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

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Aliphatic C(sp3)–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(sp3)–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 fully unbiased straight chain aliphatic amines in a regioselective fashion. These straight chain alkyl amines, though both γ and δ 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(sp3)–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 positions, with electron-rich pyridone ligands favoring selective distal δ functionalization whereas 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 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 inexactly adds up to the challenge. The employment of directing group has laid a pathway towards the proximal functionalization of sp3 C–H bonds which experiences a five-membered intermediate. Regulating the selectivity towards the distal position requires employment of effective strategies that will direct 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(sp3)–H functionalization through the participation of less favored six-membered conformation.16-20 In scheme 1A, Sh group envisioned the application of Curtin-Hammett principle to selectively functionalize the δ sp2 C–H bonds, which proceeds through the kinetically less-favored six-membered metalacycle over the more favored δ sp2 C–H bonds.21 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.22 (Scheme 1B). In all these cases, specific site-selectivity has been achieved by incorporating steric bias 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). In scheme 1D, our efforts on butyl amine, both the rigidity as well as the statistical and electronic factors, rendering the functionalization at any other position apart from δ and y positions is improbable. As soon as we start removing the substitutions at the y positions, the statistical factor starts diminishing. However, the presence of almost two substituents at the y positions make this five-membered cyclopalladation unfavourable through a combination of statistical and electronic factors. Deferring our attention towards δ substitutions, removal of each substituent engages 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 δ and y 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 δ and y positions. Our initial attempts at optimizing butyl amines with various ligands emphasized in 5 C(sp3)–H thioyalation being promoted by electron-rich pyridone moieties whereas electron-withdrawing pyridones favored the selectivity towards γ (sp3)–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 cyclopalladation. From both kinetic and theoretical insights, an electronic factor was found to be the most determining factor in controlling the five-membered vs six-membered metatlace. The formation of six-membered C–H activated intermediate primarily because of a primary C(sp3)–H bond being more facile for activation compared to a secondary C(sp3)–H one. After the formation of C–H activated product, the reaction has two possibilities. On encountering an electron-withdrawing pyridone ligand, both δ and y δ positions are equally preferred, 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 catalysts 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 metalacycle. This then undergoes several standard reactions to provide γ-thioyalated product selectively. In sharp contrast, an electron-rich pyridone...
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 significantly lesser yield. However, the δ product was exclusively favored by electron-rich pyridones and the orthogonal selectivity was controlled by the electronic nature of ligand, providing a suitable generality of methodology to varying compositions of δ and γ selective disulfides, generating orthogonal functionalization product orthogonally. To further elucidate the role of the pyridine ligands on δ and y positions selectively, the influence of the pyridine ligands for chemoselectivity was examined by natural population analysis (NPA).

Optimization of metal catalysts, oxidants, solvents and the quantity of disulfide used resulted in some cases δ-selective and for the previous entries providing electronic nature completely to pyridine ligands having electron-rich groups attached to it contributed to more selective δ C=H thioarylation. Optimizing various electron-rich pyridine ligands, the use of bulky 4-bromo and 3-hydroxy pyridine (L1) was found 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 PO4(OH) used was deemed a better fit for the protocol while Ag2CO3 was employed as the preferred oxidant over other silver or copper salts. 4-Chloro substituted disulfide led to incoordinated ligand exchange and all with other reaction conditions remaining the same and the nature of ligand only determining the orthogonality selectivity between the δ and γ 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-selectivity of 3:1 (Scheme 2, entries 2b and 2h). 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-2f). Introducing a butyl group at δ-position of butyl amine of δ-selectivity substituted butyl amine for our thioarylation protocol, in which the statistical and sterical probability of δ and y positions to be functionalized remains intact. In concert with it, deploying electron-withdrawing groups at the 3- or 5-position of pyridine ligands such as NO2, CF3 group predominantly led to selective γ thioarylation, with 2-hydroxy-3-nitro-5-methyl pyridine (L2). These results indicate that the ligand effect on chemoselectivity is predominantly controlled by electronic properties, with electron-rich disulfides ligands favoring selective distal δ functionalization while electron-deficient pyridine ligands tuning the selectivity favorably towards the γ position.

Our initial attempts focused on employing δ-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 substrates 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 combination of L1 and L2 for our thioarylation protocol, in which the statistical and sterical probability of δ and γ positions to be functionalized remains intact. In concert with it, deploying electron-withdrawing groups at the 3- or 5-position of pyridine ligands such as NO2, CF3 group predominantly led to selective γ thioarylation, with 2-hydroxy-3-nitro-5-methyl pyridine (L2). These results indicate that the ligand effect on chemoselectivity is predominantly controlled by electronic properties, with electron-rich disulfides ligands favoring selective distal δ functionalization while electron-deficient pyridine ligands tuning the selectivity favorably towards the γ position.

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 applicable for δ and γ orthogonality being maintained with both OMe as well as Cl-containing disulfides (Scheme 2, entries 2o and 2p, entries 2o and 2p). This reveals the generality of our methodology to varying compositions of δ and γ selective 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 by electronic composition of δ and γ selective disulfides, generating orthogonal selectivity between the distal δ and γ positions. 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 some cases δ-selective and for the previous entries providing electronic nature completely to pyridine ligands having electron-rich groups attached to it contributed to more selective δ C=H thioarylation. Optimizing various electron-rich pyridine ligands, the use of bulky 4-bromo and 3-hydroxy pyridine (L1) was found 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 PO4(OH) used was deemed a better fit for the protocol while Ag2CO3 was employed as the preferred oxidant over other silver or copper salts. 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-selectivity of 3:1 (Scheme 2, entries 2b and 2h). 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-2f). Introducing a butyl group at δ-position of butyl amine of δ-selectivity substituted butyl amine for our thioarylation protocol, in which the statistical and sterical probability of δ and y positions to be functionalized remains intact. In concert with it, deploying electron-withdrawing groups at the 3- or 5-position of pyridine ligands such as NO2, CF3 group predominantly led to selective γ thioarylation, with 2-hydroxy-3-nitro-5-methyl pyridine (L2). These results indicate that the ligand effect on chemoselectivity is predominantly controlled by electronic properties, with electron-rich disulfides ligands favoring selective distal δ functionalization while electron-deficient pyridine ligands tuning the selectivity favorably towards the γ position.

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 pyridine ligands which mainly partake of the formation of γ selective product gives a p value of 0.23. A positive ρ value indicates decrease in electronic density to be successful in generating higher selectivity of γ-C=H thioarylated product.51 Similarly, correlations were drawn with 4-substituted pyridine ligands which are found to generate higher δ selectivity compared to γ. A p 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-benzylxoy-2-hydroxy pyridine as ligand led to observe radical pathway, most likely to be operative while the order of radical 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 which is not (see Supporting Information for full computational details). In an attempt to garner more information about the reaction mechanism, a dimeric structure was isolated and characterized, accommodating the unbonded amide substrate, metal catalyst and ligand (Scheme 5A). Delving into the utility of the microwave protocol, we studied the catalytic and kinetic competency of this intermediate. Gratifyingly, Int. F was found to be both catalytically and kinetically competent under distinct 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.15 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 the key effect of ligands (see the Supporting Information for full computational details).

The corresponding δ and 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]-palladacycle replaced by the ligand insertion to Pd–H bond is mainly localized on ligand, and most LUMO of hydrogen elimination processes of [5,6]-palladacycle intermediates were in agreement with experimental observations where the reaction with benzyloxy-2-hydroxy (L1) resulted in corresponding δ thioarylated product. With an electron-donating ligand, ligand exchange of disulfide with the corresponding ligand determined the future pathway of the reaction. With an electron-withdrawing nature of ligand ligand exchange of di sulfide with the corresponding ligand resulted in δ thioarylated product. With an electron-donating ligand, ligand exchange of di sulfide with the corresponding ligand resulted in δ thioarylation. These results indicate that electrophilicity effects with pyridine ligand provide deeper understanding of the effect of ligands (see the Supporting Information for full computational details).

In summary, we have developed an approach to functionally fully unbiased straight chain alkyl amine 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 considered 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:


METHODS SUMMARY

Ligand enabled δ-C−H thiorylation 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 equiv., 0.2 mmol), disulfide (2 equiv., 0.2 mmol) and silver carbonate (3 equiv., 0.3 mmol) were weighed. Common laboratory syringe was used to introduce TFF (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 rotary evaporator, Desired compound was extracted using EIOAc and combined organic layer was dried over Na2SO4. Finally, it was concentrated in reduced pressure and was purified by column chromatography through silica gel (100-200 mesh size) using PET/ethyl acetate as eluent.

Ligand enabled γ-C−H thiorylation 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 equiv., 0.2 mmol), disulfide (2 equiv., 0.2 mmol) and silver carbonate (3 equiv., 0.3 mmol) were weighed. Common laboratory syringe was used to introduce TFF (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 rotary evaporator. Desired compound was extracted using EIOAc and combined organic layer was dried over Na2SO4. Finally, it was concentrated in reduced pressure and was purified by column chromatography through silica gel (100-200 mesh size) using PET/ethyl acetate as eluent.

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Author contributions

Competing interests

The authors declare no competing financial interest(s).

Additional information

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A. Substrate controlled distal amine functionalizations

B. TDG directed, ligand assisted distal amine functionalizations

C. Requirements and limitations

D. Thorpe-Ingold effect: Barrier or necessity?

E. Switching selectivity within unbiased aliphatic amines (this work)

F. Working hypothesis

G. Substrate class encoutered

Scheme 1. Evolution of functionalization at γ-(sp³)-H and δ-(sp³)-H bonds. (A) Substrate controlled distal C(sp³)-H functionalization. (B) TDG controlled distal amine functionalization. (C) Essential requirements and limitations of substrate controlled distal γ and δ C(sp³)-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 metallation. (G) Class of substrates.
<table>
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<tr>
<th>Compound</th>
<th>Yield [%]</th>
<th>Ratio γ:δ</th>
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<tbody>
<tr>
<td>2'a</td>
<td>60% [76%]</td>
<td>3:1</td>
</tr>
<tr>
<td>2'b</td>
<td>62% [84%]</td>
<td>3:1</td>
</tr>
<tr>
<td>2'c</td>
<td>45% [77%]</td>
<td>3:2:1</td>
</tr>
<tr>
<td>2'd</td>
<td>38% [79%]</td>
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</tr>
<tr>
<td>2'f</td>
<td>41% [70%]</td>
<td>5.8:1</td>
</tr>
<tr>
<td>2'g</td>
<td>34% [69%]</td>
<td>1.5:1</td>
</tr>
<tr>
<td>2'a</td>
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<td>2.1:1</td>
</tr>
<tr>
<td>2'f</td>
<td>38% [76%]</td>
<td>1.8:1</td>
</tr>
<tr>
<td>2'g</td>
<td>31% [71%]</td>
<td>1.3:1</td>
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Yields in parenthesis [ ] 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 separately isolated and characterized.

Reaction condition: 1 (0.1 mmol), R₂S₂ (2.0 equiv.), Pd(OAc)₂ (10 mol%), Ligand (20 mol%), Ag₂CO₃ (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 parenthesis [ ] 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 separately isolated and characterized.

Reaction condition: \( 1 (0.1 \text{ mmol}), R_2S_2 (2.0 \text{ equiv}), \text{Pd(OAc)}_2 (10 \text{ mol%}), \text{Ligand (20 mol%)}, \text{Ag}_2\text{CO}_3 (3 \text{ equiv}), \text{TFT (2 mL)}, 130 \degree \text{C}, 24 \text{ h} \).
A. Fluorescent active aryl sulfide cores

B. Synthesis of sulfone derivatives

C. Gram-scale reaction

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) β-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.