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Efficient Synthesis of Bulky 2,2'-Bipyridine and (*S*)-Pyridine-Oxazoline Ligands

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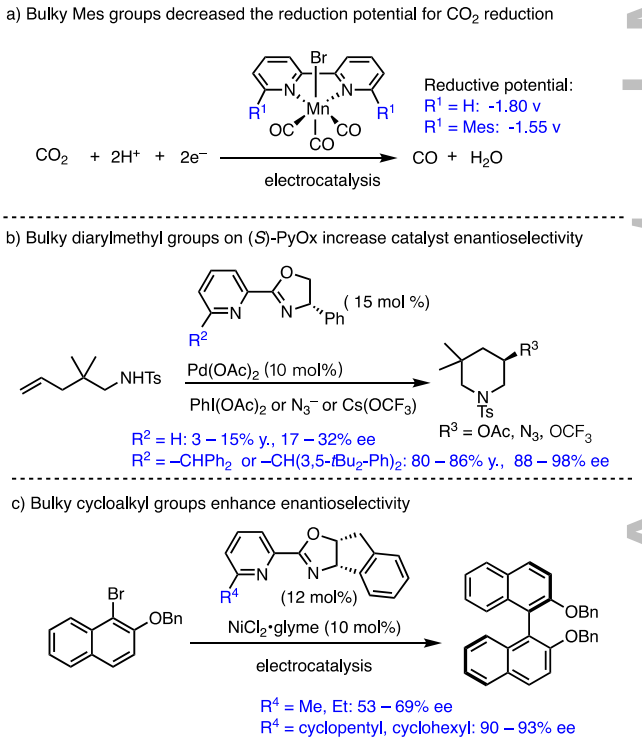
Abstract. Bulky *N,N'*-bidentate ligands can furnish catalysts with enhanced catalytic activity compared to commercially available ligands. Straightforward methods to effectively synthesize a broad range of these ligands, however, are uncommon. In this work, a simple and efficient method is developed for the synthesis of bulky *N,N'*-bidentate ligands, including 2,2'-bipyridines and enantioenriched pyridine-oxazolines. The Pd/NIXANTPHOS catalyst system enabled synthesis of a series of bulky 2,2'-bipyridine-based ligands and (*S*)-pyridine oxazoline-based enantioenriched ligands with good to excellent yields. The ligands have been benchmarked in the aminofluorination of styrene.

Keywords: bulky ligand; palladium catalysis; 2,2'-bipyridine ligands; (*S*)-pyridine-oxazoline ligands

Introduction

It is well established that new reactivity of transition metal complexes can be engendered by the use of ligands with novel steric and electronic properties. In catalysis, nowhere is this more evident than in palladium catalyzed coupling reactions with bulky monodentate phosphine ligands[1] and the Xantphos family of ligands[2]. These ligands have enabled new transformations that have had an enormous impact on synthetic chemistry. Of course, the design and synthesis of new ligands for transition metal catalysts has enable new transformations across all areas of catalysis[3]. To this end, efficient synthetic methods for the preparation of ligands with diverse structures are in high demand. While many transformations have been introduced with commercially available bidentate 2,2'-bipyridine derivatives (bpy), the use of bulky *NN'*-bidentate ligands[4] has been gaining attention. For example, bulky *N,N'*-bidentate ligands derived from 2,2'-bipyridine and enantioenriched pyridine-oxazolines have been used in metal-catalyzed carbon dioxide reduction[4c, d] (Scheme 1a), enantioselective alkene difunctionalization reactions[4e-g, 4i] (Scheme 1b) and enantioselective electrochemical homocoupling reactions[4h] (Scheme 1c) with enhanced catalytic activity. In these reactions, the bulky ligands were implemented to prevent undesirable catalyst dimerization[4c, 5] or to increase the metal center's electrophilicity toward binding olefin substrates[4f].

One drawback to these new catalytic processes is that existing methods for the synthesis of these bulky ligands involved laborious multistep procedures and only offered limited structural diversity. For example, the bulky pyridine-oxazoline ligand (**Ph$_2$PyOx**, Scheme 2a) was obtained through a 4-step synthesis with low overall yield (14%). Additionally, in order to synthesize ligands with diverse aryl groups [*e.g.* **(3,5-^{t}Bu$_2$-C$_6$H$_3$)$_2$PyOx,** Scheme 2a], two additional steps were required. The development of efficient and broadly applicable methods to synthesize bulky bidentate nitrogen-based ligands, such as 2,2'-bipyridine and pyridine-oxazoline, is expected to facilitate the development of new catalytic reactions.



Scheme 1. Examples of bulky groups enhancing reactivity with 2,2'-bipyridine and (*S*)-PyOx ligated catalysts.

Our group has developed palladium-catalyzed methods for stepwise arylation[6] of weakly acidic (pK_a>25) methyl groups

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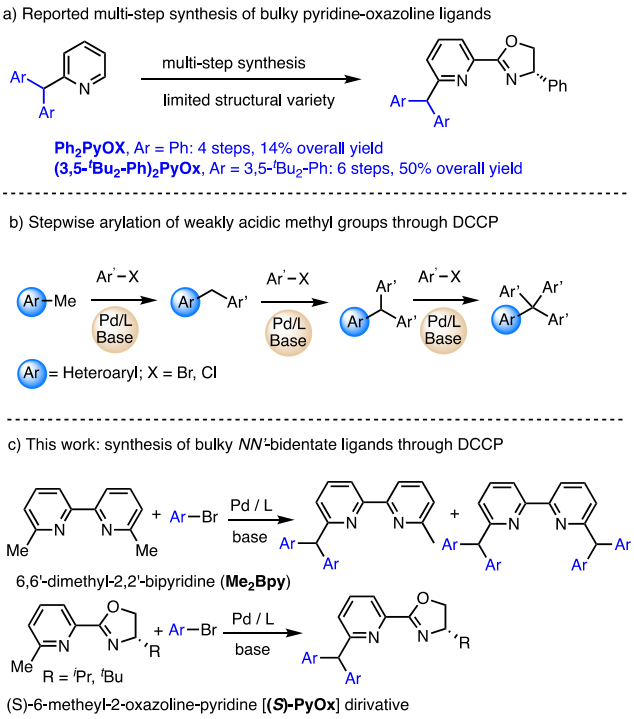
utilizing the deprotonative cross-coupling process (DCCP)[7] in the presence of bases (Scheme 2b). We[6c] and others,[8] have reported the stepwise arylation of methyl groups on nitrogen-containing hetero-aromatic rings with good to excellent yields. Inspired by these results, we envisioned a straightforward palladium-catalyzed approach for synthesis of bulky 2,2'-bipyridine and enantioenriched pyridine-oxazoline ligands through arylation of methyl groups adjacent to the pyridyl nitrogen (Scheme 2c). This method starts from commercially available 6,6'-dimethyl-2,2'-bipyridine (**Me$_2$Bpy**) and conveniently synthesized chiral (*S*)-6-methyl-2-oxazoline-pyridine [**(*S*)-PyOx)**] derivatives[9] with variable alkyl substituents at the chiral center. At the outset of our work, we anticipated that control over the extent of arylation would be possible in some cases. We envisioned that the key to obtaining ligands in high yields and selectivity would hinge on the use of appropriate amounts of aryl bromide and base. Herein, we report methods to efficiently synthesize bulky bipyridyl and enantioenriched pyridine-oxazoline ligands using palladium-catalyzed deprotonative cross-coupling approaches.

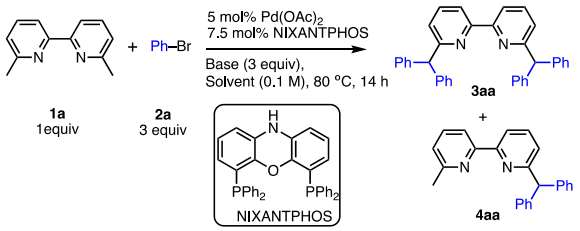


Scheme 2. Reported and proposed synthesis of bulky pyridine ligands (a,c); use of DCCP in the methyl arylation process (b).

Results and Discussion

Reaction development and optimization. Based on our previous work [6a, 6b, 7a, 7b, 10] involving van Leeuwen's NIXANTPHOS ligand[2, 11] (see Table 1 for structure), we began to study coupling of 6,6'-dimethyl-2,2'-bipyridine (**1a,** 1 equiv) and bromobenzene (**2a,** 3 equiv) with Pd(OAc)$_2$ (5 mol%) and NIXANTPHOS (7.5 mol%) as the catalyst. We targeted diarylation of the azaaryl methyl groups to provide bulky diarylmethyl substituents. In general, it is very difficult to perform mono-arylation of an azaaryl methyl group, because after the first arylation, the pK_a of the remaining hydrogens drop by over 5 orders of magnitude[12], making the subsequent deprotonation, and often arylation, faster[13]. In contrast, arylation of triarylmethane derivatives is difficult due to the increased steric hindrance, particularly when using palladium catalysts with bulky bidentate phosphine ligands[6c, 14], such as NIXANTPHOS.

Table 1. Optimization of the bis-arylation and tetra-arylation of 6,6'-dimethyl-2,2'-bipyridine



Entry	Solvent	Base	**3aa** (AY%)[a]	**4aa** (AY%)[a]
1	THF	NaO^{t}Bu	1.5	28
2	THF	KO^{t}Bu	28	48
3	THF	LiN(SiMe$_3$)$_2$	31	32
4	THF	NaN(SiMe$_3$)$_2$	29	65
5	1,4-dioxane	NaN(SiMe$_3$)$_2$	0	22
6	CPME	NaN(SiMe$_3$)$_2$	0	23
7	2-Me-THF	NaN(SiMe$_3$)$_2$	0	6
8	DME	NaN(SiMe$_3$)$_2$	58	28
9[b]	DME	NaN(SiMe$_3$)$_2$	>95	0
10[c]	DME	NaN(SiMe$_3$)$_2$	>95	0
11[d]	DME	NaN(SiMe$_3$)$_2$	>95	4
12[f]	DME	NaN(SiMe$_3$)$_2$	92	5
13[c][f]	DME	NaN(SiMe$_3$)$_2$	>95	0

[a] Assay yield determined by ^{1}H NMR using CH_2Br_2 as internal standard.
[b] 6.0 equiv of base and bromobenzene were used
[c] 5.0 equiv of NaN(SiMe$_3$)$_2$ and 6 equiv of bromobenzene were used
[d] 4.5 equiv of NaN(SiMe$_3$)$_2$ and 6 equiv of bromobenzene were used
[e] 5.0 equiv of NaN(SiMe$_3$)$_2$ and 5 equiv of bromobenzene were used
[f] Reaction time: 1 h

We initially aimed at the synthesis of bis-arylated product (**4aa**, Table 1). To begin with, 3 equiv of bromobenzene and 3 equiv of four different bases [NaO^{t}Bu, KO^{t}Bu, LiN(SiMe$_3$)$_2$ and NaN(SiMe$_3$)$_2$] were examined in THF for the coupling. These initial conditions gave the bis-arylated product (**4aa**) and tetra-arylated product (**3aa**) as mixtures with combined assay yields (AY, determined by ^{1}H NMR using CH_2Br_2 as internal standard) ranging from 29% to 94% (entries 1 – 4, Table 1). Even though use of NaN(SiMe$_3$)$_2$ gave the highest yield of **4aa** (65%), it did not offer a high selectivity of **4aa** over **3aa,** which complicated the purification. In order to find conditions to synthesize **4aa** with high yield and selectivity, NaN(SiMe$_3$)$_2$ was used with other solvents (DME, 1,4-dioxane, CPME, and 2-Me-THF). Unfortunately, these conditions gave either low reactivity (entries 5 – 7) or low selectivity (entry 8) for the synthesis of **4aa**. These results indicated that it is difficult to find conditions to synthesize bis-arylated **4aa** with high yield and selectivity. On the other hand, we were pleased to find that DME favored the formation of tetra-arylated product (**3aa**, 58%, entry 8, Table 1). This result

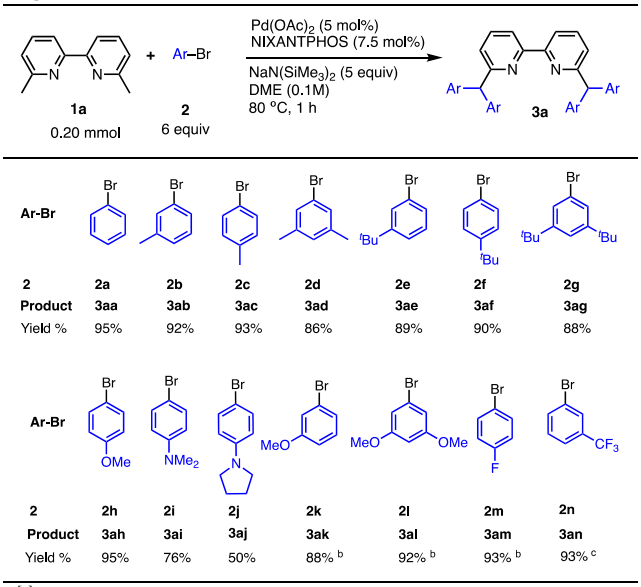
implied that increasing equivalents of base and bromobenzene should favor formation of the tetra-arylated **3aa**, as might be expected. When 6 equiv each of $NaN(SiMe_3)_2$ and bromobenzene in DME were used, **3aa** was exclusively formed (95% AY, entry 9, Table 1). Lowering the amount of $NaN(SiMe_3)_2$ to 5 equiv did not impact the yield of **3aa** (98%, entry 10, Table 1). Further lowering $NaN(SiMe_3)_2$ to 4.5 equiv (entry 11) generated a mixture of **3aa** and **4aa**. Reducing the amount of bromobenzene to 5 equiv (entry 12) also generated a mixture of **3aa** and **4aa**.

We next optimized the reaction time. Monitoring the reaction via TLC showed the reaction to be complete in 1 h, with an AY of 97% (^{1}H NMR, entry 13, Table 1). Based on the optimization above, our conditions for synthesis of tetra-arylated product **3a** used for further study were 6 equiv of aryl bromide, $Pd(OAc)_2$ (5 mol%), NIXANTPHOS (7.5 mol%), 5 equiv of $NaN(SiMe_3)_2$ and DME as solvent at 80 ºC for 1 h (entry 13).

Scope with electron rich aryl bromides. With the optimized conditions for the tetra-arylation in hand, the scope was examined (Table 2). We desired to prepare a series of tetra-arylated ligands with different steric parameters. Six aryl bromides, therefore, were chosen (Table 2, **2b – 2g)** bearing one or two methyl or *tert*-butyl groups, as aryl groups with methyl[8b] and *tert*-butyl[4g, 15] substituents are often incorporated in ligands for enhanced reactivity. The corresponding products (**3ab** – **3ag**) were obtained in good to excellent yields (86 – 93%). Use of aryl bromides with electron donating groups, including 4-OMe (**2h**), 4-NMe_2 (**2i**), and 4-pyrrolidyl (**2j**) also furnished products in good yields (**3ah** – **3aj**, 50 – 95%). The reaction was unsuccessful with 2-bromotoluene under the standard reaction conditions.

Aryl bromides with electron withdrawing groups (EWG), however, were not compatible with the current reaction conditions. For example, the use of 3-bromoanisole (**2k**) generated the corresponding product in < 10% with **1a** and **2k** being recovered. Increasing the reaction time to 12 h led to 30% yield (with the rest of **1a** and **2k** decomposed).

Table 2. Substrate scope for the tetra-arylated 2,2'-bipyridine ligands[a]

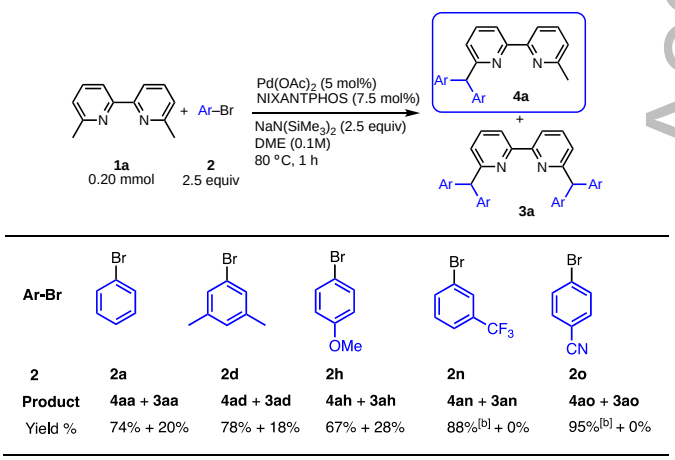


[a] Isolated yield on 0.20 mmol scale;
[b] The reaction was conducted using $LiN(SiMe_3)_2$ (5.0 equiv) in 1,4-dioxane (0.10 M) at 80º C for 12 h.
[c] The reaction was conducted using $LiN(SiMe_3)_2$ (5.0 equiv) in 1,4-dioxane (0.10 M) at 80 ºC for 24 h.

***Optimization and scope with electron poor aryl bromides*.** To enable reactivity of electron poor aryl bromides, high throughput experimentation (HTE) was used to screen solvents and bases for the reaction with 3-bromoanisole (**2k**). These studies (see the Supporting Information, Table S1, Table S2 and Figure S1) showed the combination of 1,4-dioxane and $LiN(SiMe_3)_2$ as optimal. We suspect that $LiN(SiMe_3)_2$ is more strongly aggregated in solution than $NaN(SiMe_3)_2$ making it less basic and reducing side reactions with aryl bromides bearing electron withdrawing groups. Under the newly optimized conditions **1a** and 3-bromoanisole (**2k**) were converted to the tetra-anisole 2,2'-bipyridine ligand in 88% yield (**3ak,** Table 2). Use of 1-bromo-3,5-dimethoxy-bromobenzene (**2l**) and 1-bromo-4-fluorobenzene (**2m**) furnished **3al** and **3am** in ≥92% yield. When 3-bromobenzotrifluoride (**2n**) was used, the reaction time was extended to 24 h, furnishing the product **3an** in 93% yield.

Synthesis of bis-arylated bipyridine ligands. The unsymmetrical bis-arylated products are also potentially valuable ligands with less steric bulk compared to the tetra-arylated derivatives. Therefore, an efficient synthesis of the bis-arylated products was developed by lowering the amount of base and aryl bromide to 2.5 equiv each (Table 3). Under otherwise identical conditions, bromobenzene (**2a**) and 1-bromo-3,5-dimethylbenzene (**2d**) reacted with **1a** to afford the bis-arylated products in 74 and 78% yield (**4aa**, **4ad**) with the corresponding tetra-arylated product in 20 and 18% yield (**3aa**, **3ad**), respectively. The separation of the bis- and tetra-arylated products was relatively straightforward through column chromatography using hexanes and ethyl acetate as eluent. Use of 4-bromoanisole (**2h**) afforded the bis- and tetra-arylated products as a mixture (**4ah**: 70%, **3ah**: 28%). Interestingly, aryl bromides with electron withdrawing groups (*i.e.* **2n**, 3-CF_3 group and **2o**, 4-CN group) afforded bis-arylated product exclusively in 88 and 95% yield. We note that the first arylation is slow and the second is much faster due to the ease of deprotonation of the mono-arylated intermediates. The third arylation will be slower than the first, because most of the aryl bromide has been consumed and its concentration will be low.

Table 3. Substrate scope for the bis-arylated bipyridine ligands [a]



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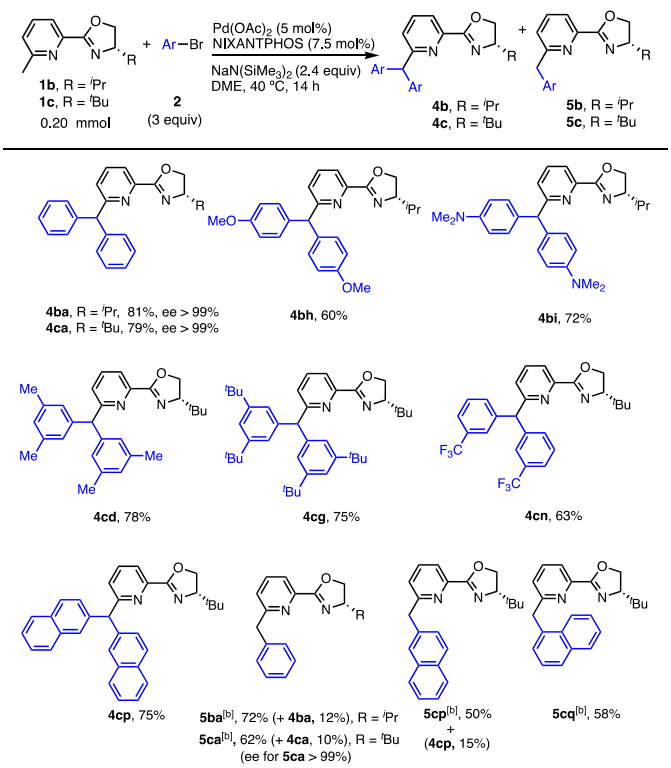
[a] Isolated yield on 0.20 mmol scale;
[b] The reaction was conducted using $LiN(SiMe_3)_2$ (2.5 equiv) in 1,4-dioxane (0.10 M) at 80 °C for 12 h.

Substrate scope of bulky chiral pyridine oxazoline ligands. We next desired to apply our method to the synthesis of a series of bulky enantioenriched pyridine oxazoline-based ligands. Not surprisingly, the preparation of our pyridine oxazoline ligands required slightly modified reaction conditions (see the Supporting Information, Table S2, for optimization). The results of this optimization process indicated use of 3 equiv of aryl bromide and 2.4 equiv of $NaN(SiMe_3)_2$ at 40 °C for 14 h was the best of the conditions examined. Using these conditions, reaction of bromobenzene (**2a,** 3 equiv) and (*S*)-4-isopropyl-2-(6-methylpyridin-2-yl)-4,5-dihydro oxazole (**1b**), or its ^{t}Bu counterpart **1c**, yielded bis-phenylated products **4ba** and **4ca** in 81 and 79% yields, respectively (Table 4).

Table 4. substrate scope of bulky (*S*)-pyridine-oxazoline-based ligands [a]

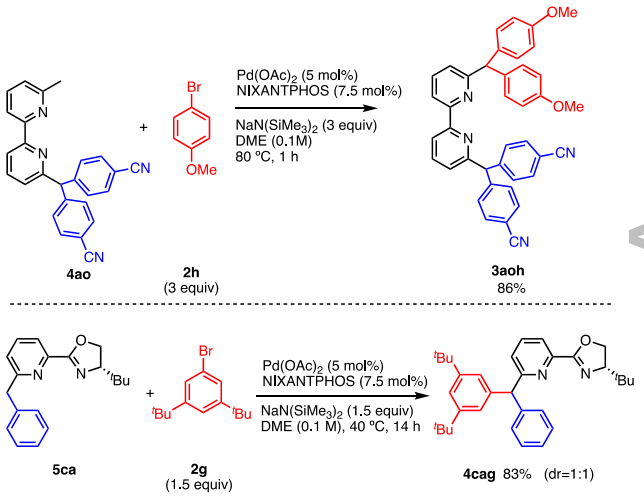


[a] Isolated yield on 0.20 mmol scale
[b] 1.5 equiv of aryl bromide and 1.5 equiv of base were used

Aryl bromides with electron donating groups (*i.e.* **2h**, 4-OMe group and **2i**, 4-NMe_2 group) also successfully coupled with **1b** to form products **4bh** and **4bi** in 60 and 72% yields. Products with aryl groups bearing 3,5-dimethyl or 3,5-di-*tert*-butyl substituents were obtained in good yields (**4cd**: 78%, **4cg**: 75%). Aryl bromide **2n** with an electron withdrawing 3-CF_3 group was also compatible with the reaction conditions, giving product **4cn** in 63%. Here, the lower temperature (40° C) may be key to the success of this electron poor aryl bromide in the presence of $NaN(SiMe_3)_2$ base [in contrast to Table 2 where the milder base $LiN(SiMe_3)_2$ had to be used at 80° C]. 2-Bromonaphthalene (**2p**) with an extended π-system was also successfully coupled with the (*S*)-PyOx ligand to form bis-arylated **4cp** in 75% yield.

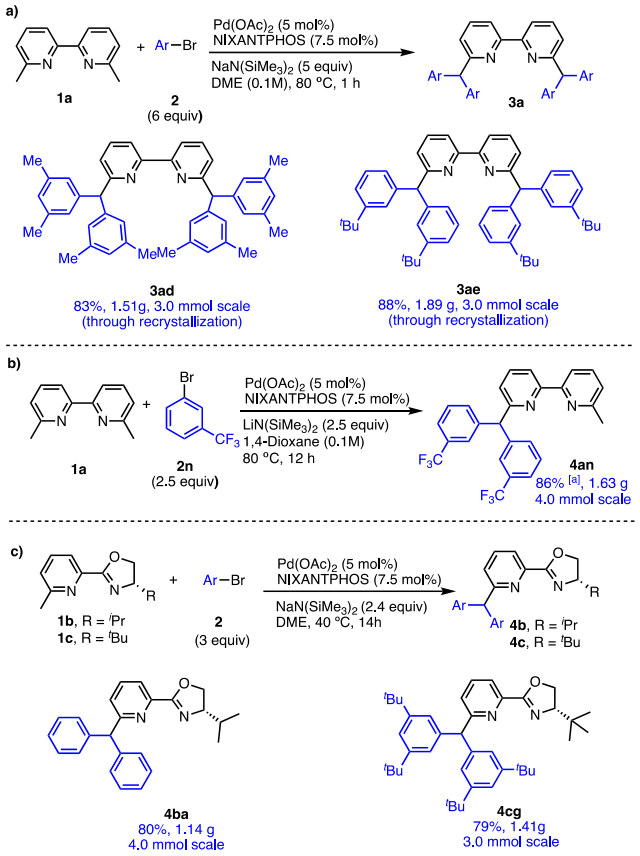
Given that (*S*)-PyOx arylations can be conducted at 40 °C, compared to the arylation of the Bpy derivatives at 80 °C, we attempted the mono-arylation of **1b** and **1c**. When 1.5 equiv bromobenzene (**2a**) and 1.5 equiv of $NaN(SiMe_3)_2$ were used with **1b** and **1c**, the corresponding mono-phenylated products **5ba** and **5ca** were obtained in 72 and 69% yield with the corresponding bis-arylated byproducts (**4ba**, 12%; **4ca**, 10%). The separation of the mono-arylated and the bis-arylated products was relatively simple through column chromatography, permitting isolation of clean mono-arylated products. Similarly, mono-arylated **5cp** with a 2-naphthyl group was obtained in 50% yield as a mixture with its bis-arylated counterpart (**4cp**, 15%). Mono-arylated **5cq** with a sterically hindered 1-naphthyl group was obtained exclusively in 58% yield without formation of its bis-arylated counterpart. This result indicated that the sterically hindered 1-naphthyl group retarded the second arylation under these conditions. Compared to the synthetic routes[4e-g] described in the Introduction involving 4 – 6 steps, this work provides an efficient method to synthesize bulky and enantioenriched (*S*)-pyridine-oxazoline ligands in two steps starting from commercially available 6-methyl-2-pyridinecarbonitrile and β-amino alcohols[9] with reasonable to good yields. Although it was viewed as unlikely that the stereocenter in the pyridine oxazoline-based ligands would be racemized by the base under these mild conditions, we viewed it as prudent to verify this hypothesis using chiral phase SFC (see Supporting Information for details). Thus, ligands **4ba**, **4ca** and **5ca** were analyzed and found to have ee values of at least 99%.

Synthesis of unsymmetrical NN'-bidentate ligands. Next, we were interested in preparing unsymmetrical Bpy ligands. Thus, starting from bis-arylated product **4ao** containing two 4-cyanophenyl groups (Scheme 3), arylation of the remaining methyl group with 4-bromoanisole (**2h**) afforded the unsymmetrical product **3aoh** in 86% yield. Similarly, further arylation of mono-phenylated (*S*)-PyOx compound **5ca**, with 1-bromo-3,5-di-*tert*-butylbenzene (**2g**) furnished bis-arylated (*S*)-PyOx product **4cag** in 83% yield as a 1:1 diastereomeric mixture.



Scheme 3. Synthesis of an unsymmetrical 2,2'-bipyridine-based ligand and bis-arylated (*S*)-PyOx ligand with two different aryl groups

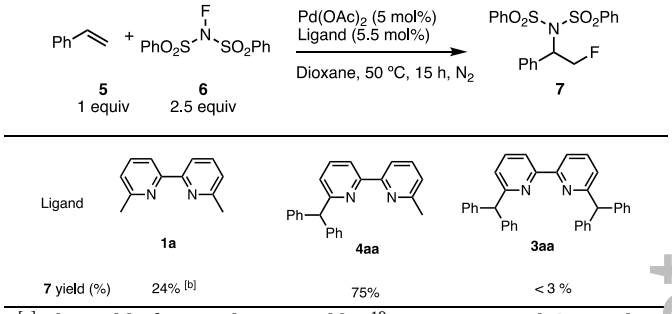
Gram scale synthesis. To demonstrate the utility of this reaction, gram-scale syntheses of tetra-arylated 2,2'-bipyridine-based ligands **3ad** and **3ae** were conducted. As shown in Scheme 4a, the products were obtained in 83 and 88% yield, respectively, after recrystallization. The gram scale synthesis of bis-arylated **4an** also offered the product in 86% yield (Scheme 4b). The synthesis of (*S*)-PyOx ligands **4ba** and **4cg** were also scaled up successfully with 80 and 79% yields (Scheme 4c). These results show that our method can be used to prepare significant quantities of ligands.



Scheme 4. Gram scale synthesis of bulky 2,2'-bipyridine-based (a,b) and (*S*)-PyOx-based ligands (c)

Catalytic activity with bulky bipyridine ligands. The aminofluorination of alkenes is a useful method to difunctionalize olefins. Liu and coworkers[16] have observed that the commercial ligand 6,6'-dimethyl-2,2'-bipyridine (**1a**) catalyzed a styrene aminofluorination reaction with a modest yield (23%). We envisioned that our bulky bipyridine ligands could be more active ligands for this aminofluorination process. This is based on the assumption that the bulky ligands should have weaker coordination with the palladium center and make the palladium center more electrophilic toward binding the styrene. Such a hypothesis has been demonstrated in Liu's work[4f]. From a preliminary activity study, we observed that our bulky bipyridine ligand **4aa** exhibited enhanced activity compared to **1a** in the styrene aminofluorination reaction[16] under the literature conditions. Interestingly, the tetra-phenylated 2,2'-bipydirine ligand (**3aa**) did not impart reactivity to the palladium. The reason for this is not clear at this time, but it may be due to the increased steric hindrance of the ligand. These preliminary reactions show that the bulky ligands prepared herein exhibit different reactivity than their commercial counterparts.

Table 5. Catalytic activity of the bulky and non-bulky 2,2'-bipyridine ligands[a].



[a] The yield of **7** was determined by ^{19}F NMR using $PhCF_3$ as the internal standard

[b] This result is consistent with literature (23%) under identical conditions.[16]

Conclusion

An efficient and convenient method is advanced to synthesize bulky *N,N'*-bidentate ligands. Using this method, twenty bulky 2,2'-bipyridine and thirteen bulky (*S*)-pyridine-oxazoline ligands were obtained in yields up to 95% and over 99% ee for the chiral PyOx ligands. Key to this method is the use of a Pd(NIXANTPHOS)-based catalyst system that we have demonstrated to perform with high efficiency in the coupling of weakly acidic azaaryl methyl groups with aryl bromides in the presence of silyl amide bases. The straightforward access to these ligands makes them attractive for catalyst development.

Experimental Section

General Methods: All reactions were carried out under dry nitrogen. Anhydrous dimethoxyethane (DME) and 1,4-dioxane were purchased from Sigma Aldrich and directly used. Unless otherwise stated, reagents were commercially available and used as received without further purification. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar or Matrix Scientific. TLC was performed with Merck TLC Silicage l60 F254 plates and detection was under UV light at 220 nm. Flash chromatography was performed with silica gel (230–400 mesh, Silicycle). The ^1H and $^{13}C\{^1H\}$ NMR spectra were obtained using a Bruker AM-500 Fourier-transform NMR spectrometer at 500 and 125 MHz or a Bruker AVIII 400 NMR spectrometer at 400 and 100 MHz, respectively. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz (Hz). The infrared spectra were obtained using a Perkin-Elmer Spectrum 100 Series FTIR spectrometer. High resolution mass spectrometry (HRMS) and low-resolution mass spectrometry data were obtained on a Waters LC-TOF mass spectrometer (model

LCT-XE Premier) or a Waters SQD mass spectrometer equipped with an Acquity HPLC using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus and are uncorrected.

General Procedure A: for the Synthesis of tetra-arylated 2,2'-bipydidine ligands

To an oven-dried 8 mL reaction vial equipped with a stir bar was charged 6,6'-dimethyl-2,2'-bipyridine (**1a**, 0.20 mmol, 1.0 equiv) and base [$NaN(SiMe_3)_2$, 5.0 equiv] in a glove box under a nitrogen atmosphere at room temperature. A stock solution containing $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol %) and NIXANTPHOS (8.3 mg, 0.015 mmol, 7.5 mol %) in 2 mL of dry DME was stirred for 10 min at 25 ºC before it was taken up by a syringe and added to the reaction vial under nitrogen. Next, aryl bromide (6.0 equiv) was added to the reaction mixture through a syringe (if the aryl bromide was a solid, it was added along with **1a** and the base). The vial was capped, removed from the glove box, and stirred for 1 h at 80 °C. The resulting cloudy, orange or red solution was cooled to room temperature, opened to air and quenched with 3 drops of water. The reaction mixture was then passed through a short pad of silica gel packed into a syringe. The pad was then rinsed with 10 mL ethyl acetate and 20 mL CH_2Cl_2 and the filtrate was collected. The volatile materials were removed under reduced pressure. The resulting crude material was loaded onto a silica gel column and purified by flash chromatography (eluted with hexanes and ethyl acetate or hexanes and CH_2Cl_2) to afford the desired products.

General Procedure B: for the synthesis of tetra-arylated 2,2'-bipydidine ligands from electron poor aryl bromides

To an oven-dried 8 mL reaction vial equipped with a stir bar was charged 6,6'-dimethyl-2,2'-bipyridine (**1a**, 0.20 mmol, 1.0 equiv) and base [$LiN(SiMe_3)_2$, 5.0 equiv] in a glove box under a nitrogen atmosphere at room temperature. A stock solution containing $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol %) and NIXANTPHOS (8.3 mg, 0.015 mmol, 7.5 mol %) in 2 mL of dry 1,4-dioxane was stirred for 10 min at 25 ºC before it was taken up by syringe and added to the reaction vial under nitrogen. Next, aryl bromide (6.0 equiv) was added to the reaction mixture through a syringe (if the aryl bromide was a solid, it was added along with **1a** and the base). The vial was capped, removed from the glove box, and stirred for 12 h or 24 h at 80 °C. The resulting cloudy, orange or red solution was cooled to room temperature, opened to air and quenched with 3 drops of water. The reaction mixture was then passed through a short pad of silica gel packed into a syringe. The pad was then rinsed with 10 mL ethyl acetate and 20 mL CH_2Cl_2 and the filtrate was collected. The volatile materials were removed under reduced pressure. The resulting crude material was loaded onto a silica gel column and purified by flash chromatography (eluted with hexanes and ethyl acetate or hexanes and CH_2Cl_2) to afford the desired products.

General Procedure C: for the Synthesis of bis-arylated 2,2'-bipydidine ligands

To an oven-dried 8 mL reaction vial equipped with a stir bar was charged 6,6'-dimethyl-2,2'-bipyridine (**1a**, 0.20 mmol, 1.0 equiv) and base [$NaN(SiMe_3)_2$ (for **4aa**, **4ad**, **4ah**) or $LiN(SiMe_3)_2$ (for **4an**, **4ao**), 2.5 equiv] in a glove box under a nitrogen atmosphere at room temperature. A stock solution containing $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol %) and NIXANTPHOS (8.3 mg, 0.015 mmol, 7.5 mol %) in 2 mL of dry in DME (for **4aa**, **4ad**, **4ah**) or 1,4-dioxane (for **4an**, **4ao**) was stirred for 10 min at 25 ºC before it was taken up by a syringe and added to the reaction vial under nitrogen. Next, aryl bromide (2.50 equiv) was added to the reaction mixture through a syringe (if the aryl bromide was a solid, it was added along with **1a** and the base). The vial was capped, removed from the glove box, and stirred for 1 – 12 h at 80 °C. The resulting cloudy, orange or red solution was cooled to room temperature, opened to air and quenched with 3 drops of water. The reaction mixture was then passed through a short pad of silica gel packed into a syringe. The pad was then rinsed with 10 mL ethyl acetate and 20 mL CH_2Cl_2 and the filtrate was collected. The volatile materials were removed under reduced pressure. The resulting crude material was loaded onto a silica gel column and purified by flash chromatography (eluted with hexanes and ethyl acetate or hexanes and CH_2Cl_2) to afford the desired products.

General procedure D: for the synthesis of bis-arylated (*S*)-PyOx ligands

To an oven-dried 8 mL reaction vial equipped with a stir bar was charged with (*S*)-6-methyl-2-oxazoline-pyridine derivatives (**1b** or **1c**, 0.20 mmol, 1.0 equiv) and base [$NaN(SiMe_3)_2$, 2.4 equiv] in a glove box under a nitrogen atmosphere at room temperature. A stock solution containing $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol %) and NIXANTPHOS (8.3 mg, 0.015 mmol, 7.5 mol %) in 2 mL of dry DME was stirred for 10 min at 25 ºC before it was taken up by a syringe and added to the reaction vial under nitrogen. Next, aryl bromide (3.0 equiv) was added to the reaction mixture through a syringe. Notice that if the aryl bromide was a solid, it was added along with **1** and the base. The vial was capped, removed from the glove box, and stirred for 14 h at 40 °C. The resulting cloudy, orange or red solution was cooled to room temperature, opened to air and quenched with 3 drops of water. The reaction mixture was then passed through a short pad of silica gel loaded into a syringe. The pad was then rinsed with 10 mL ethyl acetate and 20 mL CH_2Cl_2 and the solvent was removed under reduced pressure. The crude material was loaded onto a deactivated silica gel column and purified by flash chromatography (eluted with hexanes and ethyl acetate) to afford the desired products.

General procedure E: for the synthesis of mono-arylated (*S*)-PyOx ligands

To an oven-dried 8 mL reaction vial equipped with a stir bar was charged (*S*)-6-methyl-2-oxazoline-pyridine derivatives (**1b** or **1c**, 0.20 mmol, 1.0 equiv) and base [$NaN(SiMe_3)_2$, 1.5 equiv] in a glove box under a nitrogen atmosphere at room temperature. A stock solution containing $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol %) and NIXANTPHOS (8.3 mg, 0.015 mmol, 7.5 mol %) in 2 mL of dry DME was stirred for 10 min at 25 ºC before it was taken up by a syringe and added to the reaction vial under nitrogen. Next,

aryl bromide (1.5 equiv) was added to the reaction mixture through a syringe. Notice that if the aryl bromides was a solid, it was added along with **1** and the base. The vial was capped, removed from the glove box, and stirred for 14 h at 40 °C. The resulting cloudy, orange or red solution was cooled to room temperature, opened to air and quenched with 3 drops of water. The reaction mixture was then passed through a short pad of silica gel loaded into a syringe. The pad was then rinsed with 10 mL ethyl acetate and 20 mL CH_2Cl_2 and the solvent was removed under reduced pressure. The crude material was loaded onto a silica gel column and purified by flash chromatography (eluted with hexanes and ethyl acetate) to afford the desired products.

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FULL PAPER

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