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Copper-Catalyzed Coupling of Pyridines and Quinolines with Alkynes: A One-Step, Asymmetric Route to Functionalized Heterocycles

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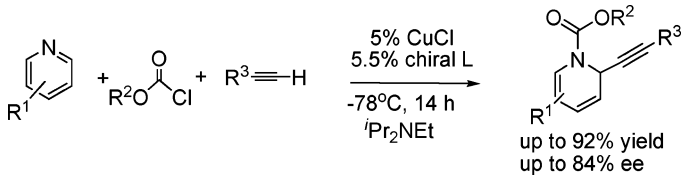

A copper (I)-catalyzed, asymmetric method to directly functionalize pyridines, quinolines, and isoquinolines with terminal alkynes is described. The reaction is readily diversified to incorporate a range of pyridine-based heterocycles and electron-rich or electron-poor alkynes. This provides a straightforward alternative to nucleophilic or cross-coupling approaches to directly derivatize these heterocycles, and yields useful propargylcarbamates.

Introduction

The ability to efficiently functionalize heterocycles such as pyridines and their derivatives (e.g., quinoline, isoquinoline, etc.) remains an important issue in synthetic chemistry. This is driven in part by the prevalence of these structures in biologically relevant molecules[1,2] as well as components in polymers,[3] ligands,[4] and various functional materials.[5] A range of methods have been developed to functionalize nitrogen-containing aromatic heterocycles. These include electrophilic aromatic substitution or metalation methodologies, as well as the now common use of metal-catalyzed cross-coupling reactions.[6] The latter are typically performed on presynthesized halogenated or metalated pyridine derivatives, or with *N*-activated heterocycles (e.g., catalytic arylation of pyridine *N*-oxides, or alkynylation of *N*-alkyl quinolinium salts).[7,8] Alternatively, the reductive functionalization of pyridine can be achieved by the addition of nucleophiles to in situ generated *N*-acyl pyridinium salts.[9] These products can be subsequently oxidized to form the

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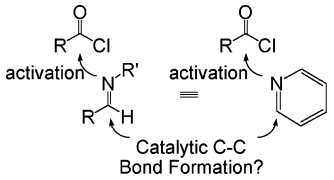


FIGURE 1. Imines and pyridine in catalytic carbon−carbon bond formation.

substituted pyridine, reduced to form piperdines, or are themselves valuable building blocks in natural product synthesis.

We and others have recently reported that imines can participate in metal-catalyzed coupling reactions with a range of cross-coupling reagents (e.g., organostannanes, organoindium compounds, or terminal alkynes).[10,11] Notably, these reactions do not require the initial halogenation of the precursor, nor strong nucleophiles or bases, providing a mild and straightforward route to α-substituted amides. In light of the resonance structure similarity between imines and nitrogen-containing heterocycles such as pyridine (Figure 1), we became intrigued with the potential that pyridine itself might participate in similar metal-catalyzed carbon−carbon bond-forming reactions, such as alkynylation to form cyclic propargylamides. Toward this end, we have preliminarily communicated one example of the simple copper-catalyzed coupling of phenylacetylene with pyridine in the presence of an acid chloride, to rapidly generate a propargylamide.[10b] While the addition of stoichiometric alkynyl−metal nucleophiles to in situ generated *N*-acyl pyridinium salts is well established,[12] as is the catalytic alkynylation of *N*-alkylated quinolines to form tertiary propargylamines,[8] this represented what was to our knowledge the first example of the direct coupling of alkynes with pyridine using simple copper salts as catalysts. More recently, the use of stoichiometric zinc salts to mediate this reaction has been reported.[14] In addition, Ma and co-workers have demonstrated that this copper-catalyzed reaction can be performed with high levels of enantioselectivity using chiral bisoxazoline ligands, although the scope of this reaction is limited to the use of electron-deficient 3-carbonyl substituted alkynes.[13]

We report herein the full details, scope, and limitations of this copper-catalyzed one-step functionalization of pyridines and related nitrogen-containing heterocycles with various simple alkynes. In addition, performing the coupling with chiral ligands provides a versatile catalytic route to enantioenriched alkynylated heterocycles.

SCHEME 1. Proposed Mechanism for the Catalytic Addition of Terminal Alkynes to Pyridine

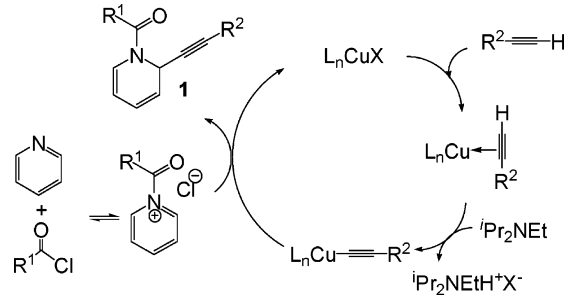
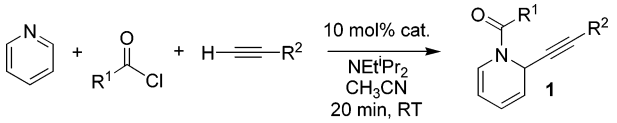


TABLE 1. Copper-Catalyzed Coupling of Pyridine, Chloroformates, and Alkynes[a]



entry	cat.	R^1	R^2	% yield **1**
1	CuI	Ph	Ph	73
2	CuI	Ph	*n*-C_4H_9	33
3	CuOTf[b]	Ph	Ph	31
4	$Zn(OTf)_2$	Ph	Ph	−
5	CuI	EtO	Ph	82
6	CuI	PhO	Ph	88
7	CuI	(9-fluorenyl) CH_2O	Ph	62
8	CuI	EtO	*n*-C_4H_9	83
9	CuI	EtO	TMS	72
10	CuI	PhO	CH_2Cl	64
11	CuI	PhO	CO_2Et	78

[a] 0.50 mmol heterocycle, 0.60 mmol acid chloride, 0.50 mmol alkyne, 0.70 mmol NEt^iPr_2, and 10 mol % catalyst in 2 mL CH_3CN. [b] $CuOTf{\cdot}C_6H_6$.

Results and Discussion

Our approach to this reaction is based upon the postulate that pyridines can be activated by acid chlorides toward a copper-catalyzed coupling with terminal alkynes in a fashion similar to that with imines, as shown in Scheme 1. As we have previously communicated, pyridine undergoes a clean coupling with phenylacetylene and benzoyl chloride in the presence of a copper iodide catalyst to generate **1** (Table 1, entry 1).[10b] While effective, attempts to couple other terminal alkynes with pyridine in the presence of benzoyl chloride resulted in very poor yields (Table 1, entry 2). Other metal salts were also found to be ineffective as catalysts (Table 1, entries 3, 4). Considering the electrophilicity of chloroformates, we examined the possibility that they might both interact more strongly with pyridine and better activate the heterocycle toward reaction. As shown in entries 5−8, a number of common nitrogen protecting group reagents (TROC, FmocCl) can participate in the coupling of pyridine with phenylacetylene, in this case providing access to synthetically useful *N*-protected cyclic amines. The yields of these reactions are similar if not better than those with acid chlorides. In addition, the use of chloroformates can allow the use of a range of functionalized alkynes as the carbon−carbon bond-forming partner with pyridine, including both electron-rich (e.g., entry 9) and electron-poor (entries 10, 11) substrates.

This copper-catalyzed multicomponent coupling is straightforward to perform (mixing of the three reagents with catalyst

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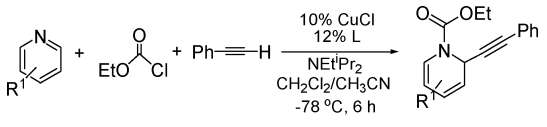
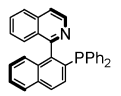
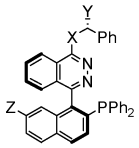
TABLE 2. Ligands in Catalytic Enantioselective Alkynylation[a]




(*R*)-QUINAP



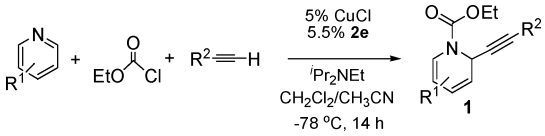
2a X = NH; Y = CH$_3$; Z = H
2b X = O; Y = CH$_3$; Z = H
2c X = NH; Y = C(Et)$_2$OH; Z = OCH$_3$
2d X = NH; Y = C(Bn)$_2$OH; Z = OCH$_3$
2e X = NH; Y = CH$_3$; Z = OCH$_3$

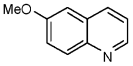
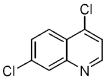
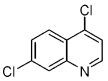
entry	heterocycle	ligand	% yield[b]	ee (%)
1	pyridine	(*R*)-Tol-BINAP	n.d.	2
2	pyridine	(*R*)-^{i}Pr-PYBOX	n.d.	0
3	pyridine	(*R*)-^{t}Bu-BOX	n.d.	1
4	pyridine	(*R*)-MONOPHOS	–	–
5	pyridine	(*R*)-MOP	72	0
6	pyridine	(*R*)-QUINAP	17	49
7	quinoline	(*R*)-QUINAP	86	43
8	quinoline	**2a**	91	53
9	quinoline	**2b**	84	41
10	quinoline	**2c**	86	75
11	quinoline	**2d**	75	66
12	quinoline	**2e**	92	81

[a] 0.10 mmol heterocycle, 0.12 mmol chloroformate, 0.11 mmol alkyne, 12 mol % ligand, 10 mol % CuCl, and 0.15 mmol ^{i}Pr$_2$NEt in CH$_3$CN/CH$_2$Cl$_2$ (5 mL). [b] n.d. = not determined.

and base for 20 min) and regioselectively generates the 1,2-addition product: cyclic propargylcarbamates. The latter are of broad utility as chiral building blocks in the synthesis of various alkaloids and other biologically relevant molecules.[15] In addition, since this reaction is mediated by copper salts, it suggests the potential for asymmetric catalysis. The enantioselective synthesis of dihydropyridine derivatives has attracted significant attention, including several very recent catalytic examples. This includes the catalytic addition of nucleophilic organolithium reagents[16] and silyl-nitriles[17] or -enolates,[18] and the copper-catalyzed alkynylation of *N*-alkyl isoquinolinium salts.[8] In addition, as previously mentioned, the addition of 3-carbonyl-substituted alkynes to *N*-acylpyridinium salts can proceed with high enantioselectivity employing bis(oxazoline) ligands,[13] although other alkyne substrates (e.g., simple phenylacetylene, alkyl-substituted alkynes, propargyl esters, etc.) yielded near racemic products.

TABLE 3. Enantioselective Alkynylation of Nitrogen Heterocycles[a]



cpd	heterocycle	alkyne	yield	ee
1a			92%	81%
1b			72%	84%
1c			88%	72%
1d			33%	80%
1e			84%	75%
1f			75%	62%
1g			82%	78%
1h			92%	70%
1i			84%	80%
1j			76%	81%

[a] 0.10 mmol heterocycle, 0.11 mmol chloroformate, 0.10 mmol alkyne, 5.5 mol % ligand, 5 mol % CuCl, and 0.14 mmol ^{i}Pr$_2$NEt in CH$_3$CN/CH$_2$Cl$_2$ (5 mL).

As shown in Table 2, the use of several commercially available chiral phosphorus- and nitrogen-donor ligands in this reaction unfortunately resulted in low to zero enantioselectivity with phenylacetylene, similar to previous reports.[13,19] Nevertheless, we were encouraged by the results with (*R*)-QUINAP, which yielded the functionalized pyridine derivative in moderate ee (49%, entry 6).[20] Similar selectivity was observed in the alkynylation of quinoline (entry 7), although in higher yield. Building upon this ligand class, further improvement of the enantioselectivity can be obtained with the PINAP derivatives **2a**–**c**, (up to 75% ee). A feature of the PINAP series of ligands is their modularity, where the substituents can be changed and the ligand subsequently resolved as column-separable diastereomers.[21] As such, two new variants of this ligand (**2d** and **2e**) were prepared, in analogy to literature procedures. In the case

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(19) CuCl was employed rather than CuI as catalyst due to its higher solubility in this solvent mixture at low temperature.

(20) This ligand has been successfully employed by Knochel in the asymmetric alkynylation of *N*-alkyliminium salts. For example: Gommermann, N.; Koradin, C.; Polborn, K.; Knochel P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

of ligand **2e**, this allows the coupling to proceed in up to 81% enantioselectivity (entry 12).

The scope of this copper-catalyzed coupling of alkynes, heterocycles, and chloroformates is shown in Table 3. Perhaps most notably, a number of nitrogen-containing heterocycles can be alkynylated via this route, provided they contain a C═N π-bonded resonance structure, including quinoline, isoquinoline, and pyridine. In addition, functionalized heterocycles can also participate in this reaction, such as those with either electron-withdrawing or -donating groups. Interestingly, even the halogenated heterocycles lead to alkynylation exclusively at the ortho position to the nitrogen, rather than cross-coupling at the halogenated carbon (**1i,j**). Finally, a range of alkynes can be employed in this chemistry, including various functionalized, electron-rich and electron-poor alkynes. Each of these multicomponent reactions proceeds in high yield and reasonable selectivity. Overall, this provides a relatively general approach to construct enantioenriched propargylcarbamate derivatives.

Conclusions

In conclusion, we have reported a general and simple copper-catalyzed method to directly couple pyridines and related heterocycles with a diverse range of alkynes. Considering the efficiency of this catalytic coupling, the availability of each of the building blocks, and the lack of any prederivatization steps, this provides a straightforward method to assemble enantioenriched dihydropyridine derivatives. Experiments directed toward the application of this approach to activate heterocycles toward other metal-catalyzed, asymmetric carbon−carbon bond-forming reactions are in progress.

Experimental Section

General Procedure for the Synthesis of Racemic 2-Alkynyl-1,2-dihydropyridines. Under a nitrogen atmosphere, pyridine (0.50 mmol) and acid chloride/chloroformate (0.60 mmol) were mixed in 1 mL of CH_3CN. To this was added the alkyne (0.50 mmol) and catalyst (10 mol %, CuI, $CuOTf{\cdot}C_6H_6$, or $Zn(OTf)_2$) in 1 mL of CH_3CN. NEt^iPr_2 was then added dropwise over 1 min, and the reaction was stirred for 20 min at ambient temperature. The solvent was then removed, and the product isolated by column chromatography with ethyl acetate/hexanes.

Ethyl 2-(phenylethynyl)pyridine-1(2H)-carboxylate (Table 1, entry 5). The above procedure was followed with pyridine, ethyl chloroformate, and phenylacetylene. Isolated yield: 82%. ^{1}H NMR (300 MHz, 60 °C, $CDCl_3$): δ 7.32−7.41 (m, 2H), 7.21−7.28 (m, 3H), 6.8 (d, 1H), 6.0 (m, 1H), 5.79 (d, 1H), 5.65 (t, 1H), 5.36 (t, 1H), 4.32 (q, 2H), 1.37 (t, 3H). ^{13}C NMR (67.9 MHz, 60 °C, $CDCl_3$): δ 153.4, 131.9, 128.1, 125.2, 122.9, 122.5, 122.3 118.6, 105.1, 86.8, 82.2, 62.5, 44.2, 14.4. HRMS (M + H) for $C_{16}H_{15}NO_2$, calculated: 254.1183, found: 254.1176.

Ethyl 2-(hex-1-ynyl)pyridine-1(2H)-carboxylate (Table 1, entry 8). The above procedure was followed with pyridine, ethyl chloroformate, and 1-hexyne. Isolated yield: 83%. ^{1}H NMR (300 MHz, 60 °C, $CDCl_3$): δ 6.72−6.77 (d, 1H), 5.87−5.95 (q, 1H), 5.49−5.58 (br, m, 2H), 5.25−5.33 (t, 1H), 4.21−4.34 (q, 2H), 2.12−2.19 (t, 2H), 1.27−1.48 (m, 5H), 0.82−0.94 (t, 3H). ^{13}C NMR (75.5 MHz, 60 °C, $CDCl_3$): δ 125.3, 121.7, 119.7, 105.1, 83.9, 77.9, 62.5, 44.0, 30.8, 21.9, 18.6, 14.5, 13.5. HRMS (M + Na) for $C_{14}H_{19}NO_2$, calculated: 256.1316, found: 256.1306.

General Procedure for the Synthesis of Enantioenriched Alkynylated Heterocycles. Under a nitrogen atmosphere, the heterocycle (0.10 mmol) and ethyl chloroformate (0.11 mmol) were mixed in 2 mL of CH_2Cl_2. Copper (I) chloride (0.35 mg, 5.00 μmol) and **2e** (2.2 mg, 5.50 μmol) were mixed in 2 mL of 1:1 CH_3CN/CH_2Cl_2. These solutions were mixed with the alkyne (0.10 mmol) in 1 mL of CH_2Cl_2, and the mixture cooled to −78 °C. EtN^iPr_2 (0.14 mmol) in 1 mL of CH_2Cl_2 was added over 30 min. The reaction was stirred 14 h, warmed to ambient temperature, and concentrated in vacuo; the product was isolated by column chromatography with ethyl acetate/hexanes. Enantioselectivity was determined using a Daicel ChiralPak OD-H or AD-H column 250 mm × 4.6 mm i.d. with hexane/2-propanol.

Ethyl-2-(phenylethynyl)quinoline-1(2*H*)-carboxylate (1a). The above procedure was followed with quinoline, ethyl chloroformate, and phenylacetylene. Isolated yield: 86%. Enantiomeric excess: 81%. Enantioselectivity was determined using a Daicel ChiralCel OD-H column 250 mm × 4.6 mm i.d. with hexane/2-propanol = 95:5, flow rate 0.5 mL/min, UV 254 nm, $t_{r(minor)}$ = 11.13 min, $t_{r(major)}$ = 12.34 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, 1H, J = 6.8 Hz), 7.33−7.07 (m, 9H), 6.60−6.52 (m, 1H), 6.15−6.06 (m, 2H), 4.42−4.22 (m, 2H), 1.37 (t, 3H, J = 9.2 Hz). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 154.1, 134.6, 132.0, 128.5, 128.3, 128.0, 126.8, 126.2, 125.4, 124.6, 124.6, 122.8, 85.9, 83.7, 62.8, 44.9, 14.7. HRMS calculated for $C_{20}H_{18}NO_2^+$: 304.1332; found: 304.1330.

Ethyl-2-((trimethylsilyl)ethynyl)quinoline-1(2*H*)-carboxylate (1b). The above procedure was followed with quinoline, ethyl chloroformate, and trimethylsilylacetylene. Isolated yield: 72%. Enantiomeric excess: 84%. Enantioselectivity was determined using a Daicel ChiralCel OD-H column 250 mm × 4.6 mm i.d. with hexane/2-propanol = 99:1, flow rate 0.5 mL/min, UV 254 nm, $t_{r(minor)}$ = 15.40 min, $t_{r(major)}$ = 16.26 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (br, 1H), 7.28−7.20 (m, 1H), 7.13−7.05 (m, 2H), 6.51 (d, 1H, J = 6.4 Hz), 6.04−5.97 (m, 1H), 5.88 (d, 1H, J = 5.3 Hz), 4.37−4.21 (m, 2H), 1.35 (t, 3H, J = 5.6 Hz), 0.05 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 134.6, 127.9, 126.8, 126.7, 126.0, 125.5, 124.5, 102.0, 88.5, 62.7, 44.9, 14.7, 0.0. HRMS calculated for $C_{17}H_{22}NO_2Si^+$: 300.1414; found: 300.1409.

Synthesis of 2d. A procedure analogous to that reported for ligands **2a**−**c** was followed.[21] Trifluoromethanesulfonic acid 1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-yl ester (1.30 g, 2.77 mmol) and (*R*)-1-amino-2-benzyl-1,3-diphenylpropan-2-ol (4.40 g, 13.9 mmol) were mixed neat in a screw-capped vial. The suspension was stirred for 24 h at 120 °C. After cooling to ambient temperature, 30 mL of methylene chloride was added, and the suspension was filtered. The filtrate was concentrated under reduced pressure. The product was isolated by column chromatography using toluene/EtOAc (10:1 to 5:1) as eluent, as a mixture of diastereomers. The product, 1-(4-((*R*)-2-benzyl-2-hydroxy-1,3-diphenylpropylamino)-phthalazin-1-yl)-7-methoxy-naphthalen-2-yl-trifluoromethanesulfonate (1.28 g, 1.62 mmol, 59% yield), was dried on a vacuum line for 24 h and then used in the next step.

A solution of $Ni(dppe)Cl_2$ (0.082 g, 0.16 mmol) in 3 mL of DMF was mixed with a solution of diphenylphosphine (0.620 g, 3.32 mmol) in 2 mL of DMF, under a nitrogen atmosphere. This red solution was heated at 120 °C for 1 h. After cooling under nitrogen, a solution of the above product (1.28 g, 1.62 mmol) in 1.5 mL of DMF was added, followed by addition of DABCO (0.73 g, 6.50 mmol) in 3 mL of DMF. The solution was then heated at 120 °C for 36 h. The mixture was then concentrated under reduced pressure. The green/black residue was then purified by column chromatography in toluene/EtOAc (pure toluene to 4:1) as eluent, as a mixture of diastereomers. Separation of the diastereomers was performed subsequently by column chromatography in toluene/EtOAc (12:1). From this, 290 mg (23%) of ligand **2d** was isolated.

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^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, 1H, J = 7.6 Hz), 7.80 (d, 1H, J = 8.4 Hz), 7.69 (d, 2H, J = 7.6 Hz), 7.60−7.03 (m, 29H), 6.40 (d, 1H, J = 7.8 Hz), 5.93 (d, 1H, J = 7.8 Hz), 3.38 (s, 3H), 3.25−2.99 (m, 3H), 2.83 (br, 2H). ^{13}C NMR (68.0 MHz, $CDCl_3$): δ 158.3, 152.8, 152.8, 152.5, 141.0, 140.9, 140.6, 138.4, 138.2, 138.0, 137.8, 137.5, 137.5, 136.9, 136.7, 134.9, 134.8, 134.2, 134.0,133.7, 133.4, 131.2, 131.1, 131.0, 129.8, 129.7, 129.5, 128.9, 128.7, 128.6, 128.4, 128.3, 128.0, 127.5, 126.9, 126.8, 126.5, 120.9, 119.7, 118.3, 105.7, 77.5, 62.0, 55.3, 44.9, 43.7. ^{31}P NMR (81.0 MHz, $CDCl_3$): δ −12.38. HRMS calculated for $C_{53}H_{45}N_3O_2P^+$: 786.3244; found: 786.3241. $[\alpha]^{24}_D$ = 182.0 (c = 1.0, $CHCl_3$).

Synthesis of Ligand 2e. A procedure analogous to that reported for ligands **2a**−**c** was followed.[21] Trifluoromethanesulfonic acid 1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-yl ester (1.30 g, 2.77 mmol) and (*R*)-α-methyl-benzylamine (1.70 g, 14.0 mmol) were mixed neat in a screw-capped vial. The suspension was stirred for 14 h at 120 °C. After cooling to ambient temperature, the product was isolated by column chromatography using hexanes/ethyl acetate (65:35) as eluent, as a mixture of diastereomers. This product, 7-methoxy-1-(4-((*R*)-1-phenylethylamino)phthalazin-1-yl)-naphthalen-2-yl trifluoromethanesulfonate (1.10 g, 1.99 mmol, 72%), was dried on a vacuum line for 24 h and then used in the next step.

A solution of $Ni(dppe)Cl_2$ (0.105 g, 0.020 mmol) in 3 mL of DMF was mixed with a solution of diphenylphosphine (0.745 g, 4.0 mmol) in 2 mL of DMF, under a nitrogen atmosphere. This red solution was heated at 120 °C for 1 h. After cooling under nitrogen, a solution of the above product (1.10 g, 1.99 mmol) in 1.5 mL of DMF was added, followed by addition of DABCO (0.90 g, 8.0 mmol) in 3 mL of DMF. The solution was then heated at 120 °C for 48 h. The mixture was then concentrated under reduced pressure. The green/black residue was then purified by column chromatography in toluene/EtOAc (pure toluene to 4:1) as eluent, as a mixture of diastereomers. Separation of the diastereomers was performed subsequently by column chromatography in toluene/EtOAc (10:1). From this, 415 mg (35%) of ligand **2e** was isolated.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (m, 3H), 7.63 (t, 1H, J = 6.9 Hz), 7.57−7.09 (m, 19H), 6.48 (s, 1H), 5.82 (quint, 1H, J = 6.9 Hz), 5.47 (br, 1H), 3.42 (s, 3H), 1.73 (d, 3H, J = 6.8 Hz). ^{13}C NMR (68.0 MHz, $CDCl_3$): δ 158.2, 152.4, 144.9, 134.7, 134.6, 134.2, 133.9, 133.6, 133.3, 131.0, 129.6, 129.4, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 127.3, 126.9, 126.9, 126.8, 120.7, 119.5, 118.0, 105.6, 55.3, 50.7, 22.5. ^{31}P NMR (81.0 MHz, $CDCl_3$): δ −12.07. HRMS calculated for $C_{39}H_{33}N_3OP^+$: 590.2356; found: 590.2350. $[\alpha]^{24}_D$ = 180.0 (c = 1.0, $CHCl_3$).

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Supporting Information Available: Spectral data on the compounds in Tables 1−3, and ligands **2d** and **2e**. This material is available free of charge via the Internet at: http://pubs.acs.org.

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