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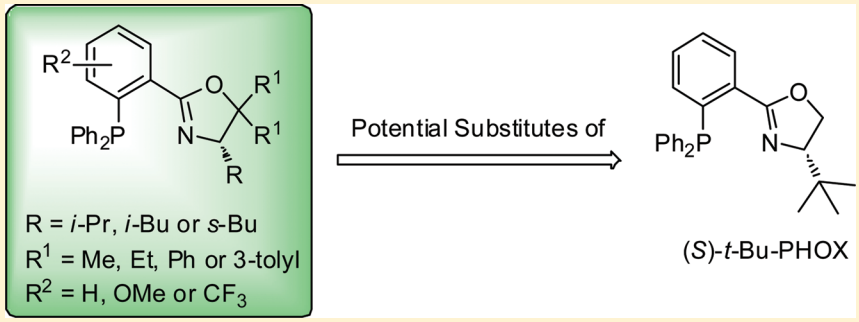
Design, Synthesis, and Applications of Potential Substitutes of *t*-Bu-Phosphinooxazoline in Pd-Catalyzed Asymmetric Transformations and Their Use for the Improvement of the Enantioselectivity in the Pd-Catalyzed Allylation Reaction of Fluorinated Allyl Enol Carbonates

Étienne Bélanger, Marie-France Pouliot, Marc-André Courtemanche, and Jean-François Paquin*

Canada Research Chair in Organic and Medicinal Chemistry, Département de chimie, Université Laval, 1045 avenue de la Médecine, Québec, QC, Canada G1V 0A6

Supporting Information



ABSTRACT: The design, synthesis, and applications of potential substitutes of *t*-Bu-PHOX in asymmetric catalysis is reported. The design relies on the incorporation of geminal substituents at C5 in combination with a substituent at C4 other than *t*-butyl (*i*-Pr, *i*-Bu, or *s*-Bu). Most of these new members of the PHOX ligand family behave similarly in terms of stereoinduction to *t*-Bu-PHOX in three palladium-catalyzed asymmetric transformations. Electronically modified ligands were also prepared and used to improve the enantioselectivity in the Pd-catalyzed allylation reaction of fluorinated allyl enol carbonates.

INTRODUCTION

The phosphinooxazoline ligands (PHOX ligands) are a versatile class of non-C_2-symmetric P,N-chiral ligands developed independently by Pfaltz, Helmchen, and Williams in 1993 (Figure 1).[1−3] The well-known members of this class of ligands (i.e., **1**−**4**, Figure 1) differ only by the substituent at C4. Within this group, the *t*-butyl-substituted one (i.e., **1**) is often the one affording the highest enantioselectivities in various asymmetric transformations[1,4,5] that in certain cases have been used as key steps in natural product synthesis.[6]

The *S*-enantiomer of this ligand ((*S*)-**1**) is commercially available; otherwise, it can be synthesized in four steps from (*S*)-*tert*-leucine ((*S*)-**6**),[7] a rather expensive non-natural amino acid (Figure 2).[8−10] On the other hand, (*R*)-*t*-Bu-PHOX ((*R*)-**1**) is not commercially available, and its synthesis requires the use of (*R*)-*tert*-leucine ((*R*)-**6**),[11] a prohibitively expensive amino acid, as starting material. Thus, (*R*)-*t*-Bu-PHOX is practically not accessible.[12] This synthetic shortcoming limits access to one enantiomeric series for any catalytic transformation using the *t*-Bu-PHOX ligand. This situation is not encountered for the other members of the PHOX ligand family (i.e., **2**−**4**, Figure 1). Ligand (*S*)-**5** was designed to address this issue, but, to date, its use in asymmetric catalysis remains limited.[7a,13]

In this context, readily accessible substitutes for *t*-Bu-PHOX that would be available in both enantiomeric series at reasonable cost would be highly valuable.

Inspired by previous results in the literature,[14−16] we envisioned that the incorporation of geminal substituents (Me, Et, Ph, 3-tolyl) at C4 of *i*-Pr-PHOX (**2**) and ligands bearing a closely related side chain at C5, such as *i*-Bu and *s*-Bu, could result in practical replacement for *t*-Bu-PHOX (**1**). These new ligands (structures **7**−**9** in Figure 3) would not only have a major economic advantage over *t*-Bu-PHOX since the cost of the starting (*S*)- or (*R*)-amino acids (**10**−**12**) is much lower, with the exception of (2*R*,3*R*)-isoleucine (**12**),[17] than the corresponding *tert*-leucines (**6**), but would also allow easy access to both enantiomers.

Herein, we describe new and readily available members of the PHOX family which have a parallel reactivity to *t*-Bu-PHOX with the key advantage of being easily accessible as both enantiomers. We have recently described our preliminary results in this area[18] and now report an expanded description of our studies including the synthesis of these ligands and their

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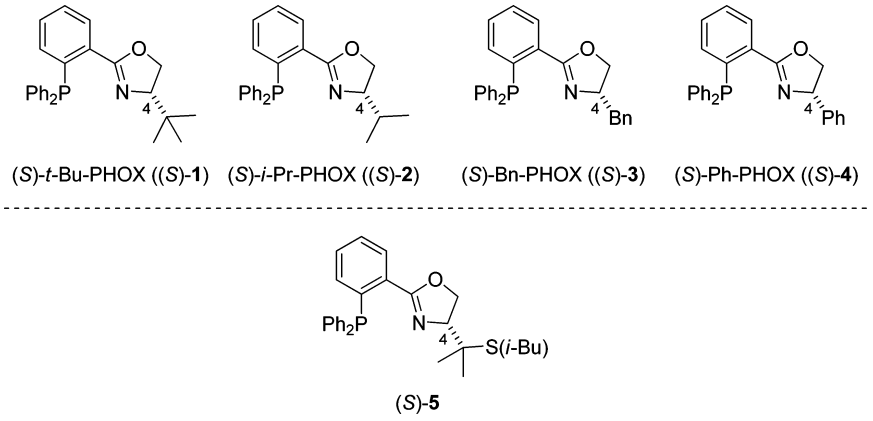

Figure 1. Some members of the PHOX ligand family.

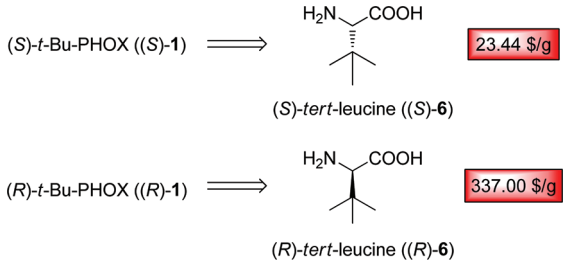

Figure 2. Synthetic precursor for the preparation of (*S*)- and (*R*)-*t*-Bu-PHOX (**1**).

application in enantioselective palladium-catalyzed transformations. We also document the preparation of electronically modified ligands and their use in improving the enantioselectivity of the Pd-catalyzed allylation reaction of fluorinated allyl enol carbonates.

RESULTS AND DISCUSSION

Synthesis of the Ligands. The retrosynthetic analysis for the synthesis of ligands **7**–**9** is shown in Figure 4. The desired ligands can be obtained from two different synthetic routes: one that parallels the original sequence used to access *t*-Bu-PHOX[7a] (via **13**–**14**) and a second route that takes advantage of a recently published approach to PHOX ligands from Stoltz's group (via **15**–**17**).[7b,c] In the first case, the C–P bond is established through a S_NAr reaction using $KPPh_2$, whereas in the second case, the key C–P bond is made through an Ullmann-type coupling developed by Buchwald.[19] The intrinsic limitation of the S_NAr reaction, where either electron-rich phosphine anions or electron-rich aryl fluorides cannot be used, potentially prevents the fine-tuning of the electronic properties of the ligand for specific reactions, and it is for that reason that the Stoltz approach was also investigated.[20] The fluoroaryl (**13**–**14**) and bromoaryl precursors (**15**–**17**) could be prepared from the corresponding amino alcohols (**18**–**20**)

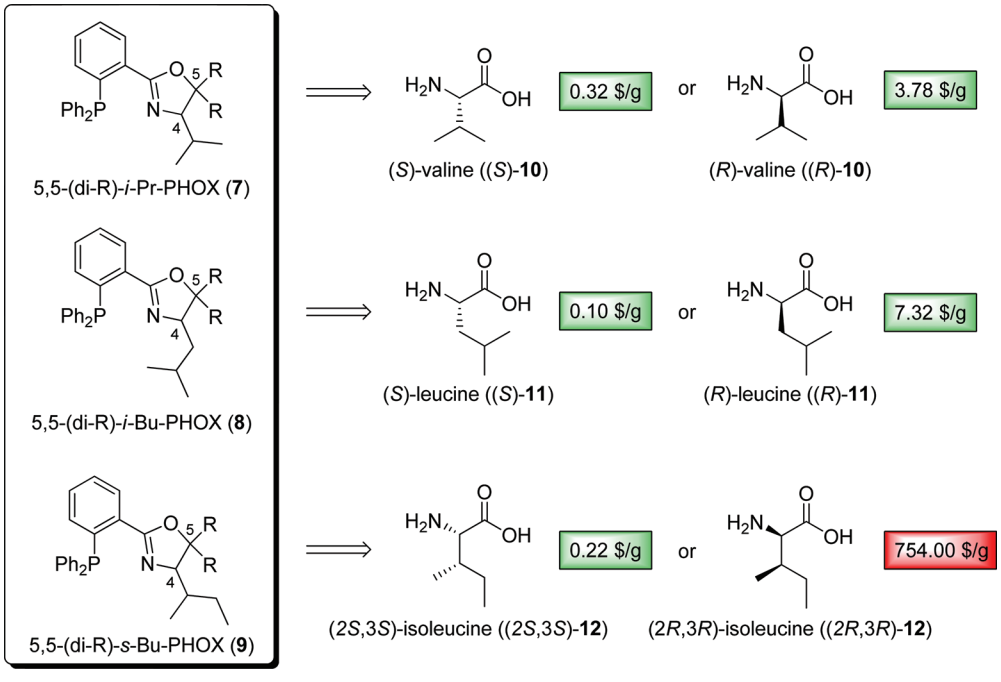

Figure 3. New ligands 5,5-(di-*R*)-*i*-Pr-PHOX (**7**), 5,5-(di-*R*)-*i*-Bu-PHOX (**8**), and 5,5-(di-*R*)-*s*-Bu-PHOX (**9**) and their respective synthetic precursors.

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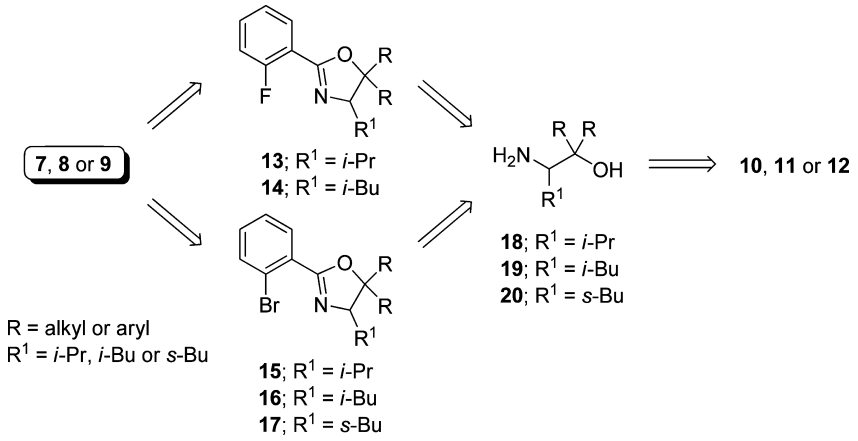
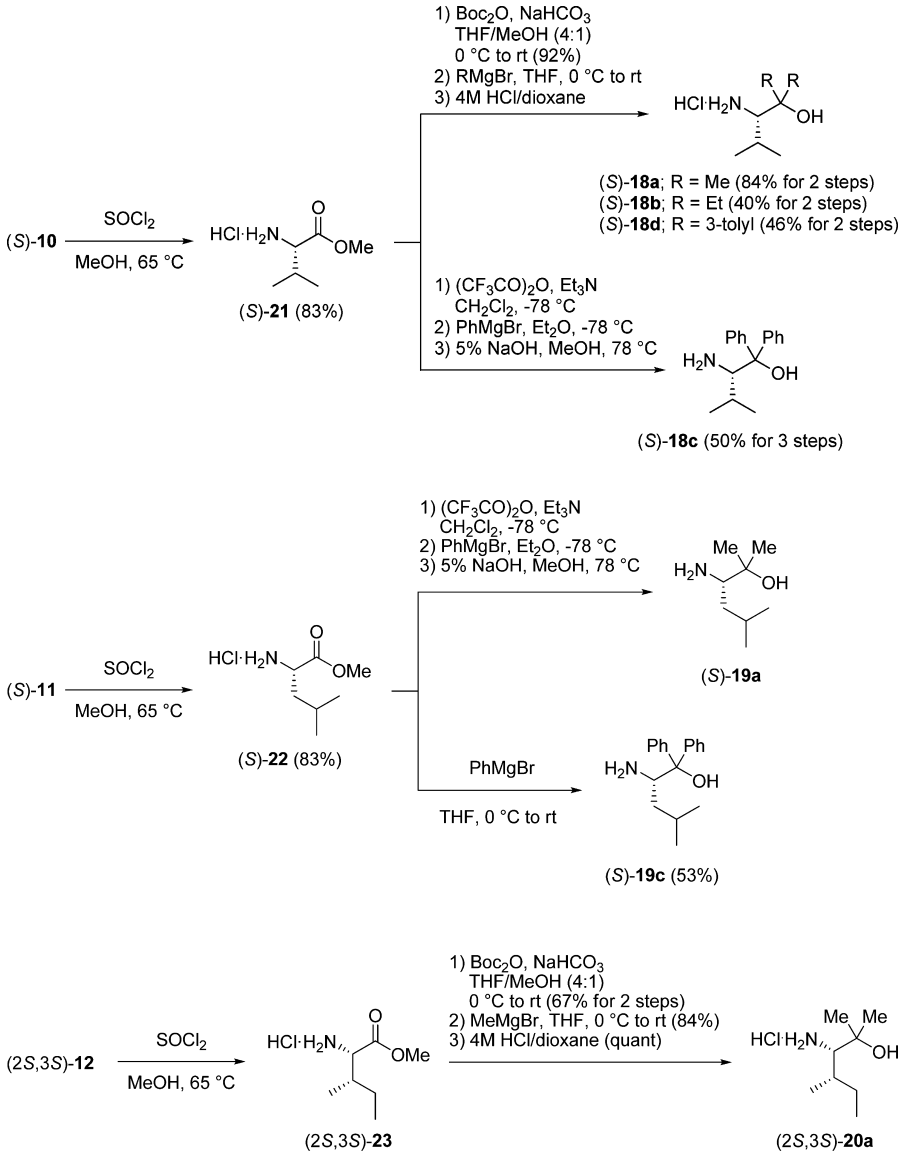


Figure 4. Retrosynthetic analysis.

Scheme 1. Synthesis of the Amino Alcohol Precursors



that could be readily obtained from the commercially available amino acids (**10**–**12**).

The following synthetic schemes illustrate the sequences used to prepare the *S*-enantiomer of the various ligands; similar routes were used when the *R*-enantiomer was also synthesized. The synthesis of the various (*S*)-amino alcohols is shown in Scheme 1. For the valine-based amino alcohol, (*S*)-valine ((*S*)-**10**) was first transformed into (*S*)-valine methyl ester

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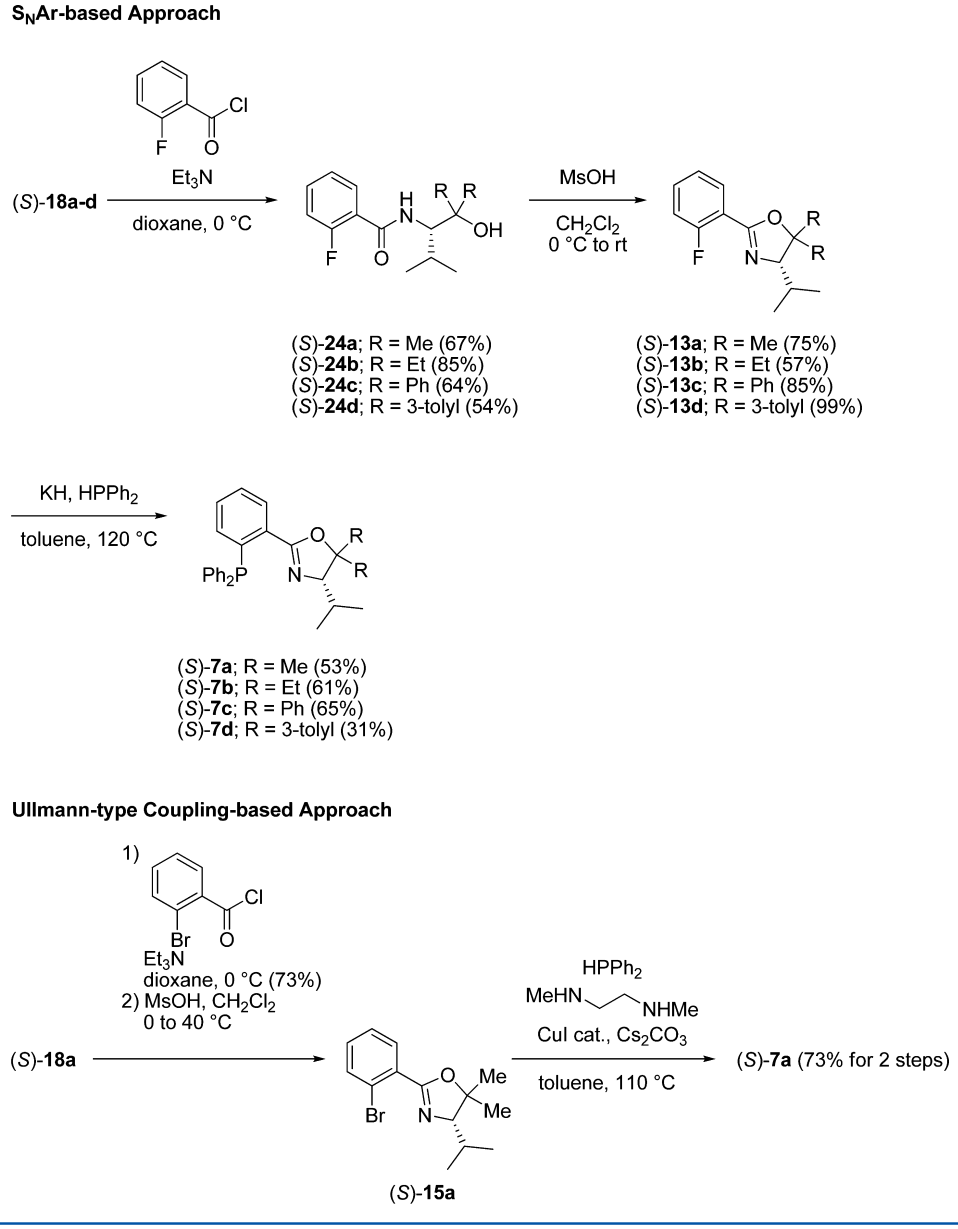
Scheme 2. Synthesis of the Valine-Based Ligands



hydrochloride salt (*S*)-**21** in 83% yield using a known procedure.[21,22] The introduction of the *gem*-dimethyl group, *gem*-diethyl group, or *gem*-di-3-tolyl was performed using a three-step process[23] involving protection of the amine and Grignard addition followed by deprotection of the Boc group under acidic conditions producing (*S*)-**18a**,[23] (*S*)-**18b**,[14e] and (*S*)-**18d** in 40−84% overall yield for the three steps. Alternatively, for the introduction of a *gem*-diphenyl group, a similar three-step process[14c] involving protection of the amine as the trifluoroacetamide and Grignard addition followed by deprotection of the amide under basic conditions was used to give access to (*S*)-**18c**[24] in 50% overall yield for the three steps. For the leucine-based amino alcohol, the (*S*)-leucine methyl ester hydrochloride (*S*)-**22**[25,26] was first prepared from (*S*)-leucine ((*S*)-**11**) using the same protocol as for the (*S*)-**10**. From (*S*)-**22**, a three-step sequence[14c] was used to prepare (*S*)-**19a** that was utilized directly for the next step (vide infra) while a direct phenyl Grignard addition furnished (*S*)-**19c**[27] in 53% yield. Finally, the isoleucine-based amino alcohol was prepared using a sequence similar to (*S*)-**18a**−**c**. Thus (2*S*,3*S*)-**20a** was prepared from (2*S*,3*S*)-**12** via (2*S*,3*S*)-**23**[28] in 56% overall yield for the four steps.

The *S*-enantiomer of the valine-based ligands (*S*)-**7a**−**d** were initially prepared using the original S_NAr approach (Scheme 2).[7a] Thus, the amino alcohols (*S*)-**18a**−**d** were reacted with 2-fluorobenzoyl chloride to afford amides (*S*)-**24a**−**d** in moderate to good yields. Cyclization under acidic conditions[14c] gave the oxazolines (*S*)-**13a**−**d** in good yields (57−99%). Finally, they were converted to the desired ligands, (*S*)-**7a**−**d**,[29] via a S_NAr reaction using $KPPh_2$ in low to moderate yields.[7a] Because of the unsatisfactory yields observed in the C−P bond-forming step, the Stoltz approach[7b,c] was also investigated for the preparation of (*S*)-**7a**. Accordingly, the amino alcohol (*S*)-**18a** was reacted with 2-bromobenzoyl chloride to give amide in good yield. The latter was cyclized, and the crude oxazoline was directly submitted to the Ullmann-type coupling developed by Buchwald[19] to afford (*S*)-**7a** in 73% yield for two steps.

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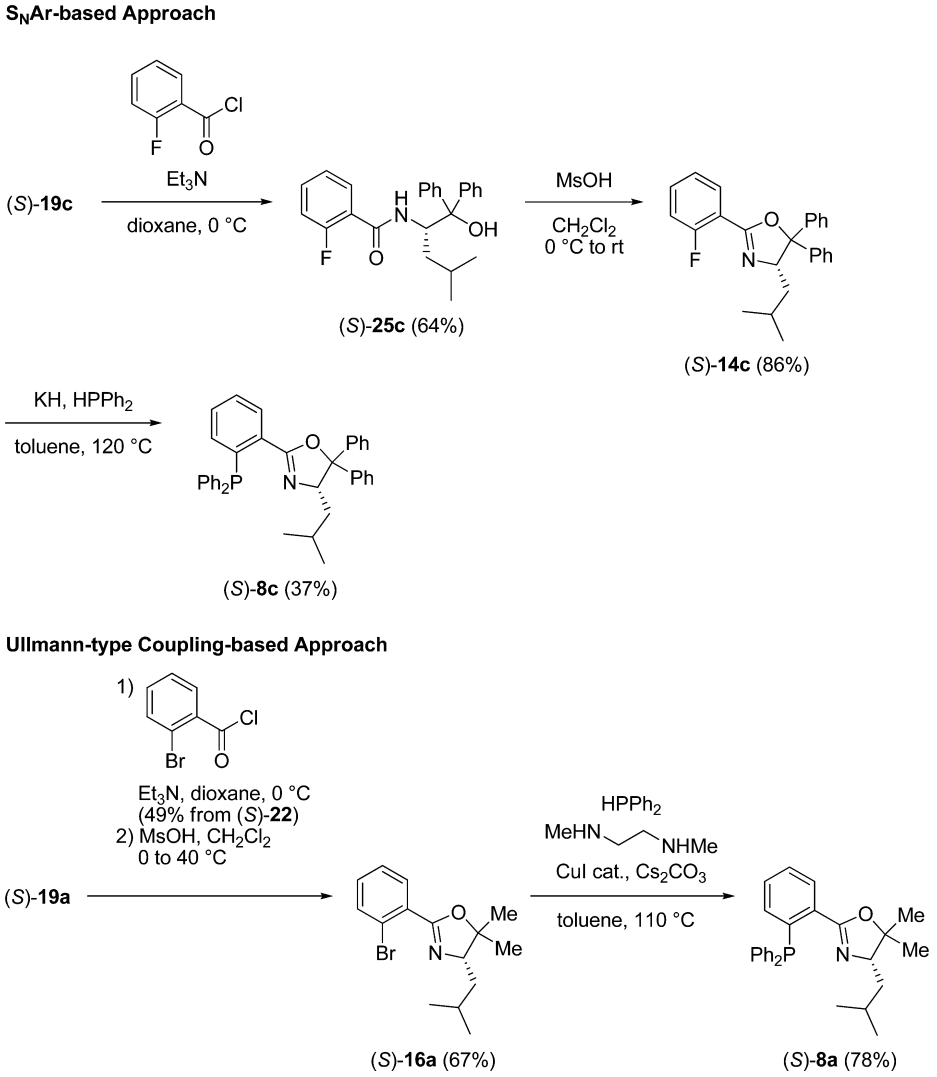
Scheme 3. Synthesis of the Leucine-Based Ligands



Similarly, the leucine-based ligands (*S*)-**8a,c** were prepared using both the S_NAr approach and the Stolz approach (Scheme 3), while the isoleucine-based ligand (*S*)-**9a** was prepared using the Stoltz approach (Scheme 4).

Exploitation of the Ligands in Asymmetric Catalysis. To evaluate the potential of the new ligands, they were tested in three different enantioselective palladium-catalyzed transformations.

First, the enantioselective Tsuji–Trost allylation reaction[30] using fluorinated silyl enol ether precursor **27** was examined (Table 1).[5a] Under the original conditions, using (*S*)-*t*-Bu-PHOX as the chiral ligand, the fluoroketone (*R*)-**28** was obtained in excellent yield and 96:4 er (entry 1). As a point of comparison, reaction with (*S*)-*i*-Pr-PHOX provided (*R*)-**28** with an excellent yield but with a lower er (90:10). Interestingly, all of the ligands derived from valine (**7a–d**, entries 3 and 5–7) gave the fluoroketone in 87–93% yield with comparable enantiomeric ratios (ca. 95:5 er). The use of the enantiomer of the ligand, (*R*)-**7a**,[31] provided the other enantiomer of the ketone, (*S*)-**28**, with identical results (entry 4). Thus, all the new valine-based ligands (**7a–d**) performed well compared to *t*-Bu-PHOX, thus demonstrating the beneficial effect of the substituents at C5 while the exact nature of the latter did not seem to play a critical role. Finally, the ligands derived from either leucine or isoleucine (entries 8–10) performed finely in terms of yield but gave lower enantiomeric ratios (92.5:7.5 to 94.5:5.5 er) compared to the valine-based ligands.

The ligands were next examined in the enantioselective Tsuji–Trost allylation reaction using fluorinated enol carbonate **29** (Table 2).[5b] While this reaction provides the same α-fluoroketones as with fluorinated silyl enol ethers, a key feature of this transformation is the important effect of the ligand-to-palladium ratio on the enantioselectivity of the α-fluoroketones since using a ligand excess (L/Pd ratio = 1.25) led to moderate results (80:20 er), while using a L/Pd ratio of 0.25 allowed the desired products to be obtained with high enantiopurity (96:4 er). While mechanistic studies are still underway to understand this phenomenon, we were curious to examine the new ligands in this reaction. Here again, under the original conditions with the optimal L/Pd ratio, using (*S*)-*t*-Bu-PHOX as the chiral ligand, the fluoroketone (*R*)-**28** was obtained in 91% yield and 96:4 er (entry 1). The reaction with (*S*)-*i*-Pr-PHOX provided (*R*)-**28** in 93% yield but with 90:10 er. With the exception of (*S*)-**7b** (79% yield, 93.5:6.5 er), all of the other ligands derived from valine (**7a,c,d**, entries 3, 6, and 7) gave the fluoroketone in excellent yield with the same enantioselectivity (95:5 er). The use of the enantiomer of the ligand, (*R*)-**7a**, provided the other enantiomer of the ketone, (*S*)-**28**, with identical results

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Scheme 4. Synthesis of the Isoleucine-Based Ligand

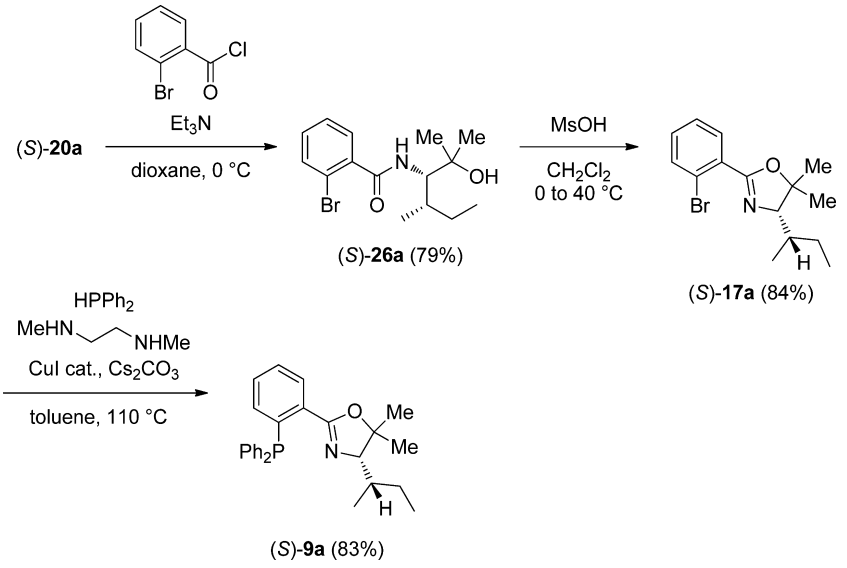
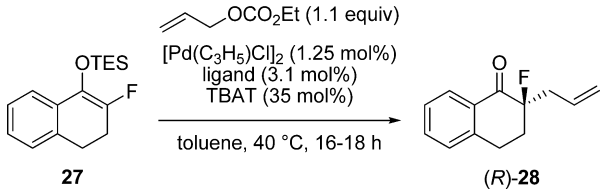


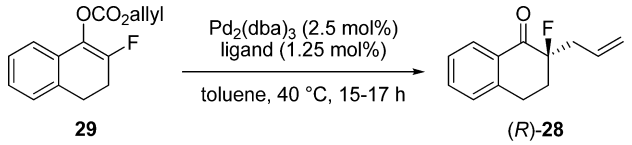
Table 1. Enantioselective Pd-Catalyzed Allylation Reaction of Fluorinated Silyl Enol Ether[a]



entry	ligand	yield (%)[b]	er[c]
1	*t*-Bu-PHOX	91	96:4
2	*i*-Pr-PHOX	93	90:10
3	(*S*)-**7a**	93	95:5
4	(*R*)-**7a**	93	5:95
5	(*S*)-**7b**	90	95:5
6	(*S*)-**7c**	87	95:5
7	(*S*)-**7d**	90	95.5:4.5
8	(*S*)-**8a**	92	93.5:6.5
9	(*S*)-**8c**	89	92.5:7.5
10	(*S*)-**9a**	92	94.5:5.5

[a]See ref 5a for details concerning the reaction conditions. [b]Isolated yield. [c]Determined by chiral HPLC.

Table 2. Enantioselective Pd-Catalyzed Allylation Reaction of Fluorinated Enol Carbonates[a]



entry	ligand	yield (%)[b]	er[c]
1	*t*-Bu-PHOX	91	96:4
2	*i*-Pr-PHOX	93	90:10
3	(*S*)-**7a**	93	95:5
4	(*R*)-**7a**	93	5:95
5	(*S*)-**7b**	79	93.5:6.5
6	(*S*)-**7c**	90	95:5
7	(*S*)-**7d**	83	95:5
8	(*S*)-**8a**	73	93:7
9	(*S*)-**9a**	80	95:5

[a]See ref 5b for details concerning the reaction conditions. [b]Isolated yield. [c]Determined by chiral HPLC.

(entry 4). Finally, ligand (*S*)-**8a**, derived from leucine, performed well in terms of yield but gave lower enantioselectivities (93:7 er), whereas ligand (*S*)-**9a**, derived from isoleucine, gave comparable results to the valine-based ligands.

Finally, the new ligands were tested in the enantioselective Heck reaction[32] between 2,3-dihydrofuran (**30**) and phenyl triflate (**31**) (Table 3). The use of PHOX ligands in this reaction, in particular, (*S*)-*t*-Bu-PHOX, was first reported by Pfaltz in 1996.[4a] Since the reported reaction time was 4 days in the original communication, we decided to conduct the reactions under microwave irradiation which has been shown by Larhed to greatly reduce the reaction time (18 h at 100 °C vs 4 days at 70 °C).[33] Using (*S*)-*t*-Bu-PHOX, the 2,5-dihydrofuran (*R*)-**32** was isolated in 81% yield and 98:2 er (entry 1). When (*S*)-*i*-Pr-PHOX was used, (*R*)-**32** was obtained in a moderate yield and 93:7 er (entry 2). In this reaction, the nature of the substituent at C5 has an impact on the enantioselectivities observed, thus using the valine-based ligand bearing a *gem*-dimethyl group at C5 ((*S*)-**7a**) furnished the product in good yield with slightly reduced enantioselectivity compared to *t*-Bu-PHOX (76% yield, 95.5:4.5 er) while ligand (*S*)-**7b** with a *gem*-diethyl group at C5 gave (*R*)-**32** with only 17% conversion with 94:6 er. Interestingly, the ligands bearing a *gem*-diphenyl ((*S*)-**7c**) or *gem*-di-3-tolyl ((*S*)-**7d**) group at C5 gave the furan with nearly identical enantioselectivity compared to *t*-Bu-PHOX (97.5:2.5 and 97:3 er, respectively), although the isolated yield was moderate when (*S*)-**7d** was used. Finally, the ligands derived from either leucine or isoleucine (entries 8 and 9) performed well in terms of enantioselectivity (ca. 95:5 er) compared to the valine-based ligands but with moderate yields.

Crystal Structure. In order to gain some insights about the chiral environment created by the addition of geminal substituents at C5, palladium complexes of ligand (*S*)-**7a**,[18] (*S*)-**8a**, and (*S*)-*t*-Bu-PHOX[18] were prepared by mixing the appropriate ligand with $PdCl_2$ in CH_2Cl_2 at 40 °C for 48 h.[34] The resulting crystals were analyzed by X-ray diffraction, and the crystal

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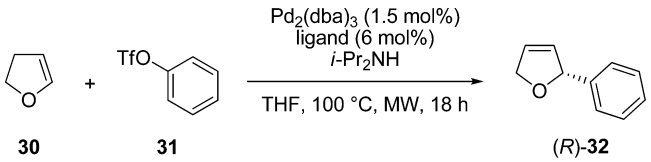
Table 3. Microwave-Assisted Enantioselective Heck Reaction of 2,3-Dihydrofuran[a]



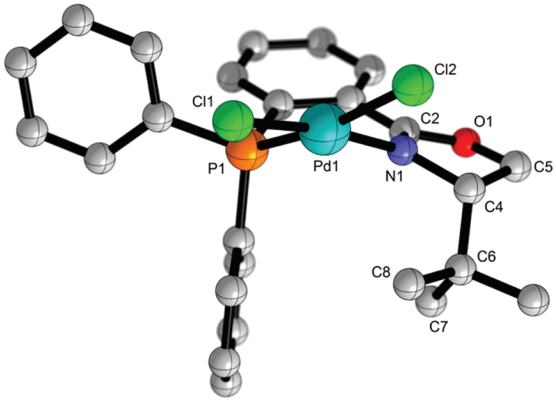
30 **31** (*R*)-**32**

entry	ligand	yield (%)[b]	er[c]
1	*t*-Bu-PHOX	81	98:2
2	*i*-Pr-PHOX	45	93:7
3	(*S*)-**7a**	76	95.5:4.5
4	(*R*)-**7a**	73	4:96
5	(*S*)-**7b**	17[d]	94:6
6	(*S*)-**7c**	81	97.5:2.5
7	(*S*)-**7d**	48	97:3
8	(*S*)-**8a**	50	95:5
9	(*S*)-**9a**	70	95.5:4.5

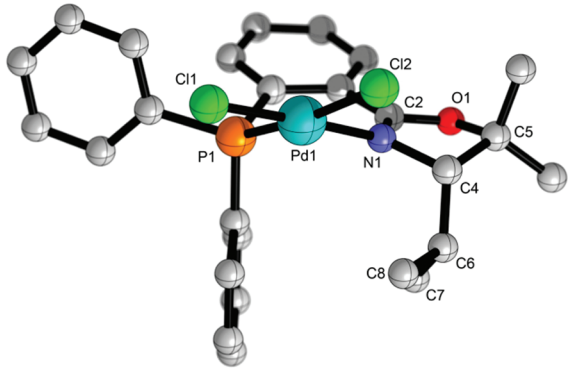
[a]See ref 33 for details concerning the reaction conditions. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Estimated conversion by ^{1}H NMR.

structures are shown in Figure 5.[35,36] In $PdCl_2[(S)$-*t*-Bu-PHOX$]$, the distance from the palladium to the methyl groups of the *i*-Pr group are 3.298 and 3.436 Å, respectively. Correspondingly, the same distances are 3.615 and 4.376 Å in $PdCl_2[(S)$-**7a**$]$ and 3.695 and 4.984 Å in $PdCl_2[(S)$-**8a**$]$. These numbers suggest a relatively similar environment around the Pd atom from the stereoinducting groups, thus an *i*-Pr or *i*-Bu group flanked by a *gem*-dimethyl group can mimic to some extent a *tert*-butyl group. However, the presence of the *gem*-dimethyl group also causes a slight distortion as indicated by the torsion angle between Cl2−Pd1−N1−C4 obtained for $PdCl_2[(S)$-**7a**$]$ (38.7°) and $PdCl_2[(S)$-**8a**$]$ (40.2°) compared to $PdCl_2[(S)$-*t*-Bu-PHOX$]$ for which a value of 47.3° was obtained. The subtle difference in terms of Pd−Me distances and torsion angles as well as the presence of the *gem*-dimethyl group at C5 may explain why in certain reactions (e.g., Heck reaction) slight differences in the enantioselectivities are observed between (*S*)-**7a** or (*S*)-**8a** and (*S*)-*t*-Bu-PHOX, whereas in others (e.g., allylation reaction) both (*S*)-**7a** and (*S*)-*t*-Bu-PHOX behave equally well, while (*S*)-**8a** gave slightly lower enantioselectivity.

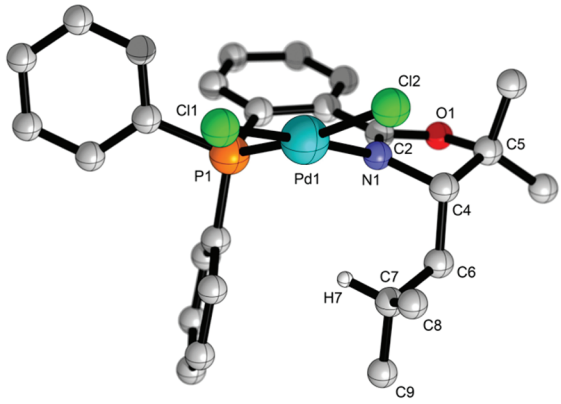
Electronic Modification. In all of the transformations presented above, the performance, in terms of stereoinduction, of the best ligands was always slightly inferior to the one using *t*-Bu-PHOX. For instance, using (*S*)-**7a** in the allylation of fluorinated silyl enol ether (Table 1, entry 3) or fluorinated allyl enol carbonate (Table 2, entry 3) produced the *α*-fluoroketone **28** with 95:5 er compared to 96:4 er with *t*-Bu-PHOX. With the hope of improving the performance in these particular reactions for eventual application in the synthesis of bioactive *α*-fluoroketones, we initially investigated the effect of lowering



$PdCl_2[(S)$-t-Bu-PHOX$]$



$PdCl_2[(S)$-**7a**$]$



$PdCl_2[(S)$-**8a**$]$

Figure 5. Crystal structure of $PdCl_2[(S)$-*t*-Bu-PHOX$]$, $PdCl_2[(S)$-**7a**$]$, and $PdCl_2[(S)$-**8a**$]$.

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temperature, a common trick to increase enantioselectivity in a given reaction.[37]

As shown in Tables 4 and 5, using *t*-Bu-PHOX and lowering the temperature led to incomplete conversion with no notable effect on the enantioselectivity (compare entries 1 and 2 in Tables 4 and 5) but with lower isolated yield or conversion. On the contrary, using ligand **7a**, decreasing the temperature to 20 °C resulted in good yield of (*R*)-**28** with nearly identical enantioselectivity (4:96 er from **27** and 4.5:95.5 er from **29**). Further decreasing the temperature to 0 °C resulted in an incomplete conversion when starting from **27** (Table 4) with a slight increase in ee. Under similar with allyl enol carbonate **29**, **28** was isolated in excellent yield with enantioselectivity similar to the one obtained with *t*-Bu-PHOX. In this case, further reduction of the temperature was not possible as low conversion was observed with a slight increase in er (Table 6, entry 5). Thus, in both systems, lowering the temperature to 20 °C was possible with ligand **7a** and allowed us to reach similar enantioselectivity as with *t*-Bu-PHOX.

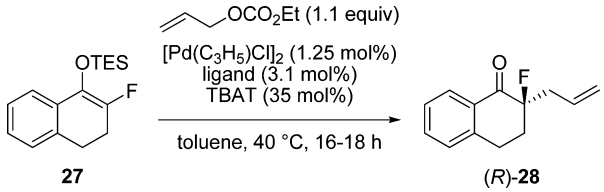
In light of these results and our desire to surpass the level of enantioinduction of *t*-Bu-PHOX, we decided to fine-tune the electronics of **7a**, a strategy that has proved beneficial in certain cases with electron-poor derivatives of *t*-Bu-PHOX derivatives.[7b,38] In that regard, we decided to synthesize two electron-poor ligands that only differed by the position of the electron-withdrawing group (CF_3) and one electron-rich ligand bearing a methoxy group for comparison. These electronically modified ligands were prepared as shown in Scheme 5 following a similar sequence as previously used for the other ligands. Thus, the acyl chloride, prepared from commercially available acid **33a** or readily available acid **33b**[39] and **33c**,[40] was reacted with alcohol (*S*)-**18a** (cf. Scheme 1), to afford the corresponding amides followed by cyclization under acidic conditions[14c] to give the oxazolines (*S*)-**35a–c**. Finally, Cu-catalyzed Ullmann-type coupling[19] of the phosphine and the aryl bromide produced the desired ligands (*S*)-**36a–c**.

The allylation of fluorinated silyl enol ether **27** was reexamined with ligand (*S*)-**36a** and (*S*)-**36c** (Scheme 6). Unfortunately, these electronically modified ligands behaved similarly to **7a** both at 20 and 0 °C (Table 4, entries 4 and 5).

The new ligands were also tested in the allylation of fluorinated allyl enol carbonate **29** (Table 6). The use of methoxy-substituted ligand (*S*)-**36a** at 20 °C led to (*R*)-**28** with good yield and 95:5 er (entry 1), while incomplete conversion was observed at −20 °C although with 96.5:3.5 er (entry 2). Superior results were obtained with CF_3-substituted ligand (*S*)-**36b**. Indeed, this ligand allowed the reaction to proceed at lower temperature as low as −20 °C. At that temperature, the α-fluoroketone **28** was isolated in 95% yield and a 97.5:2.5 er (entry 5). The isomeric CF_3-substituted ligand (*S*)-**36c** performed equally well (entry 7), and thus this electronic modulation of the ligands allowed an improved 97.5:2.5 er versus 96:4 er with *t*-Bu-PHOX.

As ligands (*S*)-**36b** and (*S*)-**36c** behaved similarly, but the latter had better physical properties, it was chosen for exploring the effect on other fluorinated allyl enol carbonate substrates (Table 7). While no effect was observed on the 7-methoxy-1-tetralone derived substrate **37a** (entries 3 and 4), improvement from 96:4 to 97:3 er was noticed with isomeric substrate **37b** (entries 5 and 6). In the case of 1-indanone derivative **37c**, the er of the α-fluoroindanone (*R*)-**38c** could be improved from 91:9 with *t*-Bu-PHOX to 93.5:6.5 with (*S*)-**36c** (entry 8). Finally, reaction of benzosuberone derivative **37d** with (*S*)-**36c**

Table 4. Effect of Temperature on the Enantioselective Pd-Catalyzed Allylation Reaction of Fluorinated Silyl Enol Ether 27[a]

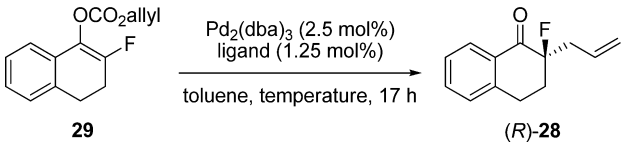


27 (*R*)-**28**

entry	ligand	temperature (°C)	yield (%)[b]	er[c]
1	(*S*)-*t*-Bu-PHOX	40	91	96:4
2	(*S*)-*t*-Bu-PHOX	20	65	96.5:3.5
3	(*S*)-**7a**	40	93	95:5
4	(*R*)-**7a**	20	72	4:96
5	(*R*)-**7a**	0	20[d]	3.5:96.5

[a]See ref 5a for details concerning the reaction conditions. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Estimated conversion by ^{1}H NMR.

Table 5. Effect of Temperature on the Enantioselective Pd-Catalyzed Allylation Reaction of Fluorinated Allyl Enol Carbonate 29[a]

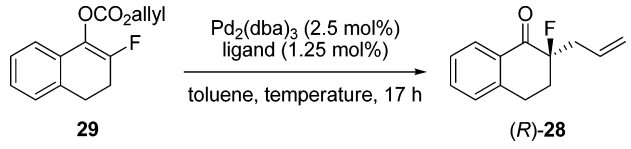


29 (*R*)-**28**

entry	ligand	temperature (°C)	yield (%)[b]	er[c]
1	(*S*)-*t*-Bu-PHOX	40	91	96:4
2	(*S*)-*t*-Bu-PHOX	20	15[d]	96:4
3	(*S*)-**7a**	40	93	95:5
4	(*R*)-**7a**	20	92	4.5:95.5
5	(*R*)-**7a**	0	90	4:96
6	(*R*)-**7a**	−20	30[d]	3:97

[a]See ref 5b for details concerning the reaction conditions. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Estimated conversion by ^{1}H NMR.

Table 6. Effect of Ligand and Temperature on the Enantioselective Pd-Catalyzed Allylation Reaction of Fluorinated Allyl Enol Carbonate 29[a]



29 (*R*)-**28**

entry	ligand	temperature (°C)	yield (%)[b]	er[c]
1	(*S*)-**36a**	20	82	95:5
2	(*S*)-**36a**	0	38[d]	96.5:3.5
3	(*S*)-**36b**	20	91	96:4
4	(*S*)-**36b**	0	99	97:3
5	(*S*)-**36b**	−20	95	97.5:2.5
6	(*S*)-**36b**	−78	trace	
7	(*S*)-**36c**	−20	94	97.5:2.5

[a]See ref 5b for details concerning the reaction conditions. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Estimated conversion by ^{1}H NMR.

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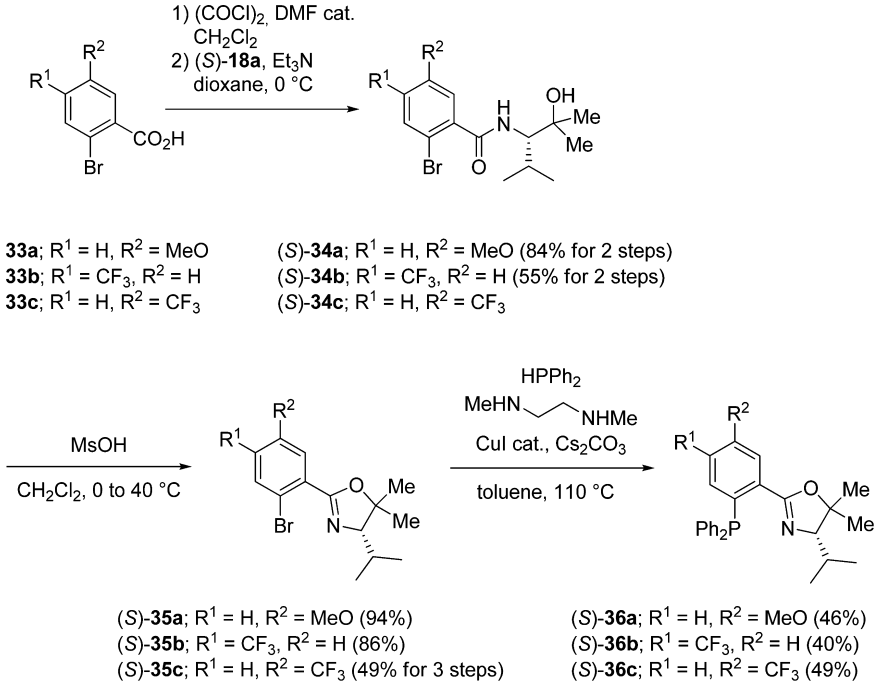
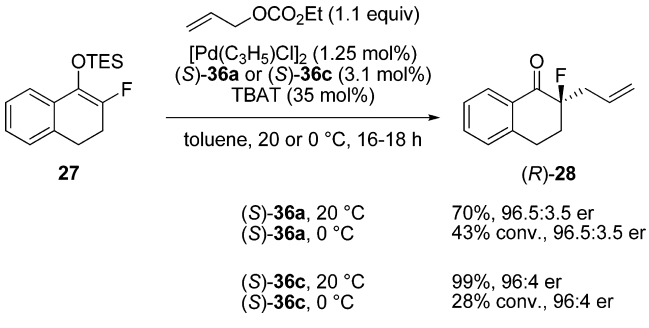
Scheme 5. Synthesis of the Electronically Modified Ligands



Scheme 6. Effect of Temperature on the Enantioselective Pd-Catalyzed Allylation Reaction of Fluorinated Silyl Enol Ether 27



gave the desired product (*R*)-**38d** in excellent yield with 95.5:4.5 er, an improvement from 94:6 er obtained with *t*-Bu-PHOX. Here, the use of (*R*)-**36c**, which would be readily accessible from (*R*)-valine, would allow access to the *S*-enantiomer of all of the α-fluoroketones.

CONCLUSION

In conclusion, we have described the design, synthesis, and applications of new and readily available members of the PHOX family as potential substitutes to *t*-Bu-PHOX in asymmetric catalysis. The ligand design incorporates two geminal substituents at C5 in combination with a substituent at C4 other than *t*-butyl (*i*-Pr, *i*-Bu, or *s*-Bu). Most of these new members of the PHOX ligand family behave similarly in terms of stereoinduction to *t*-Bu-PHOX in three palladium-catalyzed asymmetric transformations. Electronically modified ligands were also prepared and used to improve the enantioselectivity in the Pd-catalyzed allylation reaction of fluorinated allyl enol carbonates.

EXPERIMENTAL SECTION

Materials and Methods. All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions. ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded at 400 MHz (^{1}H), 100 MHz (^{13}C), 376 MHz (^{19}F), or 121 MHz (^{31}P) in $CDCl_3$ at ambient temperature using tetramethylsilane (^{1}H NMR) or residual $CHCl_3$ (^{1}H and ^{13}C NMR) as the internal standard or $CFCl_3$ (^{19}F NMR) or H_3PO_4 (^{31}P NMR) as the external standard. High-resolution mass spectra were obtained using electrospray ionization (ESI). Enantiomeric ratios were determined by HPLC analysis using OD-H or OJ-H chiral columns. The enantioselective Pd-catalyzed allylation reactions of fluorinated silyl enol ethers (Tables 1 and 4 and Scheme 6)[5a] and fluorinated allyl enol carbonates (Tables 2, 5, 6, and 7 and Scheme 6)[5b] have been carried out according to our original protocols, and products (*R*)-**28**, (*S*)-**28**, and (*R*)-**38a**–**d** have been characterized previously.[5a] Microwave-assisted enantioselective Heck reaction of 2,3-dihydrofurans has been run using known procedures (Table 3)[18,33] using a Biotage Initiator 8 apparatus, and product (*R*)-**32** has been characterized previously.[41] (*S*)-*t*-Bu-PHOX ((*S*)-**1**) and (*S*)-*i*-Pr-PHOX ((*S*)-**2**) were prepared using literature procedures.[7a]

Experimental Procedures. *Synthesis of the Amino Alcohol Precursors (Scheme 1).* (*S*)-**18a** and (*S*)-**18b** were prepared using a known procedure from (*S*)-**21**,[21] and spectroscopic data were in agreement with the literature for both (*S*)-**18a**[23] and (*S*)-**18b**.[14e] (*S*)-**18c** was prepared following a literature protocol,[14c] and spectroscopic data were in agreement with the literature.[24] (*S*)-**19a** was prepared from (*S*)-**22** following a literature protocol[14c] and was used crude for the next step. (*S*)-**19c** was prepared from (*S*)-**22** using a literature procedure.[27] The synthesis of the other amino alcohols is described in the Supporting Information.

*General Procedures for the Synthesis of the Ligands via the S_NAr Approach. Synthesis of Ligand (S)-**7a**. (S)-2-Fluoro-N-(2-hydroxy-2,4-dimethylpentan-3-yl)benzamide ((S)-**24a**): General Procedure for the Amide Formation.* To a solution of the amino alcohol (*S*)-**18a** (2.2 mmol) and dry triethylamine (0.95 mL, 6.7 mmol) in dioxane (6 mL) was added at 0 °C a solution of 2-fluorobenzoyl chloride (325 mg, 2.1 mmol) in dioxane (6 mL). After stirring for an additional 2 h, the solvent and excess of triethylamine were removed in vacuo. The residue was filtered over a short pad of silica gel, and the desired product (373 mg, 68%) was isolated as a white solid

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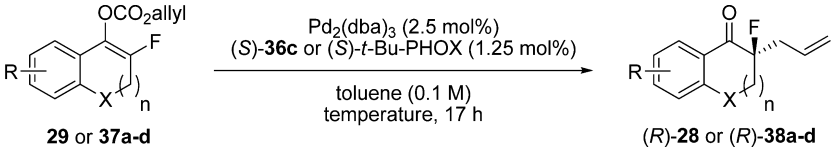
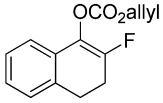
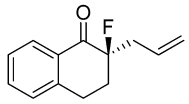
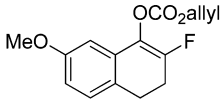
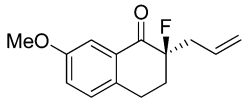
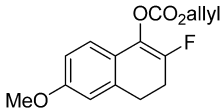
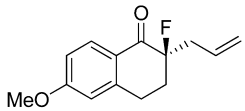
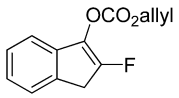
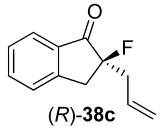
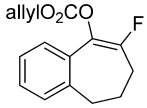
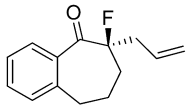
Table 7. Comparison between Ligand (*S*)-36c and *t*-Bu-PHOX in the Enantioselective Pd-Catalyzed Allylation Reaction of Various Fluorinated Allyl Enol Carbonates



29 or 37a-d (*R*)-28 or (*R*)-38a-d

entry[a]	substrate	product	ligand	temp. (°C)	yield (%)[b]	er[c]
1			(*S*)-**36c**	-20	95	97.5:2.5
2	**29**	(*R*)-**28**	*t*-Bu-PHOX	40	93	96:4
3			(*S*)-**36c**	-10	96	97:3
4	**37a**	(*R*)-**38a**	*t*-Bu-PHOX	40	92	97:3
5			(*S*)-**36c**	-10	94	97:3
6	**37b**	(*R*)-**38b**	*t*-Bu-PHOX	40	87	96:4
7			(*S*)-**36c**	-10	68	93:7
8			(*S*)-**36c**	-20	50	93.5:6.5
9	**37c**	(*R*)-**38c**	*t*-Bu-PHOX	40	91	91:9
10			(*S*)-**36c**	-10	96	95.5:4.5
11	**37d**	(*R*)-**38d**	*t*-Bu-PHOX	40	83	94:6

[a]See the Supporting Information and ref 5b for details concerning the reaction conditions. [b]Isolated yield. [c]Determined by chiral HPLC.

by flash chromatography using 20−50% Et_2O/hexane: $[\alpha]^{20}_D$ −15.9 (*c* 0.69, $CHCl_3$); mp 101.5−104.0 °C; IR (neat) ν = 3441, 3083, 2965, 2936, 1650, 1528, 1481, 1380, 1180, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (t, 1H, *J* = 7.4 Hz), 7.46 (m, 1H), 7.25 (t, 1H, *J* = 7.4 Hz), 7.15−7.03 (m, 2H), 4.05 (d, 1H, *J* = 9.9 Hz), 2.23 (m, 1H), 2.14 (br s, 1H), 1.33 (s, 3H), 1.27 (s, 3H), 1.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (d, J_{C-F} = 3.2 Hz), 162.8 (d, J_{C-F} = 247 Hz) 133.4 (d, J_{C-F} = 9.2 Hz), 132.3 (d, J_{C-F} = 2.3 Hz), 125.0 (d, J_{C-F} = 3.2 Hz), 121.7 (d, J_{C-F} = 11.2 Hz), 116.3 (d, J_{C-F} = 25.1 Hz), 73.9, 61.1, 29.5, 28.6, 27.4, 22.6, 17.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.3 (m, 1F); HRMS-ESI calcd for $C_{14}H_{20}FNO_2Na$ $[M + Na]^+$ 276.1370, found 276.1371.

*(S)-2-(2-Fluorophenyl)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole ((S)-**13a**): General Procedure for the Cyclization.* To a stirred solution of (*S*)-**24a** (709 mg, 2.8 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added dropwise MsOH (0.90 mL, 16.8 mmol), and the reaction mixture was allowed to warm to rt. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, diluted in CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic extracts were washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated. The crude material was purified with flash chromatography using 20% Et_2O/hexane to give the desired product as a colorless oil (518 mg, 75%): $[\alpha]^{22}_D$ −35.9 (*c* 0.42, $CHCl_3$); IR (neat) ν = 3044, 2972, 2873, 1646, 1459, 1340, 1228, 1058, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 1H), 7.41 (m, 1H), 7.18−7.09 (m, 2H), 3.50 (d, 1H, *J* = 8.0 Hz), 1.90 (m, 1H), 1.53 (s, 3H), 1.41 (s, 3H), 1.15 (d, 3H, *J* = 6.5 Hz), 1.04 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 160.1, 159.2 (d, J_{C-F} = 4.5 Hz), 132.7 (d, J_{C-F} = 8.4 Hz), 131.3 (d, J_{C-F} = 1.9 Hz), 124.1 (d, J_{C-F} = 3.9 Hz), 117.3 (d, J_{C-F} = 11.0 Hz), 116.9, 116.6, 86.9, 80.6, 29.3 (d, J_{C-F} = 2.4 Hz), 21.4 (d, J_{C-F} = 8.0 Hz), 20.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.5 (m, 1F); HRMS-ESI calcd for $C_{14}H_{19}FNO$ $[M + H]^+$ 236.1445, found 236.1457.

*(S)-5,5-(Dimethyl)-i-Pr-PHOX ((S)-**7a**): General Procedure for the S_NAr Reaction.* To a stirred solution of KH (85.4 mg, 2.1 mmol) in toluene (5 mL) at rt was added dropwise $HPPh_2$ (0.37 mL, 2.1 mmol). After 15 min at rt, the reaction mixture was heated to 120 °C. After 5 min at 120 °C, a solution of (*S*)-**9** (250 mg, 1.1 mmol) in toluene (10 mL) was added dropwise and the reaction mixture was heated at 120 °C overnight. The reaction was quenched by the addition of 0.5 mL of MeOH. After the reaction mixture was diluted with H_2O and Et_2O, the layers were separated and the aqueous phase was extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude product. The crude material was purified with flash chromatography using 5−10% Et_2O/hexane to give the desired product as a white solid (224 mg, 53%): $[\alpha]^{20}_D$ −28.6 (*c* 0.78, $CHCl_3$); mp 125.3−127.2 °C; IR (neat) ν = 3064, 2981, 2868, 1654, 1464, 1362, 1268, 1048, 748, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (m, 1H), 7.30 (m, 12H), 6.84 (m, 1H), 3.17 (d, 1H, *J* = 8.1 Hz),

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1.58 (m, 1H), 1.38 (s, 3H), 1.14 (s, 3H), 0.98 (d, 3H, J = 5.2 Hz), 0.86 (d, 3H, J = 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 139.3−128.1 (C−Ar), 86.8, 81.3, 29.1 (d, J_{C-P} = 6.2 Hz), 21.5, 21.4, 21.0; ^{31}P NMR (121 MHz, $CDCl_3$) δ −4.86 (s, 1P); HRMS-ESI calcd for $C_{26}H_{29}NOP$ $[M + H]^+$ 402.1981, found 402.1993.

*General Procedures for the Synthesis of the Ligands via the Ullmann-Type Coupling-Based Approach. Synthesis of Ligand (S)-**7a**. (S)-2-Bromo-N-(2-hydroxy-2,4-dimethylpentan-3-yl)-benzamide.* Following the general protocol for the amide formation using 2-bromobenzoyl chloride instead of 2-fluorobenzoyl chloride on a 6.0 mmol scale of (*S*)-**18a**, the desired product (1.37 g, 73%) was isolated as a white solid by flash chromatography using 20% acetone/hexane: $[\alpha]^{20}_D$ −2.0 (*c* 1.18, $CHCl_3$); mp 124.5−126.1 °C; IR (neat) ν = 3344, 3050, 2965, 2940, 1622, 1545, 1399, 1160, 1029, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.59 (m, 1H), 7.55−7.52 (m, 1H), 7.38−7.30 (m, 1H), 7.29−7.25 (m, 1H), 6.33−6.31 (m, 1H), 4.02 (dd, 1H, J = 10.1, 2.5 Hz), 2.29−2.22 (m, 1H), 1.35 (s, 6H), 1.08 (d, 3H, J = 6.5 Hz), 1.00 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 138.7, 133.6, 131.2, 129.6, 127.7, 119.3, 73.3, 60.9, 29.7, 28.8, 27.7, 22.6, 17.4; HRMS-ESI calcd for $C_{14}H_{21}NBrO_2$ $[M + H]^+$ 314.0750, found 314.0752.

*(S)-2-(2-Bromophenyl)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole ((S)-**15a**).* Following the general protocol for the cyclization on a 0.84 mmol scale of (*S*)-2-bromo-*N*-(2-hydroxy-2,4-dimethylpentan-3-yl)benzamide, the desired product was isolated and used without further purification. An analytically pure sample could be obtained as a colorless oil by flash chromatography using 10% Et_2O/hexane: $[\alpha]^{20}_D$ −34.0 (*c* 0.65, $CHCl_3$); IR (neat) ν = 3067, 2970, 2871, 1650, 1471, 1247, 1108, 1025, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.59 (m, 2H), 7.31 (t, 1H, J = 7.5 Hz), 7.29−7.22 (m, 1H), 3.51 (d, 1H, J = 7.8 Hz), 1.98−1.87 (m, 1H), 1.55 (s, 3H), 1.45 (s, 3H), 1.15 (d, 3H, J = 6.8 Hz), 1.05 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 133.9, 131.6, 131.5, 130.9, 127.3, 122.1, 87.7, 80.9, 29.5, 29.4, 21.6, 21.5, 20.7; HRMS-ESI calcd for $C_{14}H_{19}NBrO$ $[M + H]^+$ 299.0661, found 299.0657.

*(S)-5,5-(Dimethyl)-i-Pr-PHOX ((S)-**7a**): General Procedure for the Ullmann-Type Coupling.* A mixture of copper iodide (20.1 mg, 0.11 mmol), diphenylphosphine (0.37 mL, 2.1 mmol), and *N*,*N*′-dimethylethylenediamine (7.8 mL, 0.74 mmol) in toluene (8 mL) was stirred for 20 min at rt. After (*S*)-**19a** (0.84 mmol), cesium carbonate (1.03 g, 3.2 mmol) in toluene (7 mL) was added and the mixture was heated at 110 °C overnight. The reaction mixture was allowed to cool to rt, filtered, washed with CH_2Cl_2, and the solvent was evaporated to give the crude product. The desired product (248 mg, 73% for 2 steps) was isolated as a white solid by flash chromatography using 5−10% Et_2O/hexane.

*Synthesis of the Valine-Based Ligands via the S_NAr Approach (Scheme 2). Synthesis of Ligand (S)-**7b**. (S)-2-Fluoro-N-(2-hydroxy-2,4-diethylpentan-3-yl)benzamide ((S)-**24b**).* Following the general procedure for the amide formation on a 0.61 mmol scale of (*S*)-**18b**, the desired product (141 mg, 85%) was isolated as a colorless oil by flash chromatography using 20% acetone/hexane: $[\alpha]^{20}_D$ −3.8 (*c* 0.27, $CHCl_3$); IR (neat) ν = 3411, 2968, 1651, 1517, 1478, 1314, 1154, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.45 (m, 1H), 7.27 (t, 1H, J = 7.4 Hz), 7.16−706 (m, 2H), 4.19 (dt, 1H, J = 9.9, 2.3 Hz), 2.21 (m, 1H), 1.72−1.45 (m, 5H), 1.00 (t, 6H, J = 7.1 Hz), 0.93 (t, 3H, J = 7.5 Hz), 0.86 (t, 3H, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (d, J_{C-F} = 3.3 Hz), 160.8 (d, J_{C-F} = 247 Hz), 133.2 (d, J_{C-F} = 9.2 Hz), 132.4 (d, J_{C-F} = 2.1 Hz), 125.0 (d, J_{C-F} = 3.2 Hz), 121.8 (d, J_{C-F} = 11.5 Hz), 116.3 (d, J_{C-F} = 24.8 Hz), 78.0, 57.4, 29.0, 28.3, 28.1, 24.5, 17.3, 8.2, 8.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.2 (m, 1F); HRMS-ESI calcd for $C_{16}H_{23}FNO$ $[M + H]^+ - [H_2O]$ 264.1758, found 264.1754.

*(S)-2-(2-Fluorophenyl)-4-isopropyl-5,5-diethyl-4,5-dihydrooxazole ((S)-**13b**).* Following the general procedure for the cyclization on a 0.71 mmol scale of (*S*)-**24b**, the desired product (107 mg, 57%) was isolated as colorless oil by flash chromatography using 10% Et_2O/hexane: $[\alpha]^{22}_D$ −51.7 (*c* 0.64, $CHCl_3$); IR (neat) ν = 2967, 2882, 1648, 1456, 1341, 1225, 1111, 1061, 924, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dt, 1H, J = 7.5, 1.5 Hz), 7.41 (m, 1H), 7.13 (m, 2H), 3.69 (d, 1H, J = 6.7 Hz), 1.91 (m, 4H), 1.67 (m, 2H), 1.06 (m, 9H), 0.96 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 159.5, 158.9 (d, J_{C-F} = 4.5 Hz), 132.3 (d, J_{C-F} = 8.3 Hz), 131.1 (d, J_{C-F} = 1.8 Hz), 123.8 (d, J_{C-F} = 3.5 Hz), 116.4, 116.7, 90.7, 29.7, 28.5, 24.9, 21.9, 20.1, 8.7, 7.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.4 (m, 1F); HRMS-ESI calcd for $C_{16}H_{23}FNO$ $[M + H]^+$ 264.1758, found 264.1749.

*(S)-5,5-(Diethyl)-i-Pr-PHOX ((S)-**7b**).* Following the general procedure for the S_NAr reaction on a 0.15 mmol scale of (*S*)-**13b**, the desired product as a colorless oil (39 mg, 61%) was isolated by flash chromatography using 10% Et_2O/hexane: $[\alpha]^{20}_D$ −24.3 (*c* 1.17, $CHCl_3$); IR (neat) ν = 3053, 2966, 2880, 1652, 1470, 1336, 1276, 1088, 1045, 927, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (m, 1H), 7.36−7.24 (m, 12H), 6.84 (m, 1H), 3.42 (d, 1H, J = 8.0 Hz), 1.84−1.75 (m, 1H), 1.70−1.44 (m, 4H), 0.93−0.77 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3 (d, J_{C-P} = 3.3 Hz), 139.2−128.1 (C−Ar), 90.8, 29.5, 28.5, 25.2, 21.7, 21.2, 8.6, 8.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ −4.90 (s, 1P); HRMS-ESI calcd for $C_{28}H_{33}NOP$ $[M + H]^+$ 430.2294, found 430.2266.

*Synthesis of Ligand (S)-**7c**. (S)-2-Fluoro-N-(2-hydroxy-2,4-diphenylpentan-3-yl)benzamide ((S)-**24c**).* Following the general protocol for the amide formation on a 3.40 mmol scale of (*S*)-**18c**, the desired product (822 mg, 64%) was isolated as a white solid by flash chromatography using 20% Et_2O/pentane: $[\alpha]^{20}_D$ −74.9 (*c* 0.63, $CHCl_3$); mp 178−182 °C; IR (neat) ν = 3431, 3068, 2963, 2934, 1640, 1540, 1447, 1318, 136, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (t, 1H, J = 7.2 Hz), 7.54 (m, 4H), 7.35 (t, 3H, J = 7.5 Hz), 7.26 (m, 4H), 7.13 (m, 2H), 7.01 (t, 1H, J = 10.0 Hz), 5.27 (d, 1H, J = 9.8 Hz), 2.99 (br s, 1H), 1.94 (m, 1H), 0.99−0.97 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, J_{C-F} = 2.8 Hz), 160.1 (d, J_{C-F} = 248 Hz), 146.5, 145.7, 133.1 (d, J_{C-F} = 9.1 Hz), 131.9 (d, J_{C-F} = 2.0 Hz), 128.8, 127.3, 127.1, 125.7 (d, J_{C-F} = 13.7 Hz), 124.8 (d, J_{C-F} = 3.2 Hz), 121.8 (d, J_{C-F} = 11.8 Hz), 116.1 (d, J_{C-F} = 24.4 Hz), 82.5, 58.6, 29.5, 23.1, 17.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.3 (m, 1F); HRMS-ESI calcd for $C_{24}H_{24}FNO_2Na$ $[M + Na]^+$ 401.1683, found 401.1689.

*(S)-2-(2-Fluorophenyl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole ((S)-**13c**).* Following the general protocol for the cyclization on a 1.2 mmol scale of (*S*)-**24c**, the desired product as a white solid (364 mg, 85%) was isolated by flash chromatography using 10% Et_2O/hexane: $[\alpha]^{22}_D$ −275.4 (*c* 0.58, $CHCl_3$); mp 89−92 °C; IR (neat) ν = 3061, 2961, 2873, 1655, 1494, 1385, 1224, 1031, 909, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (t, 1H, J = 7.4 Hz), 7.62 (d, 2H, J = 7.6 Hz), 7.50−7.17 (m, 11H), 4.88 (d, 1H, J = 4.5 Hz), 1.92 (m, 1H), 1.06 (d, 3H, J = 6.7 Hz), 0.65 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9,160.3, 158.8 (d, J_{C-F} = 4.7 Hz), 145.8 140.9, 133.1 (d, J_{C-F} = 8.6 Hz), 131.5 (d, J_{C-F} = 1.6 Hz), 128.6, 128.0, 127.4 124.2 (d, J_{C-F} = 3.8 Hz), 117.0 (d, J_{C-F} = 21.9 Hz), 116.7 (d, J_{C-F} = 10.8 Hz), 92.8, 80.0, 30.6, 22.2, 17.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.6 (m, 1F); HRMS-ESI calcd for $C_{24}H_{23}FNO$ $[M + H]^+$ 360.1758, found 360.1768.

*(S)-5,5-(Diphenyl)-i-Pr-PHOX ((S)-**7c**).* Following the general protocol for the S_NAr reaction on a 0.14 mmol scale of (*S*)-**13c**, the desired product as a colorless oil (47 mg, 65%) was isolated by flash chromatography using 10% Et_2O/hexane: $[\alpha]^{20}_D$ −170.5 (*c* 0.31, $CHCl_3$); IR (neat) ν = 3064, 2955, 2926, 2868, 1657, 1434, 1328, 1254, 1139, 1098, 974, 746, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (m, 1H), 7.43−7.15 (m, 22H), 6.92 (m, 1H), 4.62 (d, 1H, J = 5.3 Hz), 1.62 (m, 1H), 0.79 (d, 3H, J = 6.8 Hz), 0.45 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 145.7, 141.3, 139.4−126.8 (C−Ar), 92.5, 81.5, 30.6, 21.5, 21.9, 17.6 (d, J_{C-P} = 1.8 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ −6.19 (s, 1P); HRMS-ESI calcd for $C_{36}H_{33}NOP$ $[M + H]^+$ 526.2294, found 526.2286.

*Synthesis of Ligand (S)-**7d**. (S)-2-Fluoro-N-(2-hydroxy-2,4-di-3-tolylpentan-3-yl)benzamide ((S)-**24d**).* Following the general procedure for the amide formation on a 1.7 mmol scale of (*S*)-**18d**, the desired product (373 mg, 54%) was isolated as a white solid by flash chromatography using 20% Et_2O/hexane: $[\alpha]^{20}_D$ −44.1 (*c* 0.43, $CHCl_3$); mp 158.3−163.3 °C; IR (neat) ν = 3436, 2960, 1631, 1526, 1481, 1314, 1126, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (t, 1H, J = 7.9 Hz), 7.42−6.94 (m, 12H), 5.21 (d, 1H, J = 9.8 Hz), 2.74 (br s, 1H), 2.35 (s, 3H), 2.25 (s, 3H), 1.91 (m, 1H), 0.98−0.95

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(m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (d, J_{C-F} = 2.5 Hz), 160.4 (d, J_{C-F} = 248 Hz), 146.2, 145.5, 138.0 (d, J_{C-F} = 4.6 Hz), 132.8 (d, J_{C-F} = 9.1 Hz), 131.7 (d, J_{C-F} = 1.9 Hz), 128.3, 127.7 (d, J_{C-F} = 7.9 Hz), 126.3, 126.1, 124.6 (d, J_{C-F} = 3.1 Hz), 122.6 (d, J_{C-F} = 5.5 Hz), 121.8 (d, J_{C-F} = 12.2 Hz), 116.1, 115.8, 82.3, 58.4, 29.3, 22.9, 21.7, 21.6, 17.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.2 (s, 1F); HRMS-ESI calcd for $C_{26}H_{27}FNO$ $[M + H]^+ - [H_2O]$ 388.2071, found 388.2061.

*(S)-2-(2-Fluorophenyl)-4-isopropyl-5,5-di-3-tolyl-4,5-dihydrooxazole ((S)-**13d**).* Following the general procedure for the cyclization on a 1.2 mmol scale of (*S*)-**24d**, the desired product as a colorless oil (444 mg, 99%) was isolated by flash chromatography using 20% Et_2O/hexane: $[\alpha]^{22}_D$ −257.4 (*c* 0.52, $CHCl_3$); IR (neat) ν = 3044, 2960, 2871, 1652, 1457, 1344, 1223, 1112, 1028, 966, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, 1H, *J* = 7.5 Hz), 7.43 (m, 3H), 7.21 (m, 6H), 7.08 (m, 2H), 4.87 (d, 1H, *J* = 4.2 Hz), 2.35 (d, 6H, *J* = 6.4 Hz), 1.90 (m, 1H), 1.09 (d, 3H, *J* = 6.9 Hz), 0.65 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 160.3, 158.9 (d, J_{C-F} = 4.7 Hz), 145.8, 140.8, 138.1,137.5, 133.0 (d, J_{C-F} = 8.5 Hz), 131.5 (d, J_{C-F} = 1.7 Hz), 128.7, 128.4, 128.1, 127.9, 127.6, 127.1, 124.4, 124.2 (d, J_{C-F} = 3.9 Hz), 123.6, 116.9 (d, J_{C-F} = 21.6 Hz), 116.8 (d, J_{C-F} = 10.8 Hz), 92.9, 79.6, 30.5, 22.4, 21.9, 17.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.4 (s, 1F); HRMS-ESI calcd for $C_{26}H_{27}FNO$ $[M + H]^+$ 388.2071, found 388.2070.

*(S)-5,5-(Di-3-tolyl)-i-Pr-PHOX ((S)-**7d**).* Following the general procedure for the S_NAr reaction on a 1.0 mmol scale of (*S*)-**13d**, the desired product as a white solid (168 mg, 31%) was isolated by flash chromatography using 7% Et_2O/hexane: $[\alpha]^{20}_D$ −188.7 (*c* 0.13, $CHCl_3$); mp 101.2−106.4 °C; IR (neat) ν = 3051, 2958, 2922, 1654, 1470, 1339, 1256, 1157, 1041, 741, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (m, 1H), 7.84−6.88 (m, 21H), 4.65 (d, 1H, *J* = 5.0 Hz), 2.37 (s, 3H), 2.33 (s, 3H), 1.65 (m, 1H), 0.82 (d, 3H, *J* = 6.7 Hz), 0.40 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 145.8, 141.2, 139.0−123.8 (C−Ar), 92.6, 81.4, 30.5, 22.0, 22.0, 21.9, 17.5 (d, J_{C-P} = 1.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ −6.48 (s, 1P); HRMS-ESI calcd for $C_{38}H_{37}NOP$ $[M + H]^+$ 554.2607, found 554.2598.

*Synthesis of the Leucine-Based Ligands via the S_NAr Approach (Scheme 3). Synthesis of Ligand (S)-**8c**. (S)-2-Fluoro-N-(2-hydroxy-2,5-diphenylhexan-3-yl)benzamide ((S)-**25c**).* Following the general procedure for the amide formation on a 1.2 mmol scale of intermediate (*S*)-**19c**, the desired product (307 mg, 64%) was isolated as a white solid by flash chromatography using 20% Et_2O/hexane: $[\alpha]^{20}_D$ −30.4 (*c* 0.64, $CHCl_3$); mp 166.3−169.3 °C; IR (neat) ν = 3415, 2953, 2919, 2868, 1637, 1534, 1447, 1293, 1150, 1059, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (td, 1H, *J* = 1.7, 7.9 Hz), 7.55 (m, 4H), 7.40−7.33 (m, 3H), 7.24 (m, 3H), 7.13 (m, 2H), 7.04−6.99 (m, 1H), 6.89 (t, 1H, *J* = 10.0 Hz), 5.33 (m, 1H), 3.27 (br s, 1H), 1.76−1.64 (m, 1H), 1.56 (t, 1H, *J* = 12.5 Hz), 1.30 (t, 1H, *J* = 12.0 Hz), 1.04 (d, 3H, *J* = 6.5 Hz), 0.86 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (d, J_{C-F} = 2.6 Hz) 162.0, 158.7, 145.2, 145.0, 133.0−115.7 (C−Ar), 81.4, 54.5, 39.7, 25.0, 24.0, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.1 (m, 1F); HRMS-ESI calcd for $C_{25}H_{25}FNO$ $[M + H]^+ - [H_2O]$ 374.1915, found 374.1907.

*(S)-2-(2-Fluorophenyl)-4-isobutyl-5,5-diphenyl-4,5-dihydrooxazole ((S)-**14c**).* Following the general protocol for the cyclization on a 0.69 mmol scale using(*S*)-**25c**, the desired pure product (246 mg, 86%) was isolated as a colorless oil by flash chromatography using 10% Et_2O/hexane: $[\alpha]^{20}_D$ −230 (*c* 0.90, $CHCl_3$); IR (neat) ν = 3060, 2954, 2930, 2868, 1651, 1457, 1222, 1111, 1030, 986, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (t, 1H, *J* = 7.2 Hz), 7.61 (d, 2H, *J* = 7.6 Hz), 7.50−7.40 (m, 3H), 7.27 (m, 8H), 5.01 (dd, 1H, *J* = 10.1, 4.5 Hz), 2.00 (m, 1H), 1.12 (m, 2H), 1.02 (d, 3H, *J* = 6.4 Hz), 0.92 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 159.7, 158.8 (d, J_{C-F} = 4.5 Hz), 144.6, 140.9, 132.9−116.6 (C−Ar), 92.7, 73.2, 43.4, 25.6, 23.9, 21.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.2 (m, 1F); HRMS-ESI calcd for $C_{25}H_{25}NFO$ $[M + H]^+$ 374.1915, found 374.1912.

*(S)-5,5-(Diphenyl)-i-Bu-PHOX ((S)-**8c**).* Following the general protocol for the S_NAr reaction on a 0.23 mmol scale of (*S*)-**14c**, the desired product as a colorless oil (46 mg, 37%) was isolated by flash chromatography using 10% Et_2O/hexane: $[\alpha]^{20}_D$ −25.0 (*c* 0.11, $CHCl_3$); IR (neat) ν = 3055, 2954, 2866, 1659, 1435, 1322, 1254, 1117, 1048, 967, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (m, 1H), 7.61−6.89 (m, 23H), 4.71 (t, 1H, *J* = 7.6 Hz), 2.37 (s, 1H), 1.71 (m, 1H), 0.88 (d, 3H, *J* = 6.4 Hz), 0.81−0.74 (m, 1H), 0.73 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 144.6, 141.2, 139.5−125.3 (C−Ar), 92.3, 73.8, 43.0 25.4, 24.0, 21.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ −5.13 (s, 1P); HRMS-ESI calcd for $C_{37}H_{35}NOP$ $[M + H]^+$ 540.2451, found 540.2441.

*General Procedures for the Synthesis of the Ligands via the Ullmann-Type Coupling-Based Approach. Synthesis of Ligand (S)-**8a**. (S)-2-Bromo-N-(2-hydroxy-2,5-dimethylhexan-3-yl)-benzamide.* Following the general protocol for the amide formation using 2-bromobenzoyl chloride instead of 2-fluorobenzoyl chloride on a 5.5 mmol scale of crude (*S*)-**19a**, the desired product (880 mg, 49% for four steps from (*S*)-**22**) was isolated as a white solid by flash chromatography using 10% acetone/hexane: $[\alpha]^{20}_D$ −30.6 (*c* 0.90, $CHCl_3$); mp 119.1−129.6 °C; IR (neat) ν = 3478, 3254, 3064, 2979, 2956, 2869, 1623, 1548, 1467, 1354, 1149, 1040, 954 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 1H, *J* = 8.0 Hz), 7.43 (d, 1H, *J* = 7.4 Hz), 7.32−7.19 (m, 2H), 6.15 (d, 1H, *J* = 9.5 Hz), 4.06 (m, 1H), 2.85−2.82 (m, 1H), 1.74 (br s, 1H), 1.45−1.39 (m, 2H), 1.29 (s, 3H), 1.23 (s, 3H), 0.97 (d, 3H, *J* = 6.4 Hz), 0.92 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 138.2, 133.4, 131.1, 129.4, 127.5, 119.1, 73.3, 56.5, 39.0, 27.7, 26.3, 25.1, 24.0, 21.5; HRMS-ESI calcd for $C_{15}H_{21}BrNO$ $[M + H]^+ - [H_2O]$ 310.0801, found 310.0793.

*(S)-2-(2-Bromophenyl)-4-isobutyl-5,5-dimethyl-4,5-dihydrooxazole ((S)-**16a**).* Following the general protocol for the cyclization on a 1.5 mmol scale using (*S*)-2-bromo-*N*-(2-hydroxy-2,4-dimethylhexan-3-yl)benzamide, the desired pure product (318 mg, 67%) was isolated as a colorless oil by flash chromatography using 10% Et_2O/hexane: $[\alpha]^{20}_D$ −72.4 (*c* 0.50, $CHCl_3$); IR (neat) ν = 2956, 2930, 2869, 1647, 1466, 1385, 1249, 1165, 1092, 1025, 909, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.28 (m, 2H), 3.88 (dd, 1H, *J* = 10.4, 4.6 Hz), 2.02−1.92 (m, 1H), 1.56 (m, 1H), 1.52 (s, 3H), 1.37 (s, 3H), 1.30−1.24 (m, 1H), 1.01 (d, 3H. *J* = 2.4 Hz), 0.99 (d, 3H, *J* = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 133.0−131.1 (C−Ar), 122.1, 87.4, 72.6, 72.4, 40.5, 28.5, 28.4, 25.7, 24.1, 24.0, 22.2, 22.1, 21.9, 21.8; HRMS-ESI calcd for $C_{15}H_{21}NBrO$ $[M + H]^+$ 310.0801, found 310.0789.

*(S)-5,5-(Dimethyl)-i-Bu-PHOX ((S)-**8a**): General Procedure for the Ullmann-Type Coupling.* A mixture of copper iodide (20.1 mg, 0.11 mmol), diphenylphosphine (0.37 mL, 2.1 mmol), and *N,N'*-dimethylethylenediamine (7.6 mL, 0.72 mmol) in toluene (8 mL) was stirred for 20 min at rt. After (*S*)-**16a** (0.82 mmol), cesium carbonate (1.0 g, 3.1 mmol) in toluene (7 mL) was added and the mixture was heated at 110 °C overnight. The reaction mixture was allowed to cool to rt, filtered, washed with CH_2Cl_2, and the solvent was evaporated to give the crude product. The desired product (265 mg, 78%) was isolated as a white solid by flash chromatography using 7% Et_2O/hexane: $[\alpha]^{20}_D$ −38.4 (*c* 0.34, $CHCl_3$); mp 74.1−75.7 °C; IR (neat) ν = 3047, 2980, 2905, 2873, 1650, 1467, 1350, 1257, 1137, 1072, 951, 724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 1H), 7.35−7.23 (m, 12H), 6.83 (m, 1H), 3.59 (dd, 1H, *J* = 10.8, 4.2 Hz), 1.74 (m, 1H), 1.31 (s, 3H), 1.23−1.16 (m, 1H), 1.10 (s, 3H), 0.99−0.92 (m, 1H), 0.89−0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 139.1−128.1 (C−Ar), 86.2, 72.7, 40.0, 28.3, 25.5, 24.1, 22.0, 21.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ −4.85 (s, 1P); HRMS-ESI calcd for $C_{27}H_{31}NOP$ $[M + H]^+$ 416.2138, found 416.2134.

*Synthesis of the Isoleucine-Based Ligand via the Ullmann-Type Coupling-Based Approach (Scheme 4). Synthesis of Ligand (S)-**9a**. 2-Bromo-N-(3S,4S)-2-hydroxy-2,5-dimethylhexan-3-yl)-benzamide ((S)-**26a**).* Following the general procedure for the amide formation on a 13.5 mmol scale of intermediate (2*S*,3*S*)-**20a**, the desired product (3.49 g, 79%) was isolated as a white solid by flash chromatography using 20% acetone/hexane: $[\alpha]^{20}_D$ −12.8 (*c* 0.67, $CHCl_3$); mp 109.5−112.9 °C; IR (neat) ν = 3408, 3360, 2967, 2934, 1635, 1505, 1464, 1378, 1178, 1044, 951 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 1H, *J* = 7.9 Hz), 7.46 (d, 1H, *J* = 7.4 Hz), 7.34−7.21 (m, 2H), 6.37 (d, 1H, *J* = 9.8 Hz), 3.97 (dd, 1H, *J* = 10.1, 2.2 Hz), 2.21

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(br s, 1H), 1.95−1.79 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H), 1.04 (d, 3H, J = 6.7 Hz), 0.89 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 133.4, 131.0, 129.4, 127.5, 119.1, 73.7, 61.3, 35.8, 29.7, 27.5, 23.6, 18.2, 12.2; HRMS-ESI calcd for $C_{15}H_{21}BrNO$ $[M + H]^+ - [H_2O]$ 310.0801, found 310.0779.

*(S)-2-(2-Bromophenyl)-4-sec-butyl-5,5-dimethyl-4,5-dihydrooxazole ((S)-**17a**).* Following the general procedure for the cyclization on a 3.0 mmol scale using (*S*)-**26a**, the desired pure product (793 mg, 84%) was isolated as a colorless oil by flash chromatography using 10% Et_2O/hexane: $[\alpha]^{20}_D$ −34.1 (*c* 1.74, $CHCl_3$); IR (neat) ν = 2967, 2932, 2875, 1650, 1465, 1387, 1247, 1085, 1036, 938, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.26 (m, 2H), 3.56 (d, 1H, J = 8.1 Hz), 1.97−1.85 (m, 1H), 1.66 (m, 1H), 1.54 (s, 3H), 1.42 (s, 3H), 1.30 (m, 1H), 1.01 (d, 3H, J = 6.6 Hz), 0.94 (t, 3H, J = 7.5, 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 133.6, 131.3, 130.8, 127.0, 121.9, 87.5, 80.0, 35.5, 29.4, 26.5, 21.3, 17.2, 11.2; HRMS-ESI calcd for $C_{15}H_{21}NBrO$ $[M + H]^+$ 310.0801, found 310.0791.

*(2S,3S)-5,5-(Dimethyl)-s-Bu-PHOX ((S)-**9a**).* Following the general procedure for the Ullmann-type coupling on a 2.1 mmol scale of (*S*)-**17a**, the desired product (724 mg, 83%) was isolated as a white solid by flash chromatography using 10% Et_2O/hexane: $[\alpha]^{20}_D$ −24.9 (*c* 0.67, $CHCl_3$); mp 118.0−119.1 °C; IR (neat) ν = 3064, 2982, 2921, 2872, 1658, 1432, 1363, 1278, 1155, 1049, 978, 850 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (m, 1H), 7.36−7.23 (m, 12H), 6.85 (m, 1H), 3.26 (d, 1H, J = 9.5 Hz), 1.81 (m, 1H), 1.41 (s, 3H), 1.34 (m, 1H), 1.15 (s, 3H), 1.05 (m, 1H), 0.83 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 139.3−128.1 (C−Ar), 86.7, 80.1, 35.3, 29.2, 27.2, 21.4, 16.8, 11.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ −4.75 (s, 1P); HRMS-ESI calcd for $C_{27}H_{31}NOP$ $[M + H]^+$ 416.2138, found 416.2138.

*Synthesis of Electronically Modified Ligands (Scheme 5). Synthesis of Ligand (S)-**36a**. (S)-2-Bromo-N-(2-hydroxy-2,4-dimethylpentan-3-yl)-5-methoxybenzamide ((S)-**34a**).* Acid **33a** (1.2 mmol scale) was first converted to the acyl chloride ($(COCl)_2$, DMF cat., CH_2Cl_2, 0 °C to rt), and the crude acyl chloride was submitted to the general procedure for the amide formation. The desired product (339 mg, 84% for 2 steps) was isolated as a white solid by flash chromatography using 20% acetone/hexane: $[\alpha]^{20}_D$ −5.0 (*c* 0.52, $CHCl_3$); mp 114.4−117.4 °C; IR (neat) ν = 3403, 2967, 2933, 1635, 1509, 1466, 1392, 1297, 1150, 1094, 1017, 819 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1H, J = 8.8 Hz), 7.01 (d, 1H, J = 2.9 Hz), 6.77 (dd, 1H, J = 8.8, 3.0 Hz), 6.48 (d, 1H, J = 9.9 Hz), 3.93 (dd, 1H, J = 10.1, 2.4 Hz), 3.76 (s, 3H), 2.27 (br s, 1H), 2.20 (m, 1H), 1.29 (s, 3H) 1.27 (s, 3H), 1.02 (d, 3H, J = 6.8 Hz), 0.96 (d, 3H, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 158.9, 139.0, 134.2, 127.7, 117.2, 115.0, 109.2, 73.5, 60.8, 55.6, 29.5, 28.6, 27.4, 22.4, 17.2; HRMS-ESI calcd for $C_{15}H_{21}NBrO_2$ $[M + H]^+ - [H_2O]$ 326.0750, found 326.0742.

*(S)-2-(2-Bromo-5-methoxyphenyl)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole ((S)-**35a**).* Following the general protocol for the cyclization on a 2.0 mmol scale of (*S*)-**34a**, the desired pure product (616 mg, 94%) was isolated as a colorless oil by flash chromatography using 10% Et_2O/hexane: $[\alpha]^{20}_D$ −28.2 (*c* 0.67, $CHCl_3$); IR (neat) ν = 2969, 2871, 1651, 1570, 1466, 1230, 1107, 1016, 936, 814 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, 1H, J = 8.8 Hz), 7.16 (d, 1H, J = 3.1 Hz), 6.81 (dd, 1H, J = 8.8, 3.1 Hz), 3.80 (s, 3H), 3.51 (d, 1H, J = 7.9 Hz), 1.98−1.87 (m, 1H), 1.55 (s, 3H), 1.45 (s, 3H), 1.16 (d, 3H, J = 6.6 Hz), 1.05 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 158.6, 134.4, 131.4, 117.8, 116.6, 112.2, 87.5, 80.7, 55.6, 29.3, 29.1, 21.3, 21.2, 20.5; HRMS-ESI calcd for $C_{15}H_{21}NBrO_2$ $[M + H]^+$ 326.0750, found 326.0737.

*(S)-5′-Methoxy-5,5-(dimethyl)-i-Pr-PHOX ((S)-**36a**).* Following the general protocol for the Ullmann-type coupling on a 1.7 mmol scale of (*S*)-**35a**, the desired product (333 mg, 46%) was isolated as a white solid by flash chromatography using 10−15% Et_2O/hexane: $[\alpha]^{20}_D$ −34.0 (*c* 0.74, $CHCl_3$); mp 131.8−132.7 °C; IR (neat) ν = 3011, 2981, 2959, 2868, 1652, 1596, 1474, 1269, 1216, 1047, 788, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 1H), 7.29 (m, 10H), 6.78 (m, 2H), 3.83 (s, 3H), 3.21 (d, 1H, J = 9.0 Hz), 1.64−1.54 (m, 1H), 1.39 (s, 3H), 1.16 (s, 3H), 0.95 (d, 3H, J = 6.5 Hz), 0.86 (d, 3H, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 159.5, 139.4−128.1 (C−Ar), 116.1, 114.9 (d, J_{C-P} = 3.9 Hz), 86.6, 81.2, 55.4, 28.9 (d, J_{C-P} = 5.9 Hz), 21.2, 21.1, 20.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ −6.98 (s, 1P); HRMS-ESI calcd for $C_{27}H_{31}NO_2P$ $[M + H]^+$ 432.2087, found 432.2079.

*Synthesis of Ligand (S)-**36b**. (S)-2-Bromo-N-(2-hydroxy-2,4-dimethylpentan-3-yl)-4-(trifluoromethyl)benzamide ((S)-**34b**).* Acid **33b**[39] (4.8 mmol scale) was first converted to the acyl chloride ($(COCl)_2$, DMF cat., CH_2Cl_2, 0 °C to rt), and the crude acyl chloride was submitted to the general procedure for the amide formation. The desired product (844 mg, 55% for 2 steps) was isolated as a white solid by flash chromatography using 20% Et_2O/hexane: $[\alpha]^{20}_D$ −1.0 (*c* 0.85, $CHCl_3$); mp 107.3−108.8 °C; IR (neat) ν = 3333, 2976, 2961, 2875, 1637, 1534, 1321, 1162, 1129, 1078, 894, 771 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.59 (s, 2H), 6.41 (d, 1H, J = 9.7 Hz), 3.98 (dd, 1H, J = 9.8, 1.9 Hz), 2.24 (m, 1H), 1.76 (s, 1H), 1.34 (s, 3H), 1.31 (s, 3H), 1.05 (d, 3H, J = 6.4 Hz), 0.97 (d, 3H, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 142.0, 133.1 (q, 1C, J_{C-F} = 33.3 Hz), 130.4 (q, 1C, J_{C-F} = 3.5 Hz), 129.8, 124.5 (q, 1C, J_{C-F} = 3.5 Hz), 120.9, 119.5, 73.5, 60.7, 29.7, 28.6, 27.5, 22.4, 17.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.2 (s, 1F); HRMS-ESI calcd for $C_{15}H_{18}NFBrO_2$ $[M + H]^+ - [H_2O]$ 364.0518, found 364.0502.

*(S)-2-(2-Bromo-4-(trifluoromethyl)phenyl)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole ((S)-(**35b**).* Following the general protocol for the cyclization on a 2.2 mmol scale of (*S*)-**34b**, the desired pure product (685 mg, 86%) was isolated as a colorless oil by flash chromatography using 10% Et_2O/hexane: $[\alpha]^{20}_D$ −30.8 (*c* 1.1, $CHCl_3$); IR (neat) ν = 2973, 2873, 1652, 1461, 1318, 1130, 1078, 1036, 846, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.78 (d, 1H, J = 8.1 Hz), 7.58 (d, 1H, J = 8.1 Hz), 3.54 (d, 1H, J = 8.0 Hz), 1.98−1.89 (m, 1H), 1.56 (s, 3H), 1.45 (s, 3H), 1.16 (d, 3H, J = 6.9 Hz), 1.06 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 134.2, 133.2 (q, 1C, J_{C-F} = 33.3 Hz), 131.8, 130.7 (m, 1C), 123.9 (q, 1C, J_{C-F} = 3.5 Hz), 122.8, 122.3 (q, 1C, J_{C-F} = 272 Hz), 88.0, 80.9, 29.3, 29.1, 21.3, 21.1, 20.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.3 (s, 1F); HRMS-ESI calcd for $C_{15}H_{18}NF_3BrO$ $[M + H]^+$ 364.0518, found 364.0502.

*(S)-4′-Trifluoromethyl-5,5-(dimethyl)-i-Pr-PHOX ((S)-**36b**).* Following the general protocol for the Ullmann-type coupling on a 1.3 mmol scale of (*S*)-**35b**, the desired product (245 mg, 40%) was isolated as a colorless oil by flash chromatography using 5% Et_2O/hexane: $[\alpha]^{20}_D$ −25.7 (*c* 0.51, $CHCl_3$); IR (neat) ν = 3071, 2972, 2872, 1651, 1435, 1319, 1227, 1088, 1046, 909, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 1H), 7.58 (d, 1H, J = 7.9 Hz), 7.31 (m, 10H), 7.06 (m, 1H), 3.17 (d, 1H, J = 9.2 Hz), 1.56 (m, 1H), 1.38 (s, 3H), 1.13 (s, 3H), 0.98 (d, 3H, J = 6.4 Hz), 0.86 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 141.4−122.6 (C−Ar), 87.2, 81.6, 29.1, 29.0, 21.5, 21.3, 20.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.4 (s, 1F); ^{31}P NMR (121 MHz, $CDCl_3$) δ −4.06 (s, 1P); HRMS-ESI calcd for $C_{27}H_{28}NF_3OP$ $[M + H]^+$ 470.1855, found 470.1851.

*Synthesis of Ligand (S)-**36c**. (S)-2-(2-Bromo-5-(trifluoromethyl)phenyl)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole ((S)-(**35c**).* Following the general protocol for the amide formation on a 1.6 mmol scale of **33c**[40] gave the desired benzamide (*S*)-**34c** that was used without further purification for the next step. Following the general procedure for the cyclization, the desired pure product (281 mg, 49% for 3 steps) was isolated as a colorless oil by flash chromatography using 5% Et_2O/hexane: $[\alpha]^{20}_D$ −29.2 (*c* 0.56, $CHCl_3$); IR (neat) ν = 2976, 2874, 1632, 1545, 1469, 1309, 1169, 1078, 1031, 829, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.76 (d, 1H, J = 8.4 Hz), 7.50 (d, 1H, J = 8.2 Hz), 3.54 (d, 1H, J = 8.1 Hz), 2.00−1.88 (m, 1H), 1.57 (s, 3H), 1.46 (s, 3H), 1.16 (d, 3H, J = 6.6 Hz), 1.06 (d, 3H, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 134.5, 129.8 (q, 1C, J_{C-F} = 33.1 Hz), 128.3 (m, 1C), 127.8 (m, 1C), 126.0, 123.8 (q, 1C, J_{C-F} = 273 Hz), 88.0, 80.9, 29.3, 29.1, 21.3, 21.2, 20.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.0 (s, 1F); HRMS-ESI calcd for $C_{15}H_{18}NF_3BrO$ $[M + H]^+$ 364.0518, found 364.0511.

*(S)-5′-Trifluoromethyl-5,5-(dimethyl)-i-Pr-PHOX ((S)-**36c**).* Following the general procedure for the Ullmann-type coupling on a 0.42 mmol scale of (*S*)-**35c**, the desired product (96 mg, 49%) was

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isolated as a white solid by flash chromatography using 2% Et_2O/hexane: $[\alpha]^{20}_D$ −29.3 (*c* 0.32, $CHCl_3$); mp 88.1−96.8 °C; IR (neat) ν = 3056, 2978, 2958, 2928, 2870, 1666, 1433, 1345, 1260, 1160, 1071, 842, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (m, 1H), 7.48 (d, 1H, *J* = 8.0 Hz), 7.30 (m, 10H), 6.94 (m, 1H), 3.15 (d, 1H, *J* = 9.3 Hz), 1.60−1.51 (m, 1H), 1.39 (s, 3H), 1.13 (s, 3H), 0.97 (d, 3H, *J* = 6.6 Hz), 0.85 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 144.7−122.7 (C−Ar), 87.2, 81.6, 29.0, 29.0, 21.6, 21.3, 20.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.0 (s, 1F); ^{31}P NMR (121 MHz, $CDCl_3$) δ −3.94 (s, 1P); HRMS-ESI calcd for $C_{27}H_{28}NF_3OP$ $[M + H]^+$ 470.1855, found 470.1851.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of the new compounds prepared and the CIF file for $PdCl_2$[(*S*)-**8a**]. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jean-francois.paquin@chm.ulaval.ca.

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