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Catalyst Pendent-Base Effects on Cyclization of Alkynyl Amines

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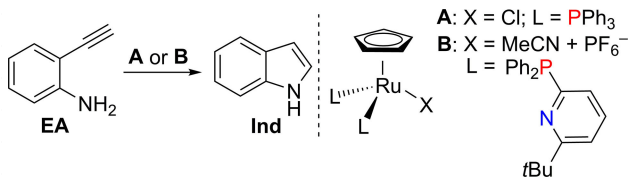
A family of [CpRu(PP)(MeCN)]PF_6 complexes (**2a–e** and **4**) were prepared in which the bis-phosphine ligand contains a pendent tertiary amine in the second-coordination sphere. **2a–e** contain $P^{Ph}{}_2N^{R'}{}_2$ ligands with two amine groups as the pendent base. Complex **4** has the $P^{Ph}{}_2N^{Ph}{}_1$ ligand with only one pendent amine. The catalytic performance of **2a–e** and **4** were assessed in the cyclization of 2-ethynyl aniline and 2-ethynylbenzyl alcohol. It was revealed that the positioning of the pendent amine near the metal active site is essential for high catalyst performance. A comparison of $P^{Ph}{}_2N^{R'}{}_2$ catalysts (**2a–e**) showed minimal difference in performance as a function of pendent amine basicity. Rather, only a threshold basicity – in which the pendent amine was more basic than the substrate – was required for high performance.

Introduction

Metal-ligand cooperative (MLC) catalysts employ ligands that work in concert with the metal to convert substrate to product.[1] The most common subset of these catalysts contain an acidic or basic site on the ligand that shuttle protons in an intramolecular fashion, allowing for high performance in a variety of transformations such as hydrogenation, dehydrogenation, dehydrogenative coupling and hydration reactions. Cyclization of alkynyl amines or alcohols gives *N*- and *O*-heterocycles respectively,[2] which are important motifs in a variety of natural products and pharmaceuticals.[3] Cyclization of the benchmark substrate 2-ethynylaniline (**EA**) to indole (**Ind**) showcases the benefit of MLC catalysts over non-cooperative catalysts (Scheme 1).[2e,f] The non-cooperative catalyst $CpRuCl(PPh_3)_2$ (**A**) achieves complete conversion with short reaction times, but the solvent is limited to pyridine, which is required as an intermolecular base to mediate proton-transfer steps.[2e] The MLC catalyst **B**, with a pendent pyridyl group on the phosphine ligand, gives **Ind** in more typical solvents (i.e. THF) and with lower catalyst loadings (2 mol% **B** vs. 10 mol% for **A**).[2f]



Scheme 1. Cyclization of 2-ethynylaniline (**EA**) with a) a non-cooperative catalyst **A** (10 mol% **A**, pyridine, 90 °C, 25 min, 84% **Ind**)[2e] and b) a cooperative catalyst **B** (2 mol% **B**, THF, 70 °C, 7 h, 87% **Ind**).[2f] [Please use corrected scheme 1 (cdx file attached) in which the structure of **A** is corrected]

The mechanism for alkynyl amine cyclization is expected to follow a similar route to the related intermolecular hydration of alkynes.[1e,2a] The simplified mechanism for cyclization includes reaction of the low-coordinate active catalyst (**I**) with the alkyne to give a vinylidene intermediate (**II**) (Figure 1). Nucleophilic attack at Cα by the substrate amine, and proton shuttling by exogenous or internal base, will give intermediate **III**. Protonolysis of the Ru–C bond by the protonated base releases the product and regenerates **I**. Experimental and computational studies of hydration reactions indicate that the highest-barrier steps include proton-transfer events.[1e,2a] Therefore, it is expected that the pK_a/pK_b and sterics of the acidic/basic site of cyclization catalysts will influence catalyst performance and that these properties offer an additional dimension for ligand tuning.

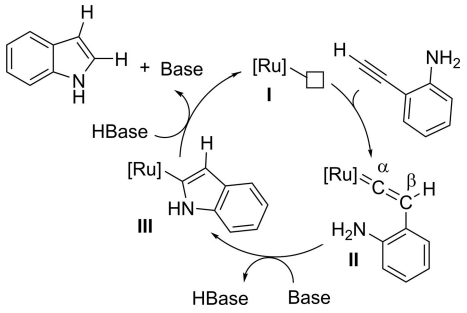


Figure 1. Simplified probable mechanism for cyclization of 2-ethynyl aniline (**EA**) based on studies[1e,2a] of catalytic alkyne hydration. The mechanism is depicted with an exogenous base, but an internal base on the ligand would serve the same role. The box in **I** indicates an open coordination site.

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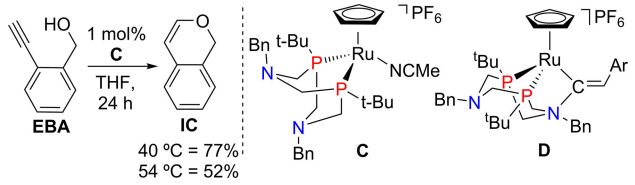
Systematic studies that evaluate the effects of the second-coordination sphere properties on catalyst performance are scarce. Such studies are challenging since many MLC ligand motifs have the acidic or basic site in the primary coordination sphere, where any changes in basicity will inevitably strongly affect the optimal steric/electronic properties for metal-mediated catalytic steps. Several ligands have the acidic or basic site in the secondary-coordination sphere (i.e. the ligand backbone), but in many cases extensive synthetic variation is non-trivial. Conversely, the $P^{R}_{2}N^{R'}_{2}$ (1,5-R′-3,7-R-1,5-diaza-3,7-diphosphacyclooctane) ligand class contains a tertiary amine in the secondary-coordination sphere that is readily synthetically varied (e.g. see ligand in **C**, Scheme 2).[4] In the case of [Ni($P^{R}_{2}N^{R'}_{2}$)$_2$]$^{2+}$ electrocatalysts, tuning the properties of the pendent base significantly altered the rates of H_2 oxidation/production.[4b,5] We have previously demonstrated that these ligands can be used to give MLC catalysts of the type [CpRu($P^{R}_{2}N^{R'}_{2}$)(MeCN)]PF_6, where derivative **C** exhibits similar performance to **B** in the cyclization of 2-ethynylbenzyl alcohol (Scheme 2). Unfortunately, this catalyst easily deactivates at elevated temperatures to give the vinyl ammonium species **D.**[6] Deactivation occurs by nucleophilic attack of the ligand pendent amine, rather than the oxygen nucleophile of the substrate, on Cα of the vinylidine intermediate (i.e. **II**). We hypothesize that a more nucleophilic substrate, such as an amine, will preferentially undergo productive turnover, rather than decomposition. Therefore, we have elected to employ 2-ethynylaniline and related compounds as representative cyclization substrates to elucidate the optimal steric and electronic parameters of the ligand basic site in MLC cyclization catalysts. Thus, we have prepared a group of [CpRu($P^{Ph}_{2}N^{R'}_{2}$)(MeCN)]PF_6 complexes that differ in the substituent on the pendent amine (R′) to systematically compare ligand structure to catalyst performance.

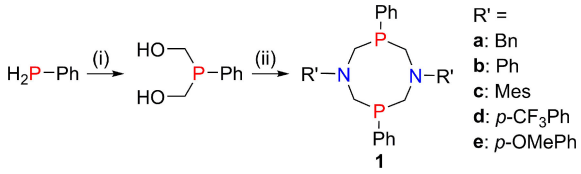


Scheme 2. Cyclization of 2-ethynylbenzyl alcohol (**EBA**) with $P^{R}_{2}N^{R'}_{2}$ catalyst **C**, and catalyst deactivation product **D**.[6a]

Results and Discussion

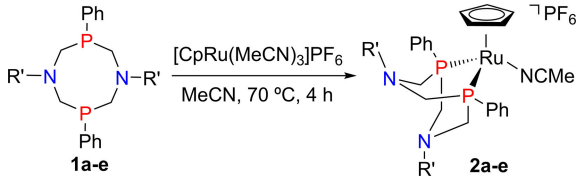
Catalyst Synthesis

A group of five $P^{R}_{2}N^{R'}_{2}$ ligands were synthesized that have the same phosphine substituent (R = Ph), but differ in the amine substituent R′ (Scheme 3). The amine substituents were selected to evaluate both steric (R′: **1a** = Bn, **1b** = Ph, **1c** = Mes) and electronic (R′: **1d** = *p*-CF_3Ph, **1b** = Ph, **1e** = *p*-MeOPh) properties. The ligands were synthesized using modified literature procedures starting from phenyl phosphine, *p*-formaldehyde and the respective amine (Scheme 3).[5,7] Derivative **1c** is a new entry into this ligand family and it was synthesized as a white solid in a poor yield (15%). Cyclization to give the 8-membered ligand is sensitive to the steric bulk of the amine since a related ligand with R′ = *t*Bu was reported to have a similarly low yield (cf. 26%).[8] X-ray quality crystals were obtained for **1d** and **1e** (R′ = *p*-CF_3Ph and *p*-OMePh, respectively). The P1-C1 bond lengths (**1d** = 1.832(2) Å; **1e** = 1.829(1) Å) are similar to that of R′ = Ph ligand **1b** (1.828–1.833 Å).[9] This suggests that the substitution at R′ has minimal long-range influence on the phosphine.



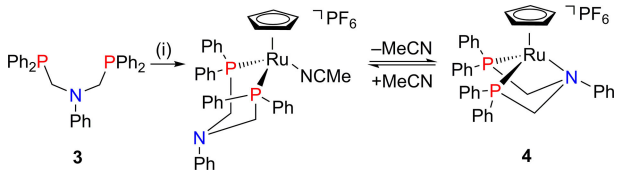
Scheme 3. Synthesis of $P^{Ph}_{2}N^{R'}_{2}$ ligands used in this study. Conditions: (i) *p*-CH_2O, EtOH, 78 °C, 4 h; (ii) dropwise H_2NR', EtOH, 78 °C, 24 h. Yield **1c** = 15%; **1a–b**, **1d–e** are known.[5,7]

Reaction of ligands **1a–e** with [CpRu(NCMe)$_3$]PF_6 in acetonitrile at 70 °C for 4 h produced the known complex **2a**[6a] and new derivatives **2b–e** in good to excellent yields (79–98%; Scheme 4). All of the complexes were characterized by ^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H} NMR and IR spectroscopies and MALDI mass spectrometry. The ^{31}P{^{1}H} NMR signals are all found at ca. 40 ppm for **2a–e**, suggesting the phosphine environment is not significantly influenced by the different R′ substituents of the pendent amine.



Scheme 4. Synthesis of Ru($P^{Ph}_{2}N^{R'}_{2}$) complexes **2a–e** by metalation of $P^{Ph}_{2}N^{R'}_{2}$ ligands (**1a–e**). Complex **2a** was previously reported.[6a]

Single crystals of **2b** were obtained and X-ray crystallography confirmed the expected structure (Figure 2). The Ru–P



Scheme 5. Synthesis of dynamic Ru($P^{Ph}_{2}N^{Ph}_{1}$) complex **4**. Conditions: (i) [CpRu(MeCN)$_3$]PF_6, MeCN, RT, 4 h. Yield **4** = 92%. [please have Scheme 5 appear after Figure 2 in text]

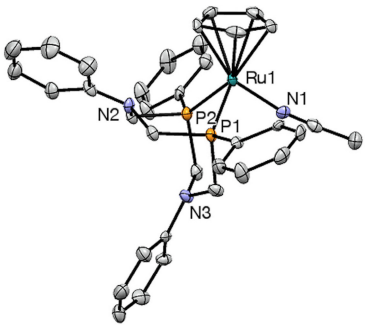


Figure 2. Displacement ellipsoid plot of **2b**. Ellipsoids are at the 50% probability level. Hydrogen atoms and PF_6^- were omitted for clarity.

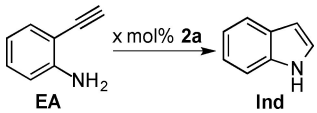
bond lengths are 2.251(2) and 2.260(2) Å (Ru–P1 and Ru–P2, respectively), which are very similar to the analogous values found for **2a**[6a] (2.2589(6) and 2.2605(6) Å). The distances between ruthenium and the Cp carbon atoms are likewise similar to **2a**. This shows that changing the R′ substituent from Bn to Ph (**2a** and **2b**, respectively) has very little impact on the solid-state bonding parameters of the primary-coordination sphere.

While the $P^R_2N^{R'}_2$ ligands contain two pendent basic sites, only the amine proximal to the acetonitrile ligand (i.e. the metal active site) in **2a–e** should participate productively in cyclization catalysis. To evaluate the necessity of the second pendent base, the known[10] bisphosphine ligand $P^{Ph}_2N^{Ph}_1$ (**3**), with one backbone amine, was prepared. Metalation of **3** with $[CpRu(NCMe)_3]PF_6$ gave **4** in high yield (Scheme 5). Instead of the typical yellow/orange solid observed for **2a–e**, complex **4** is a vibrant red solid on solvent removal. This distinct color is also observed following halide abstraction from $CpRuCl(P^R_2N^{R'}_2)$ and $Cp^*RuCl(P^R_2N^{R'}_2)$ complexes in non-coordinating solvent.[6b,11] The color in these reactions was presumed to be a consequence of ligand coordination in a κ^3-PPN mode. The appearance of the $^{31}P\{^1H\}$ NMR spectrum of isolated **4** in non-coordinating CD_2Cl_2 is highly dependent on the presence of excess acetonitrile. Rigorous removal of CH_3CN gives a spectrum with broad signals between 48.9–56.0 ppm and a minor (ca. 15%) sharp singlet at 34.3 ppm. Cooling exhibited some sharpening of the broad signals, but the sample precipitated before the signals could be fully resolved. When **4** is dissolved in CD_3CN, only the sharp singlet at 34.6 ppm is observed, which is similar to the analogous signals in **2a–e**. Additionally, dissolution in CD_3CN causes a color change from red to orange and all of the ^1H NMR signals are sharper than in CD_2Cl_2 (Figure S20 vs. S17). Therefore, this indicates that acetonitrile coordinates to **4** and the $P^{Ph}_2N^{Ph}_1$ ligand changes its coordination mode to κ^2-PP.

Catalytic Studies

The benchmark substrate 2-ethynylaniline (**EA**) was employed to optimize catalytic cyclization conditions with **2a** (Table 1). Very little difference in conversion was observed for cyclization

Table 1. Catalysis of 2-Ethynylaniline (**EA**) using **2a**.



EA **Ind**

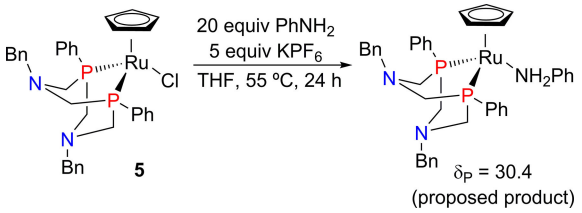
Entry	Catalyst [mol%]	Solvent	Temp [°C]	Time [h]	Yield **Ind**[a] [%]
1	2	Acetone	40	1	13
2	2	Dioxane	40	1	8
3	2	THF	40	1	12
4	2	EtOAc	40	1	13
5	2	Anisole	40	1	10
6	2	DMF	40	1	8
7	2	DMA	40	1	15
8	2	THF	40	16	30
9	2	THF	40	24	73
10	2	THF	55	24	>99
11	2	THF	55	6	>99
12	1	THF	55	6	91
13	0.1	THF	55	24	37
14[b]	1	Me-THF	70	2	>99

[a] All yields are in situ values, determined by ^1H NMR spectroscopy by quantification of **EA** and **Ind** relative to the internal standard, dimethyl terephthalate. Reactions were conducted in proteo solvents, which were removed under vacuum and the residues redissolved in $CDCl_3$ for NMR analysis. [b] Yield of **Ind** was determined by calibrated GC-FID and the yield was determined relative to the internal standard, tetralin.

conducted at 40 °C in a range of solvents (Table 1, Entry 1–7). Minor amounts of side products were observed in carbonyl-containing solvents, thus THF was selected as the optimal solvent for ongoing studies. Extending the reaction time from 1 to 24 h increased the yield of indole (**Ind**) from 12 to 73% (Entry 9). The temperature was increased to 55 °C and complete conversion was observed at 6 h (Table 1, Entry 11). Lowering the catalyst loading to 1 mol% gave 91% **Ind** after 6 h and >99% conversion was reached after 24 h. Further reduction in catalyst loading to 0.1 mol% gave a cyclization yield of 37%, which corresponds to a turnover number of 370 (Entry 13). Increasing the temperature further to 70 °C resulted in quantitative conversion to **Ind** with 1 mol% **2a** within 2 h (Table 1, Entry 14).

The high yield of **Ind** at elevated temperatures suggests that catalyst **2a** preferentially undergoes productive catalysis rather than deactivation, such as to a vinyl ammonium complex (i.e. an analog of **D**). To confirm this, cyclization of **EA** was monitored by $^{31}P\{^1H\}$ NMR spectroscopy under catalytic conditions (1.5 mol% of **2a** in THF at 50 °C). Throughout the experiment (up to 2 h), no new signal appeared in the downfield region (55–75 ppm) where **D** and related vinyl ammonium species were previously[6] observed (Figure S26). At 2 h, the reaction composition is comprised of pre-catalyst **2a** (85%) and a new minor species (ca. 10%) observed as a singlet at 30.6 ppm. This signal is in a similar location to a known benzylamine adduct formed with **2a** that has $\delta_P = 29.2$.[12] With the goal in mind of identifying the structure of this minor resting state species, the chloro complex $CpRuCl(P^{Ph}_2N^{Bn}_2)$, **5**, was synthesized and characterized by ^1H, $^{31}P\{^1H\}$, $^{13}C\{^1H\}$ NMR and IR spectroscopies, MALDI mass spectrometry and X-ray crystallography. Complex **5** was reacted with KPF_6 in THF in the

presence of aniline (Scheme 6). Only one new product signal was observed by $^{31}P\{^{1}H\}$ spectroscopy and it is a singlet at



Scheme 6. Stoichiometric reaction of **5** with aniline.

30.4 ppm. The close similarity of this shift to that of the minor species observed under catalytic conditions with **2a**, suggests that the latter is a Ru-NH_2Ar adduct. Evidence of a deactivated vinyl ammonium compound (analogous to **D**), or other deactivation species, are not observed. Rather, the catalyst predominantly exists as pre-catalyst and an amine-adduct, which are both off-cycle resting states.

With optimal conditions identified, a screen of catalysts **2a–e** and **4** was undertaken. Cyclization of **EA** was conducted in THF, at 55 °C with 0.1, 0.5, 1, and 3 mol% catalyst loadings (Figure 3). Conversion to **Ind** was quantified by GC-FID analysis

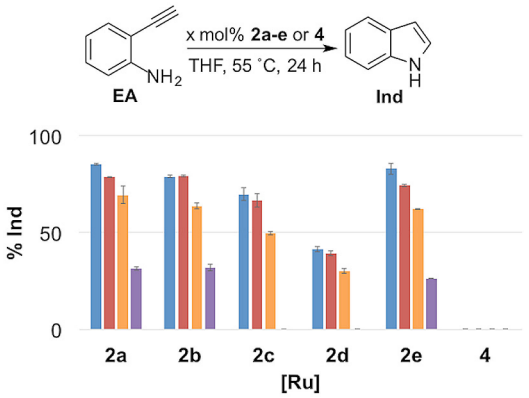


Figure 3. Cyclization yields of 2-ethynylaniline (**EA**) to indole (**Ind**) in THF at 55 °C after 24 h with catalysts **2a–e** and **4** at 3 mol% (blue), 1 mol% (red), 0.5 mol% (orange) and 0.1 mol% (purple).

of reaction solutions after a 24 h reaction time. All of the complexes were active cyclization catalysts, except the $P^{Ph}_2N^{Ph}_1$ complex **4**. Even at 3 mol% **4** shows no conversion, while its closest $P^{R}_2N^{R'}_2$ comparator **2b** gives 31% **Ind** at only 0.1 mol% loading. This corresponds to a higher activity of **2b** over **4** by at least an order of magnitude. Thus, the second metallacycle ring and pendent amine is critical for high catalyst activity. In the case of $[Ni(P^{R}_2N^{R'}_2)_2]^{2+}$ electrocatalysts, steric repulsions between the two metallacycle rings enforced the close positioning of one pendent base to the metal center.[4b,c] This positioning was deemed essential to achieve high catalytic rates.[13] A similar importance of pendent amine positioning is likely at play here and is the reason for the superior performance of $P^{Ph}_2N^{R'}_2$ catalysts **2a–e** over $P^{Ph}_2N^{Ph}_1$ catalyst **4**.

A comparison of $P^{Ph}_2N^{R'}_2$ catalysts **2a–e** with a 0.5 mol% catalyst loading (Figure 3, orange bars) reveals that the order of activity in **EA** cyclization follows **2a**≈**2b**≈**2e**>**2c**>**2d** (R′ = Bn≈Ph≈*p*-OMePh>Mes>*p*-CF_3Ph). The yield of **Ind** is ca. 15% lower with **2c** relative to **2b** (R′ = Mes and Ph, respectively). Thus, the reaction is tolerant of the increase in steric bulk at the pendent amine despite the likely steric hindrance during proton-transfer steps. Also notable from the performance trend is the poor conversion with **2d**, which has the least basic pendent amine. A comparison of ammonium pK_a values gives a rough guide to relative acidities of the substrates, possible intermediates and the protonated pendent amine of the ligand. None of ligands in **2a–e** have a pendent amine that is sufficiently basic to deprotonate aniline. Therefore, it is most likely that the ligand deprotonates the substrate after, or in concert with, nucleophilic attack on the vinylidene intermediate **II** (see Figure 1). The pendent amine of **2d** is less basic than the substrate **EA** (pK_a: $[p\text{-}CF_3C_6H_4NH_3]^+ = 8.16$, $[PhNH_3]^+ = 10.6$).[14] In contrast, catalysts **2a**,**b**,**e** are all of similar or higher basicity (pK_a: $[p\text{-}OMeC_6H_4NH_3]^+ = 12.05$, $[BnNH_3]^+ = 16.76$, $[PhNH_3]^+ = 10.6$)[14] and these three catalysts have equivalent activity. We hypothesize that, to achieve high activity, the basicity of the ligand need only be above a threshold defined by the basicity of the substrate.

A similar catalyst performance study for **2a–e** and **4** was conducted with **EBA** as the substrate (Figure 4). All of the catalysts **2a–e** showed lower performance than in cyclization of **EA**; the highest yield of isochromene (**IC**) was 32%, which was achieved with 3 mol% **2a**. The trend in activity of the $P^{Ph}_2N^{R'}_2$ catalysts followed a very similar trend to that found with **EA** where **2a**≈**2b**≈**2e**>**2d**>**2c** (R′ = Bn≈Ph≈*p*-OMePh>*p*-CF_3Ph>Mes). In all cases the pendent amine is more basic than the substrate alcohol functionality,[15] indicating that all catalysts should be equally competent at deprotonation of an intermediate formed after nucleophilic attack of the alcohol on the vinylidene. We hypothesize that the low yields of **IC** are due to competing formation of deactivation compounds, including those similar to **D**, as was confirmed previously in the

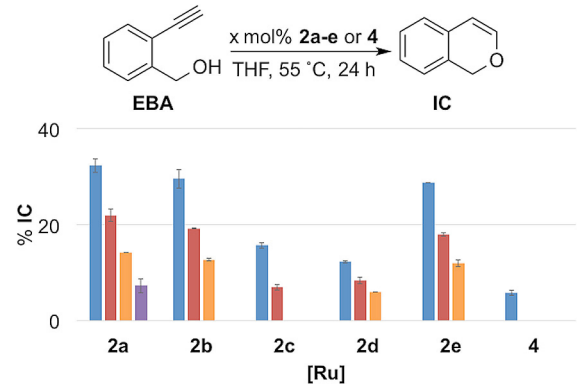


Figure 4. Cyclization yields of 2-ethynylbenzyl alcohol (**EBA**) to isochromene (**IC**) in THF at 55 °C after 24 h with catalysts **2a–e** and **4** at 3 mol% (blue), 1 mol% (red), 0.5 mol% (orange) and 0.1 mol% (purple).

cyclization of **EBA** with catalyst **C**. To confirm that deactivation, rather than low catalyst initiation, limits activity, cyclization of **EBA** was conducted with 1 mol% **2a–e** at 70 °C. Complexes **2a–c,e** gave <5% **IC** with no increase in product after 1 h, which is lower than the yields observed at 55 °C. Catalyst **2d** was slightly improved at the higher temperature, but the yield of **IC** only reached 15%. We had previously hypothesized that a sterically hindered or a poorly nucleophilic pendent amine would be less susceptible to vinyl ammonium deactivation. However, catalysts **2c** and **2d** (R′ = Mes and *p*-CF_3Ph, respectively), which were designed with these characteristics in mind, showed the lowest activity of **2a–e**. Therefore, preventing deactivation through steric or electronic tuning of the ligand was insufficient to effectively cyclize **EBA**.

The conversion of **EA** to **Ind** was monitored over time with 2 mol% **2a,b,d** at 55 °C (Figure 5). In the above studies it was

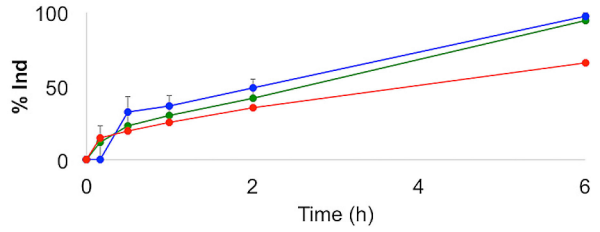


Figure 5. Cyclization of 2-ethynylaniline (**EA**) under optimal conditions (2 mol% [Ru], Me-THF, 55 °C) monitored over time. [Ru] = **2a** (R′ = Bn, green), **2b** (R′ = Ph, blue), **2d** (R′ = *p*-CF_3Ph, red).

observed that catalysts **2a** and **2b** (R′ = Bn and Ph) have similar 24 h conversion. Here it is clear that their rates are very similar and that they both reach complete conversion to **Ind** within 6 h. The activity is superior to the previously reported catalysts **A** (Scheme 1) that requires higher catalyst loading (10 mol% **A**) and the conditions are milder than those used with catalysts **A** and **B** that operate at higher temperatures (**A**: 90 °C; **B**: 70 °C).[2e,f] Notably, heating 1 mol% **2a** to 70 °C gives complete conversion to **Ind** within 2 h (Table 1, Entry 14), which is more rapid than the MLC catalyst **B** (2 mol%). At short reaction times (<2 h) catalyst **2d** (R′ = *p*-CF_3Ph) also has similar performance, but shows lower conversion than **2a** and **2b** at longer times.

We proposed above that, for amine substrates, the pendent amine of the $P^{Ph}_2N^{R'}_2$ catalysts must only be more basic than the substrate to give productive turnover. To probe this hypothesis, the cyclization of three additional substrates – 2-ethynyl-4-methoxyaniline (**EA-OMe**), 2-ethynyl-4-fluoroaniline (**EA-F**) and 2-ethynylbenzamide (**EAM**) – was conducted (Figure 6). In all cases, 2 mol% [Ru] was employed and reactions were conducted in Me-THF at 55 or 70 °C. Substrate **EA-OMe** was effectively cyclized by both catalysts **2b** and **2e** (R′ = Ph and *p*-OMePh, respectively) within 48 h at 55 °C. Catalyst **2b** is estimated to be similar or slightly less basic than the substrate (pK_a, $[PhNH_3]^+ = 10.6$, $[PhNMe_2H]^+ = 12.30$: $[p\text{-}OMeC_6H_4NH_3]^+ = 12.05$),[14] which could account for the slightly slower rate of **2b** relative to **2e**. The less basic aniline substrate **EA-F** is cyclized to ca. 85% with both **2b** and **2d** (R′ = Ph and *p*-CF_3Ph,

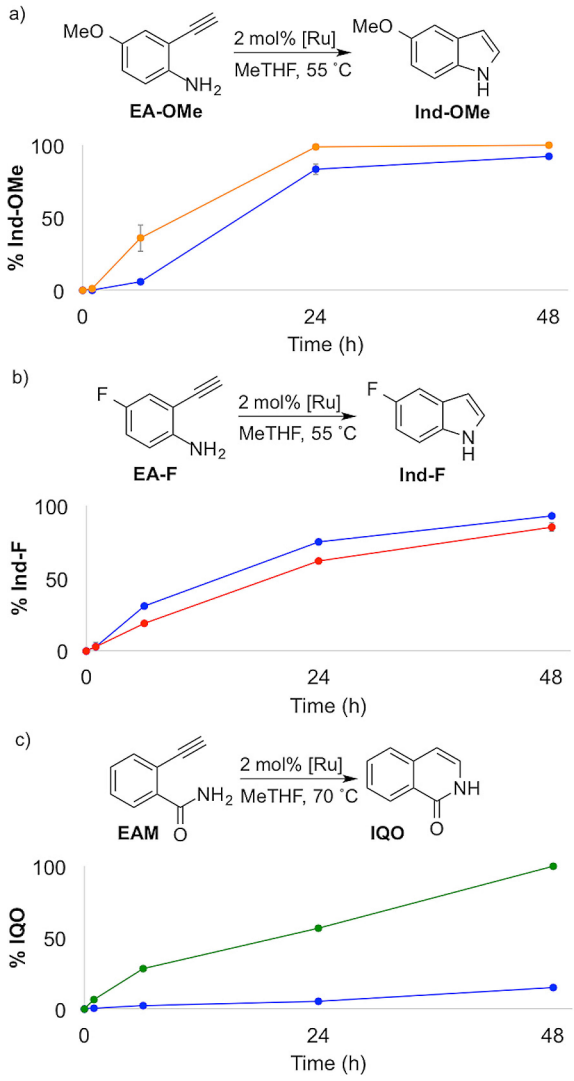


Figure 6. Cyclization conversion over time with 2 mol% [Ru] in Me-THF of: a) 2-ethynyl-4-methoxyaniline (**EA-OMe**) at 55 °C with **2b** (R′ = Ph, blue) and **2e** (R′ = *p*-MeOPh, orange); b) 2-ethynyl-4-fluoroaniline (**EA-F**) at 55 °C with **2b** (R′ = Ph, blue) and **2d** (R′ = *p*-CF_3Ph, red); and c) 2-ethynylbenzylamide (**EAM**) at 70 °C with **2a** (R′ = Bn, green) and **2b** (R′ = Ph, blue). In all cases conversion was quantified by ^{1}H NMR spectroscopy.

respectively) within 48 h at 55 °C. The **EA-F** conversion curves for **2b** and **2d** are nearly indistinguishable, which is in contrast to cyclization of **EA** with these two catalysts where **2b** was superior to **2d** (Figure 5). This supports the hypothesis that a threshold basicity of the pendent amine is important for catalyst performance. Cyclization of amide substrate **EAM** was attempted with **2a** and **2b** (R′ = Bn and Ph, respectively) at 55 °C, but <15% 1(2H)-isoquinolinone (**IQO**) was observed after 48 h. At 70 °C, **2a** gave complete conversion to **IQO** by 48 h, but conversion with **2b** reached only 15%. The poor performance of **2b** is surprising since the pendent amine in this catalyst is significantly more basic than **EAM** (pK_a: $[PhNH_3]^+ = 10.6$, $[PhCONH_3]^+ = 3.7$).[14,16] The nucleophilicity of the amide functionality in **EAM** is expected to be lower than that of the aniline substrates. Thus, the lower performance of **2b** may be a consequence of competitive deactivation through a vinyl

ammonium species of type **D**. Alternatively, the mechanistic pathway, and/or rate determining step, may be different for this substrate. Further mechanistic analysis is required to fully understand the limitations of **2b** as compared to **2a** when extending the scope beyond aniline-type substrates.

Conclusions

We have synthesized a group of $[CpRu(P^{Ph}{}_2N^{R'}{}_2)(NCMe)]PF_6$ complexes (**2a**–**e**) that differ in the steric and electronic properties of the pendent amine. These complexes were tested as catalysts in the cyclization of alkynyl amines and alcohol to give *N*- and *O*-heterocycles, respectively. This class of catalyst showed much higher activity toward aniline-type, as compared to alcohol-type, substrates. Indeed, the optimal catalysts (**2a**,**b**,**e**) generate indole under milder conditions and shorter reaction times than previously reported catalysts. The superior performance of the $P^{Ph}{}_2N^{R'}{}_2$ catalysts (**2a-e**) over the $P^{Ph}{}_2N^{Ph}{}_1$ catalyst **4**, suggests that a positioned pendent amine is essential to achieve high performance. Catalyst comparison in the cyclization of 2-ethynylaniline derivatives revealed that the yield and rates are very similar for R′ = Bn, Ph, *p*-OMePh derivatives **2a**, **2b** and **2e**, respectively. The less basic catalyst **2d** (R′ = *p*-CF_3Ph) showed inferior performance, except with the relatively low-basicity substrate 2-ethynyl-4-fluoroaniline where it had comparable performance to **2b**. This suggests that to achieve high catalyst performance, the ligand pendent base should be similar or more basic than the substrate amine of aniline substrates. Proton shuttling during catalysis is somewhat tolerant of steric bulk at the pendent amine since catalyst **2c** (R′ = Mes) shows only a minor reduction in activity as compared to **2b** (R′ = Ph) in the cyclization of 2-ethynyl aniline. Surprisingly, only catalyst **2a** was competent in the cyclization of 2-ethynylamide, indicating that there are still important aspects to the mechanism that are yet to be elucidated. We are currently extending this investigation to study the mechanism and the role of the primary-coordination sphere (i.e. the phosphine substituents, R) on catalyst performance.

Experimental Section

All air and water-sensitive reactions were manipulated under N_2 using standard Schlenk or glovebox techniques unless otherwise stated. All glassware was oven dried prior to use. $BnNH_2$ (>98%), aniline (>99%), mesitylene amine (98%), and triphenylphosphine oxide (99%) were obtained from Alfa Aesar. Phenylphosphine (99%) was obtained from Strem. 4-Trifluoroaniline (99%), tetrahydronaphthalene (99%), 2-ethynylaniline (98%), and 2-methyltetrahydrofuran (Me-THF) (>99% anhydrous) were obtained from Sigma-Aldrich. 4-methoxyaniline (98%) was obtained from Oakwood Chemicals. Chloroform-d_1 (99.8%), and dichloromethane-d_2 (99.8%) were obtained from Cambridge Isotope Laboratories. Paraformaldehyde was prepared by filtration of formaldehyde (37% by weight solution in water with 10–15% methanol) to remove any solids, removing methanol and water under vacuum until a white gel is produced. $[Ru(Cp)(MeCN)_3]PF_6$,[17] $P^{Ph}{}_2N^{R'}{}_2$ (**1a**,**b**,**d**,**e**),[5,7] and $[Ru(Cp)(P^{Ph}{}_2N^{Bn}{}_2)(NCMe)]PF_6$ (**2a**)[6a] were synthesized following literature procedures. Substrates 2-ethynyl-4-methoxyaniline (**EA-OMe**), 2-ethynyl-4-fluoroaniline (**EA-F**), and 2-ethynylamide (**EAM**) were synthesized following literature procedures.[2d,18] Dry and degassed tetrahydrofuran (THF), diethyl ether, toluene, dichloromethane (DCM), hexanes, dimethylformamide (DMF), dioxane and acetonitrile (MeCN) were obtained from an Innovative Technology 400-5 Solvent Purification System and stored under N_2. These dry and degassed solvents, except for MeCN, were stored over 4 Å molecular sieves (Fluka and activated at 150 °C under vacuum for over 12 h). Acetone was dried with Cs_2CO_3 and degassed by bubbling with N_2. Tetrahydrofuran was distilled from CaH_2 and degassed by bubbling N_2. Absolute ethanol was deoxygenated by bubbling with N_2. *N*,*N*-Dimethylacetamide and chloroform-d_1 were dried with 4 Å molecular sieves and degassed by bubbling with N_2. Benzylamine was dried with NaOH, distilled under vacuum and stored under N_2. All other chemicals were used as received.

Charge-transfer Matrix Assisted Laser Desorption/Ionization (MALDI) mass spectrometry data were collected on an AB Sciex 5800 TOF/TOF mass spectrometer using pyrene as the matrix in a 20:1 molar ratio to metal complex. Samples were spotted on the target plate as solutions in DCM. All NMR spectra were recorded on either a Varian Inova 400 or 600 MHz, a Varian Mercury 400 MHz or Bruker 400 MHz NMR spectrometer. ^1H and $^{13}C\{^1H\}$ spectra acquired in $CDCl_3$ were referenced internally against the residual solvent signal ($CHCl_3$) to TMS at 0 ppm. ^{31}P spectra were referenced externally to 85% phosphoric acid at 0.00 ppm. Infrared spectra were collected on solid samples using a PerkinElmer UATR TWO FTIR spectrometer. Elemental analysis of **5** was performed by Canadian Microanalytical Service Ltd. in Delta, BC. Satisfactory elemental analyses of **2b**–**e** and **4** were not obtained due to persistent minor, but variable, amounts of MeCN in the samples. Quantification of catalytic conversion of **EBA** or **EA** was achieved using an Agilent 7890a gas chromatography with a flame ionization detector (GC-FID), fitted with a HP-5 column. Calibration curves for **EA**, **Ind**, **EBA**, **IC** were prepared to determine the response factors. The amount of each species was quantified, relative to the internal standard (tetralin), using area counts corrected with the response factors.

General Procedure for the Synthesis of $P^{Ph}{}_2N^{R'}{}_2$ Ligands (1a–e): A modified literature procedure[7a] was followed. These reactions were manipulated under argon. Phenylphosphine (1.00 g, 9.08 mmol) was added to 100 mL Schlenk flask in a glovebox. On the Schlenk line, a 2-neck 500 mL Schlenk flask containing: a stir bar, freshly made (≤1 week) *p*-formaldehyde (3 g, 0.1 mol), and 200 mL EtOH, was fit with a reflux condenser under argon. Degassed EtOH (50 mL) was added via cannula to the 100 mL Schlenk with the primary phosphine. The primary phosphine solution was then added to the 500 mL Schlenk via cannula at room temperature. Degassed EtOH (50 mL) was added via cannula to the 100 mL Schlenk to rinse the flask and this was added to the 500 mL reaction flask. The reaction flask was heated to reflux for 4 h after which an aliquot was transferred to a degassed NMR tube by syringe. The solution was analyzed by $^{31}P\{^1H\}$ NMR spectroscopy (unlocked) to determine if any $PhPH_2$ (δ = ca. −120) remained. Once the $PhPH_2$ was consumed (ca. 4 h), the primary amine (1.05 eq) was added to the solution (still heated to 70 °C) dropwise by syringe at a rate of ca. 1 drop/10 seconds. Liquid amines (RNH_2: R = Bn, Ph, Mes, *p*-CF_3Ph) were added neat and solid amines (RNH_2: R = *p*-OMePh) were added as solutions in EtOH (25 mM). White precipitate was observed on addition of each drop, but did not persist. The reaction was left to stir at 70 °C for 24 h and then cooled to room temperature. Reactions giving ligands **1a**–**e** afforded a white precipitate, which was isolated by filtration through a filter frit and washed with acetonitrile (3×5 mL). Reactions to give ligands **1d**–**e** did not give significant precipitate on cooling to room temperature. In these cases, the ligand (**1d**–**e**) was precipitated after addition of acetonitrile (15 mL) and cooling

to −35 °C. The ligands **1 d–e** were isolated through decanting the mother liquor and washing the solid with cold acetonitrile (5-10 mL).

$P^{Ph}_2N^{Bn}_2$ (1 a): Yield = 83 %. ^{1}H and $^{31}P\{^1H\}$ NMR spectra matched literature values.[7a]

$P^{Ph}_2N^{Ph}_2$ (1 b): Yield = 87 %. ^{1}H and $^{31}P\{^1H\}$ NMR spectra matched literature values.[7b]

$P^{Ph}_2N^{Mes}_2$ (1 c) Yield = 15 %. ^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.34–7.27 (m, Ph-*H*, 3H), 7.27–7.15 (m, Ph-*H*, 7H), 6.88–6.84 (m, Ph-*H*, 1H), 6.84–6.82 (m, Ph-*H*, 2H), 6.78–6.73 (m, Ph-*H*, 1H), 4.54–4.46 (m, PCH_2N, 2H), 4.12–4.05 (m, PCH_2N, 2H), 3.84–3.77 (m, PCH_2N, 2H), 3.69–3.61 (m, PCH_2N, 2H), 2.67 (s, CH_3, 3H), 2.39 (s, CH_3, 6H), 2.20 (m, CH_3, 9H). $^{31}P\{^1H\}$ NMR (243 MHz, CD_2Cl_2): δ −22.4 (s, $P^{Ph}_2N^{Mes}_2$), −27.0 (s, $P^{Ph}_2N^{Mes}_2$). $^{13}C\{^1H\}$ NMR (151.5 MHz, CD_2Cl_2): δ 150.4–150.3 (m, C_{Ar}-N), 137.4 (C_{Ar}), 136.7 (C_{Ar}), 136.5 (C_{Ar}), 135.5 (C_{Ar}), 135.3 (C_{Ar}), 132.5-132.2 (C_{Ar}), 132.1 (d, $^2J_{C\text{-}P}$ = 16.1 Hz, C_{Ar}), 131.6 (d, $^2J_{C\text{-}P}$ = 16.1 Hz, C_{Ar}), 130.2 (C_{Ar}), 130.0 (C_{Ar}), 129.5 (C_{Ar}), 128.8–128.6 (C_{Ar}), 128.5 (d, $^3J_{C\text{-}P}$ = 6.1 Hz, C_{Ar}), 128.3 (d, $^3J_{C\text{-}P}$ = 6.1 Hz, C_{Ar}), 62.3–62.0 (m, PCH_2N), 58.2–57.9 (m, PCH_2N), 20.9–20.7 (CH_3), 20.0 (CH_3), 19.9 (CH_3), 19.3 (CH_3). MALDI MS (pyrene matrix): Calc. m/z 538.3 $[C_{34}H_{39}N_2P_2]^+$, Obs. m/z 638.3.

$P^{Ph}_2N^{PhCF3}_2$ (1 d): Yield = 75 %. ^{1}H and $^{31}P\{^1H\}$ NMR spectra matched literature values.[5] X-ray quality crystals formed from a chilled (−35 °C) solution of **1 d** in MeCN.

$P^{Ph}_2N^{PhOMe}_2$ (1 e): Yield = 90 %. ^{1}H and $^{31}P\{^1H\}$ NMR spectra matched literature values.[5] X-ray quality crystals formed from a chilled (−35 °C) solution of **1 e** in MeCN.

Synthesis of $P^{Ph}_2N^{Ph}_1$ Ligand (3): A modified procedure of the literature reported method[19] was followed. The reaction was manipulated under argon. Diphenylphosphine (1.05 g, 5.64 mmol) was added to 100 mL Schlenk flask in a glovebox. On the Schlenk line, a 2-neck 500 mL Schlenk flask containing: a stir bar, freshly made (≤ 1 week) *p*-formaldehyde (3.00 g, 0.100 mol, 18 equiv.), and 200 mL EtOH was fit with a reflux condenser under argon. Degassed EtOH (50 mL) was added via cannula to the 100 mL Schlenk with the primary phosphine. The primary phosphine solution was then added to the 500 mL Schlenk via cannula at room temperature. Degassed EtOH (50 mL) was added via cannula to the 100 mL Schlenk to rinse the flask and this was added to the 500 mL reaction flask. The reaction flask was heated under reflux for 4 h after which an aliquot was transferred to a degassed NMR tube by syringe. The solution was analyzed by $^{31}P\{^1H\}$ NMR spectroscopy (unlocked) to determine if any $PhPH_2$ remained. Once the $PhPH_2$ was consumed (4 h), the primary amine (1.05 equiv) was added neat dropwise by syringe at a rate of ca. 1 drop/10 seconds, while the reaction remained at 70 °C. White precipitate was observed on addition of each drop but did not persist. The reaction was left to stir at 70 °C for 24 h and then cooled to room temperature. The reaction afforded a white precipitate, which was isolated by filtration through a filter frit and washed with acetonitrile (3 × 5 mL). Yield = 95 %. ^{1}H and $^{31}P\{^1H\}$ NMR spectra matched literature values.

General Procedure for the Synthesis of $Ru(P^{Ph}_2N^{R'}_2)$ (2 a-e) and $Ru(P^{Ph}_2N^{Ph}_1)$ (4) Complexes: To a 100 mL Schlenk flask with a stir bar, $[CpRu(NCMe)_3]PF_6$ (0.100-0.120 mmol), ligand $P^{Ph}_2N^{R'}_2$ or $P^{Ph}_2N^{R'}_1$ (0.105-1.26 mmol, 1.05 equiv.) and acetonitrile (20 mL) was added. The flask was heated to 65 °C for 4 hours with stirring. The solvent was removed under vacuum and the remaining solid was triturated with pentane (3 × 2 mL). Acetonitrile (2 mL) was added and the resulting suspension was filtered. The solid was washed with acetonitrile until the washings were colourless. The solvent of the filtrate was removed under vacuum to produce a solid that was washed with toluene (3 x 2 mL) and diethyl ether (5 mL). The product was dried under vacuum to produce clean product. Reprecipitation of **2 a-e** from acetonitrile gave minor by-products, as judged by ^{1}H NMR spectroscopy, that are assigned to κ^3-(PPN) derivatives. To avoid mixtures, purification by reprecipitation was avoided for **2 a-e**.

$[Ru(Cp)(P^{Ph}_2N^{Bn}_2)(NCMe)]PF_6$ (2 a): ^{1}H and $^{31}P\{^1H\}$ NMR spectra matched literature values in $CDCl_3$.[6a] Spectral data in CD_2Cl_2 is provided here to ease comparisons between the various catalysts **2 a-e**. ^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.69–7.60 (m Ph-*H*, 4H), 7.56–7.48 (m, Ph-*H*, 6H), 7.41–7.16 (m, Ph-*H*, 10H), 4.78 (s, Cp-*H*, 5H), 3.89 (s, PhCH_2N, 2H), 3.71 (s, PhCH_2N, 2H), 3.29–3.17 (m, PCH_2N, 4H), 3.04–2.96 (m, PCH_2N, 2H), 2.77–2.70 (m, PCH_2N, 2H), 2.22 (s, NCCH_3, 3H). $^{31}P\{^1H\}$ NMR (243 MHz, CD_2Cl_2): δ 38.7 (s, Ru*P*), −144.4 (sept, $^1J_{P\text{-}F}$ = 712 Hz, PF_6^-).

$[Ru(Cp)(P^{Ph}_2N^{Ph}_2)(NCMe)]PF_6$ (2 b): Yield = 89 %. ^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.93–7.87 (m, Ph-*H*, 4H), 7.69–7.61 (m, Ph-*H*, 6H), 7.29 (dd, $^3J_{H\text{-}H}$ = 8.0 Hz, $^3J_{H\text{-}H}$ = 8.0 Hz, Ph-*H*, 2H), 7.25 (dd, $^3J_{H\text{-}H}$ = 8.0 Hz, $^3J_{H\text{-}H}$ = 8.0 Hz, Ph-*H*, 2H), 7.02–6.95 (m, Ph-*H*, 3H), 6.88–6.83 (m, Ph-*H*, 3H), 4.79 (s, Cp-*H*, 5H), 4.25–4.13 (m, PCH_2N, 4H), 4.00–3.91 (m, PCH_2N, 2H), 3.63–3.57 (m, PCH_2N, 2H), 2.28 (s, NCCH_3, 3H). $^{31}P\{^1H\}$ NMR (243 MHz, CD_2Cl_2): δ 39.7 (s, Ru*P*), −144.4 (sept, $^1J_{P\text{-}F}$ = 712 Hz, PF_6^-). $^{13}C\{^1H\}$ NMR (151.5 MHz, CD_2Cl_2): δ 152.5 (t, $^3J_{C\text{-}P}$ = 8 Hz, C_{Ar} -N), 151.2 (t, $^3J_{C\text{-}P}$ = 6 Hz, $^3J_{C\text{-}P}$ = 6 Hz, C_{Ar} -N), 133.6 (dd, $^1J_{C\text{-}P}$ = 19.7 Hz, $^3J_{C\text{-}P}$ = 19.7 Hz, C_{Ar} -P), 132.3-132.0 (C_{Ar}), 130.3-129.8 (C_{Ar}), 128.8 (*C*N), 122.4 (C_{Ar}), 120.9 (C_{Ar}), 118.5 (C_{Ar}), 116.8 (C_{Ar}), 82.3 (C_{Cp}), 52.8 (dd, $^1J_{C\text{-}P}$ = 17 Hz, $^3J_{C\text{-}P}$ = 17 Hz, PCH_2N), 51.1 (dd, $^1J_{C\text{-}P}$ = 22 Hz, $^3J_{C\text{-}P}$ = 22 Hz, PCH_2N), 4.7 (CH_3). MALDI MS (pyrene matrix): Calc. m/z 621.1 $[Ru(Cp)(P^{Ph}_2N^{Ph}_2)]^+$, Obs. m/z 621.1. X-ray quality crystals were formed from a concentrated solution of **2 b** in DCM to which was added toluene until the solution was slight cloudy and the solution was chilled (−35 °C).

$[Ru(Cp)(P^{Ph}_2N^{Mes}_2)(NCMe)]PF_6$ (2 c): Yield = 79 %. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.92–7.77 (m, C_{Ar}-*H*, 4H), 7.68–7.54 (m, C_{Ar}-*H*, 6H), 7.35–7.24 (m, C_{Ar}-*H*, 2H), 6.98–6.84 (m, C_{Ar}-*H*, 2H), 5.04 (s, Cp-*H*, 5H), 4.74–4.64 (m, PCH_2N, 2H), 3.80–3.63 (m, PCH_2N, 4H), 3.40–3.30 (m, PCH_2N, 2H), 2.44 (s, CH_3, 3H), . $^{31}P\{^1H\}$ NMR (243 MHz, CD_2Cl_2): δ 37.8 (s, Ru*P*), −144.4 (sept, $^1J_{P\text{-}F}$ = 712 Hz, PF_6^-). $^{13}C\{^1H\}$ NMR (151.5 MHz, CD_2Cl_2): δ 146.7 (t, $^3J_{C\text{-}P}$ = 10.1 Hz, C_{Ar}-N), 145.1 (C_{Ar}-N), 137.0 (C_{Ar}), 135.7, (C_{Ar}), 133.6 (t, $^1J_{C\text{-}P}$ = 34.2 Hz, $^3J_{C\text{-}P}$ = 34.2 Hz, C_{Ar}), 132.0 (d, $^3J_{C\text{-}P}$ = 9.8 Hz, C_{Ar}), 132.0 (d, $^2J_{C\text{-}P}$ = 9.8 Hz, C_{Ar}-P), 131.8 (C_{Ar}), 130.9–130.2 (C_{Ar}), 129.6 (d, $^3J_{C\text{-}P}$ = 8.2 Hz, C_{Ar}), 129.5 (d, $^3J_{C\text{-}P}$ = 8.2 Hz, C_{Ar}), 129.4 (*C*N), 83.1 (C_{Cp}), 52.6 (dd, $^1J_{C\text{-}P}$ = 15.7 Hz, $^3J_{C\text{-}P}$ = 15.7 Hz, PCH_2N), 51.8 (dd, $^1J_{C\text{-}P}$ = 22.2 Hz, $^3J_{C\text{-}P}$ = 22.2 Hz, PCH_2N), 22.5 (PhCH_3), 21.3–19.8 (PhCH_3), 5.4 (CH_3). MALDI MS (pyrene matrix): Calc. m/z 705.2 $[Ru(Cp)(P^{Ph}_2N^{Mes}_2)]^+$, Obs. m/z 705.2.

$[Ru(Cp)(P^{Ph}_2N^{PhCF3}_2)(NCMe)]PF_6$ (2 d): Yield = 98 %. ^{1}H NMR (600 MHz, CD_2Cl_2): δ 8.04–7.90 (m, C_{Ar}-*H*, 4H), 7.81–7.66 (m, C_{Ar}-*H*, 6H), 7.58 (d, $^3J_{H\text{-}F}$ = 7.6 Hz, C_{Ar}-*H*, 2H), 7.50 (d, $^3J_{H\text{-}F}$ = 7.5 Hz, C_{Ar}-*H*, 2H), 7.08 (d, $^3J_{H\text{-}F}$ = 7.1 Hz, C_{Ar}-*H*, 2H), 6.86 (d, $^3J_{H\text{-}F}$ = 6.9 Hz, C_{Ar}-*H*, 2H), 4.79 (s, Cp-*H*, 5H), 4.42–4.32 (m, PCH_2N, 2H), 4.26–4.12 (m, PCH_2N, 4H), 3.80–3.69 (m, PCH_2N, 2H), 2.33 (s, CH_3, 3H). $^{31}P\{^1H\}$ NMR (243 MHz, CD_2Cl_2): δ 40.6 (s, Ru*P*), −144.4 (sept, $^1J_{P\text{-}F}$ = 712 Hz, PF_6^-). $^{19}F\{^1H\}$ NMR (376.3 MHz, CD_2Cl_2): δ −61.9 (s, CF_3), −62.0 (s, CF_3), −72.3 (d, $^1J_{F\text{-}P}$ = 712 Hz, PF_6^-). $^{13}C\{^1H\}$ NMR (151.5 MHz, CD_2Cl_2): δ 154.4-154.2 (m, C_{Ar}-N), 152.8–152.6, (m, C_{Ar}-N), 132.9 (d, $^1J_{C\text{-}P}$ = 19.2 Hz, $^3J_{C\text{-}P}$ = 19.2 Hz, C_{Ar}-P), 132.7 (d, $^1J_{C\text{-}P}$ = 19.2 Hz, C_{Ar}-P), 132.5 (C_{Ar}), 132.2 (d, $^2J_{C\text{-}P}$ = 6.1 Hz, C_{Ar}), 132.1 (d, $^2J_{C\text{-}P}$ = 6.1 Hz, C_{Ar}), 130.2 (d, $^3J_{C\text{-}P}$ = 5.1 Hz, C_{Ar}), 130.1 (d, $^3J_{C\text{-}P}$ = 5.1 Hz, C_{Ar}), 129.5 (*C*N), 127.6 (quartet, $^3J_{C\text{-}F}$ = 4.7 Hz, C_{Ar}), 127.4 (quartet, $^3J_{C\text{-}F}$ = 4.0 Hz, C_{Ar}), 123.1 (found through correlation, *C*CF_3), 121.4 (found through correlation, *C*CF_3), 117.9 (m, *C*F_3), 116.9 (C_{Ar}), 116.2 (m, *C*F_3), 114.8 (C_{Ar}), 82.4 (C_{Cp}), 51.6 (dd, $^1J_{C\text{-}P}$ = 16.2 Hz, $^3J_{C\text{-}P}$ = 16.2 Hz, PCH_2N), 49.9 (dd, $^1J_{C\text{-}P}$ =

21.7 Hz, $^{3}J_{C\text{-}P}$ = 21.7 Hz, PCH_2N), 4.7 (CH_3). MALDI MS (pyrene matrix): Calc. m/z 757.1 $[Ru(Cp)(P^{Ph}{}_2N^{PhCF3}{}_2)]^+$, Obs. m/z 757.1.

$[Ru(Cp)(P^{Ph}{}_2N^{PhOMe}{}_2)(NCMe)]PF_6$ (2e): Yield = 95%. ^1H NMR (600 MHz, CD_2Cl_2): δ 7.92–7.82 (m, C_{Ar}-*H*, 4H), 7.65–7.58 (m, C_{Ar}-*H*, 6H), 7.04–6.99 (m, C_{Ar}-*H*, 2H), 6.96–6.91 (m, C_{Ar}-*H*, 2H), 6.87–6.82 (m, C_{Ar}-*H*, 4H), 4.88 (s, Cp-*H*, 5H), 4.18–4.12 (m, PCH_2N, 2H), 3.96–3.91 (m, PCH_2N, 2H), 3.77–3.66 (m, PCH_2N and OCH_3, 8H), 3.53–3.46 (m, PCH_2N, 2H), 2.37 (s, $NCCH_3$, 3H). $^{31}P\{^1H\}$ NMR (243 MHz, CD_2Cl_2): δ 39.9 (s, Ru*P*), −144.4 (sept, $^{1}J_{P\text{-}F}$ = 712 Hz, PF_6^-). $^{13}C\{^1H\}$ NMR (151.5 MHz, CD_2Cl_2): δ 156.2 ($COCH_3$), 155.2 ($COCH_3$), 147.0–146.7 (m, C_{Ar}-N), 146.3–145.8, (m, C_{Ar}-N), 133.8 (t, $^{1}J_{C\text{-}P}$ = 18.2 Hz, $^{3}J_{C\text{-}P}$ = 18.2 Hz, C_{Ar}-P), 132.8–131.5 (C_{Ar}), 130.1–129.4 (C_{Ar}), 128.8 (*C*N), 121.6 (C_{Ar}), 120.3 (C_{Ar}), 115.8–114.4 (m, C_{Ar}), 82.1 (C_{Cp}), 55.9 (OCH_3), 54.0 (found through correlation due to overlap with CD_2Cl_2, PCH_2N), 52.7(dd, $^{1}J_{C\text{-}P}$ = 21 Hz, $^{3}J_{C\text{-}P}$ = 21 Hz, PCH_2N), 4.8 (CH_3). MALDI MS (pyrene matrix): Calc. m/z 681.1 $[Ru(Cp)(P^{Ph}{}_2N^{PhOMe}{}_2)]^+$, Obs. m/z 681.2.

$[Ru(Cp)(P^{Ph}{}_2N^{Ph}{}_1)]PF_6$ (4): Yield = 92%. ^1H NMR (400 MHz, CD_2Cl_2): δ 8.17–6.87 (br, C_{Ar}-*H*, 23H), 6.72–6.37 (br, C_{Ar}-*H*, 2H), 5.81–5.17 (br, C_{Ar}-*H*, 2H), 4.97–4.37 (br, Cp-*H* and PCH_2N, 7H), 4.03–3.57 (br, PCH_2N, 2H). $^{31}P\{^1H\}$ NMR (243 MHz, CD_2Cl_2): δ 48.9-56.0 (br, Ru*P*, 85% rel. integration), 34.6 (s, Ru*P*, 15% rel. integration), −144.5 (sept, $^{1}J_{P\text{-}F}$ = 712 Hz, PF_6^-). ^1H NMR (400 MHz, CD_3CN): δ 7.80–7.26 (br, C_{Ar}-*H*, 19H), 7.22–7.10 (br, C_{Ar}-*H*, 2H), 7.00–6.85 (br, C_{Ar}-*H*, 1H), 6.69–6.46 (br, C_{Ar}-*H*, 3H), 4.78–4.68 (m, Cp-*H*, 5H), 4.68–4.51 (m, PCH_2N, 2H), 3.96–3.78 (m, PCH_2N, 2H), 2.34 (br, CH_3). $^{31}P\{^1H\}$ NMR (243 MHz, CD_3CN): 34.6 (s, Ru*P*), −144.6 (sept, $^{1}J_{P\text{-}F}$ = 706 Hz, PF_6^-). $^{13}C\{^1H\}$ NMR (151.5 MHz, CD_3CN): δ 152.7 (through ^1H-^{13}C HMBC, C_{Ar}-N), 137.8 (through ^1H-^{13}C HMBC, C_{Ar}-P), 133.9–133.5 (m, C_{Ar}), 131.6 (C_{Ar}), 131.4 (C_{Ar}), 130.3 (C_{Ar}), 129.3 (d, $^{2}J_{C\text{-}P}$ = 5.1 Hz, C_{Ar}), 129.2 (d, $^{2}J_{C\text{-}P}$ = 5.1 Hz, C_{Ar}), 123.2 (C_{Ar}), 120.2 (C_{Ar}), 83.7 (C_{Cp}), 56.3 (dd, $^{1}J_{C\text{-}P}$ = 21.2 Hz, $^{3}J_{C\text{-}P}$ = 21.2 Hz, PCH_2N),. MALDI MS (pyrene matrix): Calc. m/z 656.1 $[Ru(Cp)(P^{Ph}{}_2N^{Ph}{}_1)]^+$, Obs. m/z 656.1.

$Ru(Cl)(Cp)(P^{Ph}{}_2N^{Bn}{}_2)$ (5): $RuCl(Cp)(PPh_3)_2$ (300 mg, 0.412 mmol) and $P^{Ph}{}_2N^{Bn}{}_2$ (200 mg, 0.415 mmol) were combined under N_2 in a 100 mL Schlenk flask. Toluene (50 mL) was added via cannula. The reaction was heated to reflux and stirred for 42 h. The reaction was cooled, and the toluene was removed under vacuum. The resulting solid was triturated with hexanes (3× 30 mL). Hexanes were added (30 mL) and the suspension was filtered under air to give an orange solid. Yield: 299 mg (87%). ^1H NMR (400 MHz, CD_2Cl_2): δ 7.82–7.76 (m, Ph-*H*, 4H), 7.45–7.38 (m, Ph-*H*, 6H), 7.36–7.22 (m, Ph-*H*, 10H), 4.53 (s, Cp-*H*, 5H), 3.87 (s, $PhCH_2N$, 2H*)*, 3.59 (s, $PhCH_2N$), 3.53-3.49 (m, PCH_2N, 2H), 3.19-3.11 (m, PCH_2N, 4H), 2.63-2.56 (m, PCH_2N, 2H). $^{31}P\{^1H\}$ (162 MHz, CD_2Cl_2): δ 39.3 (s, Ru*P*). $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2): 138.0 (s, C_{Ar}), 137.9 (s, C_{Ar}), 136.9 (d, $^{1}J_{C\text{-}P}$ = 12.1 ppm, C_{Ar}), 136.8 (d, $^{1}J_{C\text{-}P}$ = 12.1 ppm, C_{Ar}), 131.5 (d, $^{3}J_{C\text{-}P}$ = 4.0 ppm, C_{Ar}), 131.5 (d, $^{3}J_{C\text{-}P}$ = 4.0 ppm, C_{Ar}), 129.9 (s, C_{Ar}), 128.4–128.2 (C_{Ar}), 127.5 (s, C_{Ar}), 127.3 (s, C_{Ar}), 79.5 (s, *Cp*), 66.1 (t, $^{3}J_{C\text{-}P}$ = 8.1 Hz, NCH_2Ph), 65.5 (t, $^{3}J_{C\text{-}P}$ = 9.1 Hz, NCH_2Ph), 52.1 (t, $^{1}J_{C\text{-}P}$ = 16.2 Hz, PCH_2N), 50.7 (t, $^{1}J_{C\text{-}P}$ = 14.1, PCH_2N). Anal. Calc. for $C_{41}H_{48}F_6N_3P_3Ru{\bullet}0.1(CH_2Cl_2)$: C, 60.86; H, 5.41; N, 4.04. Found: C, 60.78; H, 5.80; N, 3.85. MALDI MS (pyrene matrix): Calc. m/z 684.1 $[RuCp(P^{Ph}{}_2N^{Bn}{}_2)Cl]^+$, 649.1 $[RuCp(P^{Ph}{}_2N^{Bn}{}_2)]^+$, Obs. m/z 684.1, 649.1. Anal. Calc. for $C_{41}H_{48}F_6N_3P_3Ru$: C, 61.45; H, 5.45; N, 4.09. Found: C, 60.78; H, 5.80; C, 3.85. Orange X-ray quality crystals formed following vapor diffusion of hexanes into a concentrated solution of **5** in DCM.

General Procedure for the Catalytic Cyclization of Substrates: In a glovebox, the following stock solutions were prepared: **EA** (246 mg, 2.10 mmol, 0.300 M) and tetralin (185 mg, 1.4 mmol, 0.2 M) in THF (14.00 mL); **2a** (10 mg, 0.012 mmol, 6 mM) in THF (2.00 mL); **2b** (10 mg, 0.012 mmol, 6 mM) in THF (2.07 mL); **2c** (10 mg, 0.011 mmol, 6 mM) in THF (1.87 mL); **2d** (10 mg, 0.011 mmol, 6 mM) in THF (1.77 mL); **2e** (10 mg, 0.012 mmol, 6 mM) in THF (1.92 mL). Five sets (A–E) of five 4 mL vials (25 vials total) containing stir bars were charged with the **EA**/tetralin stock solution (250 μL) and additional THF (125 μL). To each vial was added catalyst stock solution (125 μL, set A = **2a**, B = **2b**, C = **2c**, D = **2d**, E = **2e**) giving a final volume of 500 μL. The final concentrations for all vials were 0.150 M in substrate and 1.5 mM in catalyst. A final vial was charged with substrate/internal standard stock solution (100 μL) for use as the time = 0 sample, required for accurate quantification of substrate and product. The vials were capped and removed from the glove box and heated to 55 °C (sets A–E) with stirring. After 0.167, 0.5, 1, 6, and 24 hours one vial from each of the sets was removed from heat, cooled, and exposed to air to quench. A 20 μL aliquot was diluted to 3 mM (0.980 μL) in acetonitrile and analyzed by GC-FID. A 10 μL aliquot of the T0 sample was diluted with acetonitrile (990 μL) and analyzed by GC-FID.

High Throughput Catalytic Procedure: A representative procedure is given for **EA**. In a glovebox, the following stock solutions were prepared: **EA** (435 mg, 3.72 mmol, 0.300 M) and tetralin (328 mg, 2.48 mmol, 0.200 M) in THF (12.390 mL). Stock solutions of catalysts (9 mM and 1.5 mM) were prepared as above. Reaction components were added to a cooled (0 °C) 8×12 reaction plate in the following order: catalyst, solvent, then substrate. Stock solutions of catalysts were robotically dispensed to their appropriate concentration amounts: 0.15, 0.75, 1.50, and 3.00 mM (0.1, 0.5, 1, 3 mol%). Solvent and substrate were added by Eppendorf pipette to the well plate and to a T0 sample. Final conditions: 150 mM Substrate, 0.1/0.5/1/3 mol% catalyst, 100 μL reaction volume in THF. The 96 well plate was sealed with a Teflon sheet, a rubber sheet and an aluminium cover, to minimize evaporation, and the plate was heated to 55 °C for 24 h. After the plate had cooled, the solutions were daughtered into a second plate and diluted to 2.5 mM (based on the starting concentration of 2-ethynylaniline) in acetonitrile for GC-FID analysis. A 10 μL aliquot of the T0 sample was diluted with acetonitrile (990 μL) and analyzed by GC-FID.

Stoichiometric Reactions with Complex 5 and Aniline: In a glovebox $Ru(Cp)(Cl)(P^{Ph}{}_2N^{Bn}{}_2)$ (7 mg, 0.01 mmol) was dissolved with $OPPh_3$ (3 mg, 0.01 mmol) in THF. An initial time = 0 (T0) spectrum was acquired by externally referenced $^{31}P\{^1H\}$ NMR spectroscopy. KPF_6 (10 mg, 0.05, 5 eq) and aniline (20 mg, 0.21 mmol, 20 eq) were added to the NMR tube, which was then heated at 55 °C in an oil bath. After times of 3 and 24 h, the tube was removed from the bath, cooled and $^{31}P\{^1H\}$ NMR spectra were acquired.

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Conflict of Interest

The authors declare no conflict of interest.

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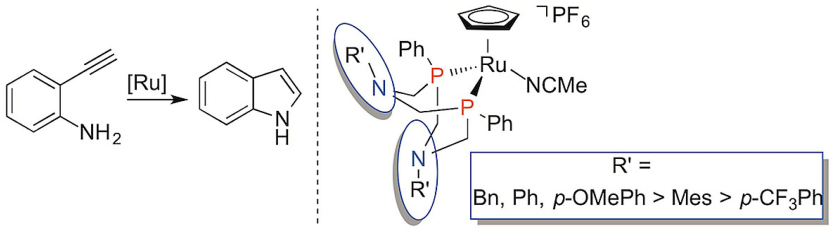

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Working together: A family of cooperative catalysts were prepared that differ systematically in the structural properties of the pendent base on the ligand framework. Optimal steric and electronic properties of the base were elucidated for the catalytic cyclization of alkynyl aniline substrates.