*-dimethyl effect in asymmetric synthesis when he reported the synthesis and application of a cheaper, yet equally efficient, *gem*-dimethyl alternative to Evans' auxiliary.[11] Davies also demonstrated that this effect exists both in the solid state and in solution through X-ray crystallographic and ^{1}H NMR NOE studies.[12,13] Seebach later reported the synthesis and application of a *gem*-diphenyl alternative to Evans' auxiliary, although this was not investigated in terms of providing a *t*-Bu mimic.[14] We sought to further examine the effect of *gem*-disubstitution on a range of different PHOX systems such as those based on thiophene (HetPHOX, ligands **1**−**6**) and ferrocene (FcPHOX, ligand **7**) (Figure 2). Both HetPHOX and FcPHOX ligands have previously been applied in a range of asymmetric transformations by our group and also the groups of Richards and Cozzi.[15−20] The present study would allow us to probe whether the *gem*-dimethyl effect is beneficial in these related oxazoline-containing ligands while searching for a suitable, cheaper alternative to the "best in class" *t*-Bu-PHOX ligand.

Received: July 30, 2015
Published: September 1, 2015

DOI: 10.1021/acs.joc.5b01764
J. Org. Chem. 2015, 80, 10151−10162

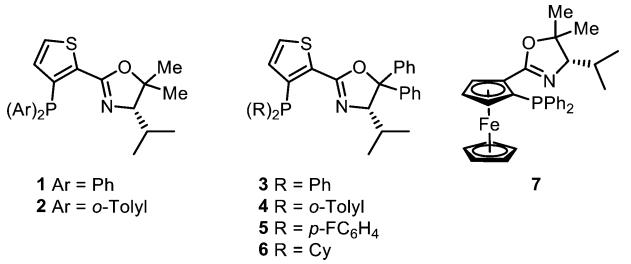
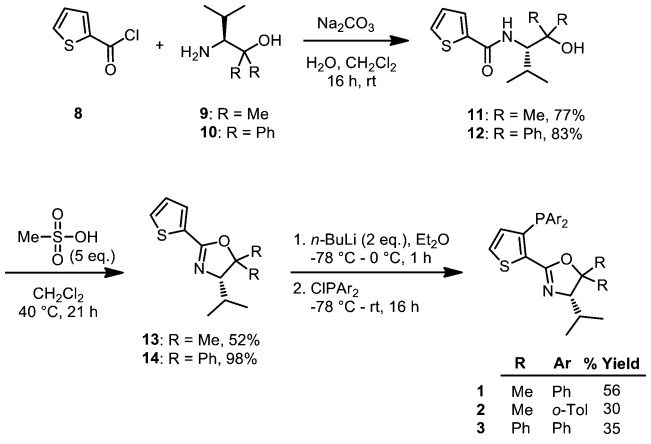


Figure 2. Novel, *gem*-disubstituted HetPHOX and FcPHOX ligands.

RESULTS AND DISCUSSION

Synthesis of HetPHOX Ligands. The synthesis of our HetPHOX ligand family began by the reaction of acid chloride **8** with *gem*-disubstituted amino alcohols **9**[21] and **10**[22] under biphasic reaction conditions to provide amides **11** and **12** in 77% and 83% yields, respectively (Scheme 1). Heating the resulting *gem*-disubstituted tertiary alcohols in the presence of methanesulfonic acid (MsOH) was enough to promote dehydration and subsequent cyclization to form oxazolines **13** and **14** in 52% and 98% yields, respectively.

Scheme 1. Synthesis of Ligands 1−3



	R	Ar	% Yield
1	Me	Ph	56
2	Me	*o*-Tol	30
3	Ph	Ph	35

HetPHOX ligands have previously been synthesized via oxazoline-directed *ortho*-lithiation with 2 equiv of *n*-BuLi, followed by quenching with the desired chlorodiarylphosphine.[15] This approach produced the HetPHOX ligands **1**−**3** in 30−56% yield in the present study (Scheme 1).

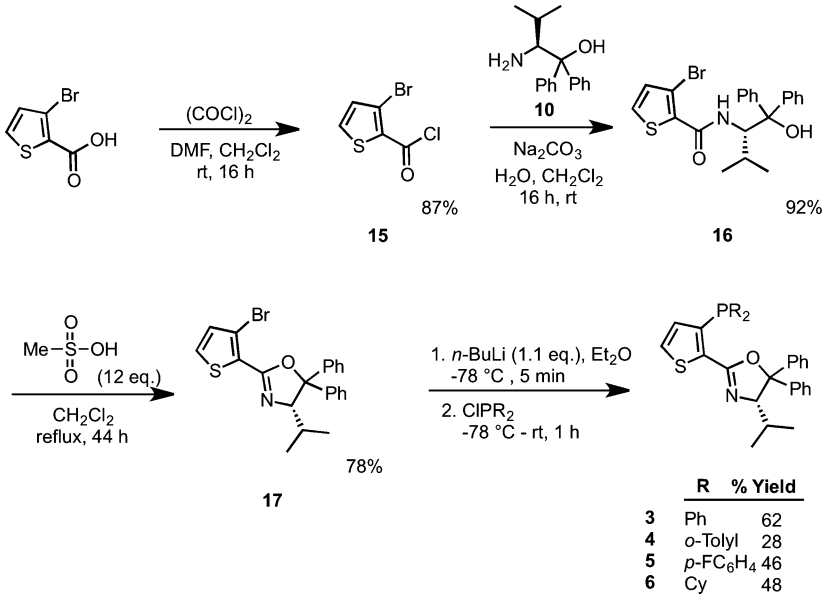
While these yields were in line with those previously obtained for HetPHOX ligands synthesized using an *ortho*-lithiation strategy,[16] it was felt that there was scope for optimization. Preliminary results (vide infra) indicated that ligand **3** showed the most interesting catalytic activity and was chosen as the target for route optimization to allow synthesis of a ligand library. A second route to the desired ligands employed lithium−bromide exchange. Therefore, the bromo-substituted acid chloride **15** was synthesized in high yield via reaction of the corresponding carboxylic acid with oxalyl chloride. Subsequent reaction with *gem*-disubstituted amino alcohol **10** provided amide **16** in 92% yield. An acid-mediated cyclization of **16** then provided oxazoline **17** in 78% yield (Scheme 2).

With bromo-substituted thiophene **17** in hand, lithium−halogen exchange with 1.1 equiv of *n*-BuLi and subsequent quench with the appropriate chlorophosphine afforded ligands **3**−**6** in 28−62% yield. Even with the addition of an extra step (synthesis of acid chloride **15**), the overall yield of ligand **3** increased from 28% to 39% using the optimized route.

Synthesis of *gem*-Disubstituted FcPHOX Ligand. Ferrocenecarboxylic acid[23] was converted into the corresponding acid chloride **18** in 94% yield before reaction with *gem*-disubstituted amino alcohol **9** in the presence of Et_3N to provide the ferrocenyl amide **19** in 70% yield (Scheme 3). Subsequent cyclization with MsOH provided the ferrocene oxazoline **20** in 82% yield.

Subsequently, a diastereoselective lithiation procedure, closely following conditions developed by Sammakia,[24] proved successful for the preparation of FcPHOX ligand **7**. Treatment of the oxazoline **20** with *s*-BuLi in the presence of TMEDA, followed by quenching with chlorodiphenylphosphine, gave

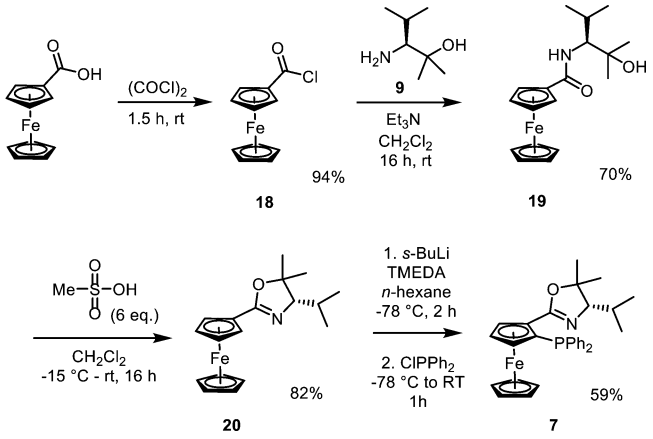
Scheme 2. Synthesis of Ligands 3−6



	R	% Yield
3	Ph	62
4	*o*-Tolyl	28
5	*p*-FC_6H_4	46
6	Cy	48

DOI: 10.1021/acs.joc.5b01764
J. Org. Chem. 2015, 80, 10151−10162

Scheme 3. Synthesis of Ferrocene Oxazoline Ligand 7



ligand **7** in 59% yield as a single diastereomer by ^{1}H NMR spectroscopy.

Application of Ligands in the Intermolecular Asymmetric Heck (IAH) Reaction. With our novel ligands in hand, we turned our attention to the asymmetric phenylation of 2,3-dihydrofuran **21** as a test reaction to evaluate our ligand class.[25−27] In the IAH reaction, [P,N] ligands such as PHOX generally provide much higher enantioselectivities and regioselectivities compared to [P,P] ligands such as BINAP; however, one of the major drawbacks with [P,N] ligands is the long reaction times required to ensure full conversion.[28,29] In order to decrease reaction time, microwave-assisted asymmetric Heck reactions have been developed by the groups of Larhed, Andersson, Diéguez, and Pámies and most recently Paquin.[8,30−32] Although a small decrease in levels of enantioselectivity is generally observed, the benefit is a greatly reduced reaction time. Paquin's microwave conditions (100 °C, 150 W for 18 h) represent a significant reduction over the 7 days usually taken required when using PHOX and HetPHOX ligands and the even more prolonged 14 days required for some FcPHOX ligands.[8] Preliminary reactions employing our novel ligand class were carried out in combination with known ligands **25** and **26** as controls (Scheme 4). The results of the initial ligand screen are reported in Table 1.

The results obtained with ligand **25** (entry 1) (84% conversion and 90% ee) closely agree with the reported results (73% yield and 91% ee).[8] Pleasingly, all of the novel ligands

Table 1. Asymmetric Phenylation of 2,3-Dihydrofuran with MW Irradiation

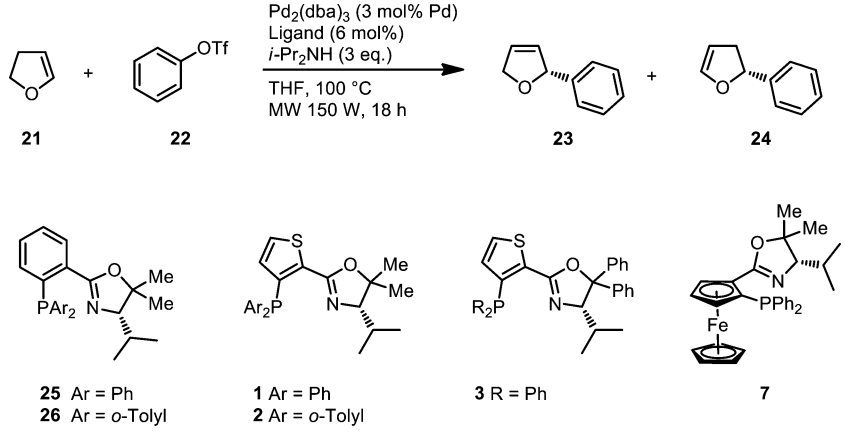
entry	ligand	conversion[a] (%)	23:24[a]	ee 23[a] (%) (*R*)	ee 24[a] (%) (*R*)
1	**25**	84	98:2	90	88
2	**26**	94	92:8	85	85
3	**1**	100	97:3	93	92
4	**2**	92	93:7	91	91
5	**3**	100	81:19	96	89
6	**7**	89	97:3	95	81

[a]Conversions were determined using tri-*n*-decane as an internal standard. Regioisomeric ratios, conversions, and enantiomeric excesses were determined by chiral GC; see the Experimental Section.

evaluated successfully catalyzed the phenylation of 2,3-dihydrofuran and provided (*R*)-**23** as the major product, with the highest observed ee (96%) induced by the palladium complex of *gem*-diphenyl-substituted ligand **3**.

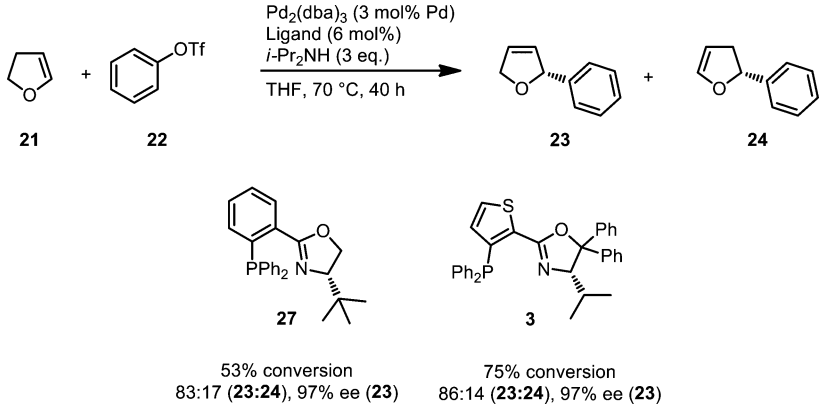
Ligand **26** was reported by Pfaltz but has not previously been evaluated in the IAH reaction.[7] Pd complexes of *o*-tolyl substituted ligand **26** facilitated formation of (*R*)-**23** in high yield but with lower levels of enantioselectivity and regioselectivity compared to its diphenylphosphine-substituted analogue **25** (entries 1 and 2). This trend was replicated with the two *gem*-dimethyl HetPHOX ligands **1** and **2** (entries 3 and 4). The reaction using diphenylphosphine-substituted ligand **1** provided better results in conversion (100% vs 92%), regioisomeric ratio (97:3 vs 93:7), and enantiomeric excess (93% vs 91%) than its di(*o*-tolyl)phosphine-substituted analogue **2**. The *gem*-diphenyl-substituted HetPHOX ligand **3** provided complete conversion and facilitated the formation of (*R*)-**23** in an excellent ee of 96%, gratifyingly matching the levels of enantioselectivity reported by Paquin with *t*-Bu-PHOX.[8] Unfortunately, an appreciable amount of the minor regioisomer was produced when ligand **3** was used (regioisomeric ratio 81:19). Finally, excellent results were obtained in the reactions catalyzed by Pd complexes of FcPHOX ligand **7** (entry 6). The kinetic product (*R*)-**23** was formed in an excellent 95% ee and, in contrast to **3**, afforded much lower levels of the thermodynamic product **24** (97:3). Where observed, the ee's of the minor isomeric product **24** were generally high to very high (81−92%) and were almost identical to the ee of the major product in many instances (entries 1−4, Table 1) with the largest ee difference being 14%

Scheme 4. Asymmetric Phenylation of 2,3-Dihydrofuran with MW Irradiation



DOI: 10.1021/acs.joc.5b01764
J. Org. Chem. 2015, 80, 10151−10162

Scheme 5. Asymmetric Phenylation of 2,3-Dihydrofuran under Conventional Heating



Scheme 6. Screening of Reaction Conditions for IAH Reaction

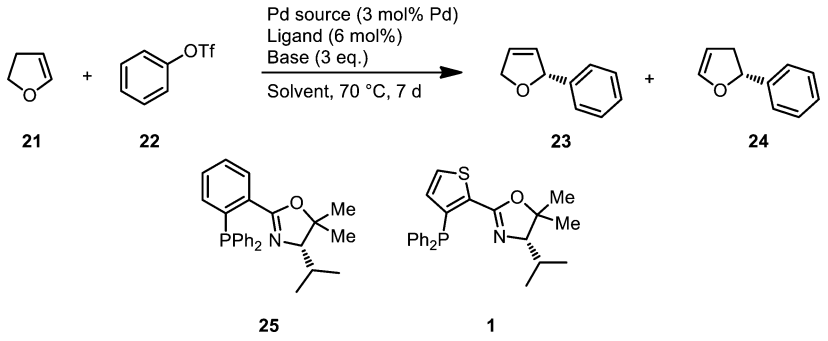


Table 2. Screening of Reaction Conditions for IAH Reaction

entry	ligand	base	Pd source	solvent	conversion[a] (%)	ee **23**[a](%) (*R*)
1	**25**	*i*-Pr$_2$NEt	Pd$_2$(dba)$_3$	THF	43	92
2	**1**	*i*-Pr$_2$NEt	Pd$_2$(dba)$_3$	THF	92	95
3	**1**	*i*-Pr$_2$NEt	Pd(OAc)$_2$	THF	63	93
4	**1**	*i*-Pr$_2$NEt	Pd$_2$(dba)$_3$	DMF	42	96
5	**1**	*i*-Pr$_2$NEt	Pd$_2$(dba)$_3$	benzene	58	95
6	**1**	PS	Pd$_2$(dba)$_3$	THF	35	90

[a]Conversions were determined using tri-*n*-decane as an internal standard. Conversions, and enantiomeric excesses were determined by chiral GC; see the Experimental Section.

(entry 6). We propose that, as with previous examples employing Pd complexes of P,N ligands, kinetic resolution, as observed by Hayashi with BINAP,[26] is not occurring to a large extent. The reaction employing ligand **3** was also monitored over time and the ratio of **23**:**24** remained reasonably constant as expected.

Comparison between Ligand 3 and *t*-Bu-PHOX 27 under Conventional Heating. Due to the increased reaction temperatures involved under microwave irradiation, levels of enantiomeric excess are generally found to be marginally lower than under conventional heating.[30] To investigate the performance of the ligands under thermal heating, side-by-side reactions with palladium complexes of *t*-Bu-PHOX **27** and the novel *gem*-diphenyl-substituted ligand **3** were carried out (Scheme 5).

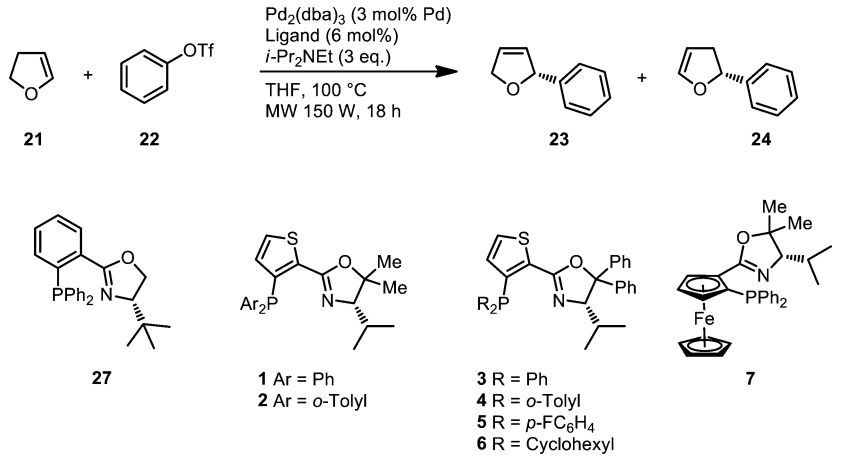
The reactions provided identical and excellent levels of enantioselectivity with ligands **3** and **27** (97% ee of (*R*)-**23**). A significantly higher level of conversion was obtained with ligand **3** over *t*-Bu-PHOX **27** (75% vs 53%). Formation of similar levels of the minor thermodynamic product **24** was observed with both ligands.

Screening of Reaction Conditions. The solvent, base, and Pd source used in the IAH reactions thus far were those reported by Paquin. It was felt that investigating variations of these conditions could prove beneficial in the present study. In particular, the choice of base for the reaction was investigated as, in previous work using HetPHOX ligands, high levels of enantioselectivity were obtained with *i*-Pr$_2$NEt and 1,8-bis(dimethylamino)naphthalene (Proton Sponge, PS).[33] The *gem*-dimethyl ligand **1** was chosen for the screen, and the conditions were evaluated in terms of the level of conversion and the ee of the kinetic product **23** (Scheme 6, Table 2).

It was found that ligand **1** provided generally high levels of ee: up to 96% with DMF as the solvent (entry 4). These results represented an improvement on the 93% ee obtained under microwave irradiation (Table 1, entry 3), similar to the increases in enantioselectivity obtained with *t*-Bu-PHOX **27** and *gem*-diphenyl ligand **3** under conventional heating (Scheme 5). There was a larger degree of variability in the levels of conversion obtained. The highest conversion observed was 92% with *i*-Pr$_2$NEt as the base (entry 2). PS has previously been successful in the IAH reaction with HetPHOX ligands but in

DOI: 10.1021/acs.joc.5b01764
J. Org. Chem. 2015, 80, 10151−10162

Scheme 7. Application of Ligands 1−7 in Asymmetric Phenylation of 2,3-Dihydrofuran



this case facilitated only low levels of conversion (35%) and the lowest observed level of ee (90%, entry 6).[16] Changing the Pd source to $Pd(OAc)_2$ proved slightly deleterious, reducing ee by 2% and conversion by 29% (entry 3 vs 2). With regard to choice of solvent, the best combination of conversion and enantioselectivity was observed when reactions were carried out in THF (entry 3, 92% conversion, 95% ee). On the basis of the above observations, it was decided to evaluate the complete ligand series using *i*-Pr_2NEt, $Pd_2(dba)_3$ and THF as optimized reaction conditions.

Application of Full Ligand Range to the Phenylation of 2,3-Dihydrofuran under Optimized Conditions and Microwave Irradiation. With the optimized reaction conditions in hand, the full series of novel ligands was applied to the IAH reaction between phenyl trifluoromethanesulfonate **22** and 2,3-dihydrofuran **21** (Scheme 7, Table 3). Changing the base from *i*-Pr_2NH to *i*-Pr_2NEt had a positive impact on the levels of conversion observed with essentially complete conversions obtained in all instances. The *gem*-dimethyl-substituted HetPHOX ligands **1** and **2** both provided (*R*)-**23** in 91% ee (entries 2 and 3), while the FcPHOX **7** ligand promoted its formation in 94% ee (entry 8). The series of *gem*-diphenyl ligands was expanded by both increasing and decreasing the electron density on the biarylphosphine (ligands **4** and **5**, respectively). In these cases, electronic variation of the phosphine had little or no impact on the levels of enantioselectivity or conversion obtained (entries 5 and 6). A poor regioisomeric ratio was obtained using *gem*-diphenyl HetPHOX ligands **3** and **4** (78:22 and 87:13 of **23**:**24**, respectively, entries 4 and 5), although reactions with the analogous bis(*p*-fluorophenyl)phosphine-containing ligand **5** produced a much lower amount of regioisomer **24** (96:4, entry 6).

Table 3. Application of Ligands 1−7 in Asymmetric Phenylation of 2,3-Dihydrofuran

entry	ligand	conversion[b] (%)	**23**:**24**[b]	ee **23**[b] (%) (*R*)
1	**27**	97	80:20	95
2	**1**	75[a]	n.d.	91
3	**2**	100	92:8	91
4	**3**	98	78:22	95
5	**4**	100	87:13	95
6	**5**	100	96:4	95
7	**6**	65[a]	n.d.	95
8	**7**	98	98:2	94

[a]Based on yield. [b]Conversions were determined using tri-*n*-decane as an internal standard. Regioisomeric ratios, conversions and enantiomeric excesses were determined by chiral GC; see the Experimental Section. n.d. = not determined.

Although levels of conversion and enantioselectivity observed using Pd complexes of *t*-Bu-PHOX **27** were excellent, the regioisomeric ratio was poorer than the literature value (99:1 **23**:**24** with 86% ee).[34] This may be attributed to the specific reaction conditions used in this study, which differ from those under which optimal results for ligand **27** were obtained.[34,35] It has been reported that, in the phenylation of 2,3-dihydrofuran under microwave irradiation at high temperatures using **27**, high levels of the minor regioisomer **24** can form (17:83 of **23**:**24** at 160 °C).[30]

Overall, the best combination of conversion, product ratio, and enantioselectivity was facilitated using FcPHOX **7** (entry 8), which provided (*R*)-**23** in 94% ee and almost complete conversion, and with by far the best isomeric ratio (98:2). The results obtained for the phenylation of 2,3-dihydrofuran **21** for our novel series of ligands compare very favorably with the literature; only a handful of ligand classes have exceeded the levels of conversion or enantioselectivity provided by *t*-Bu-PHOX.[25] It has been demonstrated in this work that under conventional heating Pd complexes of ligand **3** provide superior rates of conversion and match the levels of enantioselectivity provided by Pd complexes of *t*-Bu-PHOX **27**. It therefore appears that significant progress toward the objective of creating an effective mimic of **27** has been achieved.

Asymmetric 2-(2-Naphthyl)ation of 2,3-Dihydrofuran. To further evaluate our novel ligands, we sought to apply them in the IAH reaction between 2,3-dihydrofuran **21** and 2-naphthyl trifluoromethanesulfonate **28** (Scheme 8). This transformation has not been as widely studied as the phenylation process, yet a range of ligands have been reported for the 2-(2-naphthyl)ation of 2,3-dihydrofuran.[16,36,37] Reactions were carried out using the conditions previously described for the phenylation of 2,3-dihydrofuran (Table 4).

All ligands successfully catalyzed the 2-(2-naphthyl)ation of 2,3-dihydrofuran **21**, with (*R*)-**29** being the predominant product in all cases. Yields from the reactions catalyzed by *gem*-diphenyl-substituted ligands ranged from moderate to poor (24−62%, entries 4−7), while the *gem*-dimethyl-substituted ligands provided higher yields, with the best result provided by

DOI: 10.1021/acs.joc.5b01764
J. Org. Chem. 2015, 80, 10151−10162

Scheme 8. Asymmetric 2-(2-Naphthyl)ation of 2,3-Dihydrofuran

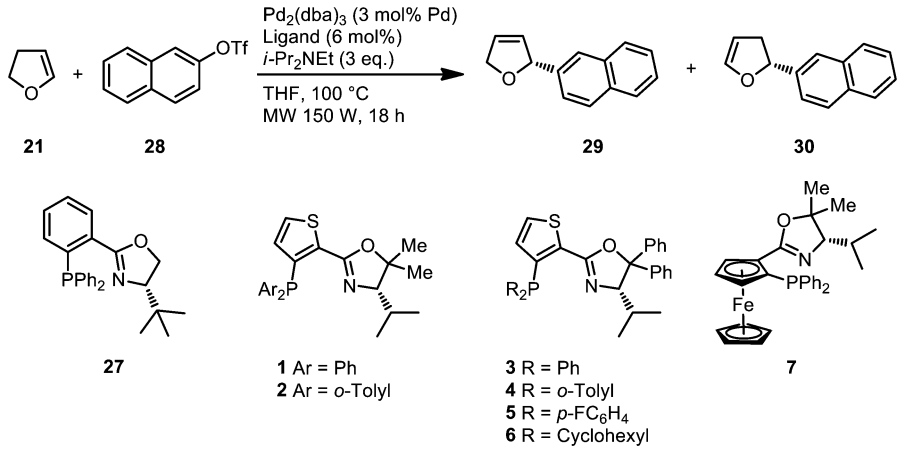


Table 4. Asymmetric 2-(2-Naphthyl)ation of 2,3-Dihydrofuran

entry	ligand	yield[a] (%)	29:30[b]	ee 29[b] (%) (*R*)	ee 30[b] (%)(*R*)
1	**27**	97	97:3	85	85
2	**1**	92	80:20	84	80
3	**2**	73	80:20	86	60
4	**3**	47	76:24	87	86
5	**4**	62	72:28	87	74
6	**5**	45	91:9	90	81
7	**6**	24	71:29	86	70
8	**7**	57	n.d.	88	n.d.

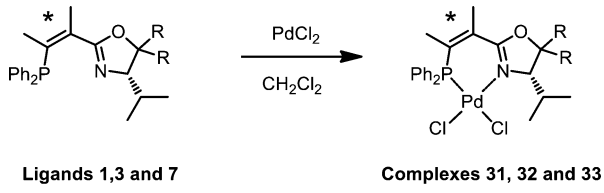
[a]Yields reported are of a regioisomeric mixture of **29** and **30** after purification by column chromatography. n.d.: not determined. [b]Regioisomeric ratios and enantiomeric excess were determined by chiral HPLC; see the Experimental Section.

ligand **1**, which provided regioisomeric products **29** and **30** in an overall 92% yield (entry 2).

The ee's obtained were lower than in the phenylation (Table 3) but were generally good to very good (84−90%) with the bis(*p*-fluorophenyl)phosphine ligand **5** facilitating the highest levels of ee (90%) and regioselectivity (91:9 of **29**:**30**), albeit in a modest 45% yield (entry 6). Where determined, significant amounts of the minor regioisomer **30** were obtained with all other novel ligands (80:20−71:29). The *t*-Bu-PHOX ligand **27** was used as a control for the experiments, and it provided a much higher regioisomeric ratio of products (97:3, entry 1). The ee's of the minor regioisomer were also moderate to good (60% to an optimal 86% ee obtained with **3**). In contrast to the phenylation of **21**, none of our novel ligands afforded a superior combination of yield, regioisomeric ratio and enantiomeric excess to *t*-Bu-PHOX **27**. However, the levels of ee observed with novel ligands **5** and **7** (entries 6 and 8, respectively) are superior to those previously obtained with *i*-Pr-substituted HetPHOX ligands and demonstrate the generality of the beneficial effect of *gem*-disubstitution on enantioselectivity.[16] As with the phenylation of 2,3-dihydrofuran, the results obtained with our novel ligand series compare favorably to the ligands reported to date in the literature. For the 2-(2-naphthyl)ation of 2,3-dihydofuran **21**, even under microwave-accelerated conditions, levels of enantioselectivity close to those obtained with *t*-Bu HetPHOX derivatives have been achieved (up to 94% ee of **29** under conventional heating).[16]

X-ray Crystallographic Investigations. In order to gain insight into the full structural effect *gem*-disubstitution had on the novel ligand classes evaluated, $PdCl_2$ complexes of the representative class members were prepared by mixing the free ligand with $PdCl_2$ (Scheme 9), and their resulting crystal structures were determined by X-ray diffraction (Figure 3).

Scheme 9. Synthesis of $PdCl_2$ Complexes of Ligands 1, 3, and 7

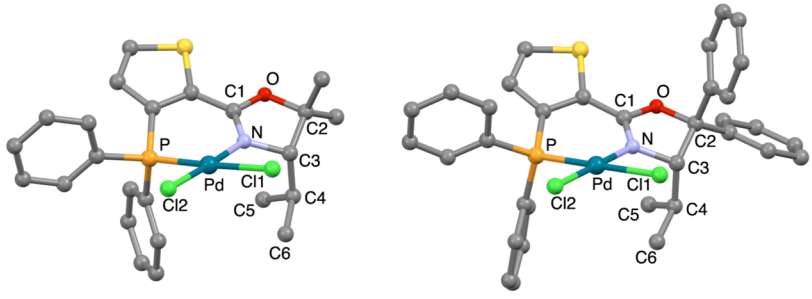


By utilizing structural data obtained by Paquin for $PdCl_2$ complexes of both *t*-Bu-PHOX **27** and its *gem*-dimethyl substituted analogue, it was possible to make a detailed comparison between these structures and our structures (Table 5).[8]

For HetPHOX complexes **31** and **32**, the distances from Pd to the two methyl groups of the *i*-Pr functionality (4.35 and 4.49 Å to CH_3 (C5), 3.63 and 3.52 Å to CH_3 (C6)) correspond closely to the same intramolecular distances for the $PdCl_2$ complexes of known ligands **25** and **27** (4.38 and 4.36 Å to CH_3 (C5), 3.61 and 3.30 Å to CH_3 (C6)). This indicates that a similar steric environment exists around the Pd center, hence rationalizing the high levels of enantiomeric excess obtained with HetPHOX ligands **1** and **3** in the IAH. For FcPHOX complex **33**, while the intramolecular distances to the two methyl groups of the *i*-Pr group are similar in magnitude, the order is inverted. The CH_3 group furthest from the Pd center in **31** and **32** is the closest to Pd in **33**.

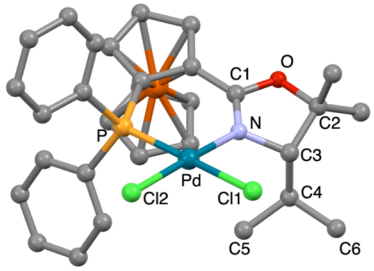
The magnitude of this difference can be quantified by examining the internal dihedral angles formed in N−C3−C4−C5. For FcPHOX complex **33**, the value of this dihedral angle is −38.0°, a 96.3° difference from the same dihedral angle in *t*-Bu-PHOX **27**. This is most likely a result of steric repulsion between the lower cyclopentadieneyl ring of the ferrocene and the *i*-Pr group, which can be seen in Figure 4. The distance between H2 of the isopropyl methyl group and H3 of the

DOI: 10.1021/acs.joc.5b01764
J. Org. Chem. 2015, 80, 10151−10162



31
$PdCl_2$ Complex of HetPHOX **1**

32
$PdCl_2$ Complex of HetPHOX **3**



33
$PdCl_2$ Complex of FcPHOX **7**

Figure 3. $PdCl_2$ complexes of HETPHOX ligands **1** and **3** and FcPHOX ligand **7**.

Table 5. Comparison of Some Key Structural Values Obtained by X-ray Crystallography

$PdCl_2$ (ligand)	Pd−C5 (Å)	Pd−C6 (Å)	N−C3−C4−C5[a] (deg)	Cl1−Pd−N−C3[b] (deg)
31	4.35	3.63	49.4	32.6
32	4.49	3.52	56.8	32.2
33	3.38	4.95	−38.0	25.2
25	4.38	3.61	50.6	38.7
27	4.36	3.30	58.3	47.3

[a]Dihedral angle formed by N−C3−C4−C5. [b]Dihedral angle formed by Cl1−Pd−N−C3.

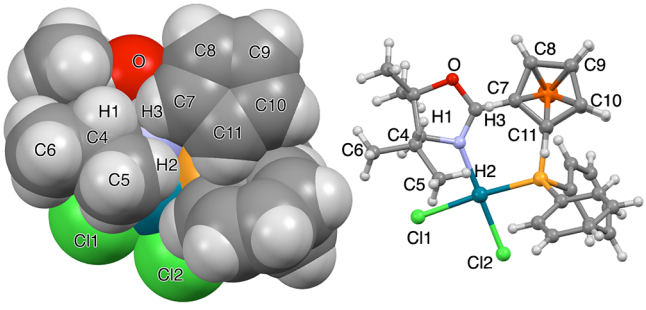


Figure 4. View looking at the lower cyclopentadienyl ring of the FcPHOX complex **33**. Spacefilling representation (left) and ball and stick model from the same perspective (right).

ferrocenyl cyclopentadienyl ring is 2.63 Å, indicating these atoms are very close in space. This H2−H3 interaction is likely preventing the *i*-Pr group from rotating in toward the metal center any further and is thus reducing the conformational bias provided by the *gem*-dimethyl substituents.

For HetPHOX complexes **31** and **32**, a much closer correlation is found between the same dihedral angles. Compound **31** forms a 49.4° dihedral N−C3−C4−C5, which is similar to the 58.3° observed in the $PdCl_2$ complex of *t*-Bu-PHOX **27**. The same dihedral for *gem*-diphenyl ligand **32** forms an angle of 56.8°, very closely correlating to the $PdCl_2$ complex of *t*-Bu-PHOX **27**. This indicates that *gem*-diphenyl substitution is more effective in biasing the orientation of the *i*-Pr group so as to mimic a *t*-Bu group. *Gem*-disubstitution also has an effect on the conformation of the oxazoline ring itself. The orientation of the oxazoline ring is distorted compared to *t*-Bu-PHOX **27**. The Cl1−Pd−N−C3 dihedral angle, which is 47.3° for ligand **27**, is altered in all three of our novel ligands. The largest divergence is found for FcPHOX complex **33** (difference of 22.1°), and the lowest variance is a still significant (14.7°) for *gem*-dimethyl complex **31**.

Mechanistic Considerations. For the arylation of 2,3-dihydrofuran **21**, the possible intermediates prior to migratory insertion utilizing palladium complexes of [P,N] ligands **1**−**7** are shown in Figure 5. The alkene can be bound to palladium by either of its faces and can bind in a *trans* fashion to either the nitrogen atom or the phosphorus atom. We would expect the more labile alkene to bind *trans* to the soft phosphorus, with the harder nitrogen *trans* to the aryl group.[38] Similar intermediates have been proposed by Hallberg and Ripa for the *t*-Bu-PHOX ligand **27** in an intramolecular Heck reaction.[39]

When the alkene approaches *trans* to the nitrogen there is little discrimination between the two faces of the alkene. Thus, if migratory insertion were to occur from the complexes C and D a low ee would be observed. However, when the alkene approaches *trans* to the phosphorus, intermediate A suffers from a high degree of steric repulsion between the *i*-Pr group of the oxazoline ring and the alkene. Conversely, intermediate B is unhindered, meaning that migratory insertion via this route would result in a high ee of (*R*) **23**/**29**, which correlates with the results we have obtained herein. These proposed transitions states may explain why the bulkier *t*-Bu oxazoline ligands generally outperform their *i*-Pr-substituted counterparts in this

DOI: 10.1021/acs.joc.5b01764
J. Org. Chem. 2015, 80, 10151−10162

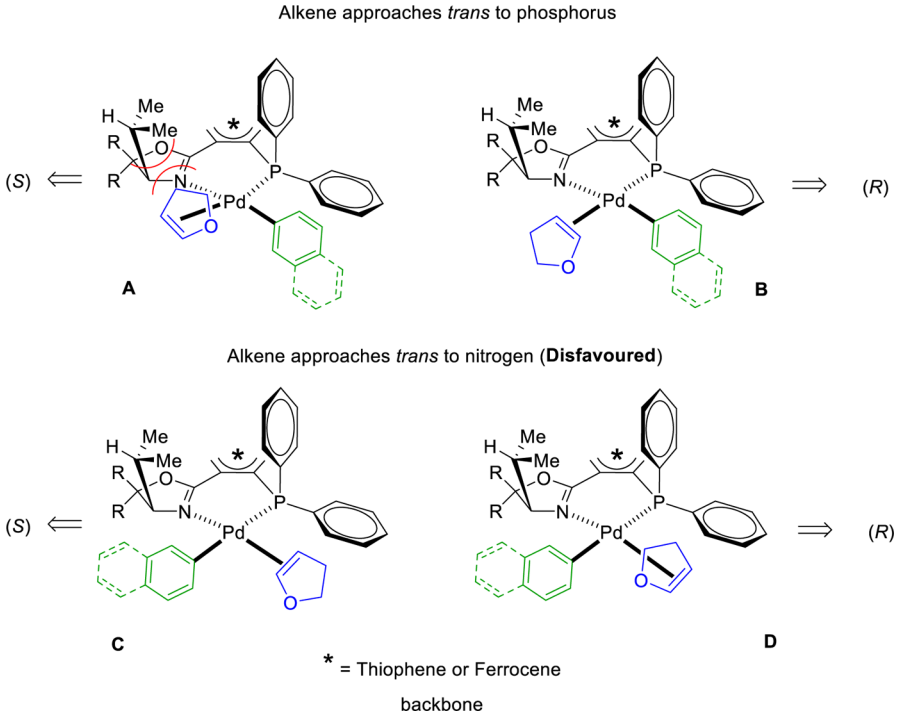


Figure 5. Possible diastereotopic ligand−Pd−substrate complexes formed with *gem*-disubstituted ligands **1**−**7** prior to migratory insertion.

reaction and, thus, why *gem*-disubstituted *i*-Pr oxazolines also provide high ee's (Figure 6). However, these transition states do not help to rationalize the regioselectivity of kinetic vs thermodynamic products for **23**/**24** or **29**/**30**.

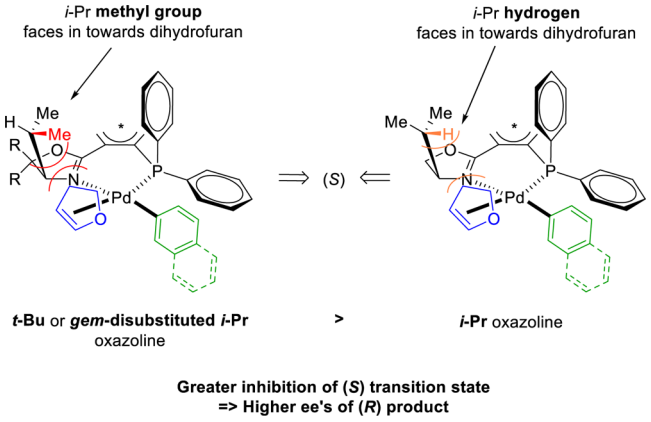


Figure 6. Comparison of *t*-Bu and *gem*-disubstituted *i*-Pr oxazoline ligands (left) with *i*-Pr oxazoline ligands (right) to rationalize why *gem*-disubstitution of *i*-Pr oxazoline ligands results in higher ee's for the IAH.

CONCLUSIONS

Seven novel *gem*-disubstituted ligands (**1**−**7**) have successfully been synthesized and applied to the asymmetric intermolecular Heck reaction, where the phenylation and 2-(2-naphthyl)ation of 2,3-dihydrofuran were investigated. Under microwave irradiation, enantiomeric excesses of up to 96% were achieved using ligand **3**, increasing to 97% under conventional heating, matching the levels of enantioselectivity observed when using "best in class" *t*-Bu-PHOX ligand **27**. An X-ray crystallographic investigation of $PdCl_2$ complexes of **1**, **3**, and **7** detailed the full structural effect of *gem*-disubstitution. Consideration of these crystal structures allowed us to propose transition states which account for the higher ee's obtained using *t*-Bu or *gem*-disubstituted *i*-Pr oxazoline ligands when compared with their *i*-Pr oxazoline counterparts. These results represent only the second example of a *gem*-disubstituted *i*-Pr oxazoline ligand successfully replicating the stereoinduction provided by Pd complexes of *t*-Bu-PHOX **27**.[10] We hope that the high enantioselectivities provided by ligand **3**, coupled with its cheap, modular synthesis, will promote its use in asymmetric catalysis.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all commercial reagents were used as received without further purification. Anhydrous diethyl ether (Et_2O), tetrahydrofuran (THF), and dichloromethane (CH_2Cl_2) were obtained from a dry solvent dispenser. Diisopropylethylamine (*i*-Pr_2NEt) was distilled from ninhydrin and KOH and stored over 3 Å molecular sieves. All microwave reactions were conducted in a CEM Discover S-class microwave reactor, which utilizes an external infrared temperature sensor.

(*S*)-*N*-(2-Hydroxy-2,4-dimethylpentan-3-yl)thiophene-2-carboxamide (11). To a solution of (*S*)-2-amino-1,1,3-trimethylbutanol (**9**) (262 mg, 2.0 mmol, 1 equiv) in CH_2Cl_2 (7 mL) was added a solution of Na_2CO_3 (636 mg, 6.0 mmol, 3 equiv) in deionized water (7 mL). The mixture was stirred vigorously, and 2-thiophenecarbonyl chloride **8** (0.30 mL, 504 mg, 2.30 mmol, 1.15 equiv) was added dropwise. The reaction mixture was allowed to stir at room temperature over 16 h. The phases were then separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 7 mL). To the combined organic phases was added methanolic 1 M KOH (1.5 mL), and the reaction was stirred for 15 min and then neutralized with 10% v/v aq HCl (10 mL). The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (20% v/v acetone in cyclohexane on SiO_2) to give the title compound as a fluffy white solid (372 mg, 77% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, J = 3.7,

DOI: 10.1021/acs.joc.5b01764
J. Org. Chem. 2015, 80, 10151−10162

1.1 Hz, 1H), 7.47 (dd, J = 5.0, 1.1 Hz, 1H), 7.08 (dd, J = 5.0, 3.7 Hz, 1H), 6.43 (d, J = 9.5 Hz, 1H), 3.94 (dd, J = 10.0, 2.7 Hz, 1H), 2.28–2.18 (m, 1H), 2.05 (br s, 1H), 1.35 (s, 3H), 1.26 (s, 3H), 1.00 (app. t, J = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 162.4, 139.2, 129.8, 127.9, 127.6, 73.7, 60.3, 29.5, 28.5, 27.4, 22.4, 17.0; IR ν_{max} (Nujol, cm^{-1}) 3419, 1632, 1531; HRMS (ESI-TOF) m/z 264.1021 [M + Na] $C_{12}H_{19}NNaO_2S$ requires 264.1034; mp 79–81 °C; $[\alpha]^{20}_D$ = −41.9 (c = 1.05, $CHCl_3$).

(*S*)-*N*-(1-Hydroxy-3-methyl-1,1-diphenylbutan-2-yl)-thiophene-2-carboxamide (12). To a solution of (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**10**) (2.54 g, 10 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added a solution of Na_2CO_3 (3.18 g, 30 mmol, 3 equiv) in deionized water (25 mL). The mixture was stirred vigorously, and 2-thiophenecarbonyl chloride **8** (1.23 mL, 11.5 mmol, 1.15 equiv) was added dropwise. The reaction mixture was allowed to stir at room temperature over 16 h. The phases were then separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). To the combined organic phases was added methanolic 1 M KOH (15 mL), and the reaction was stirred for 15 min then neutralized with 10% v/v aq HCl. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 300 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude product which was recrystallized from aqueous EtOH to give the title compound as white needles (3.04 g, 83% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.53–7.45 (m, 4H), 7.40 (dd, J = 5.0, 1.0 Hz, 1H), 7.37–7.30 (m, 3H), 7.28–7.20 (m, 3H), 7.13 (app t, J = 7.3 Hz, 1H), 7.02–6.97 (m, 1H), 6.49 (d, J = 9.8 Hz, 1H), 5.12 (app. d, J = 9.8 Hz, 1H), 2.70 (s, 1H), 1.96–1.84 (m, 1H), 0.95 (app. t, J = 6.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.9, 145.9, 145.4, 139.0, 129.6, 128.6, 128.5, 127.8, 127.5, 127.1, 127.0, 125.4, 125.3, 82.4, 58.0, 29.3, 22.9, 17.6; IR ν_{max} (Nujol, cm^{-1}) 3120, 1629, 1534; HRMS (ESI-TOF) m/z 388.1363 [M + Na] $C_{22}H_{23}NO_2NaS$ requires 388.1347; mp 212–213 °C; $[\alpha]^{20}_D$ = −119.7 (c = 0.75, $CHCl_3$).

(*S*)-4-Isopropyl-5,5-dimethyl-2-(thiophene-2-yl)-4,5-dihydrooxazole (13). A solution of (*S*)-*N*-(2-hydroxy-2,4-dimethylpentan-3-yl)thiophene-2-carboxamide (**11**) (290 mg, 1.2 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was cooled to 5 °C in an ice bath. Methanesulfonic acid (0.39 mL, 0.56 g, 6.0 mmol, 5 equiv) was added dropwise over 10 min. The reaction was transferred to a 40 °C oil bath and heated until the starting material was consumed by TLC (21 h). The reaction was quenched with saturated aq $NaHCO_3$ (10 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude yellow oil, which was purified by column chromatography (10% v/v Et_2O in cyclohexane on SiO_2) to give the title compound as a clear oil (140 mg, 52% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, J = 3.7, 1.1 Hz, 1H), 7.40 (dd, J = 5.0, 1.1 Hz, 1H), 7.05 (dd, J = 5.0, 3.7 Hz, 1H), 1.92–1.82 (m, 1H), 1.51 (s, 3H), 1.38 (s, 3H), 1.12 (d, J = 6.5 Hz, 3H), 1.02 (d, J = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 140.6, 137.1, 129.7, 129.2, 127.4, 115.3, 80.5, 29.2, 29.1, 21.3, 21.0, 20.5; IR ν_{max} (Nujol, cm^{-1}) 3076, 1531, 1061; HRMS (ESI-TOF) m/z 224.1115 [M + H] $C_{12}H_{18}NOS$ requires 224.1109; $[\alpha]^{20}_D$ = −48.9 (c = 1.29, $CHCl_3$).

(*S*)-4-Isopropyl-5,5-diphenyl-2-(thiophene-2-yl)-4,5-dihydrooxazole (14). A solution of (*S*)-*N*-(1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)thiophene-2-carboxamide (**12**) (2.66 g, 7.28 mmol, 1 equiv) in CH_2Cl_2 (200 mL) was cooled to 5 °C in an ice bath. Methanesulfonic acid (2.36 mL, 3.50 g, 36.39 mmol, 5 equiv) was added dropwise over 10 min. The reaction was transferred to a 40 °C oil bath and heated until the starting material was consumed by TLC (21 h). The reaction was quenched with saturated aq $NaHCO_3$ (100 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow oil, which was triturated in pentane and concentrated in vacuo to give the title compound as an oily semisolid (2.48 g, 98% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J = 3.7, 1.1 Hz, 1H), 7.57–7.53 (m, 2H), 7.47 (dd, J = 5.0, 1.1 Hz, 1H), 7.37–7.22 (m, 8H), 7.11 (dd, J = 5.0, 3.7 Hz, 1H), 4.77 (d, J = 4.6 Hz, 1H), 1.85 (m, 1H), 1.02 (d, J = 6.7 Hz, 3H), 0.63 (d, J = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.3, 145.3, 140.6, 130.8, 130.2, 129.7, 128.3 (2C), 127.8, 127.7 (2C), 127.6, 127.2, 126.9 (2C), 126.2 (2C), 93.0, 80.0, 30.4, 21.9, 17.0; IR ν_{max} (Nujol, cm^{-1}) 3059, 1655, 1529; HRMS (ESI-TOF) m/z 348.1420 [M + H] $C_{22}H_{22}NOS$ requires 348.1411; $[\alpha]^{20}_D$ = −354 (c = 0.55, $CHCl_3$).

(*S*)-2-(3-(Diphenylphosphanyl)thiophene-2-yl)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole (1). A solution of (*S*)-4-isopropyl-5,5-dimethyl-2-(thiophene-2-yl)-4,5-dihydrooxazole (**13**) (590 mg, 2.64 mmol, 1 equiv) in Et_2O (6 mL) was cooled to −78 °C in an acetone/liquid N_2 bath. *n*-BuLi (1.18 mL, 2.33 M in hexane, 2.76 mmol, 1.05 equiv) was added dropwise and stirring continued at −78 °C for 30 min. The reaction vessel was transferred to an ice bath, stirred at 0 °C for 30 min, and then returned to the acetone/liquid N_2 bath and recooled to −78 °C. Chlorodiphenylphosphine (0.53 mL, 2.89 mmol, 1.1 equiv) was added dropwise, and the reaction was then stirred to room temperature over 16 h. The reaction mixture was diluted with water (15 mL) and then extracted with Et_2O (3 × 40 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude residue which was purified by column chromatography (5:1 pentane/CH_2Cl_2 on SiO_2) to yield the product as a white crystalline solid (600 mg, 56% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 9H), 7.26 (m, 2H), 6.31 (dd, J = 5.1, 1.0 Hz, 1H), 3.28 (d, J = 8.2 Hz, 1H), 1.65–1.58 (m, 1H), 1.31 (s, 3H), 1.11 (s, 3H), 0.86 (app. d, J = 6.5, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.1 (d, J = 3.6 Hz), 140.8 (d, J = 27.1 Hz), 138.4 (d, J = 11.5 Hz), 137.8 (d, J = 10.5 Hz), 133.7 (d, 2C, J = 21.0 Hz), 133.5 (d, 2C, J = 20.7 Hz), 133.3, 132.7, 132.5, 128.5 (d, 2C, J = 11.2 Hz), 128.4–128.2 (m, 3C), 127.3 (d, J = 2.3 Hz), 87.6, 80.6, 29.0, 28.8, 20.9, 20.8, 20.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ −13.76 (s); IR ν_{max} (Nujol, cm^{-1}) 1638, 1061, 744; HRMS (ESI-TOF) m/z 408.1559 [M + H] $C_{24}H_{27}NOPS$ requires 408.1551; mp 140–142 °C; $[\alpha]^{20}_D$ = −176.3 (c = 0.4, $CHCl_3$).

(*S*)-2-(3-(Di-*o*-tolylphosphanyl)thiophene-2-yl)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole (2). A solution of (*S*)-4-isopropyl-5,5-dimethyl-2-(thiophene-2-yl)-4,5-dihydrooxazole (**13**) (590 mg, 2.64 mmol, 1 equiv) in Et_2O (10 mL) was cooled to −78 °C in an acetone/liquid N_2 bath. *n*-BuLi (1.18 mL, 2.33 M in hexane, 2.76 mmol, 1.05 equiv) was added dropwise, and stirring was continued at −78 °C for 30 min. The reaction vessel was transferred to an ice bath, stirred at 0 °C for 30 min, and then returned to the acetone/liquid N_2 bath and recooled to −78 °C. Chlorodi(*o*-tolyl)phosphine (1.00 g, 4 mmol, 1.5 equiv) was added in one portion, and the reaction was then stirred at room temperature over 16 h. The reaction mixture was diluted with water (15 mL) and then extracted with Et_2O (3 × 40 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to a crude residue which was purified by column chromatography (5:1 pentane/CH_2Cl_2 on SiO_2) to yield the product as a white crystalline solid (341 mg, 30% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.26 (m, 1H), 7.25–7.15 (m, 4H), 7.04 (app t, J = 7.2 Hz, 2H), 6.82–6.77 (m, 2H), 6.31 (dd, J = 5.0, 0.7 Hz, 1H), 3.30 (d, J = 8.1 Hz, 1H), 2.44 (dd, J = 10.5, 1.6 Hz, 6H), 1.63–1.56 (m, 1H), 1.31 (s, 3H), 1.09 (s, 3H), 0.83 (dd, J = 15.8, 6.5 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.2 (d, J = 3.6 Hz), 142.4 (d, J = 14.8 Hz), 142.2 (d, J = 15.1 Hz), 139.9, 139.7, 136.6 (d, J = 13.4 Hz), 136.0 (d, J = 11.7 Hz), 133.4, 132.9, 132.9, 132.7, 132.6, 129.9–129.7 (m, 2C), 128.5 (d, J = 7.4 Hz), 127.4 (d, J = 1.9 Hz), 125.9 (d, J = 13.2 Hz), 87.3, 80.5, 29.0, 28.8, 21.3 (d, J = 8.0 Hz), 21.1 (d, J = 8.5 Hz), 20.9, 20.8, 20.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ −29.75; IR ν_{max} (Nujol, cm^{-1}) 1639, 1279, 1021; HRMS (ESI-TOF) m/z 436.1886 [M + H] $C_{26}H_{31}NOPS$ requires 436.1864; mp 112–114 °C; $[\alpha]^{20}_D$ = −95.8 (c = 0.5, $CHCl_3$).

(*S*)-2-(3-(Diphenylphosphanyl)thiophene-2-yl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (3). A solution of (*S*)-2-(3-bromothiophene-2-yl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (**14**) (219 mg, 0.51 mmol, 1 equiv) in Et_2O (2 mL) was cooled in a liquid N_2/acetone bath to −78 °C. *n*-BuLi (0.23 mL, 2.33 M in hexane, 0.54 mmol, 1.05 equiv) was added dropwise and stirring continued at −78 °C for 30 min. The reaction vessel was transferred to an ice bath, stirred at 0 °C for 30 min, and then returned to the acetone/liquid N_2 bath and recooled to −78 °C. Chlorodiphenylphosphine (0.11 mL, 0.56 mmol, 1.1 equiv) was added dropwise, and

DOI: 10.1021/acs.joc.5b01764
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the reaction was then stirred to room temperature over 16 h. The reaction mixture was diluted with water (5 mL) and then extracted with Et_2O (3 × 10 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated in vacuo to a crude residue which was purified by column chromatography (5:1 pentane/CH_2Cl_2 on SiO_2) to yield the product as a slightly yellow solid (73 mg, 35% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.45 (m, 1H), 7.36−7.28 (m, 3H), 7.26−7.12 (m, 3H), 6.39 (dd, J = 5.1, 0.8 Hz, 1H), 4.72 (d, J = 4.2 Hz, 1H), 1.68 (m, 1H), 0.87 (d, J = 6.5 Hz, 1H), 0.29 (d, J = 6.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.1 (d, J = 3.3 Hz), 145.4, 140.9 (d, J = 28.1 Hz), 140.5, 138.4 (d, J = 12.5 Hz), 137.6 (d, J = 11.3 Hz), 133.8, 133.8 (d, J = 5.7 Hz, 2C), 133.6 (d, J = 6.9 Hz, 2C), 132.8 (d, J = 23.7 Hz), 128.6 (m, 2C), 128.5 (m, 2C), 128.4 (d, J = 5.7 Hz, 2C), 128.2 (2C), 128.0 (d, J = 1.6 Hz), 127.6 (2C), 127.5, 126.8, 126.7 (2C), 126.2 (m, 2C), 93.7, 80.0, 30.3, 21.7, 16.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ −15.78; IR ν_{max} (Nujol, cm^{-1}) 1630, 1035; HRMS (ESI-TOF) m/z 532.1839 [M + H] $C_{34}H_{31}NOPS$ requires 532.1864; mp 98−100 °C; $[\alpha]^{20}_D$ −244.5 (c = 1, $CHCl_3$).

(*S*)-3-Bromo-*N*-(1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)thiophene-2-carboxamide (16). To a solution of (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**10**) (2.30 g, 9.0 mmol, 1 equiv) in CH_2Cl_2 (35 mL) was added a solution of Na_2CO_3 (2.86 g, 27.0 mmol, 3 equiv) in deionized water (25 mL). The mixture was stirred vigorously, and 3-bromothiophene-2-carbonyl chloride (**15**) (2.33 g, 10.4 mmol, 1.16 equiv, prepared from the corresponding carboxylic acid and oxalyl chloride) was added portionwise over 30 min. The reaction mixture was allowed to stir at room temperature over 16 h. The phases were then separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). To the combined organic phases was added methanolic 1 M KOH (15 mL), and the reaction was stirred for 15 min and then neutralized with 10% v/v aq HCl. The phases were separated, and the aqueous phase wasextracted with CH_2Cl_2 (2 × 50 mL). The combined organics were concentrated to 100 mL in vacuo and eluted through a silica plug with CH_2Cl_2 (3 × 100 mL). The eluent was concentrated in vacuo to give the product as a white solid (3.68 g, 92% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.50 (m, 3H), 7.50−7.47 (m, 2H), 7.38 (d, J = 5.2 Hz, 1H), 7.33 (app. t, J = 7.7 Hz, 2H), 7.28−7.20 (m, 3H), 7.14 (m, 1H), 6.97 (d, J = 5.2 Hz, 1H), 5.21 (dd, J = 9.8, 2.2 Hz, 1H), 2.64 (s, 1H), 1.95−1.85 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.3, 146.0, 145.3, 135.2, 131.9, 129.9, 128.5 (2C), 128.4 (2C), 127.1, 126.9, 125.5 (2C), 125.4 (2C), 108.2, 82.2, 58.4, 29.2, 22.8, 17.7; HRMS (ESI-TOF) m/z 466.0439 [M + Na] $C_{22}H_{22}BrNO_2SNa$ requires 466.0452; IR ν_{max} (KBr disk, cm^{-1}) 3436, 3392, 2962, 1626, 1527, 1496; mp 189−194 °C; $[\alpha]^{20}_D$ = −53 (c = 1.0, CH_2Cl_2).

(*S*)-2-(3-Bromothiophene-2-yl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (17). A solution of (*S*)-3-bromo-*N*-(1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)thiophene-2-carboxamide (**16**) (3.06 g, 1.04 mmol, 1 equiv) in CH_2Cl_2 (100 mL) was cooled to 5 °C in an ice bath. Methanesulfonic acid (0.40 mL, 6.16 mmol, 6 equiv) was added dropwise over 10 min. The reaction was transferred to a 45 °C oil bath and heated for 21 h. A further portion of methanesulfonic acid (0.40 mL, 6.16 mmol, 6 equiv) was added and heating continued until the starting material was consumed by TLC (44 h total). The reaction was quenched with satd aq $NaHCO_3$ (100 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow oil, which was triturated in pentane and concentrated in vacuo to give the title compound as a white solid (2.30 g, 78% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62−7.58 (m, 2H), 7.42−7.21 (m, 9H), 7.08 (d, J = 5.3 Hz, 1H), 4.81 (d, J = 4.4 Hz, 1H), 1.92−1.82 (m, 1H), 1.04 (d, J = 6.7 Hz, 3H), 0.63 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.1, 145.2, 140.4, 132.6, 129.1, 128.3 (2 C), 127.8 (2 C), 127.8, 127.2, 126.8 (2 C), 126.1 (2 C), 125.9, 113.4, 93.5, 79.6, 30.3, 21.8, 16.7; IR ν_{max} (Nujol, cm^{-1}) 3052, 1636; HRMS (ESI-TOF) m/z 448.0363 [M + Na] $C_{22}H_{20}BrNNaOS$ requires 448.0347; mp 124−127 °C; $[\alpha]^{20}_D$ = −317 (c = 0.75, $CHCl_3$).

(*S*)-2-(3-(Dicyclohexylphosphanyl)thiophene-2-yl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (6). A solution of (*S*)-2-(3-bromothiophene-2-yl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (**17**) (419 mg, 0.98 mmol, 1 equiv) in Et_2O (20 mL) was cooled to −78 °C. *n*-BuLi (0.43 mL, 2.50 M in hexane, 1.08 mmol, 1.1 equiv) was added dropwise and stirring continued at −78 °C for 5 min. Chlorodicyclohexylphosphine (0.217 mL, 0.99 mmol, 1 equiv) was added dropwise and the cooling bath removed. The reaction mixture was allowed to stir for a further 1 h and was diluted with Et_2O (20 mL) and then quenched with water (10 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude yellow solid which was purified by column chromatography (CH_2Cl_2 on SiO_2) to yield the product as a white solid (255 mg, 48% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66−7.61 (m, 1H), 7.46−7.43 (m, 1H), 7.41 (d, J = 5.1 Hz, 1H), 7.34−7.27 (m, 2H), 7.26−7.21 (m, 1H), 7.17 (d, J = 5.0 Hz, 1H), 4.82 (d, J = 4.3 Hz, 1H), 2.05−1.57 (m, 13H), 1.35−1.05 (m, 10H), 1.04 (d, J = 6.6 Hz, 3H), 0.61 (d, J = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.7, 145.6, 140.9, 140.7 (d, J = 35.6 Hz), 135.4 (d, J = 25.4 Hz), 132.0, 128.1 (2C), 127.6 (2C), 127.5, 127.3, 127.1 (2C), 127.0, 126.5−126.4 (m, 2C), 93.4, 80.0, 35.2 (d, J = 15.2 Hz), 34.5 (d, J = 14.7 Hz), 30.5, 30.3−29.9 (m, 4C), 27.6−26.9 (m, 4C), 26.4 (d, J = 5.0 Hz, 2C), 21.9, 16.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ −14.10; IR ν_{max} (Nujol, cm^{-1}) 1637, 1424, 756; HRMS (ESI-TOF) m/z 544.2830 [M + H] $C_{34}H_{43}NOPS$ requires 544.2803; mp 151−153 °C; $[\alpha]^{20}_D$ −272 (c = 1.0, $CHCl_3$).

(*S*)-2-(3-(Bis(4-fluorophenyl)phosphanyl)thiophene-2-yl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (5). A solution of (*S*)-2-(3-bromothiophene-2-yl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (**17**) (642 mg, 1.51 mmol, 1 equiv) in Et_2O (20 mL) was cooled to −78 °C. *n*-BuLi (0.71 mL, 2.33 M in hexane, 1.65 mmol, 1.1 equiv) was added dropwise and stirring continued at −78 °C for 5 min. Chlorobis(4-fluorophenyl)phosphine (462 mg, 1.80 mmol, 1.2 equiv) was added dropwise and the cooling bath removed. The reaction mixture was allowed to stir for a further 1 h and was diluted with Et_2O (20 mL) and then quenched with water (10 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (3 × 20 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude yellow solid which was purified by column chromatography (CH_2Cl_2 on SiO_2) to yield the product as a white foam (398 mg, 46% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.42 (m, 2H), 7.36 (d, J = 5.1 Hz, 1H), 7.32−7.13 (m, 12H), 7.07−6.96 (m, 4H), 6.37 (dd, J = 5.1, 1.0 Hz, 1H), 4.71 (d, J = 4.3 Hz, 1H), 1.74−1.64 (m, 1H), 0.86 (d, J = 6.7 Hz, 3H), 0.29 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, cdcl$_3$) δ 164.6 (d, J = 4.5 Hz), 162.2 (d, J = 4.2 Hz), 156.8 (d, J = 3.3 Hz), 145.3, 140.7 (d, J = 27.4 Hz), 140.5, 135.5 (app. td, J = 22.2, 8.0 Hz, 4C), 133.8 (dd, J = 12.3, 3.5 Hz), 133.4, 133.2 (dd, J = 11.2, 3.5 Hz), 132.8 (d, J = 23.6 Hz), 128.4 (d, J = 1.9 Hz), 128.2 (2C), 127.7 (3C), 127.1, 126.8 (2C), 126.2 (m, 2C), 115.9 (dd, J = 7.8, 5.5 Hz, 2C), 115.7 (dd, J = 7.8, 5.5 Hz, 2C), 93.8 (d, J = 1.2 Hz), 80.2, 30.3, 21.8, 16.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.39 − −112.49 (m), −112.60 − −112.70 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ −18.04 (app t, J = 4.4 Hz); IR ν_{max} (Nujol, cm^{-1}) 1641, 1587, 1494; HRMS (ESI-TOF) m/z 568.1704 [M + H] $C_{34}H_{29}F_2NOPS$ requires 568.1676; mp 78−80 °C; $[\alpha]^{20}_D$ = −288.3 (c = 0.4, $CHCl_3$).

(*S*)-2-(3-(Di-*o*-tolylphosphanyl)thiophene-2-yl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (4). A solution of (*S*)-4-isopropyl-5,5-dimethyl-2-(thiophene-2-yl)-4,5-dihydrooxazole (**17**) (590 mg, 2.64 mmol, 1 equiv) in Et_2O (10 mL) was cooled to −78 °C in an acetone/liquid N_2 bath. *n*-BuLi (1.18 mL, 2.33 M in hexane, 2.76 mmol, 1.05 equiv) was added dropwise and stirring continued at −78 °C for 30 min. The reaction vessel was transferred to an ice bath, stirred at 0 °C for 30 min, and then returned to the acetone/liquid N_2 bath and recooled to −78 °C. Chlorodi(*o*-tolyl)phosphine (1.00 g, 4 mmol, 1.5 equiv) was added in one portion, and the reaction was then stirred to room temperature over 16 h. The reaction mixture was diluted with water (15 mL) and then extracted with Et_2O (3 × 40 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude residue which was purified by column chromatography (5:1 pentane/CH_2Cl_2 on SiO_2) to

DOI: 10.1021/acs.joc.5b01764
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yield the product as a white crystalline solid (341 mg, 30% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 5.1 Hz, 1H), 7.30−7.21 (m, 5H), 7.19 (t, J = 7.0 Hz, 2H), 7.15−7.04 (m, 6H), 6.86−6.80 (m, 1H), 6.38 (d, J = 5.0 Hz, 1H), 4.72 (d, J = 3.9 Hz, 1H), 2.40 (s, 6H), 1.75−1.67 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.30 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, cdcl$_3$) δ 157.4 (d, J = 2.7 Hz), 145.6, 142.5 (d, J = 12.3 Hz), 142.3 (d, J = 11.9 Hz), 139.7 (d, J = 27.5 Hz), 136.3 (d, J = 13.5 Hz), 135.8 (d, J = 12.2 Hz), 133.9 (2C), 133.4 (d, J = 25.7 Hz), 132.7 (d, J = 4.0 Hz, 2C), 130.0 (m, 2C), 128.7 (d, J = 6.9 Hz, 2C), 128.3, 128.1 (2C), 127.5 (2C), 127.4, 126.7, 126.5 (2C), 126.2 (d, J = 9.6 Hz, 2C), 126.0 (d, J = 2.7 Hz, 2C), 93.8, 79.6, 30.2, 21.7, 21.1 (d, J = 6.8 Hz), 21.0 (d, J = 7.3 Hz), 16.0; ^{31}P NMR (121 MHz, $CDCl_3$) δ −31.45; IR ν_{max} (Nujol, cm^{-1}) 1641, 1031, 748; HRMS (ESI-TOF) m/z 560.2162 [M + H] $C_{36}H_{35}NOPS$ requires 560.2177; mp 81−83 °C; $[\alpha]^{20}_D$ = −240.7 (c = 0.15, $CHCl_3$).

***N*-[1(*S*)-2-Hydroxy-2,4-dimethylpentan-3-yl]-ferrocenecarboxamide (19).** To solution of amino alcohol (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**9**) (1.11 g, 8.48 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added Et_3N (1.27 mL, 8.90 mmol, 1.05 equiv). In a separate flask, ferrocene acid chloride **18** (2.12 g, 8.48 mmol, 1 equiv) was dissolved in CH_2Cl_2 (50 mL). The solution of ferrocene acid chloride was added dropwise to the main reaction flask at rt. The reaction was allowed stir at room temperature over 16 h and was then concentrated in vacuo to a crude residue which was purified by column chromatography (20:1 CH_2Cl_2/MeOH on SiO_2) to yield the product as an orange solid (2.05 g, 70% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.09 (m, 1H), 4.71 (m, 2H), 4.36 (m, 2H), 4.25 (s, 5H), 3.91 (m, 1H), 2.22−2.17 (m, 1H), 1.34 (s, 3H), 1.29 (s, 3H), 1.03−1.01 (m, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.9, 75.8, 72.8, 69.3 (s, 2C), 68.6 (s, 5C), 67.3, 67.0, 59.0, 28.5, 27.3, 26.3, 21.6, 16.1; IR ν_{max} (CH_2Cl_2, cm^{-1}) 3426, 1635; HRMS (ESI-TOF) m/z 366.1146 [M + Na] $C_{18}H_{25}FeNO_2Na$ requires 366.1132; mp 131−133 °C; $[\alpha]^{20}_D$ = −4.8 (c = 0.35, $CHCl_3$).

[4(*S*)-Isopropyl-5,5-dimethyl-2-oxazolin-2-yl]ferrocene (20). A solution of *N*-[1(*S*)-2-hydroxy-2,4-dimethylpentan-3-yl]-ferrocenecarboxamide (**19**) (2.045 g, 5.93 mmol, 1 equiv) in CH_2Cl_2 (65 mL) was cooled to −15 °C in an ice/NaCl bath. Methanesulfonic acid (2.30 mL, 35.4, mmol, 6 equiv) was added dropwise over 10 min. The reaction was then allowed to stir to room temperature over 16 h. The reaction was quenched with saturated aq $NaHCO_3$ (100 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude yellow oil, which was purified by column chromatography (10% v/v Et_2O in cyclohexane on SiO_2) to give the title compound as an orange solid (1.59 g, 82% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75−4.71 (m, 2H), 4.32−4.27 (m, 2H), 4.19 (s, 5H), 3.33 (d, J = 7.4 Hz, 1H), 1.90−1.77 (m, 1H), 1.48 (s, 3H), 1.39 (s, 3H), 1.09 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H); ^{13} C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.1, 85.6, 80.2, 71.7, 70.0, 69.9, 69.5 (s, 5C), 68.9, 68.9, 29.5, 29.2, 21.4, 21.3, 20.2; IR ν_{max} (CH_2Cl_2, cm^{-1}) 3437, 1643, 1265; HRMS (ESI-TOF) m/z 326.1219 [M + H] $C_{18}H_{24}NOFe$ requires 326.1207; mp 68−71 °C; $[\alpha]^{20}_D$ = −51.4 (c = 0.5, $CHCl_3$).

1-[4(*S*)-Isopropyl-5,5-dimethyl-2-oxazolin-2-yl]-2(*S*)-(diphenylphosphino)ferrocene (7). A Schlenk tube was charged with [4(*S*)-isopropyl-5,5-dimethyl-2-oxazolin-2-yl]ferrocene (**20**) (327 mg, 1.01 mmol, 1 equiv). Anhydrous *n*-hexane (10 mL) was added via syringe with stirring to form a suspension. TMEDA (1.90 mL, 1.3 mmol, 1.5 equiv) was added dropwise, and formation of an orange solution was observed. The reaction flask was placed in a liquid N_2/acetone bath at −78 °C and allowed to equilibrate for 20 min. *s*-BuLi (1.0 mL, 1.3 M in cyclohexane, 1.3 mmol, 1.3 equiv) was added dropwise and the reaction stirred at −78 °C for a further 1.5 h. The reaction flask was then transferred to a 0 °C ice bath for 30 min, and chlorodiphenylphosphine (0.37 mL, 2.0 mmol, 2 equiv) was added dropwise. Immediate formation of a yellow suspension was observed. The reaction was kept in the ice bath and allowed warm to room temperature over 16 h. The reaction mixture was transferred to a separatory funnel containing 10% w/v aq NH_4Cl (20 mL). After vigorous mixing, the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL), and the organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to give a crude product, which was purified by column chromatography (8:1 cyclohexane/EtOAc on SiO_2) to give the title compound an orange solid (280 mg, 54% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.43 (m, 3H), 7.37−7.33 (m, 4H), 7.23−7.19 (m, 5H), 4.98 (m, 1H), 4.33 (app t, J = 2.4 Hz, 1H), 4.23 (s, 5H), 3.52 (m, 1H), 3.14 (d, J = 8.1 Hz, 1H), 1.69−1.57 (m, 1H), 1.47 (s, 3H), 0.91 (d, J = 6.5 Hz, 1H), 0.88 (d, J = 6.5 Hz, 1H), 0.84 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.6, 139.9 (d, J = 12.8 Hz), 138.6 (d, J = 14.0 Hz), 134.9 (d, J = 21.3 Hz, 2C), 132.6 (d, J = 19.5 Hz, 2C), 128.8, 128.12 (d, J = 6.9 Hz, 2C), 128.0 (d, J = 6.9 Hz, 2C), 127.8, 86.4, 80.2, 78.3, 75.9, 74.0, 72.2, 70.7 (s, 5C), 70.6, 29.3, 29.0, 20.9, 20.6, 20.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ −16.68; IR ν_{max} (Nujol, cm^{-1}) 3380, 1628, 1524; HRMS (ESI-TOF) m/z 510.1669 [M + H] $C_{30}H_{33}NOFeP$ requires 510.1649; mp 52−54 °C; $[\alpha]^{20}_D$ = +23.2 (c = 0.35, $CHCl_3$).

Preparation of Racemic Heck Products. Racemic Heck products for use in GC and HPLC were synthesized by known methods. 2-Phenyl-2,5-dihydrofuran (**23**),[40] 2-Phenyl-2,3-dihydrofuran (**24**),[41] and 2-(2-naphthyl)-2,3-dihydrofuran (**30**).[42] Racemic 2-(2-naphthyl)-2,5-dihydrofuran (**29**) was prepared using racemic *i*-Pr-PHOX.

General Procedure for the Asymmetric Intermolecular Heck (IAH) Reactions. $Pd_2(dba)_3$ (8 mg, 0.009 mmol, 0.05 equiv) and ligand (0.035 mmol, 0.06 equiv) were added to a 10 mL microwave vial containing a stir bar, which then was sealed with a septum. The vial was connected to a Schlenk line using a needle and was evacuated and backfilled with nitrogen (3×). THF (2 mL) was added and the purple solution stirred at room temperature until the purple color dissipated and a yellow/brown solution was observed (10−60 min). The vessel was sequentially charged by syringe with 2,3-dihydrofuran (227 μL, 3.0 mmol, 5 equiv), aryl trifluoromethanesulfonate (0.60 mmol, 1 equiv), *n*-tridecane (37 μL, 0.15 mmol, 0.25 equiv), and *i*-Pr_2NEt (250 μL, 1.8 mmol, 3 equiv). The vessel was then transferred to the microwave reactor and cyclically irradiated at 150 W with stirring to an internal temperature of 100 °C for 18 h. After being cooled to room temperature, the reaction mixture was diluted with pentane (5 mL) and stirred for 1 min, causing precipitation of *i*-Pr_2NEt·HOTf. The suspension was filtered through a 1 cm plug of $MgSO_4$, eluting with Et_2O (10 mL). The filtrate was concentrated in vacuo and sampled for GC analysis or HPLC analysis and, in the case of the 2-naphthylation of 2,3-dihydrofuran, subsequently purified by flash chromatography.

For the phenylation of 2,3-dihydrofuran, conversion and levels of enantiomeric excess were determined concurrently in a single GC analysis (γ-CD-TFA, 30.0 m, 0.25 mm i.d. 80−90 °C at 0.3 °C/min, 90−120 °C at 2 °C/min, hold 10 min, 120−80 °C at 15 °C/min, 103 kPa, inj 200 °C, det. 220 °C). t_R (*S*)-**23** 44.68 min, t_R (*R*)-**23** 45.14 min, t_R (*S*)-**24** 38.96 min, t_R (*R*)-**24** 39.32 min). Conversion was determined by using *n*-tridecane as an internal standard.

For 2-(2-naphthyl)ation of 2,3-dihydrofuran, levels of enantiomeric excess were determined by chiral HPLC (Chiralcel OD 0.46 × 25 cm, heptane/*i*-PrOH 99:1, 1 mL/min, 25 °C). t_R (*S*)-**29** 10.66 min, t_R (*R*)-**29** 12.61 min, t_R (*S*)-**30** 6.73 min, t_R (*R*)-**30** 7.51 min. Absolute configurations were inferred by reference to the literature. Equal absorbance was assumed for **29** and **30** at 256 nm for the purpose of determining the product ratio.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01764. CCDC 1415495−1415497 contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

X-ray data (CIF)

DOI: 10.1021/acs.joc.5b01764
J. Org. Chem. 2015, 80, 10151−10162

Full analysis for all new compounds including NMR, X-ray, and chromatographic data (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: patrick.guiry@ucd.ie.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the UCD School of Chemistry for the award of a research scholarship to D.M. We thank the Irish Research Council (IRC) for the award of a research scholarship (RS/2012/607) to C.N. We also thank UCD School of Chemistry for the use of analytical facilities and the technical staff, Dr. Yannick Ortin and Geraldine Fitzpatrick for NMR spectroscopy and Adam Coburn and Kevin Conboy for mass spectrometry.

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DOI: 10.1021/acs.joc.5b01764
J. Org. Chem. 2015, 80, 10151−10162