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Research Article

Ligand-Controlled Orthogonal Selectivity between δ and γ Positions of Long-Chain Picolinamides

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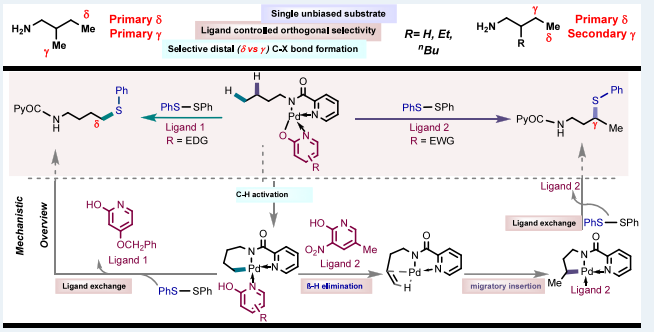
ABSTRACT: Aliphatic C(sp^3)−H bonds are inherently difficult to activate, owing to their inertness and chemical indistinguishability. This challenge has been overcome mostly by a directing group approach; however, the regioselectivity in distal aliphatic positions has mostly been substrate-dependent, with substrate bias being a prerequisite for distal C(sp^3)−H activation, a direct consequence of the Thorpe−Ingold effect. Extending the methodology to straight-chain aliphatic substrates, in which all the available positions are compatible toward functionalization, has been a long-standing problem. To this aim, we attempted to develop a ligand-enabled orthogonal selectivity between the distal δ and γ positions of long-chain picolinamides in a regioselective fashion. These alkyl amines, with the assistance of a picolinic acid directing group, can be orthogonally functionalized between their γ and δ positions just by changing the ligand, with all other reaction parameters remaining constant, signifying the immense importance of the ligand in controlling the selectivity between the aforementioned positions of such inert C(sp^3)−H bonds. Experimental as well as DFT studies have been carried out to generalize the nature of the ligand that would be successful in promoting orthogonal selectivity between these positions, with electron-rich pyridone ligands favoring selective distal δ functionalization while electron-deficient pyridone ligands tuning the selectivity favorably toward the γ position. This regioselective orthogonal selectivity tuned from γ to δ positions has also been mechanistically established through control reactions, kinetic studies, and theoretical calculations.



KEYWORDS: *distal orthogonal selectivity, Pd-catalyzed δ and γ thioarylation, long-chain picolinamides, β-hydride elimination, pyridone ligand-controlled, density functional theory, electron-rich pyridone ligand, electron-deficient pyridone ligand*

1. INTRODUCTION

The advent of C−H activation has opened up vast levels of synthetic strategies toward a diverse range of organic transformations.[1−4] The drawback involving the specific site selectivity can be overcome by the judicious use of C−H activation techniques. However, the similar bond strengths and chemical properties of sp^3 C−H bonds make it inherently difficult for selective distal functionalization. The inertness of aliphatic C−H bonds and the corresponding difficulty for transition metals to distinguish between the similar methyl and methylene C−H bonds add up to the challenge. Recently, various strategies have been adopted to activate the less favored methylene positions over the more favored methyl groups of aliphatic carboxylic acids.[5] The employment of a directing group has laid a platform toward the proximal functionalization of sp^3 C−H bonds, which go through a five-membered intermediate. Regulating the selectivity toward the distal position requires employment of effective strategies that will modify the metalation step toward a six-membered palladation over the more favored five-membered one.[6] In recent times, several groups have applied the use of the directing group strategy to enable distal C(sp^3)−H functionalization through the participation of less favored six-membered cyclometalation (Scheme 1A).[7,8] In 2016, Shi's group envisioned the application of the Curtin−Hammett principle to selectively functionalize the δ sp^3 C−H bonds, which proceeds through the kinetically less favored six-membered metallacycle over the more favored five-membered one.[9] Few years later, Yu's group used the transient directing group strategy to functionalize the distal position of aliphatic amines, with functionalization depending on the design of the biased substrate with specific available positions[10] (Scheme 1B). In all these cases, specific site selectivity has been achieved

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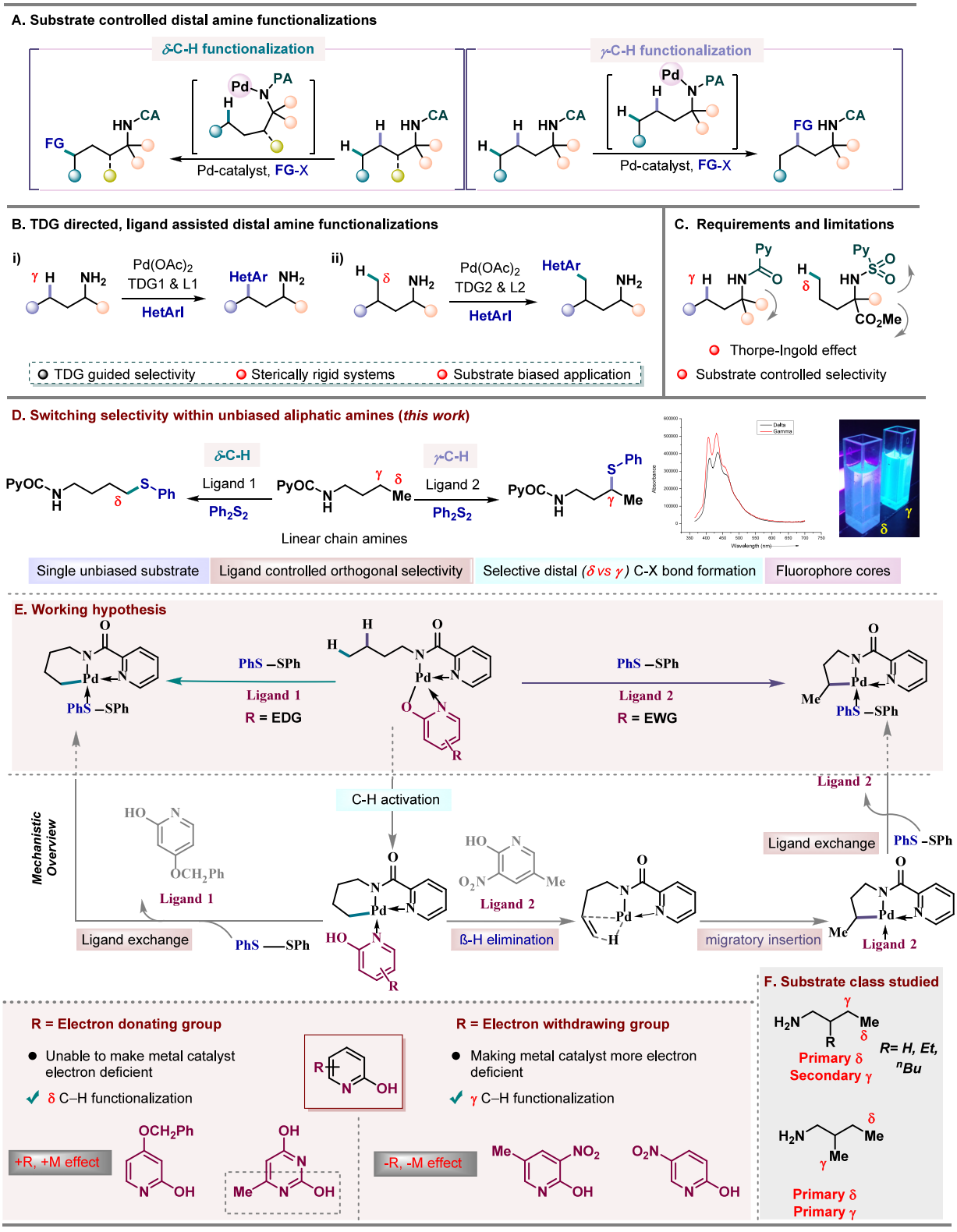
Scheme 1. Evolution of Functionalization at γ C(sp^3)−H and δ C(sp^3)−H Bonds: (A) Substrate-Controlled Distal C(sp^3)−H Functionalization, (B) TDG-Controlled Distal Amine Functionalization, (C) Essential Requirements and Limitations of Substrate-Controlled Distal γ and δ C(sp^3)−H Functionalization, (D) Ligand-Controlled Orthogonal Selectivity between γ and δ Positions of the Same Aliphatic Amine, (E) Working Hypothesis of the Nature of the Ligand Controlling the Five-Membered vs Six-Membered Metalation, and (F) Substrate Classes Studied



by incorporating steric bias on characteristically different substrates, thus promoting distal C−H activation by blocking all the other available positions, in turn making functionalization at the proximal position improbable, both statistically and

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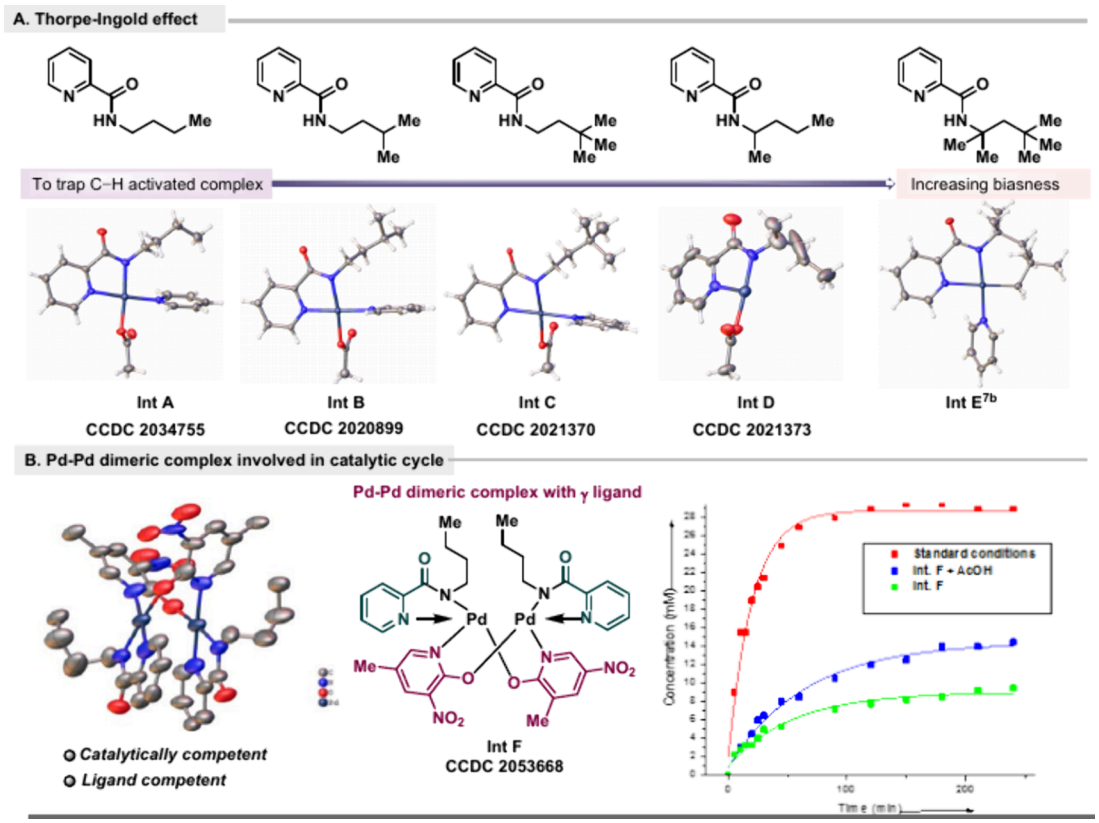
Scheme 2. Organometallic Intermediates Involved in δ and γ C(sp^3)−H Functionalization: (A) Culmination of the Thorpe−Ingold Effect and (B) Pd−Pd Dimeric Complex Involved in the Catalytic Cycle and Essential Part of the Reaction Protocol



sterically (Scheme 1C). Complementary approaches to functionalize such positions have mostly been achieved by a radical pathway utilizing direct rhodium-catalyzed decomposition of diazo compounds.[11] Another strategy that has been adopted for functionalizing a large range of sp^3 C−H bonds has been the use of hydrogen atom transfer (HAT) reactions.[12] Pioneered by various groups,[13−15] these HAT approaches have been able to overcome the challenge of activating distal aliphatic C−H bonds without the requirement of a preinserted coordinating site. The exploration of an aliphatic amine with both proximal γ and distal δ positions available for functionalization and where ligand modulation can achieve orthogonal selectivity between these γ and δ positions via C−H activation has not yet been undertaken. The challenge therefore lies in choosing such an alkyl moiety and tuning the reaction conditions in a way to achieve orthogonal site selectivity between the distal δ and γ C−H bonds of the same molecule, thus providing the generality and in turn improving the synthetic applicability of the protocol.

The use of ligands has played a significant role in the overall advent of C−H activation. Over the past few decades, more focus has been implemented on the role of ancillary ligands to accelerate the process of transition metal catalysis in C−H activation.[16] A better σ-donating ligand binding allows the space for a comparatively poor donor substrate to get bound with the metal center, such as in the case of Pd(II) where an electron-donating ligand will prefer the C−H bond cleavage to go via concerted-metalation deprotonation step (CMD), whereas an electron-withdrawing ligand will lead the pathway toward electrophilic palladation.[17] Looking at additional insight into the mechanism of ligands like chiral carboxylates,[18] monoprotected amino acids[19] reveal their incredible influence on controlling the stereoselectivity of the products. Consequently, in recent years, there has been a resurgence of the involvement of 2-hydroxypyridine or pyridone ligands in the C−H activation methodology. Such pyridone ligands primarily assist in reducing the activation barrier of the C−H cleavage step by forming a stable palladium−pyridone complex, in turn accelerating the C−H activation step.[20] This enormous importance of the ligand made us dwell deep into the crucial role that it might have in controlling the site selectivity of the distal C−H bonds in alkanes. Correspondingly, we observed the electronic effect of pyridone motifs to have a significant effect on controlling the overall site selectivity between γ and δ positions (Scheme 1D,E). An electron-deficient pyridone motif, by virtue of making the metal catalyst more electron-deficient, shifts the selectivity toward γ functionalization, while pyridones having an electron-donating group attached to it predominantly leads to the δ-selective thioarylation (Scheme 1E).

The presence of thioaryl motifs as important structural cores is observed in diverse pharmaceutical drugs and complex molecules.[21,22] Additionally, organosulfur compounds are known for their presence in various biological systems, thus holding a prime position in drug derivatives and complex molecules alike.[23] Inspired by the demand for the incorporation of a thioaryl motif into distal positions of aliphatic moieties and the generation of ligand-modulated orthogonal selectivity between the distal δ and γ positions on the same alkyl amine, we herein report the orthogonal thioarylation between the γ and δ positions of long-chain aliphatic picolinamides via the modulation of a ligand (Scheme 1D,E).

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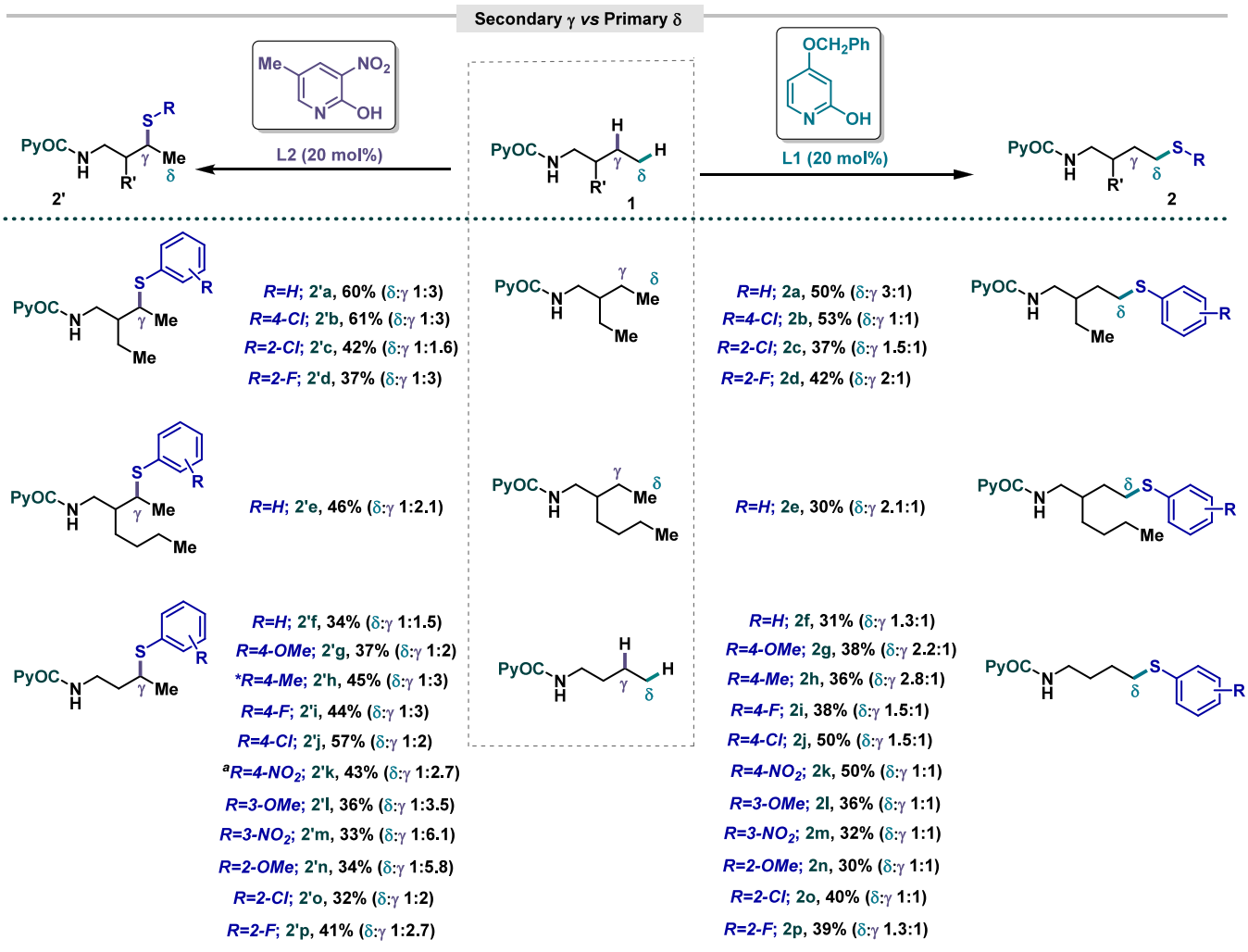
Table 1. Scope of Ligand-Controlled Orthogonal Selectivity between Long-Chain Picolinamides Having Secondary γ versus Primary δ C−H Bonds[a]



[a]Selectivities mentioned are from MNR or HPLC of the crude reaction mixture. Isolated yields. Both the gamma (γ) and delta (δ) compounds are separately isolated and characterized. TMB was used as an internal standard for NMR of the crude reaction mixture. For HPLC of the crude reaction mixture, reactions were run in a chiral OD-H column with a ratio of hexane:EtOAc of 95:5. [a]2-OH-5-CF_3 as the ligand. *Isoquinoline-3-carboxylic acid was used as the directing group. Reaction conditions: **1** (0.1 mmol), R_2S_2 (2.0 equiv), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), AgOAc (3 equiv), TFT (2 mL), 130 °C, 24 h.

2. MATERIALS AND METHODS

In previous reports, the judicious choice of substrates gave way for six-membered cyclopalladation over the corresponding five-membered one. At the outset of our studies, we set about understanding the nature of intermediates that will be successful in promoting such distal site selectivity of aliphatic amines guided by picolinic acid-based directing groups. The α substitution controls the rigidity of the cyclometalated intermediate, while the substitutions at the γ position play with the statistical factor, rendering the functionalization improbable at any other position apart from δ (Scheme 2A, **Int. E**).[8b] Once we introduce the removal of substitutions from the γ positions, the statistical factor begins to diminish. However, the presence of at most two substituents at the γ position makes the five-membered cyclopalladation unfavorable through a combination of statistical and steric factors (Scheme 2A, **Int. B**). On the other hand, removal of each α substituent destabilizes the C−H-activated intermediate, which is a direct consequence of the Thorpe−Ingold effect (Scheme 2A, **Int. C** and **D**). Thus, X-ray crystallography shows that while systems with flexibility at the α and γ positions struggle to stabilize the C−H-activated intermediate, this instability does not prevent effective functionalization but the lifetime of the intermediates (Scheme 2A). Despite kinetic instability, thermodynamics drive the reaction forward, enabling facile C−H functionalization. Focusing our efforts on butyl amine, wherein both the rigidity and the statistical inaccessibility are lost, renders both γ and δ positions feasible for C−H activation (Scheme 2A, **Int. A**). Further, the Thorpe−Ingold effect loses its prominence. The question that arises then is how do we control the five-membered vs six-membered cyclopalladation? However, in such a case, we found the formation of six-membered δ C−H activation to be more favored over the corresponding γ C−H-activated intermediate mainly because of a primary C(sp^3)−H bond being more facile for activation compared to a secondary C(sp^3)−H one.[24] Consequently, we presumed that using auxiliary mediated butyl amine as a

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substrate should give us selective δ C−H thioarylation under a set of reaction conditions, but we could only obtain a 1:1 selectivity of the γ- and δ-functionalized products.[25] The challenge therefore lies in developing reaction conditions that will enable selective functionalization in each of the distal δ and γ positions. For our initial attempts at functionalizing the active positions of such long-chain picolinamides, we utilized a range of 2-hydroxy-substituted pyridine ligands. We observed that employing a pyridone ligand having an electron-withdrawing group at the 3 or 5 position helped us attain selective γ C(sp^3)−H thioarylation, while reversing the electron density on the pyridone ring, that is, utilizing one with an electron-rich group at the 4 position, provided a selective δ-thioarylated product. To gain further insights toward such a change in selective functionalization by varying the electronic nature of the ligand, we carried out DFT studies. From computational analysis, we observed that the influence of pyridone ligands toward chemoselectivity could be examined by natural population analysis (NPA). The NPA charges of the nitrogen atom of pyridone containing an electron-rich motif attached to it (4-benzyloxy-2-hydroxy pyridine, **L1**) is found to be lower compared to one having an electron-deficient moiety on the pyridone ring (2-hydroxy-3-nitro-5-methylpyridine, **L2**). These results indicate that the ligand effect on chemoselectivity can be guided by electronic repulsions, with electron-rich pyridone ligands hypothesized to favor selective distal δ functionalization while electron-deficient pyridone ligands expected to tune the selectivity favorably toward the γ position, correlating with our experimental observations. Consequently, we hypothesized that β-H elimination plays an important role in driving the reaction protocol. After the formation of the δ C−H-activated intermediate, the reaction pathway has two possibilities. An electron-withdrawing pyridone ligand by virtue of making the Pd-metal more electron-deficient opens up the possibilities of a facile β-H elimination to transform the six-membered C−H-activated intermediate to a corresponding five-membered metallacycle. A similar Pd-catalyzed remote desaturation of aliphatic amines via β-H elimination has been explored in detail by Gevorgyan and Yu groups involving ferrocene and benzoquinone motifs as ligands, respectively.[26] This five-membered intermediate then undergoes several standard steps to provide the γ-thioarylated product selectively. In sharp contrast, an electron-rich pyridone ligand, due to its inability to transform the Pd into a more electron-deficient species, does not adhere to β-H elimination. In turn, it undergoes ligand exchange with the disulfide, accommodating it to generate the δ-thioarylated product in a selective fashion. Consequently, the δ-selective product was found to be favored by electron-rich pyridones, and the preference in selectivity can be controlled by tuning the electronic nature of the ligand, providing a suitable generality of the nature of the ligand that could control the formation of δ- and γ-functionalized products orthogonally. Indeed from both kinetic and theoretical insights, a combination of statistical and electronic factors was found to be crucial in an attempt to induce orthogonal selectivity between the γ and δ C(sp^3)−H positions.

We focused on employing β-substituted butyl amine as a substrate guided by a picolinic acid-based auxiliary and selecting suitable ligands that will generate orthogonal selectivity between the δ and γ positions. This forms a class of substrates involving primary δ C−H bonds and secondary γ C−H bonds, where both positions are compatible for selective functionalization. Our initial hypothesis and theoretical insights led us to developing a suitable ligand−substrate compatibility that will provide orthogonal selectivity between such γ and δ positions of β-ethyl-substituted butyl amine for our thioarylation protocol. In conjunction with it, we found 2-hydroxy-3-nitro-5-methylpyridine (**L2**) to be the optimum ligand among all providing us with a yield of 60% and a δ:γ selectivity of 1:3 (Table 1, entry **2'a**). Gratifyingly, we could isolate and X-ray crystallographically characterize a Pd−Pd dimeric complex, accommodating the amide substrate, metal catalyst, and **L2** ligand (Figure 2B, **Int. F**). We observed **Int. F** to be catalytically competent under the reaction conditions, suggesting it to be a crucial component in the reaction mechanism. From the kinetic competency of **Int. F**, it was observed that this intermediate is less active than $Pd(OAc)_2$. However, the activity of **Int. F** can be enhanced by the external addition of AcOH, suggesting the acetate anion to have a primary role in the overall reaction mechanism. Similarly, reversing the electronic nature completely to pyridone ligands having electron-rich groups attached to it contributed to more selective δ C−H thioarylation. Optimizing various electron-rich pyridone ligands, the use of 4-benzyloxy-2-hydroxy pyridine (**L1**) was found to be the optimal ligand with a δ:γ selectivity of 3:1 and a product yield of 51% (Table 1, entry **2a**). Among all metal catalysts, $Pd(OAc)_2$ seemed to be significantly better for the protocol, while Ag_2CO_3 was employed as the preferred oxidant over other silver or copper salts.[25] α,α,α-Trifluorotoluene was utilized as a solvent for both γ and δ C−H thioarylation, and the reactions were carried out at 130 °C for a duration of 24 h. With the final optimized conditions for both the cases and with all other reaction conditions remaining the same and the nature of the ligand only determining the orthogonal selectivity between the γ and δ positions, we delved into understanding the scope and limitations of our protocol. 4-Chloro-substituted disulfide led to incongruously low δ selectivity utilizing **L1** as the ligand; however, employing **L2** as the ligand provided a 62% yield of the desired product with a δ:γ selectivity of 1:3 (Table 1, entries **2b** and **2'b**). Nonetheless, 2-substituted disulfides gave the corresponding δ- and γ-functionalized products orthogonally employing **L1** and **L2** as ligands, respectively, with moderate yields and selectivity (Table 1, entries **2c**−**2d** and **2'c**−**2'd**). Introducing a butyl group at the β position of an auxiliary-mediated butyl amine was also found to be compatible in synthesizing the orthogonal δ- and γ-thioarylated compounds with the corresponding ligands (**L1** for δ selectivity and **L2** for γ selectivity). Diphenyl disulfide proved consistent in generating the orthogonal selectivity in such motifs (Table 1, entries **2e** and **2'e**). Interestingly for selective δ functionalization, the shorter alkyl chain of 2-ethylhexylamine was preferentially functionalized over the longer one presumably because of the more favorable primary C−H activation compared to the secondary ones.[24] Upon having an idea about the nature of substitution at the β position of such auxiliary-mediated butyl amines and their compatibility toward producing orthogonal selectivity between the γ and δ positions, we proceeded to examine the possibility of synthesizing such orthogonally functionalized products on substrates devoid of any branching. We examined the compatibility of picolinic acid-protected butyl amine toward our optimized reaction protocol, an aliphatic amine having a primary δ sp^3 C−H bond and a secondary γ C−H bond. Gratifyingly, we observed orthogonal selective δ- and γ-thioarylated products, albeit with moderate yields and selectivities, only by tuning the electronic

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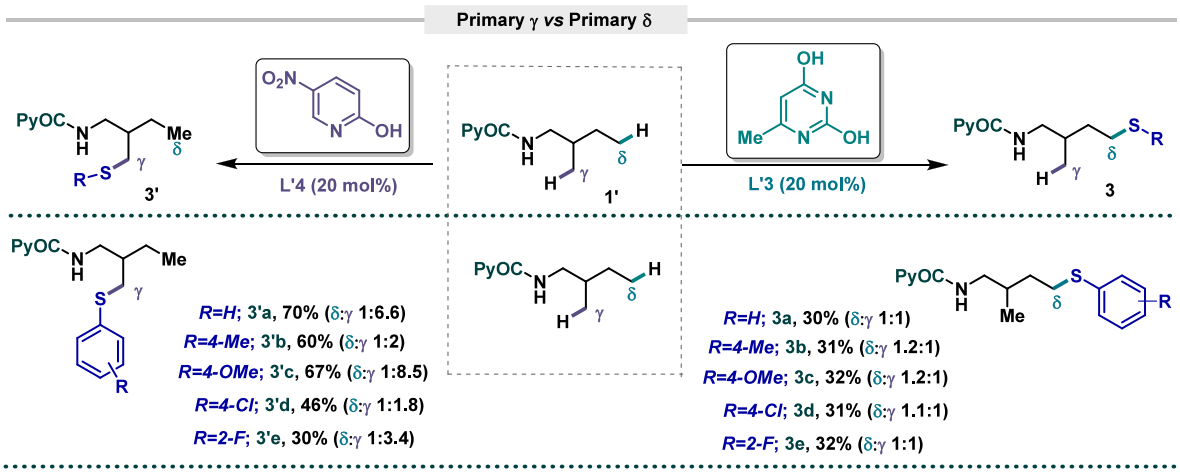
Table 2. Scope of Ligand-Controlled Orthogonal Selectivity between Long-Chain Picolinamides Having Primary γ vs Primary δ C−H Bonds[a]



[a]Selectivities mentioned are from NMR or HPLC of the crude reaction mixture. Isolated yields. Both the gamma (γ) and delta (δ) compounds are separately isolated and characterized. For NMR of the reaction mixture, TMB was used as an internal standard. For HPLC of the reaction mixture, reactions were run in a chiral OD-H column with a hexane:EtOAc ratio of 95:5. Reaction conditions: **1** (0.1 mmol), R_2S_2 (2.0 equiv), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), AgOAc (3 equiv), TFT (2 mL), 130 °C, 24 h.

nature of the ligand. A variety of disulfides were found to be consistent toward generating orthogonal selective products. Employing an electron-rich disulfide predominantly tilts the selectivity toward the δ position, while greater γ selecitivity was observed in the case of disulfides having an electron-deficient motif attached to it. In the case of 1,2-bis(4-methoxyphenyl)-disulfide, utilizing **L1** as a ligand, the δ-thioarylated product was obtained with a δ:γ selectivity of 2.2:1 (Table 1, entry **2g**). Under the same reaction conditions, just tuning the ligand to **L2** provided a γ-selective thioarylated product (Table 1, entry **2'g**). Interestingly, the reaction performed more efficiently with the use of an isoquinoline-mediated directing group in the case of *p*-tolyldisulfide, resulting in concise generation of the γ-selective product in a δ:γ ratio of 1:3 (Table 1, entry **2'h**).[25] Other halogen substituents as well as electron-deficient moieties such as the $-NO_2$ group at the 4 position of the disulfide group worked suitably well with **L1** and **L2** as ligands to generate the orthogonal δ- and γ-thioarylated products (Table 1, entries **2i**−**2k** and **2'i**−**2'k**). Likewise, the electronic nature of 3-substituted disulfides also did not have much detrimental effect toward the δ and γ selectivity. Exercising **L2** as a ligand led to moderate yields as well as selectivity of the γ-thioarylated product with not only electron-rich disulfides such as 1,2-bis(3-methoxyphenyl)disulfide but also with 1,2-bis(3-nitrophenyl)disulfide, a significantly electron-deficient disulfide (Table 1, entries **2'l** and **2'm**). Similarly, the expected δ-thioarylated product could also be synthesized using **L1** as a ligand, with both the disulfides, however with a mixed selectivity of 1:1 (Table 1, entries **2l** and **2m**). Extending it further to 2-substituted disulfides, the protocol was found to be compatible, with the δ and γ orthogonal selectivity being maintained with both −OMe as well as −Cl-containing disulfides (Table 1, entries **2n** and **2o** and **2'n** and **2'o**). This reveals the generality of our methodology with varying degrees of long-chain picolinamides as well as disulfides, generating orthogonal selectivity between the distal δ and γ positions on the same aliphatic amine guided by an auxiliary, just by tuning the ligand, with all other reaction parameters remaining constant.

Having gained insight into systems bearing primary δ and secondary γ C−H bonds, we turned our attention to substrates in which the selectivity has to be determined between primary δ and primary γ C−H bonds. We examined the instance of 2-methyl butyl amine to be the most general example of such classes of long-chain picolinamides. Optimization of metal catalysts, oxidants, solvents, and the quantity of disulfide used resulted in the same conditions being employed for the previous class of substrates to be consistent for this class, for both selective γ and δ C−H thioarylation. Optimization of ligands gave rise to similar conclusions with regard to previously successful substituted pyridone ligands for selective γ functionalization but proved ineffective for thioarylation of primary δ C−H bonds. Consistent with our hypothesis of an electron-withdrawing group on the pyridone ligands improving the capability of the reaction to proceed through a five-membered metallacycle, the 2-hydroxy-5-nitro pyridine (**L'4**) ligand was found to be the best among them with a 68% yield and a δ:γ selectivity of 1:6.6. However, unlike our studies on a previous class of substrates (primary δ and secondary γ sp^3 C−H bonds), electron-rich groups on the pyridone ligand failed to provide us with a selective δ-thioarylated product. Inspired by literature reports utilizing pyridine and quinoline ligands for aliphatic C(sp^3)−H functionalization,[27] we started studying a series of pyridine and quinoline ligands, only to observe all these ligands being successful in generating selective the γ C−H thioarylated product compared to our desired δ-functionalized product. We hypothesized that in the event of a competition between two primary C−H bonds, the tendency of the protocol proceeding through more favored five-membered metalation becomes more probable compared to the involvement of the less favored six-membered cyclometallic intermediate, thus the reason for excellent γ selectivity over the δ C−H bond for a wide range of ligands. Hypothesizing the need to incorporate a stronger coordinating ligand along with the requirement of an electron-donating effect on the ligand to shift it from a favored five-membered to a less favored six-membered one and in turn overcoming the more suitable γ functionalization to change the selectivity toward the less

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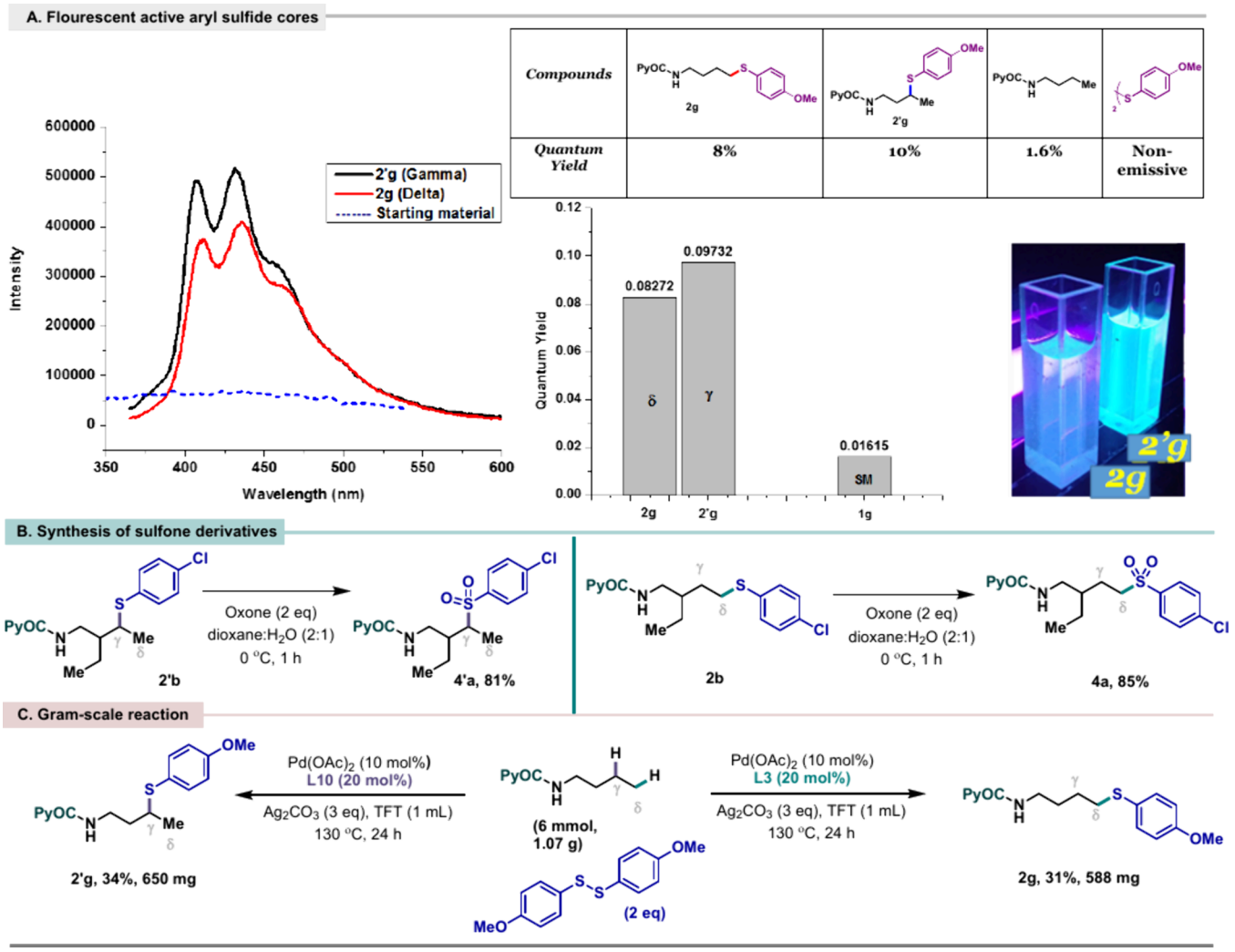
Scheme 3. Applications and Scalability of Our Methodology: (A) Fluorescence Activity of the Synthesized Compounds, (B) Synthesis of γ and δ Sulfones from Their Respective Characterized Thioarylated Compounds, and (C) Gram-Scale Reaction in Each of the γ and δ Case



preferred δ position, we forged the idea of employment of 2-hydroxy-pyrimidine ligands with an electron-donating group embedded in it. Consequently we started optimizing various electron-rich hydroxy-substituted pyrimidine ligands. Intriguingly, the application of a dihydroxy-pyrimidine ligand proved successful in reversing the selectivity, with 6-methylpyrimidine-2,4-diol (**L'3**) proving to be the optimum ligand for δ thioarylation with a yield of 33% albeit with a δ:γ selectivity of 1:1. Undertaking the reaction with all other ligands proved unsuccessful in generating selective δ-functionalized product; however, with the use of hydroxy-substituted pyrimidine ligands, we were able to reverse the selectivity from the inherently kinetically favored γ position toward a slightly δ-selective nature of the product, which is a highly disfavored position for the given class of substrates. Upon the development of optimized conditions, we set about understanding the scope and limitations of our protocol. With picolinic acid-mediated 2-methyl butyl amine as the substrate, a range of disulfides were adaptable for both selective γ and δ thioarylation. Enabling **L'4** as the ligand, a range of substituted disulfides were found to be compatible for selective γ C−H functionalization with excellent yields and selectivities (Table 2, entries **3'a**−**3'e**). Focusing on our objective of successfully enabling orthogonal selectivity between the γ and δ positions, the corresponding δ C−H thioarylated products with the same disulfides were also successfully obtained engaging **L'3** as the desired ligand for the δ C−H bond, albeit with poorer selectivities (Table 2, entries **3a**−**3e**). Both the nature of disulfide and substituents in the alkyl amine seem to have a relatively small effect on the selectivity trend. However, unfortunately, an obvious trend on the effect of the electronics of diaryl disulfide toward the selectivity of γ- and δ-functionalized products cannot be completely extracted.

Following an understanding of the scope and limitations of our protocol, we attempted to acquire potential applications of our newly developed compounds. Sulfur quantum dots are a new class of metal-free fluorescent nanomaterials, which have been probed with significant detail in the past 5 or 6 years primarily because of their applications in bioimaging and biosensing.[28] Additionally, sulfoxide or sulfone with electron-deficient characteristics is an attractive source for electron injection and transportation.[28e] Consequently, such sulfur-based compounds are an appealing building block for the new generation of OLED's. Since our synthesized δ and γ sulfide derivatives are prone to conversion to sulfones and due to the ability of sulfur-containing compounds acting as effective

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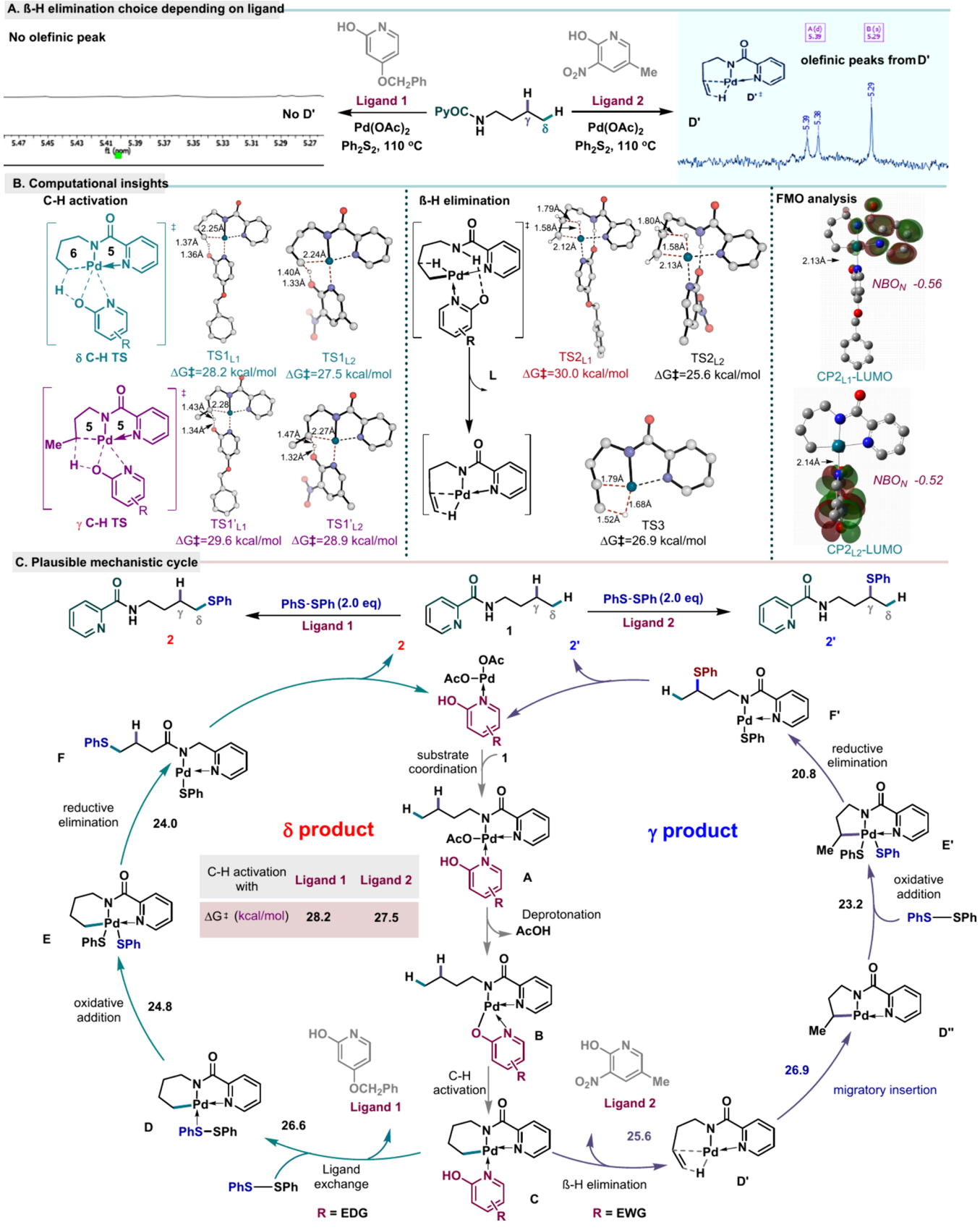
Scheme 4. Kinetic and DFT Investigations: (A) β−H Elimination Choice Depending on the Nature of the Ligand, (B) Computational Insights toward Orthogonal Selectivity, and (C) Plausible Mechanistic Cycle



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fluorescent materials, we designed to probe the fluorescent activity of our compounds. Our studies involved observing the photophysical properties with respect to the emission and absorption maxima in chloroform (Table 1, entries **2'g** and **2g**). We observed the pair of compounds to be fluorescent active. As shown in Scheme 3A, the emission wavelengths of compound **2g** lie in the blue-green region of the spectrum with an emission maximum of 435 nm. Similarly, its corresponding γ analogue **2'g** also shows an emission maximum of 431 nm corresponding to its blue-green emission as depicted in Scheme 3A. On comparing with our starting analogues, substrate **1g** and the corresponding disulfides (4-methoxy disulfide, 4-fluoro disulfide, and 4-nitro disulfide), we observed all of the starting materials to have a significantly lower quantum yield compared to our synthesized δ and γ sulfide derivatives (Scheme 3A). While the disulfides are nonemissive in nature, our starting analogue **1g** shows a quantum yield of about 1.6%, which depicts that fluorescence activity is observed from our synthesized thioarylated compound and not generated from the core motif. Correspondingly, our derivatized δ and γ products could be employed as low-toxicity metal-free fluorescent dyes and materials having a quantum yield between 8 and 10%. Interestingly, we observed the γ compound (**2'g**) to have a slightly higher quantum yield (10%) compared to its δ analogue (**2g**) (8%). This could be attributed to the slightly higher intramolecular H-bonding that is possible within the γ isomer (due to proximity) compared with the δ-thioarylated compound. The intramolecular H-bonding lowers the energy of the amide n orbital, consequently increasing the energy of the n−π^* state.[29] This reduces the probability of undergoing intersystem crossing, thereby showing a greater fluorescence activity and higher quantum yield. Additionally to understand the practicability of our transformation, we applied our orthogonal γ and δ products to oxidation with oxone generating sulfone of the corresponding products successfully in each of the cases (Scheme 3B, entries **4a** and **4'a**). The feasibility of our transformation was further established by the gram-scale synthesis of both our γ and δ protocols with similar yields and selectivity as in the small-scale reactions, extending our methodology to the synthesis of desired products in large quantities as well (Scheme 3C, entries **2g** and **2'g**).

In an attempt to give a conclusive justification to the hypothesis about the electronic nature of ligands, a series of kinetic experiments were carried out. Undertaking the Hammett plot with 3-substituted pyridone ligands, which mainly partake in the formation of γ-selective product, gives a ρ value of 0.23 (Scheme 5B). A positive ρ value indicates a decrease in electron density to be successful in generating higher selectivity of the γ C−H thioarylated product.[30] Similar correlations were drawn with 4-substituted pyridone ligands, which are found to generate higher δ selectivity compared to the γ product. A ρ value of −0.16 was obtained, suggesting the increase in electron density to be imperative for generating higher selectivity of δ C−H thioarylation.

Further, order determination studies with 4-benzyloxy-2-hydroxypyridine as a ligand led to order with respect to the disulfide moiety to be zero, while the order with respect to the amide, ligand, and catalyst to be unity, suggestive of the fact that the amide, ligand, and the metal catalyst might be involved in the rate-determining step while the disulfide moiety is not (see the Supporting Information for further details). From the kinetic studies, it was observed that an individual variation of the metal catalyst and the ligand gave an order of 1 each, suggesting both the metal catalyst and the ligand are likely to be involved in the rate-determining step of the reaction protocol. Additionally, we carried out order studies with a dependent variation of the metal catalyst and the ligand (x mol % of the catalyst +2x mol % of the ligand).[31] We observed an order close to 1.2, which suggests probable involvement of the metal−ligand complex in the rate-determining step of the reaction mechanism. Finally, to investigate whether a radical reaction is in force, up to three equivalents of radical scavengers were added under the standard reaction conditions.[32] The reaction yield and selectivity remaining unchanged in such an instance suggest a radical mechanism to be highly unlikely. With these findings in hand, density functional theory (DFT) calculations were used to gain insight into the origin of orthogonal selectivity and provide deeper understanding of the effect of ligands (see the Supporting Information for full computational details).

The corresponding δ and γ C−H cleavage transition states with ligand **L1** and **L2** are presented in Scheme 4B. The transition structure **TS1** for δ C−H activation has the characteristic [5,6]-palladacycle and **TS1'** for γ C−H activation has the characteristic [5,5]-palladacycle. The calculations showed that C−H bond activation for δ functionalization is 1.4 kcal/mol more favorable than that of γ functionalization with both ligands. It was obvious that the [5,6]-membered coordination with the favored ring strain is preferred over the [5,5]-membered coordination.

These results indicate that C−H cleavage is not the selectivity-determining step for the γ-selective product. Lin's group reported that the β-hydrogen elimination reactions of five- or six-membered rings occurs easily in several metallacyclic complexes.[33] The corresponding β-hydrogen elimination processes of [5,6]-palladacycle intermediates were compared to investigate the effect of ligands on site selectivity. β-H Elimination with ligand **L2** via transition state $\mathbf{TS2}_{L1}$ requires an activation barrier of 25.6 kcal/mol. Subsequent intramolecular alkene migratory insertion to the Pd−H bond via transition state **TS3** was found to have an activation energy of 26.9 kcal/mol from a [5,5]-palladacycle complex, which can give the corresponding γ product. When the pyridone ligand **L2** is replaced by the ligand **L1**, the relative free energy of β-hydrogen elimination $\mathbf{TS2}_{L2}$ is 4.4 kcal/mol higher than that of the transition state $\mathbf{TS2}_{L1}$. Our calculations indicate that β-H elimination of [5,6]-palladacycle with ligand **L2** is feasible, while it was found to be unfavorable with ligand **L1**. These results are in agreement with experimental observations where the reaction with 4-benzyloxy-2-hydroxy pyridine (**L1**) resulted in a δ-thioarylated product, and 2-hydroxy-3-nitro-5-methyl pyridine (**L2**) resulted in the corresponding γ-functionalized product. The complete free energy profiles of favorable selectivity between δ and γ positions with ligands **L1** and **L2** are presented in the Supporting Information. On the basis of these data, the C−H activation process is the rate- and site selectivity-determining step for the δ-selective product. The β-hydrogen elimination process is identified as the site selectivity dominant step for the γ-selective product. This result is consistent with our first-order kinetics and experimental studies. Experimentally, undertaking the reaction with **L2** as the ligand in the presence of a disulfide coupling partner, olefin peaks were observed at 5.39 and 5.29 ppm, justifying the involvement of β-H elimination to form the intermediate **D'** (Scheme 4A). In contrast, a similar reaction

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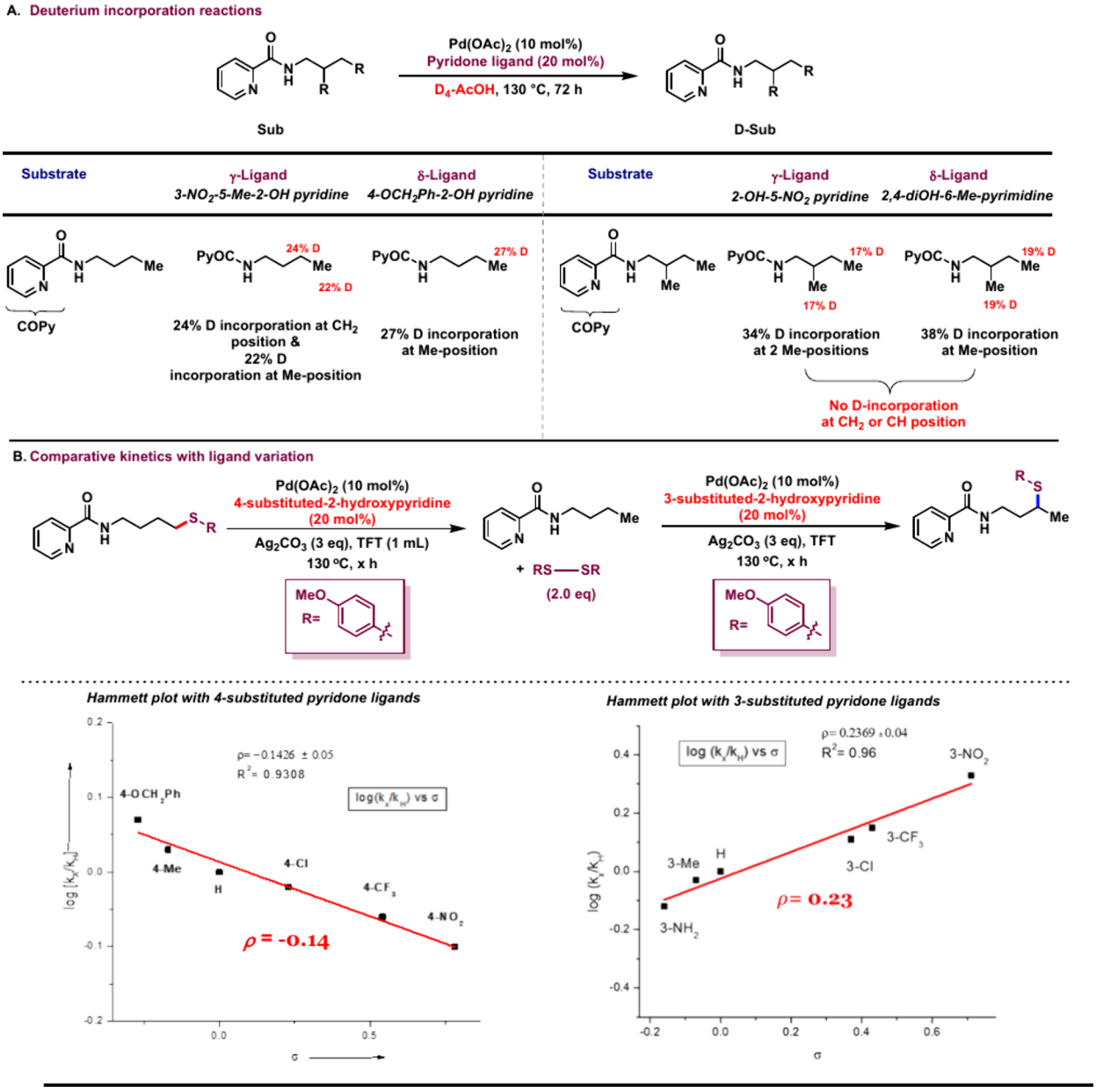
Scheme 5. Mechanistic Investigations: (A) Deuterium Incorporation Reaction on Both Classes of Substrates and (B) Hammett Plots with 3-Substituted and 4-Substituted Pyridone Ligands



with **L1** as a ligand gave rise to no such olefin peak, enhancing the nonparticipation of β-H elimination for the δ-thioarylated product; rather, a ligand exchange pathway is operative. Additionally, undertaking the reaction with 3-buten-1-amine as a substrate in the presence of **L2** as a ligand showed the presence of the same two olefin peaks at 5.39 and 5.29 ppm, supporting further the involvement of intermediate **D'** through the β-H elimination pathway for regioselective γ C−H functionalization. To further reveal the significant role of ligands in the origin of regioselectivity, NPA charge and FMO analyses were performed to the key [5,6]-palladacycle intermediates. The NPA charges of N atoms of $\mathbf{CP2}_{L1}$ and $\mathbf{CP2}_{L2}$ are −0.56 and −0.52, respectively, which indicates that the electrophilicity of $\mathbf{CP2}_{L2}$ is slightly higher than that of $\mathbf{CP2}_{L1}$ and easier to accept electrons. Calculated LUMOs in Scheme 4B show that the LUMO of $\mathbf{CP2}_{L2}$ is mainly localized on the ligand, and most of the LUMO of $\mathbf{CP2}_{L1}$ is localized on the substrate, which also implies the electron-withdrawing nature of ligand **L2**. These results indicate that electrophilicity effects with the pyridine ligand provide the greatest contribution to the γ C−H selectivity. In the case of systems having a primary γ C−H bond and a primary δ C−H bond, the protocol follows a different mechanism. A similar migration, which is prone to other classes of substrates, would result in γ methylene thioarylation of the aliphatic chain. However, we observe selective γ methyl functionalization over the methylene positions, which suggests that the two ligands distinctively control the position of the C−H activation step. Additionally, on conducting deuteration experiments with 2-methyl butyl amine substrate (**1'**), we found no deuteration to occur at the CH_2 or CH position. Using the corresponding γ ligand (2-hydroxy-5-nitro pyridine), 34% D-incorporation was observed only at the terminal methyl positions (Scheme 5A). No deuteration was observed at the methylene position or at the

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tertiary CH position. Similarly, using the corresponding δ ligand (2,4-dihydroxy-6-methyl pyrimidine), 38% D-incorporation was observed only at the terminal methyl positions. In stark comparison, with a butyl amine substrate (1), using the δ ligand (4-benzyloxy-2-hydroxy pyridine), we obtained 27% D-incorporation only at the terminal methyl positions. No deuteration was observed at the methylene position. Similarly, using the corresponding γ ligand (2-hydroxy-3-nitro-5-methylpyridine), 24% D-incorporation was observed at the desired methylene position, and 22% D-incorporation was observed at the terminal methyl position. This result explains why we get a preferential δ C−H activation initially with both ligands followed by a β-hydride elimination to produce the γ C−H-activated intermediate in the case of electron-deficient pyridone ligands. Thus, two different mechanisms are likely to be observed for the butyl amine substrate (**1**) and 2-methyl butyl amine substrate (**1'**). Further mechanistic investigations along with theoretical calculations are currently underway in our laboratory.

Through all the above performed kinetic and theoretical understandings, a plausible mechanistic cycle is proposed as in Scheme 4C. The Pd(II) species catalyst first coordinates with the substrate followed by deprotonation of the counteranion to result in the formation of intermediate **B**, having a bidentate form of coordination of the ligand. The δ C−H activation occurs by concerted-metalation deprotonation (CMD) to form a [5,6]-palladacycle, and the nature of the ligand determines the future pathway of the reaction. With an electron-donating ligand, ligand exchange of disulfide with the corresponding ligand succeeds in this step accompanied by oxidative addition with disulfide followed by reductive elimination and protonation resulting in formation of the corresponding δ-thioarylated product. With an electron-withdrawing ligand, β-hydrogen elimination and migratory insertion are favored to form the [5,5]-palladacycle complex, preceding the similar subsequent steps to favor the formation of the γ C−H thioarylated product.

3. CONCLUSIONS

In summary, we have developed an approach to functionalize long-chain alkyl picolinamides orthogonally between the γ and δ positions, solely by the tuning of the ligand. Two classes of amines having varying substituted γ and δ C−H bonds have been tested along with a variety of diverse disulfides. The choice of the ligand is highly significant to adjust the selectivity in each class of substrates. The strategy developed herein can be used as a general principle for the selective functionalization of γ and δ C−H bonds in the case of two classes of aliphatic amines, thus paving the way for a general classification of the types of ligands and reaction conditions required to functionalize both the positions in such alkyl C−H bonds.

3.1. General Procedure for Ligand-Enabled δ C−H Thioarylation of Long-Chain Picolinamides. In a clean, oven-dried screw-cap reaction tube containing a magnetic stir bar, long-chain picolinamides (0.1 mmol), $Pd(OAc)_2$ (10 mol %, 0.01 mmol), corresponding ligand (20 mol %, 0.02 mmol), disulfide (2 equiv, 0.2 mmol), and silver carbonate (3 equiv, 0.3 mmol) were weighed. A common laboratory syringe was used to introduce TFT (2 mL) into the reaction mixture. Then, the tube was placed in a preheated oil bath at 130 °C, and the reaction was stirred (at 1000 rpm) vigorously for 24 h. After taking out the reaction, it was cooled to room temperature and filtered through a Celite pad using ethyl acetate (30 mL). The solvent was removed in a rotatory evaporator. The desired compound was extracted using EtOAc, and the combined organic layer was dried over Na_2SO_4. Finally, it was concentrated in reduced pressure and was purified by column chromatography through silica gel (100−200 mesh size) using PET-ether/ethyl acetate as an eluent.

3.2. General Procedure for Ligand-Enabled γ C−H Thioarylation of Long-Chain Picolinamides. In a clean, oven-dried screw-cap reaction tube containing a magnetic stir bar, long-chain picolinamides (0.1 mmol), $Pd(OAc)_2$ (10 mol %, 0.01 mmol), corresponding ligand (20 mol %, 0.02 mmol), disulfide (2 equiv, 0.2 mmol), and silver carbonate (3 equiv, 0.3 mmol) were weighed. A common laboratory syringe was used to introduce TFT (2 mL) into the reaction mixture. Then, the tube was placed in a preheated oil bath at 130 °C, and the reaction was stirred (at 1000 rpm) vigorously for 24 h. After detaching the reaction, it was cooled to room temperature and filtered through a Celite pad using ethyl acetate (30 mL). The solvent was removed in a rotatory evaporator. The desired compound was extracted using EtOAc, and the combined organic layer was dried over Na_2SO_4. Finally, it was concentrated in reduced pressure and was purified by column chromatography through silica gel (100−200 mesh size) using PET-ether/ethyl acetate as an eluent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c03126.

Full experimental details for the preparation of all new compounds and their spectroscopic and chromatographic data as well as DFT studies (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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