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Mechanistic Model for Enantioselective Intramolecular Alkene Cyanoamidation via Palladium-Catalyzed C−CN Bond Activation

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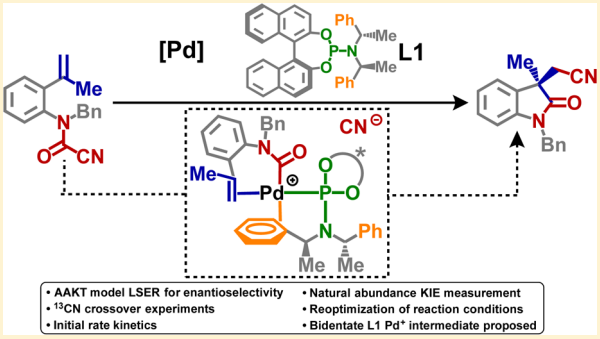
Supporting Information

ABSTRACT: We studied key aspects of the mechanism of Pd-catalyzed C−CN bond activation and intramolecular enantioselective alkene cyanoamidation. An Abboud−Abraham−Kamlet−Taft (AAKT) linear solvation energy relationship (LSER) model for enantioselectivity was established. We investigated the impact of Lewis acid (BPh_3), Lewis base (DMPU), and no additives. BPh_3 additive led to diminished enantioselectivity and differing results in ^{13}CN crossover experiments, initial rate kinetics, and natural abundance $^{12}C/^{13}C$ kinetic isotope effect measurements. We propose two catalytic mechanisms to account for our experimental results. We propose that the DMPU/nonadditive pathway passes through a κ^2-phosphoramidite-stabilized Pd^+ intermediate, resulting in high enantioselectivity. BPh_3 prevents the dissociation of CN^-, leading to a less rigid κ^2-phosphoramidite-neutral Pd intermediate.



INTRODUCTION

Metal-catalyzed C−C bond activation is an intriguing challenge in organic synthesis due to the nonpolar C−C σ-bond being thermodynamically stable and typically unreactive.[1−5] Fundamental research sparked the development of general C−C σ-bond activation strategies for homogeneous catalysis including strain-promoted,[6−9] chelation-assisted,[10−13] and C−CN[14] bond activation. Pd or Ni oxidative addition into C−CN bonds, combined with intramolecular or intermolecular migratory insertion across C−C π-bonds, has proven particularly attractive for catalytic reaction development. Hallmarks of C−CN bond activation methodologies include the production of two new C−C bonds, high atom economy, and retention of the CN functional group. Variations include alkylcyanation,[15] allylcyanation,[16] alkynlcyanation,[17] arylcyanation,[18−21] acylcyanation,[22−24] cyanoesterification,[25−27] and cyanoamidation.[25,28−31]

Lewis acid additives, typically B, Al, or Zn, are often additives in catalytic C−CN bond activation.[15,17,19,21,23,25] However, Lewis acid additives have contrasting effects in stoichiometric processes, making their overall impact on catalysis difficult to assess. Nolan et al. noted that Lewis acid additives increased the rate of reductive elimination of $TMSCH_2$−CN from Pd(dppp).[32] Jones and colleagues demonstrated that BPh_3 additive in the activation of Me−CN promoted oxidative addition with Pd(dippe)[33] but favored reductive elimination with Ni(dippe).[34] In their studies of stoichiometric allyl C−CN bond activation with Ni(dippe), a process involved in DuPont's synthesis of adiponitrile, complete chemoselectivity for C−CN bond activation, versus competing C−H activation, was observed upon addition of BPh_3. BPh_3 also assisted dissociation of CN^- from the (NC)Ni(dippe) complex.[35]

Despite the considerable expansion of catalytic C−CN bond activation methodologies in organic synthesis, mechanistic study of these reactions has been sparse. In a seminal mechanistic study of the catalytic variant of allyl C−CN bond activation, Jones demonstrated a relationship between solvent polarity and the regioselectivity of the reaction and also measured activation parameters for C−CN bond cleavage.[36] Beyond this, insights into the mechanism of catalytic C−CN bond activation reactions have been primarily based on X-ray structures[19,25,26] of isolated intermediates as well as insights from divergent reactivity observed with atypical substrates from some methodology studies.[18,20,30]

This void in mechanistic understanding, especially with regards to enantioselective Pd-catalyzed C−CN bond activation reactions and our inability to predict the impact of Lewis acid additives, motivated us to explore these topics. To the best of our knowledge, CN crossover, initial rate kinetics, and kinetic isotope effects (KIE) have not been investigated in detail. We performed these experiments as well as studied solvent effects for asymmetric alkene cyanoamidation. Our findings support a mechanistic model in which Lewis acid additive results in an altered coordination environment around the catalyst during the enantiodetermining step. We expect our findings will impact and guide further development of asymmetric C−CN bond activation processes in fine chemical synthesis.

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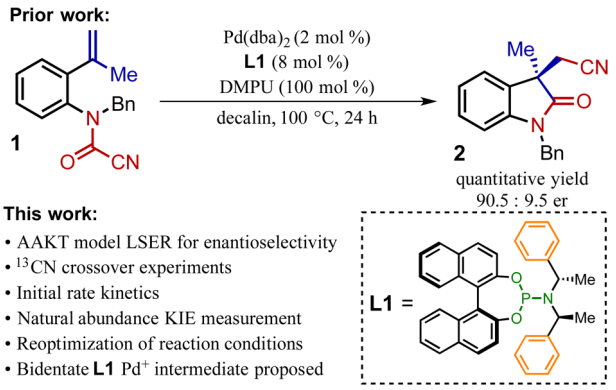
The Pd-catalyzed intramolecular enantioselective cyanoamidation of cyanoformamide **1**, developed by Takemoto et al., was selected for study (Scheme 1).[29] The reaction has high

Scheme 1. Enantioselective Alkene Cyanoamidation

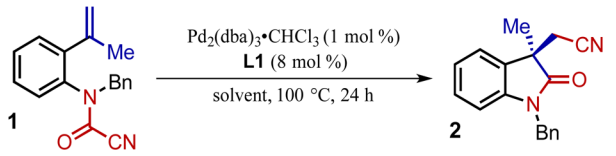


synthetic potential, forming a chiral oxindole **2**, with good enantioselectivity, good yield, and no observable byproducts. The reaction conditions are also distinct among catalytic C–CN bond activation reactions in that a polar/Lewis base additive, cyclic urea DMPU (dimethyltetrahydropyrimidinone), is incorporated. We are unaware of any other studies involving Lewis base additives. Additionally, the highest enantioselectivity was obtained using the uncommonly deployed decalin as solvent.

RESULTS AND DISCUSSION

Our initial attempts to reproduce the conversion of **1** into oxindole **2** consistently gave product with an er of 89:11 (Table 1, entry 1, >10 runs).[37] Interestingly, decalin in the absence of

Table 1. AAKT Model LSER for Enantioselectivity



entry	solvent	er[a]	entry	solvent	er[a]
1	decalin[b]	89:11	11	MEK	83:17
2	decalin	89:11	12	dioxane	82:18
3	toluene	85:15	13	$PhCF_3$	82:18
4	toluene[b]	85:15	14	DCE	79:21
5	DMPU[c]		15	NMP	79:21
6	decalin[d]	80:20	16	DMF	76:24
7	toluene[d]	77:23	17	MeCN	71:29
8	cyclohexane	89:11	18	heptane	84:16
9	*m*-xylene	85:15	19	PFMCH	75:25
10	2-propanol	84:16			

[a]Complete conversion to **2** observed by ^{1}H NMR. [b]With 100 mol % of DMPU. [c]No reaction. [d]With 100 mol % of BPh_3.

DMPU at 100 °C gave full conversion with an identical er of 89:11 (entry 2). Toluene gave quantitative conversion and an er of 85:15 (entry 3). As observed with decalin, the addition of 100 mol % of DMPU did not affect the er (entry 4). DMPU as the solvent resulted in no reaction of **1** (entry 5). Substituting 100 mol % of Lewis acid BPh_3 for DMPU in both decalin and toluene decreased the er significantly (entries 6 and 7).

We investigated the potential for interactions within the cybotactic region to affect the enantioselectivity by performing an additional 10 cyanoamidation reactions with solvents of varying dielectric constant (ε). All 10 reactions resulted in complete conversion to oxindole **2** with a significant range in er (entries 8–17). Specifically, cyanoamidation in cyclohexane gave **2** with an er of 89:11, identical to that of decalin. Acetonitrile, with the highest dielectric constant, gave **2** with an er of 71:29. There was a general trend of nonpolar solvents leading to higher er; however, single linear regression analysis of er and dielectric constant gave $R^2 = 0.665$.[38−41] We used the Abboud–Abraham–Kamlet–Taft (AAKT) multiparameter solvatochromic equation (eq 1), which is a more comprehensive assessment of solvent polarity, to establish a linear solvation energy relationship (LSER) with the er data (Figure 1).[42−44] The three AAKT parameters, π^* (polarizability/

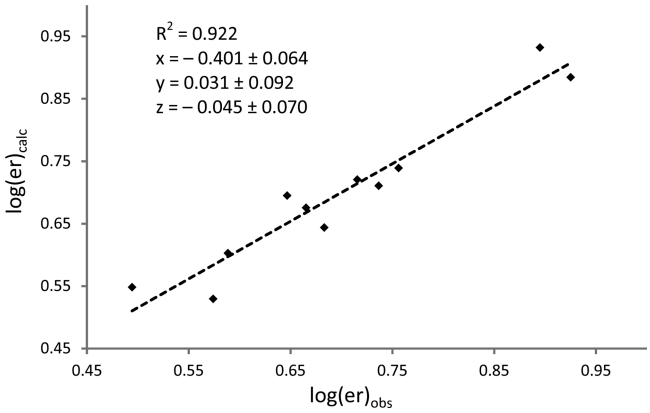


Figure 1. Plot of observed log(er) vs calculated log(er) with multiparameter AAKT regression analysis.

dipolarity), α (hydrogen bond acidity), and β (hydrogen bond basicity), gave a $R^2 = 0.798$ (see Supporting Information for parameter values). A Grubb's test of the residuals led us to exclude the MeCN data, for which an anomalously low er was observed.[45] The revised LSER gave an improved fit with $R^2 = 0.922$. The resulting parameter coefficients for π^*, α, and β indicated solvent polarizability/dipolarity as the major contributor to the fit. Single regression analysis with only π^* gave a fit of $R^2 = 0.917$. The discovery of an inverse correlation between solvent polarizability/dipolarity and er led us to screen solvents with lower π^* values than decalin ($\pi^* = 0.11$) and cyclohexane ($\pi^* = 0$). Heptane ($\pi^* = -0.08$) and perfluoromethylcyclohexane (PFMCH) ($\pi^* = -0.40$) as solvents resulted in full conversion to oxindole **2**, but with a lower than predicted er (entries 18 and 19). This is likely accounted for by the reactions remaining heterogeneous. All other reactions were homogeneous at 100 °C.

$$\log(er) = c + x\pi^* + y\alpha + z\beta \quad (1)$$

In the previous work, it was conjectured that a Pd^+ intermediate resulting from the dissociation of CN^- would not form during the catalytic cycle because the bidentate phosphine ligands screened did not perform well in comparison to phosphoramidite **L1**.[31] We synthesized a ^{13}CN-labeled methyl-substituted cyanoformamide **3*** to investigate this hypothesis.[15] A 1:1 mixture of **1** and **3*** underwent cyanoamidation with 100 mol % of DMPU. Unexpectedly, crossover of the ^{13}CN label was observed in both decalin and

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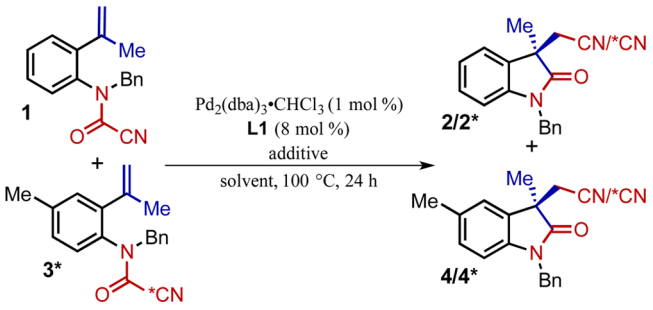
toluene, producing ~1:1:1:1 distribution of **2**, **2***, **4**, and **4*** (Table 2, entries 1 and 2).[23,29,46] In the absence of DMPU, full

Table 2. ^{13}CN Crossover Experiments



entry	solvent	additive	4*/2*	er of 2
1	decalin	DMPU (100 mol %)	47:53	
2	toluene	DMPU (100 mol %)	51:49	
3	decalin		49:51	
4	toluene		51:49	
5	toluene	BPh_3 (50 mol %)	36:64	80:20
6	toluene	BPh_3 (100 mol %)	35:65	77:23
7	toluene	BPh_3 (200 mol %)	30:70	73:27

crossover was also observed (entries 3 and 4). Upon the addition of 100 mol % of BPh_3, the ratio of **2***/**4*** favored **4***, showing partial retention of the ^{13}CN label (entry 6). An experiment with 50 mol % of BPh_3 gave a similar result (entry 5). However, more of the ^{13}CN label was retained when 200 mol % of BPh_3 was added (entry 7). Heating the mixture of **1** and **3*** in the absence of catalyst resulted in no crossover of the ^{13}CN label (see Supporting Information).

We hypothesized that a mechanism for crossover could involve the coordination of a second **L1**, facilitating CN^- dissociation from Pd. To test this hypothesis, the crossover experiment was performed with 4 mol % of **L1** (2:1 instead of 4:1 **L1**/Pd) with the expectation that some of the label would be retained (see Supporting Information). However, complete crossover was observed, and the er of **2** was unchanged. When **L1** loading was reduced to 2 mol % (1:1 **L1**/Pd), negligible change in er was observed, thus suggesting a mechanism where only one **L1** is ligated to the metal center at the enantiodetermining step. Crossover studies of oxindoles **2** and **4*** showed no crossover of the ^{13}CN label after 24 h at 100 °C, suggesting reductive elimination is irreversible. Likewise, resubjecting enantioenriched oxindole **2** induced no change in er, showing the enantiodetermining step is irreversible.

The drastic difference in reactivity observed with the addition of BPh_3 and the lack of evidence that DMPU has a significant effect on the reaction led us to study the initial rate kinetics of the reactions under both sets of conditions. We performed initial rate kinetics with ^{1}H NMR spectroscopy in toluene-d_8 at 90 °C (see Supporting Information).[47] By varying DMPU concentrations relative to **1**, we observed an *inhibitory* effect of increased [DMPU] on the overall rate. DMPU inhibition matches with our prior observation that DMPU cannot serve as a solvent for the reaction. In contrast, BPh_3 showed a general *increase* in the rate of the reaction, following classic saturation kinetics that plateaued at [BPh_3] greater than 100 mol % relative to **1**. However, the increase in rate is only 28% relative to the rate without added BPh_3 (see Supporting Information).

We investigated the turnover-limiting step by determining the ^{12}C/^{13}C KIE of the reaction with 100 mol % of DMPU or BPh_3 in decalin. Reactions were run on gram scale to >85% conversion to oxindole **2**. The starting cyanoformamide **1** was then reisolated and analyzed using quantitative ^{13}C NMR spectroscopy.[48,49] Each reaction with BPh_3 or DMPU showed statistically significant, but different, levels of isotopic enrichment at the carbonyl carbon (C1) as well as the CN carbon (C2) (Figure 2). Negligible enrichments were observed at the

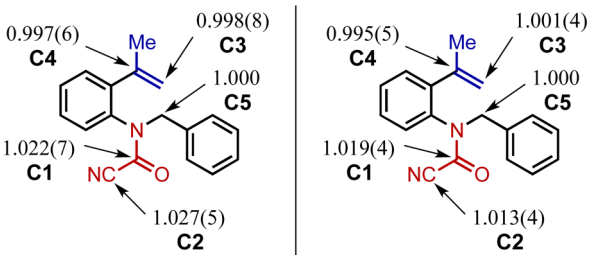
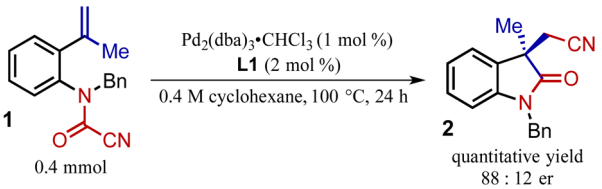


Figure 2. Map of ^{13}C enrichment after natural abundance measurement of the ^{12}C/^{13}C KIE: 100 mol % of DMPU (left); 100 mol % of BPh_3 (right).

olefinic carbons (C3 and C4). These results indicate that C–CN bond activation via oxidative addition is the turnover-limiting step of the reaction.

The results of our experiments led us to attempt cyanoamidation under reoptimized conditions (Scheme 2).

Scheme 2. Optimized Alkene Cyanoamidation



Cyclohexane was used as solvent as it was shown at small scale (0.1 mmol) to give the same er as decalin. The ligand loading was decreased from 8 to 2 mol % (1:1 **L1**/Pd) as it was shown to have no effect on conversion or er in toluene. The reaction was scaled to 0.4 mmol, and the concentration was increased to 0.4 M. The revised cyanoamidation conditions resulted in quantitative yield of **2** with an er of 88:12.

We forward two mechanistic models consistent with our results. Without BPh_3, we propose that η^2-coordination of Pd to the CN of **1** will form **A**, in accordance with structures from Jones et al. (Figure 3, left).[33] From **A**, turnover-limiting *cis* oxidative addition into the C–CN bond forms intermediate **B**. Crossover may then occur by dissociation of CN^- from **B**, forming cation **C**. Although the proposed cationic intermediate is favored with increased solvent polarity, our AAKT LSER of enantioselectivity indicated that higher er was achieved with lower π^* value solvents, as long as the reaction was homogeneous at 100 °C. We propose enhancement of enantioselectivity by intramolecular stabilization of the Pd^+ via the secondary coordination of a phenethyl arm of **L1**, creating a more rigid bidentate chiral ligand structure. Higher π^* value solvents increase intermolecular interactions between solvent dipoles and Pd^+, likely disrupting the desirable Ph–Pd coordination.[31,50] Trost et al. proposed an analogous secondary coordination in phosphoramidate/Pd-catalyzed enantioselective

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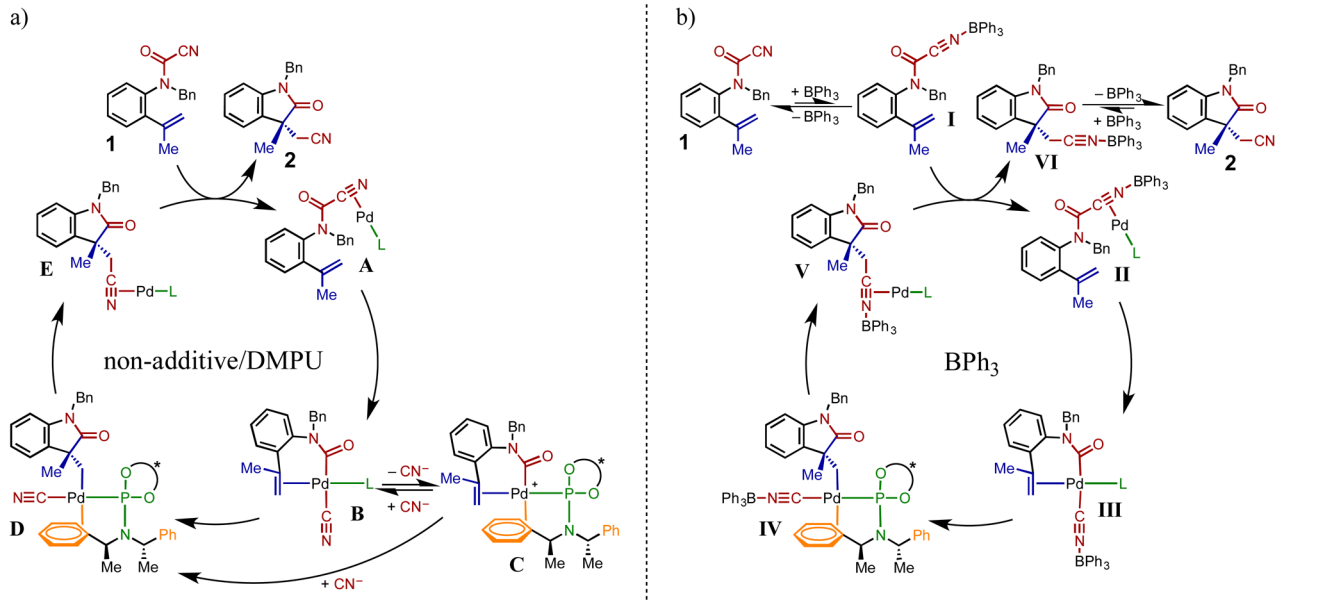

Figure 3. Proposed catalytic cycle for (a) nonadditive/DMPU and (b) BPh_3 additive.

trimethylenemethane reactions.[51,52] Higher enantioselectivity achieved via bidentate Pd^+ intermediates also finds precedent in the cationic pathway for the asymmetric Heck reaction.[53−55] Considering this insight, reaction optimization with other substrates should include screening for the most nonpolar solvent that still provides homogeneous reaction mixtures. In this highly enantioselective pathway, migratory insertion from **C** to **D** may be in competition with a lower selectivity pathway to **D** from **B**. Irreversible reductive elimination completes the cycle, forming **E** and **2** after coordination of **1**.

The addition of BPh_3 opens a new pathway that operates *concurrently* with the non-BPh_3-catalyzed pathway. The two pathways operating concurrently is supported by the diminished, but nonzero observed, KIE as well as the ^{13}C label being partially, but not completely, retained in crossover experiments with BPh_3 additive. This new pathway begins with BPh_3 coordination to the nitrogen in **1** to form **I**.[33] ^{11}B and ^{13}C NMR spectra were taken of pure BPh_3 and a 1:1 mixture of BPh_3 and **1** in toluene-d_8. No change was observed in the spectra (see Supporting Information), indicating the equilibrium does not favor the Lewis pair.[56] We hypothesize that coordination of Pd to **I** is turnover-limiting based on the relative decrease in magnitude of the $^{12}C/^{13}C$ isotope enrichment observed at C1 and C2 in the BPh_3 additive KIE experiment. Also, there is no enrichment observed at C3 or C4, indicating that the turnover-limiting step did not change to migratory insertion or reductive elimination. The catalytic cycle with BPh_3 does not include a Pd^+ species, reflecting our observation that the ^{13}CN label in **3*** is retained to a larger extent in the product **4***. Also, the decreased er obtained in reactions with added BPh_3 further supports CN^- coordination during the enantiodetermining step, preventing the formation of **C**.[21] BPh_3 may prevent CN^- dissociation due to a stronger Pd−CN bond upon formation of the Lewis adduct.[33] In both cases, only one **L1** is coordinated to Pd, based on the observation that decreasing the **L1**/Pd ratio to 1:1 does not affect the er of the reaction.[51]

The inherent er of the BPh_3 pathway can be estimated with the assumption that the ^{13}CN label is fully retained if all the material proceeds through the BPh_3-catalyzed pathway. The calculated er for the exclusively BPh_3-catalyzed pathway would be 62:38 (see Supporting Information for calculation). This result suggests that developing chiral catalysts that can accomplish C−CN bond activation without the use of Lewis acid will be advantageous to developing more enantioselective reactions.

CONCLUSION

In conclusion, the results obtained from the LSER, ^{13}CN crossover, kinetics, and $^{12}C/^{13}C$ KIE experiments led us to propose a rigid bidentate **L1** Pd^+ intermediate as the origin of high enantioselectivity, counter to previous conjecture.[11] Lewis acid BPh_3 opens a second operable catalytic cycle that increases the reaction rate but leads to diminished enantioselectivity, due to the retention of CN^- preventing the formation of the Pd^+ intermediate. DMPU inhibits the rate of the reaction but does not impact enantioselectivity. We have developed improved mechanistic models for alkene cyanoamidation that will guide development of asymmetric reactions involving C−CN bond activation.

EXPERIMENTAL SECTION

General Information. All reactions were carried out using oven-dried glassware. Cyanoformamide **1** and **3*** were prepared by literature procedures.[29] Solvents were dried and degassed prior to use or used fresh from new bottles. $Pd_2(dba)_3{\cdot}CHCl_3$ was purified by literature procedure from Pd_2dba_3, which was purchased from commercial sources.[57] Phosphoramidite **L1** was prepared according to a literature procedure.[58] All other chemicals were purchased from commercial vendors and used as received. All cyanoamidation reactions were carried out in a nitrogen-filled glovebox in 1 dram vials sealed with PTFE lined caps or 5 mm NMR tubes. Heating was applied by aluminum blocks. Analytical thin layer chromatography was carried out using 0.25 mm silica plates. Flash chromatography was performed using 230−400 mesh (particle size 0.04−0.063 mm) silica gel. ^1H NMR (300 and 500 MHz), ^{13}C NMR (75, 100, and 125 MHz), and ^{11}B NMR (128 MHz) spectra were obtained on FT NMR instruments. ^1H NMR spectra were reported as δ values in parts per million relative to tetramethylsilane (TMS); ^{13}C NMR spectra were referenced to $CDCl_3$ at 77.16 ppm, and ^{11}B NMR spectra were absolute referenced to TMS from a ^1H NMR spectrum obtained on the same instrument.

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General Procedure for 0.1 mmol Scale Cyanoamidation. Under N_2 atmosphere in a glovebox, 0.0276 g (0.1 mmol) of cyanoformamide **1**, 0.0043 g (0.008 mmol) of **L1**, and 0.0010 g (0.001 mmol) of $Pd_2(dba)_3{\cdot}CHCl_3$ were massed in a 1 dram screw top reaction vial. If DMPU was used in the reaction, 0.0128 g (12 μL) (0.1 mmol) was added via microsyringe. If BPh_3 was used, 0.0242 g (0.1 mmol) or other desired quantity was massed in the reaction vial. One milliliter of the solvent was added via syringe as well as a 5 mm stir bar, and the reaction vial was sealed. The reactions were heated at 100 °C for 24 h in an aluminum heating block on a preheated hot plate in a glovebox. Once completed, the reactions were allowed to cool to room temperature and removed from the glovebox. Depending on the solvent boiling point, the reaction mixtures were concentrated either in vacuo by rotatory evaporation or with a Kügelrohr. The crude oxindole **2** was then dissolved in ∼1 mL of $CDCl_3$ and filtered through a 0.2 μm syringe filter. ^{1}H NMR was taken to determine conversion to oxindole: HPLC [Chiralcel OD-H, hexane/2-propanol = 90/10, 1.0 mL/min, λ = 254 nm, retention times (major) 14.3 min, (minor) 17.5 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (s, 3H), 2.64 (d, 1H, J = 16.5 Hz), 2.90 (d, 1H, J = 16.5 Hz), 4.93 (s, 2H), 6.78 (d, 1H, J = 7.6 Hz), 7.09 (t, 1H, J = 7.6 Hz), 7.27 (m, 6H), 7.47 (m, 1H).

General Procedure for ^{13}CN Crossover Experiments. Under N_2 atmosphere in a glovebox, 0.024 g (0.087 mmol) of cyanoformamide **1** and 0.025 g (0.086 mmol) of ^{13}CN-labeled cyanoformamide **3***, 0.0075 g (0.014 mmol) of **L1**, and 0.0017 g (0.0017 mmol) of $Pd_2(dba)_3{\cdot}CHCl_3$ were weighed in a screw top 1 dram reaction vial. If DMPU was used in the reaction, 21 μL (0.022 g) (0.17 mmol) was added via microsyringe. If BPh_3 was used, 0.042 g (0.17 mmol) or other desired quantity was massed in the reaction vial. Next, 1.74 mL of solvent (toluene or decalin) was added via syringe as well as a 5 mm stir bar, and the reaction vial was sealed. The reactions were heated at 100 °C for 24 h in an aluminum heating block on a preheated hot plate in a glovebox. Once completed, the reactions were allowed to cool to room temperature and removed from the glovebox. The reaction mixtures were concentrated in vacuo by rotatory evaporation. The crude mixture of oxindoles **2**, **2***, **4**, and **4*** was then dissolved in ∼1 mL of $CDCl_3$ and filtered through a 0.2 μm syringe filter. ^{1}H NMR spectra were then taken to determine conversion to oxindole. The extent of crossover was determined of integration of ^{13}C NMR spectra (see Supporting Information): HPLC [Chiralcel OD-H, hexane/2-propanol = 90/10, 1.0 mL/min, λ = 254 nm, retention times (major) 14.3 min, (minor) 17.5 min.

Initial Rate Kinetics Method. In a nitrogen-filled glovebox, two stock solutions were made in toluene-d_8: stock A (0.2 M cyanoformamide, 0.002 M $Pd_2(dba)_3$, and 0.016 M **L1**) and stock B (0.4 M additive (BPh_3 or DMPU)). Next, 1.2 mL of stock A was added to separate vials, and then stock B was added to make solutions of 0, 0.1, 0.25, 0.5, 1, and 2 equiv of additive. Toluene-d_8 was then added to bring the total volume to 2.4 mL in all vials. Next, 0.7 mL from each vial was added to separate NMR tubes so that each reaction was run in triplicate, and the tubes were sealed with plastic caps and the caps secured with electrical tape. The tubes were then placed in the NMR spectrometer autosampler and sequentially monitored via variable-temperature NMR spectroscopy at 90 °C (calibrated using pure glycol standard) for 1 h (roughly 10% conversion). Spectra were processed using the integrals graph function in MestReNova after we performed phase and baseline corrections. The data were exported to Microsoft Excel, and the data fit with a linear line to obtain rates. All data were normalized to obtain mM/s rates based on the integral of the peak at 3.93 ppm being from the starting material, which is 90% of the total starting material (as it is one of two peaks corresponding to rotational isomers that are resolved in the spectra, with the lesser isomer being 10% of the total). The rates obtained were averaged and standard deviations obtained. The average rates were plotted with error bars equivalent to the standard deviation against the concentration of additive in the experiment (see Supporting Information for plots).

General Procedure for Collection of Sample for ^{12}C/^{13}C Kinetic Isotope Effect Determination. A 250 mL round-bottom flask was charged with a stir bar, $Pd_2(dba)_3$ (0.140 mmol), and phosphoramidite **L1** (1.16 mmol) in a glovebox under nitrogen atmosphere. Decalin was then added to the catalyst (40 mL). Cyanoformamide **1** was added (7.25 mmol), and the reaction mixture was diluted with additional decalin until the reaction mixture was 0.1 M (72 mL total). DMPU (7.25 mmol) was added, and the reaction flask was sealed with a rubber septum and electrical tape. The flask was then removed from the glovebox; a nitrogen inlet was inserted with positive nitrogen pressure, and the reaction was heated to 100 °C in an oil bath.

After 1 h, a 0.1 mL sample was removed and filtered through a plug of silica gel. The silica gel was rinsed first with hexanes to remove decalin and then with ethyl acetate to flush off the product and starting material. The sample was concentrated, and an NMR spectrum of the crude material was taken to determine the approximate percent conversion. This process was repeated until the reaction was determined to be ∼90% complete.

The reaction mixture was removed from the oil bath, diluted with cold hexanes, and immersed in an ice bath to quickly cool to room temperature. The reaction mixture was then flushed down a large column of silica to remove the catalyst. Decalin was removed by first flushing the column of silica with hexanes (∼250 mL). Then, the column was rinsed several times with ethyl acetate (∼500 mL combined) to ensure all the starting material was obtained. The solution was then concentrated, and silica gel column chromatography was used to separate the enriched starting material from the product (90:10 hexane/EtOAc as eluent). Concentration of fractions yielded enriched **1** for the natural abundance KIE ^{13}C NMR experiment.

Pure samples of the recovered enriched **1** and unreacted substrate **1** were quantitatively analyzed by ^{13}C NMR spectroscopy. Spectra were obtained on a Bruker Avance III 500 MHz spectrometer (125 MHz, $CDCl_3$) at 300 K with an inverse-gated decoupling pulse sequence and calibrated 30° pulses, collecting 256k points total. T_1 values were measured prior to obtaining data, and D_1 values were set to 120 s with acquisition times of 11.5 s. Five acquisitions were obtained for each sample. Each spectrum was processed using a −1.00 Hz exponential and a 3.00 Hz Gaussian apodization, as well as a third-order Bernstein polynomial baseline correction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00196.

General procedure, HPLC data, rate kinetics, KIE measurement (PDF)

Spectra, kinetics plots, LSER, HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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