Ligand controlled orthogonal selectivity between distal positions of fully unbiased aliphatic amines

Soumya Kumar Sinha[1ǂ], Nupur Goswami[1ǂ], Yingzi Li[2ǂ], Suman Maji[1], Anjana S. S.[1], Srimanta Guin[1], Robert S. Paton[2]* and Debabrata Maiti[1]*

[1]Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India. dmaiti@iitb.ac.in
[2]Department of Chemistry, Colorado State University, Fort Collins, CO 80523-1872, USA. robert.paton@colostate.edu

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 directing group approach however the regioselectivity in distal aliphatic positions has mostly been substrate dependent, with substrate biasness being a pre-requisite for distal C(sp^3)–H activation; a direct consequence of the Thorpe-Ingold effect. Extending the methodology to fully unbiased straight chain aliphatic substrates, in which all the available positions are sterically and statistically equally probable for functionalization and in which the Thorpe-Ingold effect loses its significance, has been a long-standing problem. To this aim, we developed a ligand enabled orthogonal selectivity between the proximal γ and distal δ positions of such fully unbiased straight chain aliphatic amines in a regioselective fashion. These straight chain alkyl amines, though both δ and γ positions are equally probable for functionalization, can be orthogonally functionalized between these two positions just by changing the ligand, all other reaction parameters remaining constant; signifying the immense importance of ligand in controlling the selectivity between the aforementioned positions of such inert aliphatic C(sp^3)–H bonds. Experimental as well as DFT studies have been carried out to generalize the nature of ligand that would be promoting the orthogonal selectivity between these positons, with electron-rich pyridone ligands favoring selective distal δ functionalization while electron-deficient pyridone ligands tuning the selectivity favorably towards the γ position. This regioselective orthogonal selectivity tuned from γ to δ positions have also been mechanistically established through control reactions, kinetic studies and theoretical calculations.

The advent of C–H activation has opened up vast levels of synthetic strategies towards a diverse range of organic transformations.[1-14] The drawback involving the specific site-selectivity can be overcome by the judicious use of C–H activation techniques. However, the similar bond strength and chemical properties of indistinguishable 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 metal to distinguish between the similar primary and secondary bonds inexplicably adds up to the challenge. The employment of directing group has laid a platform towards the proximal functionalization of sp^3 C–H bonds which experiences a five-membered intermediate. Regulating the selectivity towards the distal position requires employment of effective strategies that will modify the metalation step towards a six-membered palladation over the more favored five-membered one.[15] In recent times, several groups have applied the use of directing group strategy to enable distal C(sp^3)–H functionalization through the participation of less favored six-membered cyclometalation (**Scheme 1A**). [16-25] In 2016, Shi group envisioned the application of Curtin-Hammett principle to selectively functionalize the δ sp^3 C–H bonds, which proceeds through the kinetically less-favored six-membered metalacycle over the more favored γ sp^3 C–H bonds.[26] Two years later, Yu group employed the transient directing group strategy to functionalize the distal position of aliphatic amines, although the nature of functionalization is dependent on designing of the biased substrate and positions that are available for functionalization[27] (**Scheme 1B**). In all these cases, specific site-selectivity has been achieved by incorporating steric biasness on the substrate, thus promoting distal C–H activation by blocking all the available positions for the kinetically favored proximal one, in turn making proximal positions both statistically and sterically inaccessible for functionalization; a direct consequence of Thorpe-Ingold effect (**Scheme 1C**). The implementation of a straight chain alkyl amine, in which both proximal γ and distal δ positions are statistically and sterically equally accessible for functionalization, and in which simple modulation of ligands results in orthogonal selectivity between these γ and δ positions has not been explored. In such cases, where both positions are open for functionalization, Thorpe-Ingold effect loses its significance rendering both γ and δ positions equally prone for functionalization. The challenge therefore lay in choosing a fully unbiased organic moiety and tuning the reaction conditions in a way to achieve orthogonal site-selectivity between the distal γ and δ C–H functionalization of the same molecule, thus providing the generality and in turn improving the synthetic applicability of the protocol.

The use of ligands has had 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.[28-30] A better σ-donating ligand binding allows the space for a comparatively poor donor substrate to get bound with the metal centre, such as, in case of Pd(II) 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 towards electrophilic palladation.[31] Looking at additional insight into the mechanism of ligands like chiral carboxylates,[32] mono-protected amino acids[33] reveal its incredible influence in controlling the stereoselectivity of the products. In recent years, there has been a resurgence in 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 C–H activation step.[34-36] This enormous importance of ligand made us dwell deep into the crucial role it might have in controlling the site-selectivity of the similar distal bonds in alkanes, which are otherwise inherently impossible to distinguish and functionalize. The presence of thioaryl groups is unmatched in pharmaceutical drugs and complex molecules.[37-40] Organosulphur compounds are known for their prevalence in infinite array of biological systems, rendering itself indisputable in drug derivatives and complex molecules alike.[41] 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 fully unbiased aliphatic amine, in turn overcoming the stark similarity of both positions to generate high site-selectivity; we herein report the realization of orthogonal thioarylation between the γ and δ positions of completely unbiased aliphatic amines *via* the modulation of ligand (**Scheme 1E**).

In the previous reports, the judicious choice of substrates give way for six-membered cyclopalladation over the corresponding five-membered one. At the outset of our studies, we set about understanding the nature of intermediate that will be successful in promoting such distal site-selectivity of aliphatic amines. 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 at any other position apart from δ improbable. As soon as we start removing the substitutions at the γ positions, the statistical factor starts diminishing. However, the presence of atmost two substituents at the γ positions make the five-membered cyclopalladation unfavourable through a combination of statistical and steric factors. Divulging our attention towards α substitutions, removal of each substituent engages in destabilizing the C–H activated intermediate, which is a direct consequence of the Thorpe-Ingold effect (**Scheme 1D,** Int. **B-E**). Focusing our efforts on butyl amine, both the rigidity as well as the statistical and sterically inaccessibility is lost, rendering both γ and δ positions equally prone for C–H activation (**Scheme 1D,** 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 in such a case? The challenge therefore lay in shrewd choice of ligands that will enable the orthogonal selectivity among the distal δ and γ positions. Our initial attempts at optimizing butyl amines with various ligands emanated in δ C(sp^3)–H thioarylation being promoted by electron-rich pyridone moieties while electron-withdrawing pyridones favored the selectivity towards γ C(sp^3)–H bond. Consequently five-membered cyclopalladation was accommodated by pyridones having an electron-withdrawing group attached to it and electron-donating groups promoted the orthogonal kinetically unfavored six-membered cyclometalation. From both kinetic and theoretical insights, electronic factor was found to be the most determining factor in controlling the five-membered vs six-membered metalation. The formation of six-membered δ C–H activation is favored over the corresponding γ C–H activated intermediate primarily because of a primary C(sp^3)–H bond being more facile for activation compared to a secondary C(sp^3)–H one. After the formation of δ C–H activated product, the reaction has two possibilities. On encountering an electron-withdrawing pyridone ligand, β-H elimination is favored significantly, primarily due to the strong metal-alkene bonding interactions which reduces the activation barriers for reaction pathway. The electron-deficient pyridone ligands in combination with the metal catalyst can suitably provide empty orbital to accept the electrons from the β-hydrogen atom; facilitating smooth β-H elimination to give the desired five-membered metallacycle. This then undergoes several standard reactions to provide γ-thioarylated product selectively. In sharp contrast, an electron-rich pyridone

ǂThese authors contributed equally to this work. *e-mail: [1]dmaiti@iitb.ac.in [2]robert.paton@colostate.edu

ligand, due to its inability to provide an empty orbital, does not confer itself to facile β-H elimination, in turn undergoing ligand exchange and accommodating the disulfide to generate the δ-thioarylated product in selective fashion. Consequently, the selectivity of δ product was found to be favored by electron-rich pyridones and the orthogonal selectivity was controlled by the electronic nature of ligand; providing a suitable generality of the nature of ligand that could control the formation of δ and γ-functionalized product orthogonally. To further elucidate the role of the pyridine ligands on δ and γ positions selectivity, the influence of the pyridine ligands for chemoselectivity was examined by natural population analysis (NPA). The NPA charges of the nitrogen atom of the 4-benzyloxy-2-hydroxy pyridine (**L1**) is -0.558, while it's -0.477 on the 2-hydroxy-3-nitro-5-methyl pyridine (**L2**). These results indicate that the ligand effect on chemoselectivity is mainly controlled by electronic repulsions, with electron-rich pyridone ligands favoring selective distal δ functionalization while electron-deficient pyridone ligands tuning the selectivity favorably towards the γ position.

Our initial attempts focused on employing ß-substituted butyl amine as substrate and selecting suitable ligands that will generate orthogonal selectivity between the δ and γ positions. This forms a class of substrate involving primary δ C–H bonds and secondary γ C–H bonds, where both δ and γ positions are equally prone for functionalization. Our initial hypothesis and theoretical insights led us to developing the suitable ligand-substrate compatibility that will provide orthogonal selectivity within γ and δ positions of ß-ethyl substituted butyl amine for our thioarylation protocol, in which the statistical and sterical probability of δ and γ positions to be functionalized remains intact. In conjuction with it, deploying electron-withdrawing groups at the 3- or 5-position of pyridone ligands such as $-NO_2$, $-CF_3$ group predominantly led to selective γ thioarylation, with 2-hydroxy-3-nitro-5-methyl pyridine (**L2**) being the optimum one among them with an yield of 60% and a γ:δ selectivity of 3:1 (**Scheme 2,** entry **2'a**). 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 bulky 4-benzyloxy-2-hydroxy pyridine (**L1**) was obtained to be the optimal ligand with δ:γ selectivity of 3:1 and product yield of 51% (**Scheme 2,** entry **2a**). Among all metal catalysts, $Pd(OAc)_2$ was seemed to be significantly better for the protocol while Ag_2CO_3 was employed as the preferred oxidant over other silver or copper salts.[42] α,α,α-Trifluorotoluene was utilized as solvent for both γ and δ C–H thioarylation and the reactions were carried out at 130 ℃ for a duration of 24 hours. With the final optimized conditions for both the cases and with all other reaction conditions remaining the same and the nature of 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 ligand, however employing **L2** as ligand provided 62% yield of the desired product with a γ:δ selectivity of 3:1 (**Scheme 2**, 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 selectivities (**Scheme 2**, entries **2c-2d**, entries **2'c-2'd**). Introducing a butyl group at ß-position of 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). Substituted as well as unsubstituted disulphides proved consistent in generating the orthogonal selectivity in such unbiased aliphatic amines (**Scheme 2,** entries **2e-2f**, entries **2'e-2'f**). Interestingly, the shorter alkyl chain of 2-ethyl hexylamine was preferentially functionalized over the longer one presumably because of the more favorable primary C–H activation compared to the secondary ones.[43] Upon having an idea about the nature of substitution at the ß-position of butyl amines and their compatibility towards producing orthogonal selectivity between the γ and δ positions, we proceeded to examine the possibility of synthesizing such orthogonally functionalized products on completely unbiased substrate, that is a substrate devoid of any branching. The most general example of such an amine having equal statistical and sterical probability of functionalizing the δ and γ positions, is butyl amine. Fascinatingly, the electronic nature of 4-substituted disulfides was found to control the nature of orthogonal selective products. Employing an electron-rich disulphide predominantly tilts the selectivity towards the δ-position while greater γ-selecitivity was observed in case of disulfides having an electron-deficient motif attached to it. In case of 1,2-bis(4-methoxyphenyl)disulfide, utilizing **L1** as ligand, δ thioarylated product was obtained with a δ:γ selectivity of 2.2:1 (**Scheme 2**, entry **2h**). Under the same reaction conditions, just by tuning the ligand to **L2** provided a γ-selective thioarylated product (**Scheme 2**, entry **2'h**). Interestingly, the reaction performed more efficiently with a better design of the directing group in case of p-tolyldisulfide, resulting in concise generation of γ selective product in a γ:δ ratio of 3:1 (**Scheme 2**, entry **2'i**). Other halogen substituents as well as electron-deficient moieties such as $-NO_2$ group at the 4-position of disulphide group worked suitably well with **L1** and **L2** as ligands to generate the orthogonal δ and γ thioarylated products (**Scheme 2**, entries **2j-2l**, entries **2'j-2'l**). Likewise, electronic nature of 3-substituted disulfides also did not have much detrimental effect towards the δ and γ selectivity. Exercising **L2** as 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(4-methoxyphenyl)disulfide but also with 1,2-bis(4-nitrophenyl)disulfide, a significantly electron-deficient disulfide (**Scheme 2**, entries **2'm** and **2'n**). Similarly, the expected δ thioarylated product could also be selectively synthesized using **L1** as ligand, with both the disulfides (**Scheme 2**, entries **2m** and **2n**). 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 (**Scheme 2**, entries **2o** and **2p**, entries **2'o** and **2'p**). This reveals the generality of our methodology to varying degree of amines as well as disulfides, generating orthogonal selectivity between the distal δ and γ positions, just by tuning the ligand, 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 fully unbiased 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 butylamine to be the most general example of such classes of completely unbiased aliphatic amines. Optimization of metal catalysts, oxidants, solvents and the quantity of disulfide used resulted in 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 regards 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 electron-withdrawing group on the pyridone ligands improving the capability of the reaction to proceed through a five-membered metallacycle, 2-hydroxy-5-nitro pyridine (**L'4**) ligand was found to be the best among them with 68% yield and γ:δ selectivity of 7:1. Inspired by literature reports utilizing pyridine and quinoline ligands for aliphatic C(sp^3)–H functionalization,[44-46] we started studying a series of pyridine and quinoline ligands, only to observe all these ligands being successful in generating selective 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 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 towards the less 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 an yield of 33% and a δ:γ selectivity of 1:1. Upon development of optimized conditions, we set about understanding the scope and limitations of our protocol. With 2-methyl-butylamine 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 (**Scheme 3**, entries **3'a-3'e**). Focussing 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 δ C–H bond, albeit with poorer selectivities (**Scheme 3**, entries **3a-3e**).

Compounds containing sulfur imbibed into it are known to show fluorescent activity and thus can be used as effective fluorescent materials.[47-50] Delving further into this, we wanted to observe the fluorescent properties of our synthesized γ and δ compounds. Our studies involved the characterization of three pairs of compounds (**Scheme 2**, entries **2'h** and **2h**, entries **2'j** and **2j**, entries **2'l** and **2l**) and we collected the emission spectra at their absorption maxima of all these three pairs. Gratifyingly, we observed all the compounds to be fluorescent active with the γ product having a greater quantum yield or being a better fluorescent molecule than its corresponding δ analogue (**Scheme 4A**). Interestingly, we further observed the quantum yield to be higher for compounds having an electron-donating group attached to it compared to those which have an electron-withdrawing moiety, justifying the greater fluorescent activity of the electron-rich δ and γ product. 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 4B**, 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 4C**, entries **4b and 4'b**).

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 partakes the formation of γ selective product gives a ρ value of 0.23. A positive ρ value indicates decrease in electron-density to be successful in generating higher selectivity of γ C–H thioarylated product.[51] Similar correlations were drawn with 4-substituted pyridone ligands which are found to generate higher δ selectivity compared to γ. A ρ value of -0.16 was

obtained, suggesting the increase of electron-density to be imperative for generating higher selectivity of δ C–H thioarylation.[42] Further, order determination studies with 4-benzyloxy-2-hydroxypyridine as ligand led to order with respect to disulfide moiety to be zero while the order with respect to amide, ligand and catalyst to be unity; suggestive of the fact that amide, ligand and the metal catalyst might be involved in the rate determining step while the disulfide moiety is not (see Supporting Information for further details). In an attempt to garner more information about the reaction mechanism, a dimeric structure was isolated and characterized, accommodating the unbiased amide substrate, metal catalyst and ligand (**Scheme 5B**, Int. **F**). Delving into the utility of this intermediate in our reaction protocol, we studied the catalytic and kinetic competency of this intermediate. Gratifyingly, Int. **F** was found to be both catalytically and kinetically competent under the reaction conditions suggesting the involvement of the intermediate in our 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.[52] Reaction yield and selectivity remaining unchanged in such an instance suggests 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 5C**. 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 group reported that the β-hydrogen elimination reactions of five- or six-membered-ring occurs easily in several metallacyclic complexes.[53] 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 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 pyridine 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 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 benzyloxy-2-hydroxy (**L1)** pyridine resulted in δ-thioarylated product and 2-hydroxy-3-nitro-5-methyl (**L2**) resulted in corresponding γ functionalized product. The complete free energy profile of favorable selectivity between δ and γ position with ligand **L1** and **L2** are presented in Supporting Information. On the basis of these data, the C–H activation process is the rate- and site-selectivity-determining step for 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 KIE experimental studies. Experimentally, undertaking the reaction with **L2** as ligand in the presence of 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 $\mathbf{D'^{\ddagger}}$ (**Scheme 5A**). In contrast, similar reaction with **L1** as ligand gave rise to no such olefin peak, enhancing the non-participation 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 substrate in presence of **L2** as ligand showed the presence of same two olefin peaks at 5.39 and 5.29 ppm, supporting further the involvement of intermediate $\mathbf{D'^{\ddagger}}$ 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 analysis 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 higher than that of $\mathbf{CP2_{L1}}$ and easier to accept electrons. Calculated LUMOs in **Scheme 5C** show that the LUMO of $\mathbf{CP2_{L2}}$ is mainly localized on ligand, and most LUMO of $\mathbf{CP2_{L1}}$ is localized on the substrate, which also imply the electron-withdrawing nature of ligand **L2**. These results indicate that electrophilicity effects with pyridine ligand provide the greatest contribution to the γ C–H selectivity. Through all the above performed kinetic and theoretical understandings, a plausible mechanistic cycle is proposed as in **Scheme 5D**. The Pd(II) species catalyst first coordinates with the substrate, followed by deprotonation of the counter anion to result in the formation of intermediate **B**, having bidentate form of coordination of the ligand. The δ C−H activation occurs by concerted-metalation deprotonation (CMD) to form a [5,6]-palladacycle, 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 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 is favored to form the [5,5]-palladacycle complex; preceding the similar subsequent steps to favor the formation of γ-C–H thioarylated product.

In summary, we have developed an approach to functionalize fully unbiased straight chain alkyl amines orthogonally between the γ and δ positions, solely by the tuning of ligand. Two classes of amines having varying substituted γ and δ C–H bonds have been tested along with variety of diverse disulfides. The choice of ligand is highly significant to adjusting 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 case of systems having comparable and equally accessible such bonds, thus paving the way for a general classification of the type of ligands and reaction conditions required to functionalize both the positions in such simple straight chain alkyl amines.

References:

1. McMurray, L., O'Hara, F. & Gaunt, M. J. Recent developments in natural product synthesis using metal-catalysed C–H bond functionalisation. *Chem. Soc. Rev.* **40**, 1885–1898 (2011).
2. Wencel-Delord, J. & Glorius, F. C–H bond activation enables the rapid construction and late-stage diversification of functional molecules. *Nat. Chem.* **5**, 369–375 (2013).
3. Dalton, T., Faber, T. & Glorius, F. C–H Activation: Toward Sustainability and Applications. *ACS Cent. Sci.* **7**, 245–261 (2021).
4. Davies, H. M. L. & Morton, D. Recent Advances in C–H Functionalization. *J. Org. Chem.* **81**, 343-350 (2016).
5. Sinha, S. K., Panja, S., Grover, J., Hazra, P. S., Pandit, S., Bairagi, Y., Zhang, X. & Maiti, D. Dual Ligand Enabled Nondirected C–H Chalcogenation of Arenes and Heteroarenes. *J. Am. Chem. Soc.* **144**, 12032-12042 (2022).
6. Abrams, D. J., Provencher, P. A. & Sorensen, E. J. Recent Applications of C–H Functionalization in Complex Natural Product Synthesis. *Chem. Soc. Rev.*, **47**, 8925-8967 (2018).
7. Crabtree, R. H. & Lei, A. Introduction: CH Activation. *Chem. Rev.* **117**, 8481-8482 (2017).
8. Sinha, S. K., Guin, S., Maiti, S., Biswas, J. P., Porey, S. & Maiti, D. Toolbox for Distal C–H Bond Functionalizations in Organic Molecules. *Chem. Rev.* **122**, 5682-5841 (2021).
9. Dutta, U., Maiti, S., Bhattacharya, T. & Maiti, D. Arene Diversification *via* Distal C(sp^2)–H Functionalization. *Science* **372**, 701 (2021).
10. Meng, G., Lam, N. Y. S., Lucas, E. L., Saint-Denis, T. G., Verma, P., Chekshin, N. & Yu, J. -Q. Achieving Site-Selectivity for C–H Activation Processes Based on Distance and Geometry: A Carpenter's Approach. *J. Am. Chem. Soc.* **142**, 10571-10591 (2020).
11. Dey, A., Sinha, S. K., Achar, T. K. & Maiti, D. Accessing Remote meta- and para-C(sp^2)–H Bonds with Covalently Attached Directing Groups. *Angew. Chem. Int. Ed.* **58**, 10820-10843 (2019).
12. Goswami, N., Bhattacharya, T. & Maiti, D. Transient Directing Ligands for Selective Metal-Catalyzed C–H Activation. *Nat. Rev. Chem.* **5**, 646-659 (2021).
13. Chen, Z., Rong, M.–Y., Nie, J., Zhu, X.–F., Shi, B.–F. & Ma, J.–A. Catalytic Alkylation of Unactivated C(*sp3*)–H Bonds for C(*sp3*)–C(*sp3*) Bond Formation. *Chem. Soc. Rev.* **48**, 4921–4942 (2019).
14. Dutta, U. & Maiti, D. Emergence of Pyrimidine-Based *meta*-Directing Group: Journey from Weak to Strong Coordination in Diversifying *meta*-C–H Functionalization. *Acc. Chem. Res.* **55**, 354-372 (2022).
15. He, G. & Chen, G. A Practical Strategy for the Structural Diversification of Aliphatic Scaffolds through the Palladium-Catalyzed Picolinamide-Directed Remote Functionalization of Unactivated C(sp^3)–H Bonds. *Angew. Chem. Int. Ed.* **50**, 5192-5196 (2011).
16. Ye, X., He, Z., Ahmed, T., Weise, K., Akhmedov, N. G., Peterson, J. L. & Shi, X. 1,2,3-Triazoles as versatile directing group for selective sp2 and sp3 C–H activation: cyclization vs substitution. *Chem. Sci.*, **4**, 3712-3716 (2013).
17. Guin, S., Deb, A., Dolui, P., Chakraborty, S., Singh, V. K. & Maiti, D. Promoting Highly Diastereoselective γ-C−H Chalcogenation of α- Amino Acids and Aliphatic Carboxylic Acids. *ACS Catal.*, **8**, 2664-2669 (2018).
18. Xia, G., Weng, J., Liu, L., Verma, P., Li, Z. & Yu, J. –Q. Reversing conventional site-selectivity in C(sp3)–H bond activation. *Nat. Chem.* **11**, 571-577 (2019).
19. Wu, Y., Chen, Y. –Q., Liu, T., Eastgate, M. D. & Yu, J. –Q. Pd-Catalyzed γ-C(sp3)–H Arylation of Free Amines Using a Transient Directing Group. *J. Am. Chem. Soc.* **138**, 14554-14557 (2016).
20. Das, J., Guin, S. & Maiti, D. Diverse Strategies for Transition Metal Catalyzed Distal C(sp^3)–H Functionalizations. *Chem. Sci.* **11**, 10887-10909 (2020).
21. Zhan, B. –B., Li, Y., Xu, J. –W., Nie, X. –L., Fan, J., Jin, L. & Shi, B. –F. Site-Selective δ-C(sp^3)–H Alkylation of Amino Acids and Peptides with Maleimides via a Six-Membered Palladacycle. *Angew. Chem. Int. Ed.* **57**, 5858-5862 (2018).
22. Guin, S., Dolui, P., Zhang, X., Paul, S., Singh, V. K., Pradhan, S., Chandrashekar, H. B., S. S. Anjana., Paton, R. S. & Maiti, D. Iterative Arylation of Amino Acids and Aliphatic Amines via δ-C(sp3)−H Activation:

Experimental and Computational Exploration. *Angew. Chem. Int. Ed.* **58**, 5633-5638 (2019).
23. Lin, H., Pan, X., Barsamian, A. L., Kamenecka, T. M. & Bannister, T. D. Native Directed Site-Selective δ-C(sp3)–H and δ-C(sp2)–H Arylation of Primary Amines. *ACS Catal.* **6**, 4887-4891 (2019).
24. Chandrashekar, H. B., Dolui. P., Li, B., Mandal, A., Liu, H., Guin, S., Ge, H. & Maiti, D. Ligand-Enabled δ-C(sp^3)−H Borylation of Aliphatic Amines. *Angew. Chem. Int. Ed.* **60**, 18194-18200 (2021).
25. Zhang, Q. & Shi, B.–F. Site-Selective Functionalization of Remote Aliphatic C–H Bonds *via* C–H Metalation. *Chem. Sci.* **12**, 841-852 (2021).
26. Xu, J. –W., Zhang, Z. –Z., Rao, W. –H. & Shi, B. –F. Site-Selective Alkenylation of δ-C(sp^3)−H Bonds with Alkynes via a Six-Membered Palladacycle. *J. Am. Chem. Soc.* **138**, 10750-10753 (2016).
27. Chen, Y. –Q., Wang, Z., Wu, Y., Wisniewski, S. R., Qiao, J. X., Ewing, W. R., Eastgate, M. D. & Yu, J. –Q. Overcoming the Limitations of γ- and δ-C−H Arylation of Amines through Ligand Development. *J. Am. Chem. Soc.* **140**, 17884-17894 (2018).
28. Lyons, T. W. & Sanford, M. Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions. *Chem. Rev.* **110**, 1147-1169 (2010).
29. He, C., Whitehurst, W. G. & Gaunt, M. J. Palladium-Catalyzed C(sp^3)–H Bond Functionalization of Aliphatic Amines. *Chem* **5**, 1031-1058 (2019).
30. Gensch, T., Hopkinson, M. N., Glorius, F. & Wencel-Delord, J. Mild metal-catalyzed C–H activation: examples and concepts. *Chem. Soc. Rev.* **45**, 2900-2936 (2016).
31. Lapointe, D. & Fagnou, K. Overview of the Mechanistic Work on the Concerted Metallation–Deprotonation Pathway. *Chem. Lett.* **39**, 1118-1126 (2010).
32. Ryabov, A. D., Sakodinskya, I. K. & Yatsimirsky, A. K. Kinetics and mechanism of ortho-palladation of ring-substituted NN-dimethylbenzylamines. *J. Chem. Soc., Dalton Trans.,* 2629-2638 (1985).
33. Sokolov, V. I., Troitskaya, L. L. & Reutov, O. A. Asymmetric induction in the course of internal palladation of enantiomeric 1-dimethylaminoethylferrocene. *J. Organomet. Chem.* **133**, C28-C30 (1977).
34. Engle, K. M. & Yu, J. –Q. Developing Ligands for Palladium(II)-Catalyzed C–H Functionalization: Intimate Dialogue between Ligand and Substrate. *J. Org. Chem.* **78**, 8927-8955 (2013).
35. Shao, Q., Wu, K., Zhuang, Z., Qian, S. & Yu, J. –Q. From $Pd(OAc)_2$ to Chiral Catalysts: The Discovery and Development of Bifunctional Mono-*N*-Protected Amino Acid Ligands for Diverse C−H Functionalization Reactions. *Acc. Chem. Res.* **53**, 833-851 (2020).
36. Brookhart, M., Green, M. L. H. & Parkin, G. Agostic Interactions in Transition Metal Compounds. *Proc. Natl. Acad. Sci. USA* **104**, 6908-6914 (2007).
37. Frausto da Silva, J. R. & Williams, R. J. P. The Biological Chemistry of the Elements: The Inorganic Chemistry of Life, Second Edition; Oxford University Press: New York, **2001**.
38. Mellah, M., Voituriez, A. & Schulz, E. Chiral Sulfur Ligands for Asymmetric Catalysis. *Chem. Rev.* **107**, 5133-5209 (2007).
39. Feng, M., Tang, B., Liang, S. H. & Jiang, X. Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry. *Curr. Top. Med. Chem.***16**, 1200-1216 (2016).
40. Zhao, C., Rakesh, K. P., Ravidar, L., Fang, W. –Y. & Qin, H. –L. Pharmaceutical and medicinal significance of sulfur (SVI)-Containing motifs for drug discovery: A critical review. *Eur. J. Med. Chem.* **162**, 679-734 (2019).
41. Ilardi, E. A., Vitaku, E. & Njardarson, J. T. Data-Mining for Sulfur and Fluorine: An Evaluation of Pharmaceuticals To Reveal Opportunities for Drug Design and Discovery. *J. Med. Chem.* 5**7**, 2832-2842 (2014).
42. See Supporting Information for Full Details.
43. Davies, H. M. L. & Liao, K. Dirhodium tetracarboxylates as catalysts for selective intermolecular C–H functionalization. *Nat. Rev. Chem.* **3**, 347-360 (2019).
44. He, C. & Gaunt, M. J. Ligand-assisted palladium-catalyzed C–H alkenylation of aliphatic amines for the synthesis of functionalized pyrrolidines. *Chem. Sci.* **8**, 3586−3592 (2017).
45. He, J., Wasa, M., Chan, K. S. L., Shao, Q. & Yu, J. –Q. Palladium-Catalyzed Transformations of Alkyl C−H Bonds. *Chem. Rev.* **117**, 8754–8786 (2017).
46. Mandal, N. & Datta, A. Harnessing the Efficacy of 2-Pyridone Ligands for Pd-Catalyzed (β/γ)-C(sp3)–H Activations. *J. Org. Chem.* ***85***, 13228-13238 (2020).
47. Ruan, H. & Zhou, L. Synthesis of Fluorescent Sulfur Quantum Dots for Bioimaging and Biosensing. *Front Bioeng Biotechnol.* **10**, 909727 (2022).
48. Li, C., Wang, Y., Jiang, H. & Wang, X., Biosensors Based on Advanced Sulfur-Containing Nanomaterials. *Sensors.* **20**, 3488 (2022).
49. Lv, Z., Chen, Z., Feng, S., Wang, D. & Liu, H. A sulfur-containing fluorescent hybrid porous polymer for selective detection and adsorption of Hg2+ ions. *Polym. Chem.*, **13**, 2320-2330 (2022).
50. Kang, Y., Guo, Y., Shi, H., Ye, S. & Zhang, B. Synthesis and Characterization of Novel 1,4-Di(o-thioaryl)benzene Buta-1,3-diynes. *ChemistrySelect* **3**, 7054-7059 (2018).
51. Jensen, K. H., Webb, J. D. & Sigman, M. S. Advancing the Mechanistic Understanding of an Enantioselective Palladium-Catalyzed Alkene Difunctionalization Reaction. *J. Am. Chem. Soc.* **132**, 17471-17482 (2010).
52. Wright, P. J. & English, A. M. Scavenging with TEMPO• To Identify Peptide- and Protein-Based Radicals by Mass Spectrometry: Advantages of Spin Scavenging over Spin Trapping. *J. Am. Chem. Soc.* **125**, 8655-8665 (2003).
53. Huang, X., Zhu, J. & Lin, Z. ß-Hydrogen Elimination of Five-Membered-Ring Metallacycles. Is It Possible? *Organometallics* **23**, 4154-4159 (2004).

METHODS SUMMARY

Ligand enabled δ C–H thioarylation of aliphatic amine:

In a clean, oven–dried screw cap reaction tube containing magnetic stir-bar, amine (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. 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 were stirred (at 1000 rpm) vigorously for 24 h. After taking out the reaction, it was cooled to room temperature and filtered through celite pad using ethyl acetate (30 mL). Solvent was removed in rotatory evaporator. Desired compound was extracted using EtOAc and 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 eluent.

Ligand enabled γ C–H thioarylation of aliphatic amine:

In a clean, oven–dried screw cap reaction tube containing magnetic stir-bar, amine (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. 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 were stirred (at 1000 rpm) vigorously for 24 h. After detaching the reaction, it was cooled to room temperature and filtered through celite pad using ethyl acetate (30 ml). Solvent was removed in rotatory evaporator. Desired compound was extracted using EtOAc and 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 eluent.

Acknowledgements

Financial support received from SERB, India is gratefully acknowledged (CRG/2022/004197). Financial support received from UGC-India (Fellowship to S.K.S. and N. G.) and from CSIR-India (Fellowship to S.M.) is gratefully acknowledged. R.S.P. acknowledges support from the NSF (CHE-1955876) and computational resources from the RMACC Summit supercomputer supported by the NSF (ACI-1532235 and ACI-1532236), the University of Colorado Boulder and Colorado State University, and the Extreme Science and Engineering Discovery Environment (XSEDE) through allocation TG-CHE180056.

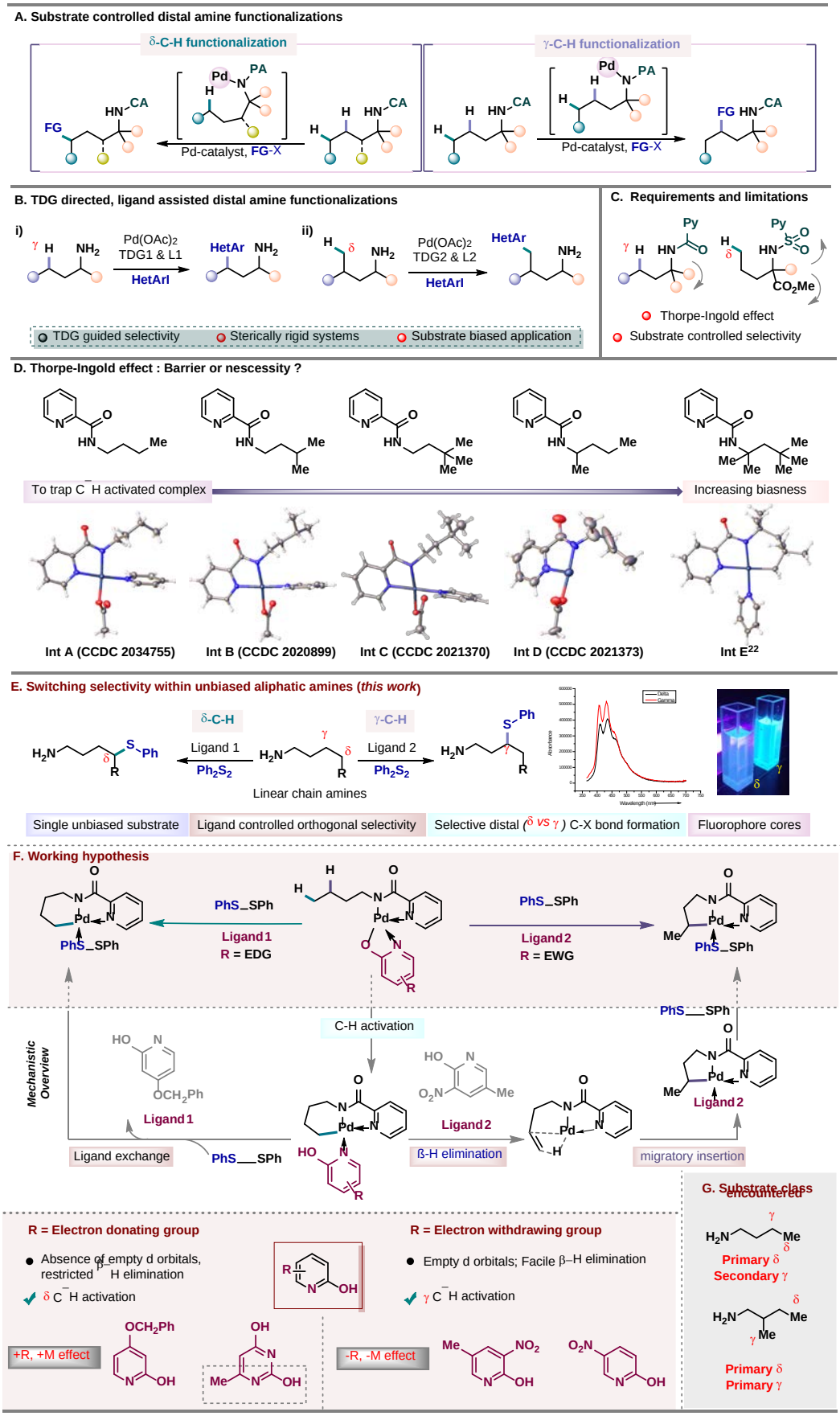
Author contributions

Competing interests

The authors declare no competing financial interest(s).

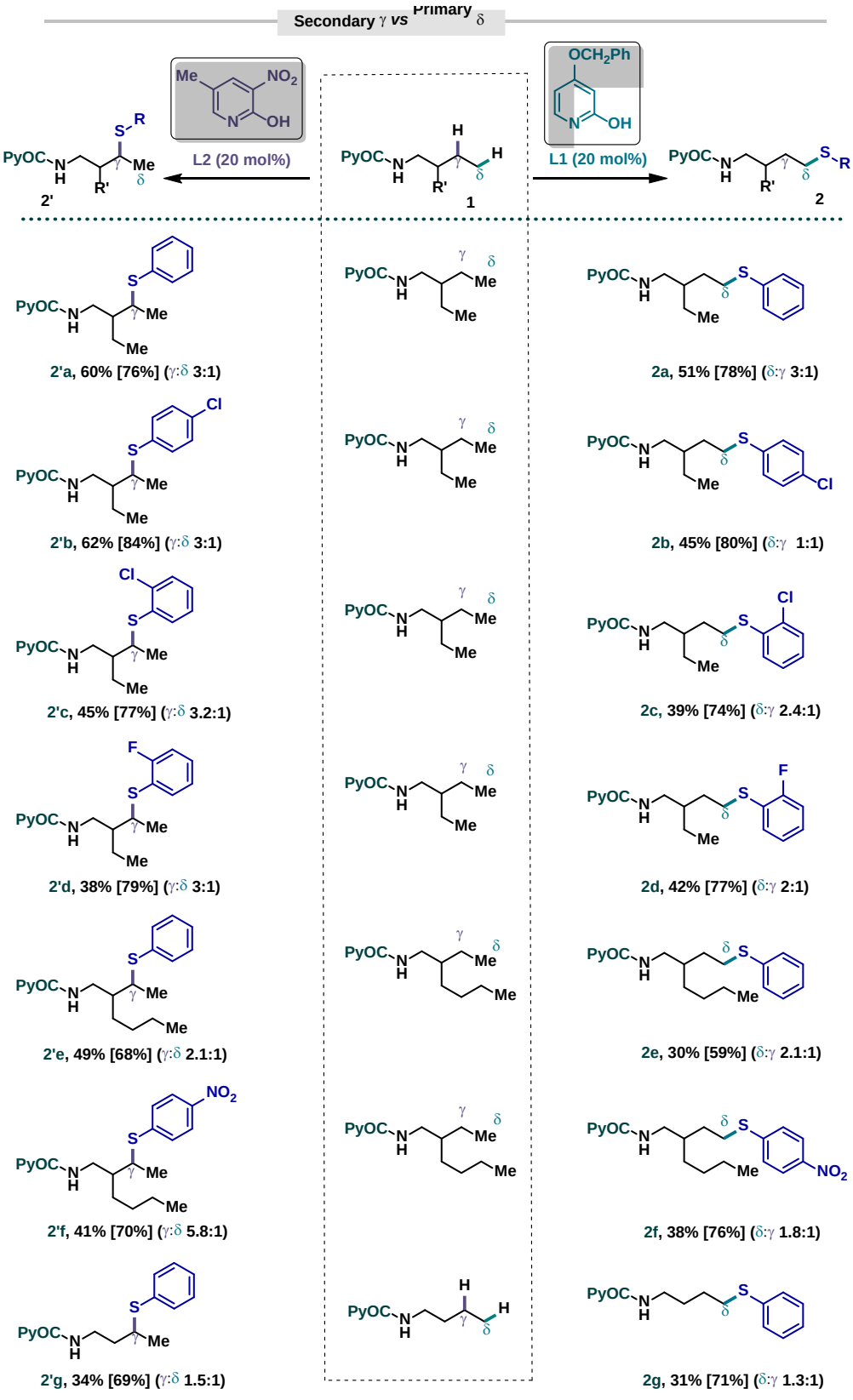
Additional information

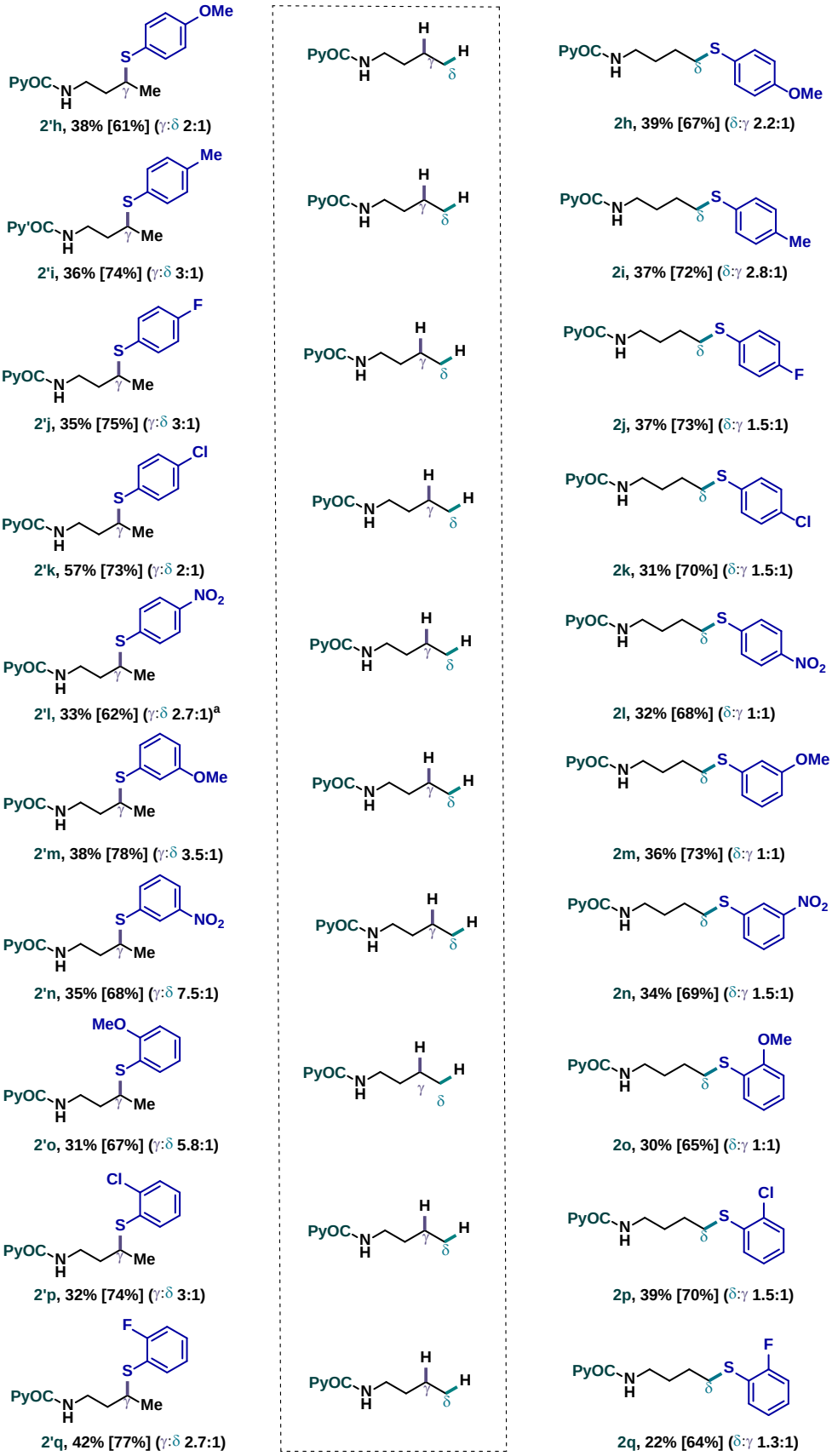
Correspondence and requests for materials should be addressed to D.M. (dmaiti@iitb.ac.in) and (robert.paton@colostate.edu).



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**) Thorpe-Ingold effect: barrier or necessity? (**E**) Ligand controlled orthogonal selectivity between γ and δ positions of the same fully unbiased aliphatic amine. (**F**) Working hypothesis of the nature of ligand controlling the 5-membered vs 6-membered metalation. (**G**) Class of substrates.

.

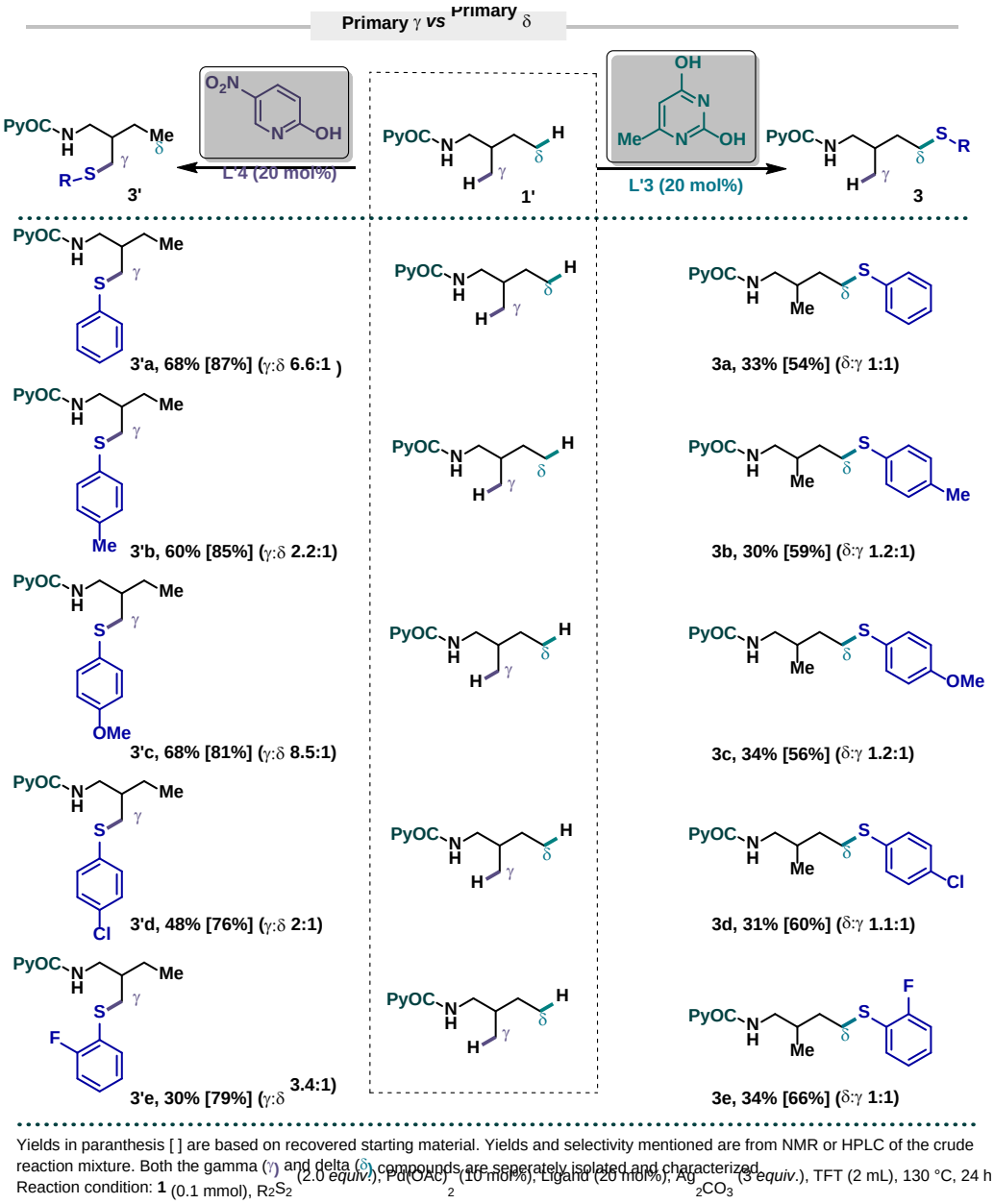

Secondary γ vs Primary δ
L2 (20 mol%)
L1 (20 mol%)
2'
1
2
2'a, 60% [76%] (γ:δ 3:1)
2a, 51% [78%] (δ:γ 3:1)
2'b, 62% [84%] (γ:δ 3:1)
2b, 45% [80%] (δ:γ 1:1)
2'c, 45% [77%] (γ:δ 3.2:1)
2c, 39% [74%] (δ:γ 2.4:1)
2'd, 38% [79%] (γ:δ 3:1)
2d, 42% [77%] (δ:γ 2:1)
2'e, 49% [68%] (γ:δ 2.1:1)
2e, 30% [59%] (δ:γ 2.1:1)
2'f, 41% [70%] (γ:δ 5.8:1)
2f, 38% [76%] (δ:γ 1.8:1)
2'g, 34% [69%] (γ:δ 1.5:1)
2g, 31% [71%] (δ:γ 1.3:1)



Yields in paranthesis [ ] are based on recovered starting material. Yields and selectivity mentioned are from NMR or HPLC of the crude reaction mixture. Both the gamma (γ) and delta (δ) compounds are seperately isolated and characterized. [a]2-OH-5-CF_3 as ligand. Py' is isoquinoline DG

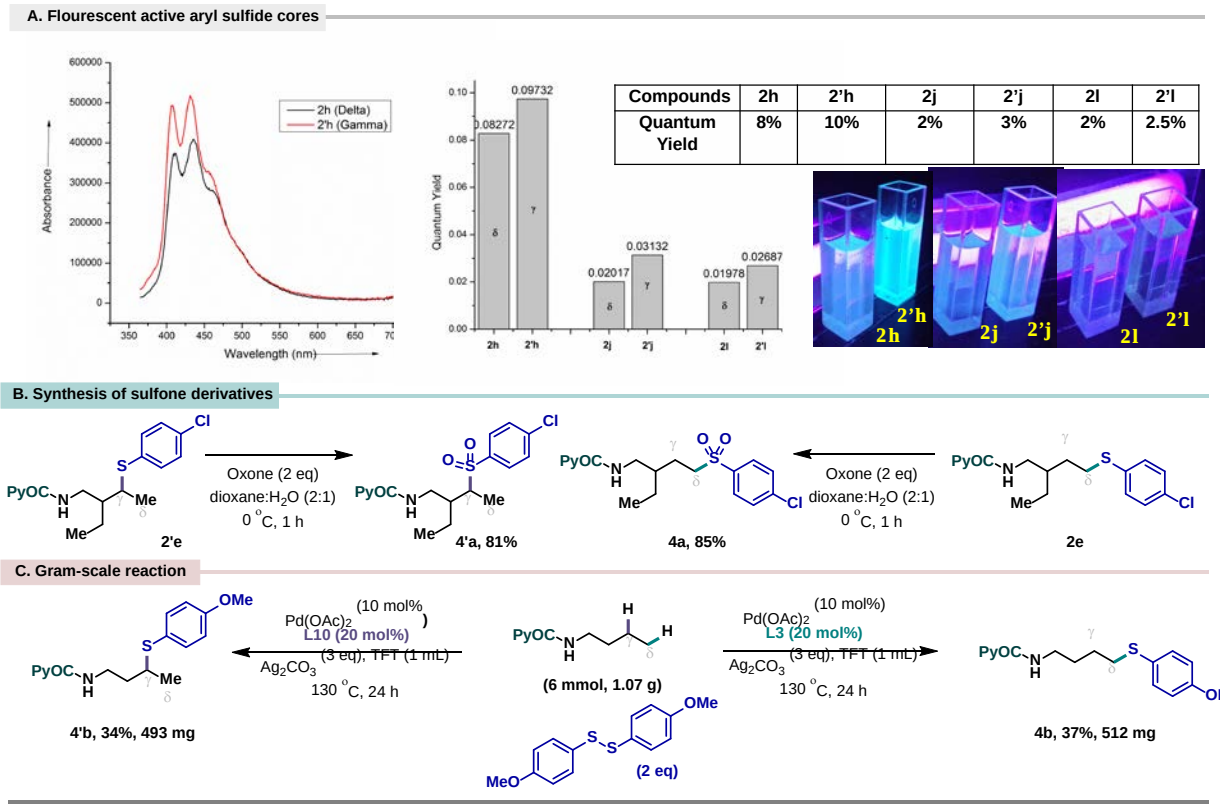
Reaction condition: **1** (0.1 mmol), R_2S_2 (2.0 *equiv.*), $Pd(OAc)_2$ (10 mol%), Ligand (20 mol%), Ag_2CO_3 (3 *equiv.*), TFT (2 mL), 130 °C, 24 h

Scheme 2. Scope of ligand controlled orthogonal selectivity between amines having secondary γ vs primary δ C–H bonds.



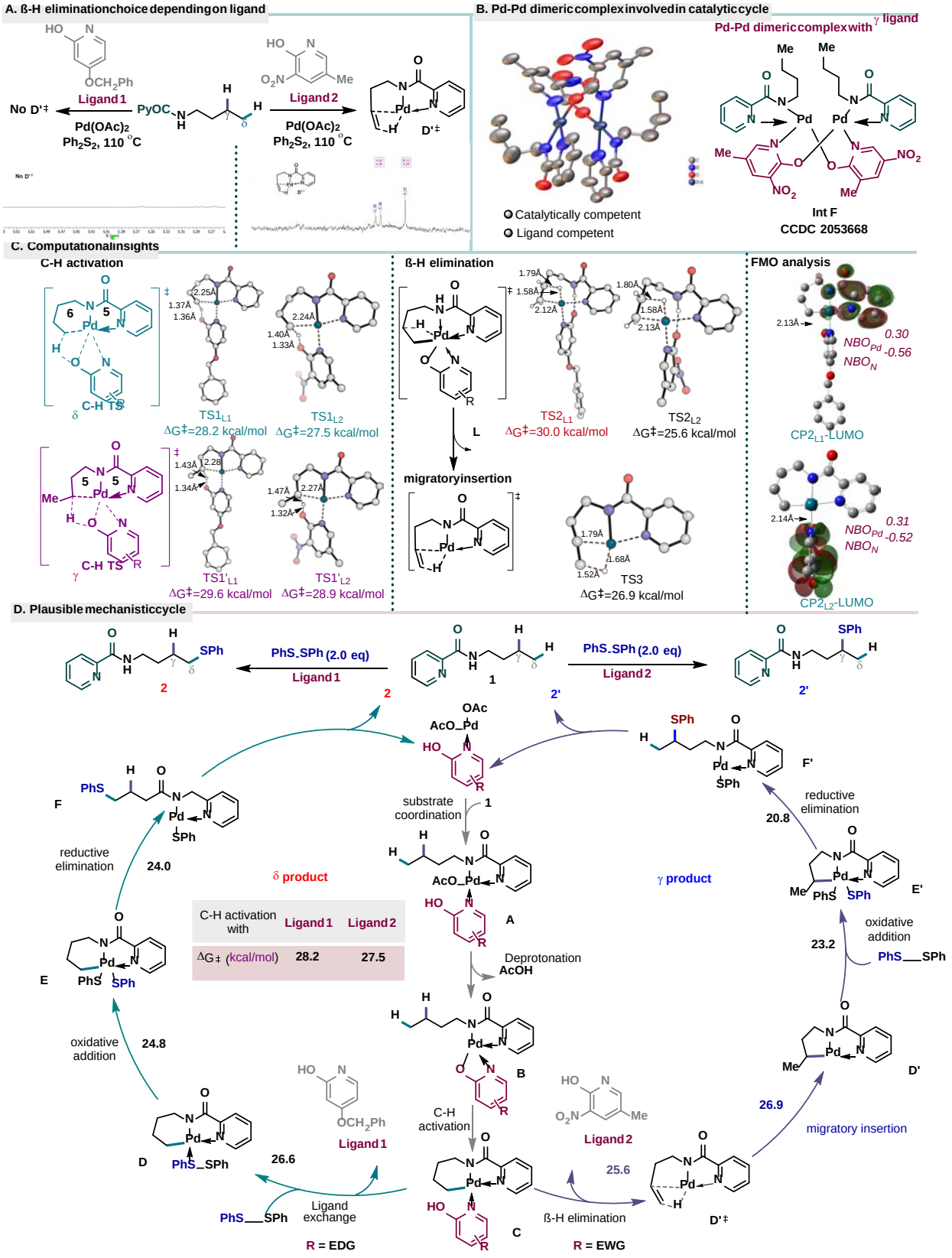
Yields in paranthesis [ ] are based on recovered starting material. Yields and selectivity mentioned are from NMR or HPLC of the crude reaction mixture. Both the gamma (γ) and delta (δ) compounds are seperately isolated and characterized.
Reaction condition: **1** (0.1 mmol), R_2S_2 (2.0 *equiv.*), $Pd(OAc)_2$ (10 mol%), Ligand (20 mol%), Ag_2CO_3 (3 *equiv.*), TFT (2 mL), 130 °C, 24 h

Scheme 3. Scope of ligand controlled orthogonal selectivity between amines having primary γ vs primary δ C–H bonds.



Compounds	2h	2'h	2j	2'j	2l	2'l
Quantum Yield	8%	10%	2%	3%	2%	2.5%

Scheme 4. 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. (**C**) Gram scale reaction in each of γ and δ case.



Scheme 5. Kinetic and DFT investigations. (**A**) ß–H elimination choice depending on nature of ligand. (**B**) Pd-Pd complex involved in mechanistic cycle. (**C**) Computational insights towards orthogonal selectivity (**D**) Plausible mechanistic cycle.