Rewritten Chain of Thought for the Production of the OAI-M1-03 Research Proposal

1 Preamble

This document contains a rewritten summary of the reasoning that led to the OAI-M1-03 research proposal to add oxidants such as TEMPO to Chan–Lam coupling on primary sulfonamides with boronic acids. GPT-5.4 was prompted with high-level research directions of the form "consider whether high level strategy X can be usefully applied to improve reaction class Y", for example, increasing substrate scope for Chan–Lam coupling. GPT-5.4 was also used to rank proposals according to criteria such as tractability and novelty. At the end of each phase, a short list of the highest-ranked proposals was considered by human chemists, and a few proposals were propagated to the next phase along with suggestions for further refinement. This document is structured as 3 phases to indicate where steering prompts were used.

2 Phase 1: Initial Exploration of Better Conditions for Chan–Lam Coupling

2.1 From a green-solvent idea to a mechanistic question

The initial target is a process-oriented Chan–Lam C–N method: lower copper, no external ligand, air as oxidant, and an aqueous or nonvolatile polar medium. Electron-poor and heteroaryl boronic acids, ortho-substituted partners, and aliphatic amines are the important stress cases because slow transmetalation, protodeboronation, coordination, and amine oxidation may compete. Electrochemical, nickel, heterogeneous, and photochemical methods address adjacent limitations but move away from the simplest aerobic copper(II) aryl coupling.

Deep eutectic solvents first seem like the best route. Cicco et al. (2023) show that $Cu(OAc)_2$ in choline acetate/urea (1:2) enables ligand-free aerobic coupling of organoboron reagents and primary amines at room temperature, with recycling and scale-up. The drawbacks are equally important: 20 mol% copper, *t*-BuOK, careful drying, weaker yields with electron-withdrawing anilines, and only moderate performance for several primary alkyl amines. A related glycerol/K_2CO_3/PEG-200 medium offers lower viscosity, whereas choline chloride media become less attractive because ethaline can decompose. These observations shift the target from a generically “green” solvent to a low-copper, base-free reaction. Aqueous DMSO is the conservative reference, and diluted choline acetate/urea tests whether an ionic hydrogen-bond network adds value without the viscosity of the neat medium.

A mechanistic study supplies a more focused idea: $B(OH)_3$, formed during transmetalation, may stabilize copper intermediates and support a base-free pathway through a six-membered aryl-migration transition state. The calculated transmetalation energy span is $26.4\,\text{kcal}\,\text{mol}^{-1}$, followed by a $25.4\,\text{kcal}\,\text{mol}^{-1}$ disproportionation/reductive-elimination barrier. The model also predicts effects from organoboron:amine stoichiometry and aryl electronics; electron-rich arylboronic acids should have lower barriers, and inverse stoichiometry may generate more $B(OH)_3$. Excess boronic acid, however, may also increase biaryl homocoupling.

Several adjacent branches do not survive scrutiny. Enantioconvergent $C(sp^3)$–N coupling of alkyl boronates uses a radical relay and is too remote from conventional aryl Chan–Lam chemistry. Propylene carbonate is plausible but initially lacks direct precedent. Sulfonamides seem likely to complicate product assignment, and inexpensive amino-acid ligands might stabilize copper in water, but glycine, proline, histidine, and related searches do not provide enough Chan–Lam support. I therefore retain primary or secondary amines with one N–H site and drop amino-acid ligation as the central claim.

The boric-acid hypothesis remains uncertain. $B(OH)_3$ may stabilize productive copper intermediates and assist Cu(I)-to-Cu(II) regeneration, but it may instead reduce amine nucleophilicity, change copper solubility, or work only in a particular solvent. A eutectic medium may enhance the effect or merely introduce viscosity and water sensitivity.

2.2 Intermediate plan: test boric-acid promotion with ordinary amines

The first plan crosses 50 electron-rich, electron-poor, heteroaryl, and ortho-substituted boronic acids with 10 anilines, aminopyridines, primary alkyl amines, and secondary cyclic amines. Difficult examples such as 3-pyridyl, 2-thienyl, and 2,6-difluorophenyl boronic acids with aliphatic secondary amines should distinguish genuine rescue from good performance on easy partners.

Matched conditions compare aqueous-DMSO and choline acetate/urea base-mediated benchmarks, a no-base control, added $B(OH)_3$ at several copper loadings, excess boronic acid, hydrated or diluted eutectic media, and alternative copper salts. The published glycerol/K_2CO_3/PEG-200 composition remains exploratory rather than inventing an uncertain formula; if its preparation is ambiguous, hydrated choline acetate/urea remains the primary medium. This matters because an apparent improvement may reflect mixing and transport rather than chemistry. Desired product, biaryl homocoupling, and identifiable protodeboronation products matter more than conversion alone.

A follow-up matrix lowers copper from roughly 5 to 0.25 mol%, varies $B(OH)_3$ from zero to one equivalent, changes water content and boronic-acid stoichiometry, and compares copper sources. The target is broad activity at no more than 1–2 mol% copper without strong base, not maximum yield on easy partners. A reproducible promoter effect at matched copper loading and solvent, followed by retention of activity as copper decreases, supports the hypothesis. A solvent-only effect, suppression, or no consistent benefit remains informative and may instead justify a mild-base process.

2.3 Pivot to primary sulfonamides

The ordinary-amine design is broad, but its central gap remains weak because base-free Chan–Lam methods already exist. Primary sulfonamides provide a sharper target. Gandhi et al.'s 2024 preprint and 2025 paper identify only nineteen examples in earlier reports and patents, then establish broader monoselective conditions across 3,904 reactions. The results show that sulfonamide N-arylation remains highly substrate-dependent: these nucleophiles are weak, and the second N–H bond permits diarylation. At the same time, monoarylated and diarylated products have distinct masses, so overarylation becomes a measurable selectivity problem rather than an ambiguous side reaction. I briefly consider potassium aryltrifluoroborates, but hydrolysis and solubility introduce another uncertain mechanism, so arylboronic acids remain preferable.

The direct sulfonamide study favors 1,2-dichloroethane with K_2CO_3 or K_3PO_4; CsF and KO*t*Bu also work. On preparative translation, heterogeneous mixtures affect reproducibility, while KO*t*Bu in ethanol/water improves selectivity. These results establish feasibility but retain chlorinated or volatile solvent and strong base. Propylene carbonate/water becomes a lower-volatility experimental hypothesis, with DMSO/water as the reference rather than assuming that the new solvent works.

The promoter concept also changes. CsF has direct sulfonamide precedent and may alter boron speciation or copper redox behavior, while $B(OH)_3$ may stabilize copper intermediates but has only computational support for amine coupling. The closest additional clue is a 2015 C–O Chan–Lam–Evans study in which CuF_2 improves coupling and fluoride-assisted B–C cleavage is proposed. This is suggestive, not direct C–N evidence. KO*t*Bu/ethanol gives a clear tetracoordinate alkoxyboronate by ^{11}B NMR, whereas CsF produces only a partial shift, so fluoride may not replace alkoxide for every sulfonamide. $B(OH)_3$ also cannot compensate if deprotonation, rather than transmetalation or copper turnover, is limiting.

2.4 Intermediate plan: separate fluoride, boric acid, and solvent effects

The revised screen crosses 50 aryl or heteroaryl boronic acids with 10 primary sulfonamides. High-copper $Cu(OAc)_2$ references use 2,6-lutidine, K_2CO_3, or CsF in DMSO/water. Lower-copper conditions compare no additive, $B(OH)_3$ alone, CsF alone, and CsF+$B(OH)_3$, first in DMSO/water and then in PC/water at two ratios. Reactions use 20 mM sulfonamide, 1.5 equivalents boronic acid, air, 60 °C, and 16 hours. LC/MS separately follows monoarylation, diarylation, biaryl formation, and protodeboronation. A hydrated deep eutectic medium drops out because its evidence is generic and its viscosity adds a confounder.

A second matrix crosses copper at 0.25, 0.5, 1, or 2 mol% with no additive, $B(OH)_3$, CsF, or both in the better PC/water ratio. Lower copper counts as an improvement only if conversion remains near the high-copper reference across broad substrate space, mono:di selectivity remains high, and homocoupling stays controlled. Failure of $B(OH)_3$ alone points toward inadequate sulfonamide activation; CsF-only success without synergy weakens the stabilization model; activity in DMSO but not PC exposes solvent or speciation problems; and $CsF/B(OH)_3$ antagonism falsifies the co-promotion hypothesis.

2.5 Current phase plan: a sharper co-promotion test

The project now asks whether $B(OH)_3$ and fluoride cooperate to improve copper turnover and boron transfer, while PC/H_2O provides a more practical polar medium. Replacing CsF with inexpensive KF creates a useful process distinction. Prudlik et al.'s 2025 solvent study supports propylene carbonate as a more sustainable polar medium but does not establish Chan–Lam performance. Results from computation, $C(sp^3)$–N coupling, C–O coupling, and electrosynthesis motivate controls without proving the proposed aryl-sulfonamide chemistry. Aryltrifluoroborates, BPin reagents, CuF_2 slurries, and phase-transfer additives stay excluded because they add hydrolysis, solubility, or attribution problems.

Cycle 1 uses 50 diverse (hetero)arylboronic acids and 10 primary sulfonamides, spanning electronics, sterics, heteroaryl content, and sulfonamide acidity while excluding extra N–H sites. Three 20 mol% $Cu(OAc)_2$ baselines use 2,6-lutidine, K_2CO_3, or CsF in $DMSO/H_2O$. Seven 1 mol% Cu conditions compare CsF alone, KF alone, $B(OH)_3$ alone, $B(OH)_3$ with either fluoride in $DMSO/H_2O$, and the same promoter/fluoride pairs in PC/H_2O. The promoter-only row remains even if it fails because it distinguishes synergy from independent additive effects, while matched solvent pairs isolate the PC contribution.

The common reaction frame is 20 mM sulfonamide and 30 mM boronic acid under air at 60 °C for 16 hours. Analysis measures desired monoarylation, diarylation, biaryl, and protodeboronation. A useful outcome approaches baseline conversion with KF, PC/H_2O, and no more than 1 mol% copper while improving mono:di selectivity and limiting biaryl formation.

The first stoichiometric idea merely varies boronic-acid equivalents and does not truly invert the partners. The repaired design swaps which substrate is present at 30 versus 20 mM: boron excess uses 20 mM sulfonamide and 30 mM boronic acid, whereas sulfonamide excess uses 30 and 20 mM, respectively. Total substrate concentration stays constant. This creates a direct test of whether sulfonamide excess suppresses diarylation and homocoupling, even if conversion decreases, and whether the proposed $B(OH)_3$ effect depends on which partner is limiting.

Cycle 2 selects 300 informative pairs and applies 16 conditions: four copper concentrations from 0.05 to 0.40 mM, $B(OH)_3$ absent or present, and the two reciprocal stoichiometries. The preferred solvent and fluoride follow from Cycle 1 rather than being assumed. Separate copper stocks preserve reliable dosing at high and low loading, while sufficient water, mixing, dilution, and removal of particulates address solubility and KF precipitation. The central test is whether low copper works for a meaningful substrate subset while preserving monoarylation and impurity control; only then do representative reactions move to preparative confirmation.

3 Phase 2: Mechanistic Hypothesis Expansion

Chemists looked at the highest-ranked generated samples from phase 1 and suggested we keep the substrate scope the same but ask the model to explore different reaction conditions.

3.1 Separating coordination and oxidation effects

The substrate set stays fixed at 50 aryl or heteroaryl boronic acids crossed with 10 primary sulfonamides, so the new chemistry has to come from the conditions. Copper source, base-free coupling, alternate organoboron forms, electrochemistry, photochemistry, ligands, and exogenous oxidants all initially seem possible. Changing the organoboron reagent changes a coupling partner, while photochemical and electrochemical routes create a different reaction regime. Ligand and soluble-oxidant effects provide a cleaner orthogonal question.

Gandhi and co-workers show that primary-sulfonamide Chan–Lam N-arylation is strongly substrate-dependent and prone to overarylation. Their broad campaign already supplies monoselective conditions and a prediction model, so another general-condition screen adds little. A narrower gap is a systematic map of ancillary-ligand and oxidation effects at low copper loading across the retained substrate matrix.

Han and co-workers provide the closest ligand precedent in a related weak-N-nucleophile class. A ligand-coordinated copper species suppresses a nonligated pathway, while a multidentate PyBox ligand blocks

S,N-bis-chelation and favors N-bound C–N reductive elimination. Ligand electronics change chemoselectivity more than conversion, suggesting that coordination can control product identity without controlling the slowest step. This mechanism may not transfer from sulfenamides to sulfonamides, but it makes ligand-controlled selectivity plausible. Other copper couplings use TMEDA or N,N,O-tridentate ligands with broad heterocycle compatibility; these reactions justify ligand classes rather than predict success here.

Oxidation also remains worth testing. Han's ligand-controlled system gives little product without external O_2 and substantially less under air than under O_2. Other C–N Chan–Lam reactions use DTBP or MnO_2. These examples make oxidant identity a credible variable without proving that Cu(I) reoxidation limits primary-sulfonamide coupling. Strong chelation may inhibit transmetalation, while peroxide additives may increase phenol formation or protodeboronation.

The working hypothesis is that low-copper outcomes divide into coordination-sensitive and oxidation-sensitive regimes. Ligand-specific rescue of heteroaryl pairs may indicate coordination control. A broad response to DTBP or TBHP may indicate an oxidation-dependent turnover limitation. Side products must distinguish productive changes from decomposition: more phenol or protodeboronation under peroxide conditions signals oxidative boronic-acid loss, while more biaryl signals unproductive aryl–aryl coupling. Weak heteroaryl performance could still arise from copper binding, slow transmetalation, or protodeboronation. Strong ligands may stabilize a productive species or block transmetalation and nucleophile binding. External oxidants may accelerate copper turnover or merely create decomposition. Cu(III) stabilization, mononuclear versus dinuclear pathways, and oxygen delivery remain hypotheses rather than facts.

3.1.1 Intermediate plan: ligand–oxidant response map

The first broad experiment uses all 500 substrate pairs under ten conditions, for 5,000 reactions. A high-copper reference and a ligand-free 1 mol% Cu reference anchor the comparison. Six low-copper conditions use 2,2′-bipyridine, 1,10-phenanthroline, TMEDA, DMEDA, PyBox, or 8-hydroxyquinoline. Two more combine phenanthroline with DTBP or TEMPO. TEMPO is an uncertain mechanistic probe, not an assumed promoter.

The low-copper series fixes $Cu(OAc)_2$, KF, stoichiometry, temperature, time, and solvent composition. Sulfonamide is 20 mM, boronic acid is 30 mM, temperature is 60 °C, and time is 16 h. At 50 μL total volume, 20 mM sulfonamide corresponds to 1 μmol. A 1 mol% Cu condition contains 0.2 mM copper, delivered as 5 μL of a 2 mM stock. A 10 mol% ligand condition contains 2 mM ligand, delivered as 5 μL of a 20 mM stock. Two equivalents of KF or peroxide correspond to 40 mM. Analysis follows monoarylated product, N,N-diarylation, biaryl, phenol, and protodeboronation.

A focused follow-up selects 300 pairs with ligand-dependent heteroaryl behavior, substantial diarylation, or electronically and sterically difficult boronic acids. A provisional 2 ligand $\times$ 2 copper-loading $\times$ 4 oxidant matrix compares 0.25 or 1 mol% Cu under air, DTBP, TBHP, or TEMPO, giving 16 conditions and 4,800 reactions. This design remains contingent: if oxidation has no meaningful effect, uninformative oxidant levels give way to ligand-free or ligand-concentration controls. If an oxidant raises product only alongside phenol or protodeboronation, it does not represent productive turnover.

Solvent composition can confound these comparisons. DMSO-based substrate, catalyst, and ligand stocks can make a nominal carbonate condition nearly half DMSO. Aqueous copper and carbonate-based ligand or oxidant stocks reduce this fraction, but exact DMSO, water, and carbonate contents must either match or remain explicit. The desired output is a response map rather than one best condition. Ligand-specific improvement without added side products supports coordination control; broad oxidant-dependent improvement at lower copper supports a turnover effect; general inhibition by strong chelators supports blocked transmetalation or nucleophile binding.

3.2 Testing an acetate-bridged transmetalation model

The ligand–oxidant plan clarifies one axis, but copper counterion and carboxylate identity offer a cleaner test of a more specific transmetalation model. $Cu(OAc)_2$, $Cu(OTf)_2$, $CuCl_2$, $Cu(BF_4)_2$, and CuF_2 differ in Lewis acidity, aggregation, solubility, and transmetalation behavior. Comparing non-acetate salts with and without KOAc directly asks whether acetate rescues their reactivity. If an acetate-bridged dicopper–boron assembly is important, acetate should rescue a non-acetate salt; failure of rescue argues against that simple model. Other carboxylates can then test whether changes in copper speciation alter monoarylation, diarylation, or biaryl formation.

The first literature searches are noisy. A recent amination study identifies boron-to-copper transmetalation as a central limitation, but its alkyl-radical solution does not transfer directly to arylboronic-acid/sulfonamide coupling. An older counteranion study supplies the more direct rationale by placing acetate in a dinuclear copper–boron assembly before transmetalation. Buffered pH might separate sulfonamide deprotonation from copper binding, yet there is little direct precedent. Lewis acids could mask heteroaryl donors but are less directly interpretable. Strong oxidants and Cu(I)/Cu(II) comparisons add redox confounders, leaving counterion plus exogenous carboxylate as the sharper question.

Recent examples triangulate rather than prove the hypothesis. The primary-sulfonamide study establishes substrate dependence and overarylation. A CuF_2/DTBP study shows that CuF_2 can support N-arylation of weak N-nucleophiles, but peroxide and protic-medium effects prevent attribution to fluoride alone. A recent review supplies $Cu(BF_4)_2$ and CuF_2 examples, although catalyst form, oxidant, solvent, and nucleophile differ. A solvent study supports propylene carbonate as a more sustainable polar aprotic component, not as a proven Chan–Lam enhancer. The specific gap is therefore counterion and controlled-carboxylate addition for primary sulfonamides at low copper.

3.2.1 Intermediate plan: salt and carboxylate rescue

The broad 500-pair experiment again uses ten conditions. It contains a 20 mol% $Cu(OAc)_2$ control in DMSO/water, low-copper $Cu(OAc)_2$ controls in DMSO/water and propylene-carbonate/water, $Cu(OTf)_2$, $Cu(BF_4)_2$, and $CuCl_2$ each with and without one equivalent KOAc, and CuF_2 without added acetate. Lutidine, substrate ratio, temperature, time, and atmosphere remain fixed. The decisive comparisons are each non-acetate salt with versus without KOAc.

At 50 μL, 5.0 μL of 0.20 M sulfonamide gives 20 mM, 7.5 μL of 0.20 M boronic acid gives 30 mM or 1.5 equivalents, 2.0 μL of 1.0 M 2,6-lutidine gives 40 mM or 2 equivalents, and 1.0 μL of 1.0 M KOAc gives 20 mM or 1 equivalent. Five microliters of 4 mM copper stock gives 0.4 mM copper, or 2 mol%. The 20 mol% control requires 200 nmol copper, obtainable from 5.0 μL of 40 mM stock or 10.0 μL of 20 mM stock.

The initial thought is to use 1 mol% copper throughout, but aerobic ligand-free conditions may then produce too little signal. Fixing DTBP might improve turnover, yet it introduces radical chemistry and compromises the counterion question. Raising temperature could increase protodeboronation. A uniform 2 mol% copper loading under air at 60 °C preserves the paired comparisons while improving detectability. A follow-up can then test lower loadings.

Substrate and lutidine stocks contribute about 14.5 μL DMSO per well, nearly 30% of the volume. Propylene carbonate/water is therefore the bulk fill rather than the exact final solvent ratio, and carryover must match across paired conditions. CuF_2 solubility and salt precipitation remain practical uncertainties. The analytical readout tracks monoarylated product, diarylated product, biaryl, and protodeboronation products.

A focused experiment selects 300 pairs based on acetate response, heteroaryl behavior, or diarylation. It compares $Cu(OAc)_2$ with the best non-acetate salt in a 2 salt $\times$ 2 copper-loading $\times$ 4 carboxylate matrix. The carboxylates are none, acetate, pivalate, and trifluoroacetate; copper is 0.25 or 1 mol%. This separates a general counterion effect from acetate rescue and carboxylate-dependent selectivity. Cycle-one sparsity remains possible, CuF_2 may depend on the peroxide context in which it is reported, and carboxylates change basicity and solubility as well as aggregation. A reproducible rescue pattern or a clear failure of that pattern is informative, but neither proves copper nuclearity.

3.3 Returning to ligand control with sharper falsification

The counterion question is clean, but the direct sulfonamide problem remains weak nucleophilicity and overarylation. Fluoride and boric-acid activation already address transmetalation, while another broad base or solvent screen lacks a sharp hypothesis. Redox mediation initially seems attractive because low copper may make Cu(I) reoxidation limiting. Copper/nitroxyl aerobic chemistry shows that such combinations can operate with nitrogen nucleophiles and water, but direct thermal TEMPO-mediated Chan–Lam precedent is weak. Peroxide-enabled arylation of amides and other weak nitrogen nucleophiles is closer, yet it uses different boron reagents and conditions. Peroxide is therefore better treated as a diagnostic perturbation than as the central claim.

Ligand-controlled copper speciation gives a more discriminating question. Hu et al. (2024) report that phenanthroline and salen can promote Chan–Lam reactions under milder conditions. Han et al. (2024) show that PyBox controls chemoselectivity in sulfenamide Chan–Lam chemistry by preventing S,N-bis-chelation. This analogy is imperfect, but it motivates asking whether chelating ligands outcompete inhibitory coordination by sulfonamides or heteroaryl boronic acids.

The refined hypothesis is that phenanthroline, bipyridine, PyBox, or related ligands favor productive copper species, accelerate C–N bond formation with weak sulfonamides at low copper loading, and suppress diarylation or biaryl homocoupling. A disproportionate PyBox benefit for heteroaryl boronic acids would support inhibitory substrate binding. The stronger claim that these ligands enforce a mononuclear Cu(III) pathway remains provisional; conversion and side-product maps can challenge it but cannot establish nuclearity.

3.3.1 Intermediate plan: broad ligand-response map

The 500-pair matrix runs under ten conditions, again totaling 5,000 reactions. Three controls distinguish a conventional 20 mol% $Cu(OAc)_2$ DMSO/water condition, a 1 mol% copper DMSO/water condition, and a 1 mol% copper propylene-carbonate-rich condition. The ligand series tests pyridine, phenanthroline, bipyridine, PyBox, and salen at 5 mol% with 1 mol% copper. Phenanthroline/TBHP and PyBox/TBHP branches ask whether stronger oxidation adds benefit after ligand binding is addressed.

Reactions contain 20 mM sulfonamide, 30 mM boronic acid, and 50 μL total volume and run at 60 °C for 16 h under air. The propylene-carbonate condition is not literally binary PC/water because substrate, base, and ligand stocks introduce substantial DMSO; it is a reproducible PC/DMSO/water ternary medium. At 50 μL, 5 μL of 0.20 M sulfonamide gives 1.0 μmol, 7.5 μL of 0.20 M boronic acid gives 1.5 μmol, 5 μL of 2 mM copper gives 1 mol% copper, and 1 μL of 50 mM ligand stock gives 5 mol% ligand.

LC–MS follows monoarylation, diarylation, biaryl homocoupling, protodeboronation, and phenol formation. A ligand matters only if it improves a broad fraction of pairs relative to the low-copper ligand-free control while increasing mono:di selectivity and reducing biaryl. Preferential improvement of heteroaryl substrates supports the coordination hypothesis. Similar improvement across all classes points instead to a general rate, solubility, or oxidation effect. Inhibition by the strongest ligands indicates Cu(II) trapping or impeded transmetalation and directly challenges the proposed mechanism.

The follow-up selects about 300 ligand-responsive cases, heteroaryl and electron-poor boronic acids, and diarylation-prone sulfonamides. The two best ligands are compared at 0.25, 0.5, and 1 mol% $Cu(OAc)_2$ with either 2,6-lutidine or K_3PO_4. Ligand-free controls anchor the comparison, and TBHP at the lowest copper loading tests whether oxidative turnover becomes limiting only after productive ligation is established. Sixteen conditions across 300 pairs give 4,800 reactions. A peroxide response without ligand dependence points back toward oxidation-limited turnover; ligand benefit without a peroxide effect supports a speciation or bond-forming explanation. Scale-up, isolated-product confirmation, and orthogonal spectroscopic or kinetic work remain necessary before claiming a mononuclear pathway.

3.4 Mapping productive and destructive oxidation

The repeated need to use peroxide as a diagnostic suggests that oxidant identity deserves its own study rather than remaining a side branch. Cu(I) salts, micellar media, in-situ sulfonamide silylation, heterogeneous copper, boroxines, and alternate bases either introduce solubility and transport ambiguity or return too closely to boron activation. Oxidants can instead separate productive copper turnover, radical capture, and destructive boronic-acid oxidation. Air, peroxides, persulfate, Oxone, benzoquinone, and TEMPO may produce distinct patterns in monoarylation, diarylation, phenol, biaryl, and aryl–TEMPO adducts.

The recent literature does not provide direct proof. A mediated electrochemical Chan–Lam study shows that redox mediators can accelerate low-valent-copper oxidation but does not establish a thermal sulfonamide method. Nickel Chan–Lam chemistry and Cu/Fe sulfonamide coupling show broader catalyst sensitivity but move away from copper/boronic-acid N-arylation. Hypervalent iodine, Selectfluor, and NFSI could create high-valent copper rapidly, yet their extra oxidation or fluorination chemistry makes an initial comparison difficult to interpret. An H_2O_2-supported copper C–N reaction supplies adjacent support only.

Roy et al. (2025) provide the strongest recent precedent: CuF_2/DTBP enables Chan–Lam N-arylation of oxazolidinones, amides, amines, and azoles. Peroxide-assisted coupling of weak nucleophiles is therefore plausible, but transfer from arylboronic pinacol esters to arylboronic acids and primary sulfonamides remains uncertain. A paper whose title initially appears directly relevant does not establish sulfonamide-nitrogen arylation in its abstract, so it cannot support the claim. Gandhi and co-workers still define the direct gap. Liang and Han show that catalyst and pathway control alter selectivity, while Xiao et al. (2025) show that radical capture by Cu(II) can bypass difficult transmetalation in alkylboronic-ester C(sp^3)–N coupling. The substrates and bond class differ, so the alkyl result is only a reason to test whether radical-generating oxidants create a distinct regime here.

The hypothesis must therefore remain broader than "oxidation is rate-limiting." External oxidants may reoxidize copper, generate aryl radicals that enter by copper capture, or destroy boronic acid to phenol and biaryl. Better conversion alone cannot discriminate among these outcomes. TEMPO can affect radicals, copper coordination, or electron transfer, and no single side product uniquely assigns a mechanism. Consistent substrate-dependent patterns across matched conditions are required.

3.4.1 Intermediate plan: oxidant-regime screen

Three controls compare high-copper air, low-copper air in DMSO/water, and low-copper air in propylene-carbonate/water. Seven low-copper conditions contain TBHP, DTBP, H_2O_2, $K_2S_2O_8$, Oxone, benzoquinone, or TEMPO. This produces ten conditions across all 500 pairs. Each reaction is analyzed for desired monoarylation, diarylation, phenol, biaryl, and aryl–TEMPO products. Carbonate-containing media support representative redox chemistry, including TEMPO-mediated oxidation, but this establishes solvent plausibility rather than target-reaction precedent. DMSO/water controls and water-dependent salt solubility remain important.

A quinone benefit with little phenol or biaryl supports improved copper turnover. A peroxide benefit accompanied by substrate-dependent aryl–TEMPO formation makes radical capture plausible. Phenol or biaryl without product indicates destructive oxidation. High mono-selectivity under an inorganic oxidant identifies a useful condition but does not prove a purely two-electron pathway.

The focused experiment selects about 300 oxidant-responsive, diarylation-prone, hindered, electron-poor, heteroaryl, and radical-signature pairs. A 16-condition factorial compares the best inorganic oxidant and peroxide, two low copper loadings, lutidine and K_3PO_4, and benzoquinone absent or present. A quinone benefit confined to weakly oxidizing conditions supports a turnover role. A peroxide advantage restricted to certain boronic-acid classes may indicate a different pathway. Strong base dependence points toward nucleophile activation rather than redox alone. Cu(I), Selectfluor, and hypervalent iodine remain excluded because they add stability, solubility, fluorination, or oxidation ambiguity. The goal is a substrate-dependent mechanistic map, not simply a low-copper winning condition.

3.5 Considering a reversible organoboron reservoir

Oxidant mapping still leaves the selectivity problem: repeated transmetalation may feed diarylation and biaryl formation even when copper turnover is adequate. A distinct idea is to alter organoboron speciation with diols. Pinacol, catechol, neopentyl glycol, ethylene glycol, or glycerol may reversibly buffer free boronic acid, slowing repeated transmetalation and suppressing diarylation or biaryl homocoupling. The opposite is equally plausible: a boronate may transfer more readily than the free acid, or a diol may chelate copper and inhibit turnover. Conversion, mono:diarylation, biaryl, phenol/protodeboronation, and persistent boronate signals all need measurement.

There is no clear direct diol-additive study in aryl-boronic-acid Chan–Lam coupling. Vantourout and co-workers identify off-cycle organoboron inhibition, oxidation/protodeboronation, and sensitivity to Cu(I)-to-Cu(II) oxidation in Chan–Lam amination. Pinacol can interfere with Cu(II), so diols may act through boron sequestration, copper poisoning, or both. The primary-sulfonamide data make mono:diarylation the central selectivity response, but a loss of total product cannot masquerade as improvement.

An alkylboronic-ester study identifies boron-to-copper transmetalation as limiting in a different C(sp^3)–N context. Separate work confirms reversible, pH-dependent boronic-acid/diol ester formation outside cross-coupling. Together these results support the question, not the predicted answer: the diol-bound pool may be a kinetic buffer, an activated boronate, or an inhibitory sink. Pinacol and ethylene glycol form five-membered boronates, neopentyl glycol forms a six-membered boronate, catechol adds strong boron binding and metal-chelation risk, and glycerol supplies a hydrophilic polyol case. Lower diarylation and biaryl with retained conversion supports control of boron availability. Loss of conversion supports inhibition, while increased conversion rejects the slow-release model and favors activated boronate transfer.

3.5.1 Intermediate plan: diol-buffered boron speciation

All 500 pairs run under ten conditions. Controls are 20 mol% and 1 mol% $Cu(OAc)_2$ with 2,6-lutidine in DMSO/H_2O 9:1, plus 1 mol% Cu in propylene carbonate/H_2O 7:3. The low-copper propylene-carbonate rows add pinacol at 1 or 2 equivalents, catechol, neopentyl glycol, ethylene glycol, glycerol, or neopentyl glycol plus KF.

Fixed conditions are 20 mM sulfonamide, 30 mM boronic acid, 2 equivalents 2,6-lutidine, 50 μL, 60 °C, and 16 h. Five microliters of 0.2 M sulfonamide gives 20 mM; 7.5 μL of 0.2 M boronic acid gives 30 mM; 5 μL of 2 mM $Cu(OAc)_2$ gives 1 mol% Cu; and 2.5 μL of 0.4 M diol gives 1 equivalent. DMSO carryover stays consistent. Triage favors moderate conversion with improved mono:diarylation and reduced biaryl or phenol; a ratio gain is not meaningful if product formation collapses.

About 300 pairs with diarylation, difficult boronic acids, strong diol response, or possible fluoride rescue then enter a 2 × 2 × 2 × 2 design: pinacol versus neopentyl glycol, 0.5 versus 2 equivalents diol, no KF versus 2 equivalents KF, and 0.25 versus 1 mol% Cu. Five microliters of 0.5 mM or 2 mM copper stock gives 0.25 or 1 mol% Cu, respectively.

Fluoride restoration of conversion with erosion of diol-derived selectivity supports a reversible boron reservoir. Persistent inhibition despite fluoride suggests copper binding or another off-cycle sink. Suppression of both biaryl and diarylation supports reduced organoboron transfer; diarylation-only suppression suggests a later or sulfonamide-side effect. Diol–copper interactions show whether inhibition intensifies as catalyst concentration falls. Solubility, glycerol viscosity, catechol inhibition, fluoride precipitation, and DMSO fraction can confound the conclusions, so selected outcomes require preparative confirmation and structural analysis.

3.6 Refining ligand denticity and mild redox mediation

The organoboron-reservoir idea is falsifiable but weakly precedented. Returning to copper coordination allows a more direct comparison of bidentate and tridentate ligands. Weak sulfonamide nucleophilicity may coexist with nonproductive copper binding, so ligand denticity and electronics could alter monoarylation, diarylation, phenol formation, and biaryl homocoupling. A nickel Chan–Lam study shows that electron-rich bipyridine can outperform parent bipyridine and several other ligands, but this remains adjacent evidence.

Han et al. show more directly that tridentate PyBox prevents S,N-bis-chelation in sulfenamide coupling, produces a Cu(II)-derived resting state, and redirects N- versus S-arylation; nitrogen deprotonation precedes reductive elimination. This suggests, but does not establish, that primary sulfonamides form inhibitory N,O-bound copper species. Tridentate ligands may suppress those species, or they may block productive nucleophile binding. A ligand-free/bidentate/tridentate comparison can distinguish these outcomes. A tridentate advantage, especially for donor-rich sulfonamides, supports coordination-sphere saturation; strong-ligand inhibition falsifies it.

Low-copper turnover may still be redox- or transmetalation-limited. Benzoquinone remains a mild diagnostic rather than an assumed solution. Benefit from benzoquinone alone suggests Cu reoxidation limits the reaction; synergy with PyBox suggests coupled redox and coordination effects. $Cu(TFA)_2$ enters once because it supports the PyBox/sulfenamide precedent. Propylene carbonate remains reserved for the focused experiment so that the initial ligand comparison is not confounded.

3.6.1 Intermediate plan: bidentate versus tridentate control

The ten broad conditions are 20 mol% and 1 mol% $Cu(OAc)_2$ ligand-free controls; 1 mol% $Cu(OAc)_2$ with 2,2′-bipyridine, 4,4′-dimethoxy-2,2′-bipyridine, 1,10-phenanthroline, terpyridine, or PyBox; benzoquinone without ligand; PyBox plus benzoquinone; and $Cu(TFA)_2$ plus PyBox. Fixed conditions are 20 mM sulfonamide, 30 mM boronic acid, 2 equivalents 2,6-lutidine, DMSO/water, 60 °C, and 16 h. Ligand is 10 mol% and benzoquinone is 0.5 equivalent, giving 5,000 reactions across the 500 pairs.

In 50 μL, the low-copper conditions contain 5.0 μL of 0.20 M sulfonamide, 7.5 μL of 0.20 M boronic acid, 5.0 μL of 2 mM Cu, 2.0 μL of 1.0 M 2,6-lutidine, 1.0 μL of 0.10 M ligand when present, and 2.5 μL of 0.20 M benzoquinone when present. This gives 20 mM sulfonamide, 30 mM boronic acid, 1 mol% Cu, 2 equivalents base, 10 mol% ligand, and 0.5 equivalent mediator. Ten ligand equivalents per copper may itself cause inhibition, which remains informative.

The focused matrix selects 300 pairs representing ligand rescue, diarylation, difficult heteroaryl or electron-poor boronic acids, and large tridentate–bidentate contrasts. A 2 × 2 × 2 × 2 design compares the best bidentate with the best tridentate ligand, benzoquinone absent or present, Cu at 0.25 or 1 mol%, and DMSO/water with propylene-carbonate/water, giving 4,800 reactions. A tridentate main effect supports suppression of nonproductive coordination; a benzoquinone main effect supports redox limitation; a ligand–solvent interaction indicates medium-dependent speciation; and no tridentate benefit rejects the saturation model. Substrate descriptors test whether effects track sulfonamide acidity and donor count or boronic-acid electronics and sterics.

3.7 Isolating base, counterion, and ion-pairing effects

The ligand study still leaves base entangled with sulfonamide deprotonation, boronate formation, copper ligation, oxidation potential, protodeboronation, and copper precipitation. A matched counterion study can separate some of these roles more cleanly than an unrelated collection ranked only by pK_a. Photochemical and electrochemical variants change the activation mode too much; strong peroxides and bifluoride create decomposition or handling concerns; micellar and heterogeneous systems complicate mixing and interpretation; diol trapping may protect boronic acids but also suppress transmetalation. Ligand suppression of sulfonamide chelation and benzoquinone mediation now belong to separate hypotheses.

The useful literature converges on Gandhi and Doyle's primary-sulfonamide study, Xiao and Yang's discussion of boron-to-copper transmetalation, Liang's sulfenamide S-arylation, Vantourout's mechanistic study, and Pooventhiran's computation on boric-acid promotion. Direct searches do not reveal a compelling diol, buffer, N-oxide, or alternative-oxidant solution to the counterion problem. Gandhi and Doyle show weak-nucleophile and diarylation problems plus strong base and solvent dependence. DCE with K_2CO_3 or K_3PO_4 performs broadly, while CsF and KO*t*Bu also emerge as general bases. They raise counterion-dependent copper oxidation potential as one possible reason inorganic bases facilitate redox events, but their practical conditions still use 20 mol% Cu and DCE or EtOH/water. The question remains whether matched counterions support much lower copper in high-boiling mixed solvents.

Pooventhiran's calculations suggest that boric-acid coordination can lower transmetalation energy and ease Cu(I)-to-Cu(II) regeneration. This does not imply that alkali-metal ions behave similarly, but it reinforces the sensitivity of transmetalation and regeneration to the local coordination environment. The sources motivate a test without establishing its result.

Carbonate and fluoride provide two distinct anions, while K^+ versus Cs^+ supplies a matched cation comparison. Adding 18-crown-6 perturbs cation association. If K^+ plus crown approaches the corresponding Cs^+ condition, increased anion availability or salt solubility is likely important. If a K/Cs difference persists after crown addition, cation-specific copper speciation or ion pairing remains plausible. Neither result alone proves a change in oxidation potential. Phenol, protodeboronation, and biaryl must accompany product measurements so accelerated boronic-acid consumption is not mistaken for productive turnover.

3.7.1 Intermediate plan: matched cation–anion matrix

The 500-pair experiment uses ten conditions. Two references are a 20 mol% Cu/lutidine condition and a 1 mol% Cu/lutidine condition. The remaining eight form a 2 × 2 × 2 design: carbonate versus fluoride, K^+ versus Cs^+, and crown ether absent versus present, all at 1 mol% Cu.

The fixed recipe is 20 mM sulfonamide, 30 mM boronic acid, 2 equivalents base, 60 °C, and 16 h. At 50 μL, 5 μL of 0.20 M sulfonamide and 7.5 μL of 0.20 M boronic acid give the target concentrations. Five microliters of 2 mM copper gives 0.20 mM, or 1 mol% relative to sulfonamide. Two microliters of 1.0 M base gives 40 mM. Five microliters of 0.20 M crown gives 20 mM, half the base concentration. The high-copper reference reaches 4 mM copper. The crown loading is large enough to alter bulk ion pairing, but it may also interact with copper or change solvation; that ambiguity remains part of the interpretation.

The follow-up selects about 300 pairs spanning strong K/Cs responders, weak responders, diarylation-prone sulfonamides, heteroaryl and electron-poor boronic acids, and representative failures. The better-supported anion is fixed. A $2 \times 2 \times 2 \times 2$ design varies K^+ versus Cs^+, crown absent versus present, 0.25 versus 1 mol% Cu, and DMSO/water versus propylene-carbonate/water. Propylene carbonate is a deliberate alternate polar medium, not an assumed optimum; the factor probes ion pairing and solvation as well as transferability.

Convergence of crown-treated K^+ with Cs^+ supports anion availability or solubility. Persistence of a cation difference leaves cation-specific copper speciation plausible. A solvent–cation interaction indicates a role for ion pairing or solvation. Survival of the effect at 0.25 mol% Cu argues that it influences catalytic turnover rather than only stoichiometric copper chemistry. A null or substrate-specific result rejects a general counterion-control claim. Only after relevant mixtures emerge should electrochemical or spectroscopic measurements test whether copper redox properties actually change; until then, "cation redox tuning" and "naked-anion activation" remain competing explanations.

3.8 Integrating ligand control with radical and redox probes

The matched-ion design avoids ligand effects, but soluble N-donor ligands remain the cleanest direct way to alter copper speciation without changing substrates. Initial evidence from Cu(I) chemistry emphasizes boronic-acid homocoupling, while nickel/bipyridine coupling shows that ligand electronics affect C–N product, phenol, and biaryl formation; neither resolves the copper/sulfonamide problem. Han, Kozlowski, Jia, and co-workers provide the stronger related precedent: PyBox prevents S,N-bis-chelation in sulfenamide Chan–Lam coupling, spectroscopy identifies a Cu(II)-derived resting state, computation places nitrogen deprotonation before reductive elimination, and ligand–substrate interactions control pathway selection. The sulfenamide analogy remains evidence for a variable, not proof of the sulfonamide mechanism.

Xiao and co-workers add a redox question. Conventional boron-to-copper transmetalation limits alkyl Chan–Lam coupling, while radical capture by Cu(II) produces a Cu(III) intermediate and bypasses that barrier. This does not establish a radical route here, but it suggests that a redox additive may improve copper turnover or inhibit the reaction by trapping radicals.

The direct primary-sulfonamide data show weak nucleophilicity, substrate dependence, overarylation, and nitrogen binding to copper throughout the catalytic cycle. Base and solvent strongly affect boronic-acid speciation. CsF and KO*t*Bu are broadly productive; KO*t*Bu forms a tetracoordinate alkoxyboronate, whereas CsF changes the boronic-acid environment only partially. Earlier reports do not systematically map ligand denticity and redox mediation for this substrate class.

Bipyridine, neocuproine, terpyridine, and PyBox therefore probe distinct coordination effects against a fixed productive-base background. Bipyridine may stabilize Cu(I); neocuproine adds steric pressure that may suppress product rebinding; terpyridine and PyBox test whether tridentate coordination blocks N,O-chelation. TEMPO is deliberately ambiguous. Cooperative Cu/TEMPO chemistry shows that it can mediate redox exchange and that bipyridine tunes the Cu(I/II) potential, but excess ligand blocks substrate access. Modest ligand loading and a benzoquinone comparator are necessary.

Three patterns discriminate the hypotheses. A ligand-only benefit supports chelation control. Improvement from both TEMPO and benzoquinone supports a copper-redox bottleneck. TEMPO inhibition with benzoquinone improvement supports radical interception. A change in ligand effect between DMSO/water and propylene carbonate/water may indicate competition between solvent and ligand at copper.

3.8.1 Intermediate plan: ligand–mediator interaction map

The first 5,000-reaction matrix compares a high-copper benchmark, a low-copper ligand-free control, four ligands, and the same four ligands with TEMPO across all 500 pairs. The background uses CsF, water-containing DMSO, and 1.5 equivalents boronic acid. Conversion, mono:diarylation, biaryl, phenol/protodeboronation, and possible aryl–TEMPO adducts define the response.

A focused 24-condition experiment retains 200 informative successes and failures. It compares no ligand versus the best ligand; no mediator, TEMPO, or benzoquinone; 0.25 versus 1 mol% copper; and DMSO/water versus propylene-carbonate/water. The $2 \times 3 \times 2 \times 2$ design gives 4,800 reactions. Retaining failures is essential because the purpose is to locate mechanistic boundaries rather than collect only high-yielding cases. An older direct $Cu(OAc)_2$/TEMPO Chan–Lam precedent strengthens feasibility without proving TEMPO's role with primary sulfonamides. The plan remains useful without a universal best condition if the patterns distinguish chelation, redox, and radical explanations.

3.9 Current plan: terminal-oxidant dependence at low copper

The recurring redox ambiguity can now be isolated more directly. Copper counterions, carboxylates, buffer, water fraction, CuF_2, fluoride cations, and micelles either overlap the fluoride/boric-acid study, introduce intertwined solubility effects, or risk a descriptive screen. A broad ligand or radical-mediator matrix overlaps the coordination-sphere work. Terminal oxidant identity supplies the cleaner question: does aerobic copper turnover become limiting at no more than 1 mol% copper?

Primary-sulfonamide Chan–Lam coupling remains highly substrate-dependent and prone to overarylation, and prior reports often require high or stoichiometric copper. Heterocyclic and electron-poor sulfonamides perform better on average, but optimum conditions still depend on sulfonamide identity. Liang et al. establish the requirement for Cu(I)-to-Cu(II) reoxidation. Han, Jia, Kozlowski, and co-workers show that preventing S,N-bis-chelation changes chemoselectivity in a related sulfenamide coupling, confirming that copper speciation and substrate binding can redirect the reaction. Xiao et al. show radical capture bypassing two-electron transmetalation in an alkylboronic-ester system. A photoinduced persulfate study on alkyl boronic acids is likewise not direct validation of this thermal aryl system; persulfate remains a mechanistic comparator.

The current hypothesis is that atmospheric Cu(I) reoxidation limits a subset of substrate pairs at low copper loading. NMO or benzoquinone should rescue those pairs with less biaryl than Oxone or ammonium persulfate. Selectfluor supplies a stronger electrophilic condition, while H_2O_2 tests whether an oxidant instead converts boronic acids to phenols. Broad mild-oxidant rescue with little phenol supports redox-limited turnover. Radical-capable rescue with more biaryl indicates a different oxidative regime. Oxidant-insensitive pairs remain more consistent with transmetalation, deprotonation, or inhibitory binding. These are conditional inferences, not direct observations of elementary steps.

All 500 substrate pairs enter ten conditions, giving 5,000 reactions. Two 20 mol% $Cu(OAc)_2$ benchmarks use either 2,6-lutidine in DMSO/water 9:1 or CsF in DMSO/water 7:3. The matched low-copper series uses 1 mol% $Cu(OAc)_2$ and 2 equivalents CsF in DMSO/water 7:3 under air, then adds NMO, benzoquinone, Selectfluor, H_2O_2, Oxone, or ammonium persulfate. A final NMO condition uses propylene carbonate/water 7:3.

Each 50 μL reaction contains 20 mM sulfonamide and 30 mM boronic acid and runs at 60 °C for 16 h. The recipe uses 5.0 μL of 0.20 M sulfonamide and 7.5 μL of 0.20 M boronic acid. Ten microliters of 20 mM copper stock gives the 20 mol% benchmark, while 5 μL of 2 mM stock gives 1 mol% copper. Four microliters of 0.50 M CsF gives 40 mM. Two microliters of a 0.50 M oxidant stock gives 1 equivalent, while 4 μL gives 2 equivalents.

LC–MS/PDA follows monoarylated product, N,N-diarylated product, biaryl, phenol, and other major oxidation products. A promising mild oxidant improves the low-copper air control broadly while preserving about 10:1 mono:di selectivity and keeping biaryl below roughly 15% area. H_2O_2 producing phenol, or persulfate increasing both target and biaryl, remains informative even if preparatively poor.

The focused experiment selects 300 pairs spanning mild-oxidant responders, nonresponders, diarylation-prone systems, hindered and electron-poor boronic acids, heteroaryl partners, and representative high performers. Sixteen conditions vary copper at 0.25, 0.5, and 1 mol%; oxidant as none, the best mild oxidant, or the best radical-capable oxidant; and solvent as DMSO/water or propylene-carbonate/water. Two low-priority radical/low-copper solvent combinations are omitted, giving 4,800 reactions.

The unresolved issue is whether external oxidants accelerate copper turnover or merely oxidize the boronic acid. Broad clean rescue by NMO or benzoquinone supports the intended interpretation. Side-product-heavy rescue under Oxone or persulfate supports pathway divergence or nonspecific oxidation. Failure of all oxidants points away from Cu(I) reoxidation. Preparative validation should include examples from every response class rather than only the highest-yielding reactions.

4 Phase 3: Oxidant-Screen Refinement and Final Experimental Design

Chemists looked at the highest-ranked generated samples from phase 2 and suggested we keep the backbone structure of the plan the same while asking the model to polish small design choices.

4.1 Reframing the condition question

The low-copper oxidant hypothesis is worth preserving, but the initial matrix does not yet isolate copper redox turnover. The copper arithmetic is correct: a 50 μL reaction at 20 mM sulfonamide contains 1.0 μmol substrate, and 5 μL of a 2 mM copper stock supplies 10 nmol, or 1 mol %. Mechanistically, however, primary-sulfonamide Chan–Lam coupling can fail through weak nucleophilicity, poor boron-to-copper transfer, copper deactivation, protodeboronation, or secondary diarylation.

Gandhi/Doyle 2025 provides the direct benchmark. Its large primary-sulfonamide study describes strong substrate dependence and overarylation. The optimized preparative condition uses 20 mol % $Cu(OAc)_2$, KO$t-$Bu, water, ethanol, oxygen, 60 °C, and 18 h. More importantly, additional oxygen slightly increases target formation in a comparator condition while also increasing N, N-diarylation. Faster oxidation can therefore improve turnover and worsen selectivity.

Three controls are necessary: high-Cu/lutidine/air, high-Cu/CsF/air, and low-Cu/CsF/air. Every oxidant should be compared with the low-Cu air control for target response and with the high-Cu controls for mono/di selectivity.

Walker et al. supports the redox premise: in amine Chan–Lam coupling, rapid reoxidation of low-valent copper regenerates catalyst and improves rates relative to air. This makes redox-limited turnover plausible, but not proven, for primary sulfonamides. Sang/Gestwicki 2025 supplies an alternative. Their alkylboron system is limited by sluggish boron-to-copper transmetalation and bypasses it through radical capture. The chemistry differs, but it warns that oxidant-insensitive sulfonamide pairs may instead be limited by transmetalation, deprotonation, binding, or copper sequestration. Han and Liang further show that copper coordination can redirect related sulfenamide Chan–Lam pathways. A ligand may stabilize low-level copper, but it adds another variable, so the first matrix remains ligandless.

No direct primary-sulfonamide study compares the proposed oxidants. NMO, *p*-benzoquinone, Selectfluor, hydrogen peroxide, Oxone, and ammonium persulfate should therefore be treated as distinct oxidation probes, not predetermined mechanistic labels. Target and side-product patterns determine whether a condition provides clean turnover or introduces radical-like chemistry.

Stock-solvent carryover is the largest compositional confound. Substrate stocks already contribute 12.5 μL DMSO to a 50 μL reaction, while aqueous copper, CsF, and oxidants alter water content. A fixed-slot design solves this. Each low-Cu reaction receives 5 μL sulfonamide stock, 7.5 μL boronic-acid stock, 5 μL of 2 mM $Cu(OAc)_2 \cdot H_2O$, 4 μL of 0.50 M CsF, a 4 μL oxidant slot, a 4 μL compensation slot, and 20.5 μL make-up solvent. A 0.25 M oxidant stock supplies one equivalent. Aqueous oxidants receive DMSO compensation; *p*-benzoquinone in DMSO receives water. The final DMSO/water ratio stays near 62:38.

All oxidants begin at one equivalent to avoid solubility and salt-loading confounds. Hydrogen peroxide remains informative but can decompose and generate gas with copper, so venting is necessary. A single 55 °C, 18 h condition balances turnover against diarylation and oxidant decomposition.

CsF stays fixed because it is soluble and has direct sulfonamide precedent. KO$t-$Bu initially appears attractive because it gives better selectivity and stronger boronate activation in the Gandhi/Doyle system, but changing to it also changes solvent, water sensitivity, and boron speciation. Propylene carbonate also remains exploratory: its physical properties are attractive, but no direct precedent appears, and stock carryover gives an actual PC:DMSO:H_2O ratio near 37:33:30. It is therefore a PC-containing condition, not a PC-rich solvent replacement.

4.2 Intermediate plan

The first Cycle 1 plan retains the same 500 substrate pairs and ten conditions. Three are the air baselines. Six use 1 mol % Cu, two equivalents CsF, and one equivalent of NMO, *p*-benzoquinone, Selectfluor, hydrogen peroxide, Oxone, or ammonium persulfate. The tenth uses NMO in the PC-containing medium. Substrates enter first, base/oxidant/solvent mixtures next, and copper last.

Cycle 2 selects 300 informative pairs. A nine-condition core crosses 0.25, 0.5, and 1.0 mol % Cu with air, the best cleaner oxidant, and the best aggressive oxidant. Five conditions test PC translation, and two test oxidant dose. Copper delivery remains fixed at 5 μL by changing stock concentration. If Cycle 1 shows no oxidant effect, the dose conditions can instead vary CsF to probe boronate activation.

LC–MS/PDA should track target monoarylation, N, N-diarylation, biaryl, phenol, protodeboronation, and clear oxidant-specific products. Success is a reproducible within-pair target increase without a proportionate loss of mono/di selectivity or rise in biaryl and phenol. Clean rescue supports redox limitation; target gain with destructive side products indicates competing oxidation; and no oxidant response despite high-Cu rescue points toward transmetalation, activation, coordination, or mass-transfer limits.

4.3 Tightening the oxidant screen

The mechanistic axis remains useful, but the oxidant panel contains redundant failure modes. H_2O_2, Oxone, and persulfate all create the desired mild-versus-radical contrast, while using all three adds gas, salt, precipitation, and solvent-oxidation concerns. CsF also affects boronic-acid speciation and possibly copper redox behavior, so replacing it globally would confound the oxidant question. It remains in the main screen, with any base change confined to a diagnostic branch.

The Gandhi/Brown/Doyle study sharpens this concern. Across 3,904 reactions, it identifies only 19 prior sulfonamide examples in 18 reports and finds strong substrate dependence. Sixteen of twenty-two sulfonamides prefer conditions other than the most general set, and alternative conditions can increase overarylation. The study finds productive CsF and KO$t-$Bu conditions, base-dependent ^{11}B NMR changes consistent with altered boronic-acid speciation, and improved reproducibility with added water. Thus, an oxidant-insensitive reaction may be limited before copper reoxidation.

Walker et al. show that a redox mediator can accelerate Cu(I) oxidation and improve Chan–Lam coupling relative to air, supporting a mediator probe without proving the same mechanism here. Sang/Gestwicki and Xiao et al. identify boron-to-copper transmetalation as a bottleneck in related alkylboron C–N coupling. Han and Liang further show that copper resting state, ligation, and coordination can control Chan–Lam selectivity. These analogies preserve transmetalation and speciation as alternatives rather than allowing every low-copper failure to be labeled redox-limited.

The revised ten-condition screen keeps the three baselines—20 mol % Cu/lutidine/air, 20 mol % Cu/CsF/air, and 1 mol % Cu/CsF/air—then uses NMO, *p*-benzoquinone, Selectfluor, TBHP, APS, TEMPO plus air, and an NMO condition in a propylene-carbonate-rich medium. H_2O_2 drops out because gas generation and DMSO oxidation can create variable behavior. Oxone drops out because it adds another salt-heavy strong oxidant without enough distinct information. TEMPO remains deliberately ambiguous: improvement suggests mediated aerobic turnover, while inhibition with fewer side products suggests radical interception or catalyst inhibition.

Cycle 1 uses 50 boronic acids × 10 primary sulfonamides = 500 pairs and 5,000 reactions. Each 50 μL reaction contains 20 mM sulfonamide and 30 mM boronic acid, or 1.0 and 1.5 μmol. One mol percent Cu is 10 nmol, now supplied by 2.5 μL of 4.0 mM $Cu(OAc)_2$. Four microliters of 0.25 M oxidant supplies 1.0 μmol; 4 μL of 0.05 M TEMPO supplies 0.20 μmol, or 20 mol %; and 4 μL of 0.50 M CsF supplies 2.0 μmol, or two equivalents. A fixed oxidant slot and solvent-compensation slot keep the main low-copper conditions compositionally matched. The PC condition is only PC-rich because DMSO and water still enter with the stocks.

4.4 Revised intermediate plan

Cycle 2 still selects 300 pairs and applies sixteen conditions, giving 4,800 reactions. Nine core conditions cross 0.25, 0.5, and 1.0 mol % Cu with air, the best mild oxidant, and the best radical/peroxide oxidant. Four PC-rich conditions compare 0.5 and 1.0 mol % Cu under air or the mild oxidant. Two sentinel conditions use 0.5 mol % Cu and replace CsF with KO$t-$Bu, with and without the mild oxidant, in DMSO/diglyme/water. One final condition tests half-dose mild oxidant.

The KO$t-$Bu branch remains small because its favorable literature behavior occurs in another solvent environment. A rescue is informative, but failure does not rule out transmetalation. With a fixed 2.5 μL copper slot, 1, 2, and 4 mM Cu stocks supply 0.25, 0.5, and 1.0 mol % exactly. The half-dose condition asks whether air contributes enough turnover to preserve target signal while reducing overoxidation.

Each condition is compared with the same pair's low-copper air control. The readout tracks monoarylated target, diarylated product, biaryl, phenol, and protodeboronation products; exact-mass conflicts remain qualitative. Broad improvement with mild oxidants and little additional side chemistry supports redox-limited turnover. Increased target plus biaryl or phenol under TBHP or APS indicates productive oxidation accompanied by radical/peroxide chemistry. A KO$t-$Bu rescue of an oxidant-insensitive pair supports a transmetalation/speciation limitation.

This plan aims for a pair-specific mechanistic map rather than a universal oxidant ranking. Cycle 1 identifies oxidant-sensitive, peroxide-sensitive, TEMPO-sensitive, diarylation-prone, and unresponsive pairs. Cycle 2 tests whether those responses persist across copper loading, PC-rich solvent, oxidant half-dose, and the limited KO$t-$Bu alternative.

4.5 Refining the mechanistic contrast

The current design still risks variable oxygen transfer, high salt and oxidant burden, unclear analytical readouts, and a Cycle 2 KO$t-$Bu branch that changes base and solvent simultaneously. A 2 mol % Cu/air condition is a cleaner control: it tests whether an oxidant simply compensates for insufficient catalyst inventory. Higher CsF loading or a diglyme cosolvent can probe transmetalation/speciation with less confounding than an immediate KO$t-$Bu switch.

The primary-sulfonamide precedent also connects counterion identity to copper oxidation potential and reports heterogeneity, mass-transfer, and oxygen-atmosphere differences during scale translation. Under KO*t*–Bu/ethanol conditions, water improves reproducibility, while boron NMR supports strong alkoxyboronate formation; CsF only partly activates the boronic acid. Oxidation therefore cannot be the only possible bottleneck.

Walker, Manabe, Brusoe, and Sevov make Cu reoxidation a credible rate-relevant variable by showing that a mediator can rapidly oxidize low-valent copper and improve Chan–Lam performance relative to air. TEMPO nevertheless remains only a probe, not an assumed equivalent of that mediator. Xiao and co-workers identify boron-to-copper transmetalation as limiting in an alkylboronate Chan–Lam system, while Han and co-workers identify a Cu(II)-derived resting state and ligand-controlled chemoselectivity in sulfenamide coupling. Redox turnover, copper coordination, and transmetalation therefore remain competing explanations.

4.6 Current plan

Cycle 1 now keeps all conditions in one DMSO/water family. The ten conditions are 20 mol % Cu/2,6-lutidine/air; 20 mol % Cu/CsF/air; 1 mol % Cu/CsF/air; 1 mol % Cu/CsF with NMO, *p*-benzoquinone, Selectfluor, aqueous TBHP, ammonium persulfate, or TEMPO/air; and 2 mol % Cu/CsF/air. The three non-peroxide oxidants test cleaner Cu reoxidation, TBHP and persulfate provide radical/peroxide contrasts, TEMPO probes mediation or radical interception, and 2 mol % Cu tests catalyst inventory. H_2O_2 and Oxone remain excluded because their decomposition, gas, and salt burden weaken microscale reproducibility.

Each reaction uses 20 mM sulfonamide, 30 mM arylboronic acid, 50 μL total volume, $Cu(OAc)_2 \cdot H_2O$, 55 °C, and 18 hours. Fill, headspace, venting, shaking, Cu-last addition, and solvent-compensation slots remain constant. A fixed 2.5 μL Cu slot uses 4 mM stock for 1 mol % and 8 mM for 2 mol %. One-equivalent oxidants occupy a 4 μL slot, with the opposite solvent added for compensation.

The quench contains EDTA to bind copper and sulfite or thiosulfate to destroy residual oxidant. Analysis follows monoarylated target, N,N-diarylated product, biaryl, protodeboronation product, phenol, and oxidant-specific products where mass-distinct. Within each substrate pair, target/internal-standard signal, mono:di ratio, and a combined side-product index matter more than an uncertain absolute microscale yield. A mild oxidant supports the hypothesis when it improves target signal over 1 mol % air without the side-product burden of TBHP or persulfate.

Cycle 2 replaces the confounded KO$t-$Bu branch with sixteen conditions. Nine cross 0.25, 0.5, and 1 mol % Cu with air, the best mild oxidant, and the best peroxide/persulfate oxidant. Four propylene-carbonate-enriched conditions cross 0.5 and 1 mol % Cu with air or the best mild oxidant. Two speciation sentinels use 0.5 mol % Cu plus the best mild oxidant with either 4 equivalents CsF or a DMSO/diglyme/water mixture. One condition uses half an equivalent of the best mild oxidant. The half-dose test distinguishes turnover assistance from high stoichiometric oxidant demand.

The 300-pair subset preserves high-signal, oxidant-sensitive, baseline-productive but oxidant-insensitive, diarylation-prone, peroxide-signature, mediator-sensitive, and structurally diverse cases. The parent library remains 50 arylboronic acids and 10 primary sulfonamides, with ambiguity flags for extra free NH or multiple nucleophilic nitrogen sites.

An oxidant response at fixed Cu supports redox sensitivity. Recovery by 2 mol % Cu/air instead suggests a catalyst-inventory limitation, while superiority of 1 mol % Cu plus mild oxidant points to an oxidant-specific effect. Increased biaryl, phenol, or protodeboronation under TBHP or persulfate marks peroxide/radical side chemistry. Response only to higher CsF or diglyme supports a speciation/transmetalation bottleneck. Propylene-carbonate conditions test whether these rankings survive solvent translation.