TEMPO Improves Generality and Decreases Oxidative Deboronation in Chan–Lam Couplings of Primary Sulfonamides

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ABSTRACT

Primary sulfonamides are valuable motifs in medicinal chemistry but remain challenging substrates for Chan–Lam *N*-arylation because of low nucleophilicity and boronic acid degradation. Here, we report a high-throughput study of TEMPO-promoted Chan–Lam coupling between primary sulfonamides and arylboronic acids. Across two microscale screening campaigns comprising 10,080 reactions, we evaluated oxidant identity, oxidant loading, copper source and loading, base, solvent, temperature, and substrate structure. Stoichiometric TEMPO emerged as a surprising yet uniquely effective additive, improving desired C–N bond formation while suppressing oxidative deboronation relative to oxidant-free and most of the strongly oxidizing conditions. Under the optimized condition, using 2 equivalents of TEMPO and 20 mol% $Cu(OAc)_2$, the mean estimated product yield increased to 25.2% (from 16.6%), and the fraction of reactions exceeding 30% yield increased over twofold to 37.5% (from 15.6%). Bench-scale validation confirmed the beneficial effect of TEMPO in eleven of fourteen representative substrate pairs, with LC-PDA-MS yields improving over twofold in the majority of cases. Notably, we observe consistent gains for electron-poor boronic acids across the high-throughput campaign and the bench-scale validation. Evaluation of structurally related additives showed that 4-hydroxy-TEMPO maintained comparable performance, offering a potentially lower-cost and more readily removable alternative to TEMPO. These results identify aminoxyl additives as a surprising tool for improving primary sulfonamide Chan–Lam couplings, with potential application on the industrial scale.

1. Introduction

An oxidative nucleophile–nucleophile coupling protocol,[1a,b, 2, 3] now widely known as the Chan–Lam (Chan–Lam, CL) coupling, enables the formation of C–N, C–O, and C–S bonds through the copper-catalyzed cross-coupling of organoboron reagents (such as boronic acids, pinacol esters, stannanes, or siloxanes) with various N–H, O–H, and S–H containing nucleophiles. Unlike palladium-catalyzed alternatives,[4] where the electrophilic substrate drives transition-metal turnover, CL reaction fundamentally requires an external terminal oxidant to regenerate the active Cu(II) catalyst from the Cu(I) species generated post-reductive elimination.[5] The primary synthetic value of CL amination lies in its mild operating parameters — it can operate at room temperature, utilizes inexpensive, low-toxicity copper catalysts, and is highly tolerant of ambient air and moisture. These features have made it an indispensable tool in medicinal chemistry and industrial process development.[6,7]

A major limitation of CL coupling is the presence of rapid, competitive side reactions that degrade the organoboron coupling partner before productive cross-coupling can occur.[8-10] Among these, oxidative deboronation is a key side reaction, in which oxidative cleavage of the carbon–boron bond generates phenolic byproducts.[8,9] These phenols can then undergo competitive Chan–Lam etherification with the remaining organoboron reagent to form diaryl ethers, severely depleting the boron stoichiometry and complicating product purification. Consequently, traditional protocols often require a large excess of the organoboron partner (typically 1.5 to 3.0 equivalents) to achieve complete conversion. Addressing these persistent inefficiencies requires a detailed understanding of both the productive catalytic cycle and the off-cycle pathways that govern copper speciation and organoboron degradation.

Recent mechanistic studies[8,9] have shown that Chan–Lam efficiency is strongly influenced by off-cycle copper speciation and Cu(I) reoxidation. Vantourout, Watson, and co-workers demonstrated that, in reactions of boronic pinacol esters, liberated pinacol can sequester copper as inactive [CuII(pinacol)$_2$] complexes, and that boric acid can improve turnover by trapping free diol, buffering acetate, and accelerating Cu(I) oxidation. However, aerobic Cu(I) reoxidation may also generate reduced oxygen byproducts such as peroxides or Cu–oxygen intermediates that promote protodeboronation/oxidative deboronation of the organoboron reagent.[8,9]

We therefore asked whether mild redox additives could improve the balance between productive copper turnover and these competing degradation pathways. TEMPO (2,2,6,6-tetramethylpiperidinyloxyl) was selected among others as a promising candidate because it is a mild, shelf-stable radical oxidant known to modulate Cu redox chemistry, although its precise role in Chan–Lam C–N coupling remains unresolved. Although Cu/TEMPO systems are well established in aerobic alcohol oxidation (the Stahl oxidation),[11a-c] their application as pure redox mediators to turn over C–N cross-coupling cycles remains remarkably neglected since the early work of Lam and co-workers.[1]

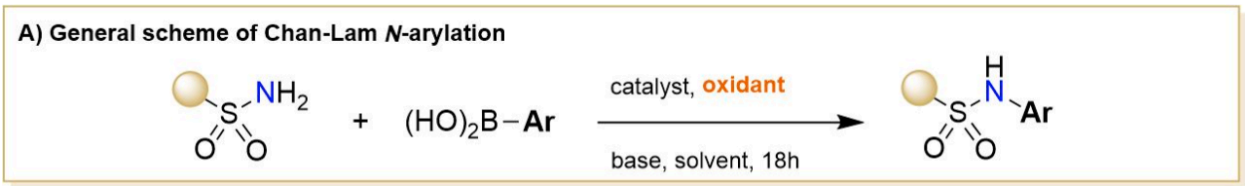
In this seminal study by Lam et al., TEMPO only occasionally outperformed molecular oxygen as the terminal oxidant, although it should be noted that the study evaluated only a limited number of examples within any given nucleophile class. As a result, atmospheric O_2 became the entrenched oxidation strategy in Chan–Lam coupling.

Subsequent studies demonstrating the efficacy of alternative oxidation strategies have focused predominantly on di-tert-butyl peroxide and related bulky organic peroxides.[12a-f] Beyond these examples, reports employing alternative oxidants or redox mediators remain relatively limited and fragmented.[13a-d] Remarkably, despite its inclusion in the original Chan–Lam study, TEMPO has received little subsequent attention. We identified only two studies that deliberately incorporated TEMPO into methodology development: a heterogeneous copper-mediated protocol[14] and a recently reported oxidative annulation of aminopyridines with arylboronic acids employing 4-OH TEMPO as an oxidant.[15]

Motivated by these observations, we revisited the role of TEMPO in Chan–Lam coupling using high-throughput experimentation (HTE). To the best of our knowledge, this study provides the first broad evaluation of the impact of TEMPO on Chan–Lam coupling across a diverse substrate set, while also examining its relationship with boronic acid-derived side reactivity. Furthermore, it establishes the first TEMPO-assisted Chan–Lam protocol developed specifically for sulfonamide arylation.

Primary sulfonamides ($R–SO_2NH_2$) were selected as the target nucleophile class due to their prevalence in medicinal chemistry and attractive physicochemical properties.[16a-c] At the same time, they remain challenging substrates for direct Chan–Lam *N*-arylation. The strongly electron-withdrawing sulfonyl group renders them weak and highly polar nitrogen nucleophiles, whose reactivity is sensitive to reaction parameters such as base, solvent, copper source, and the identity of the organoboron coupling partner.

We undertook a large-scale high-throughput experimentation campaign to map oxidant-dependent trends in reactivity and side product formation. Gandhi, Brown, Doyle, and co-workers recently generated a 3,904-reaction high-throughput dataset to identify effective conditions for primary sulfonamide Chan–Lam *N*-arylation.[17] We use their results to determine the starting baseline conditions (see Experimental section for details). As shown in Figure 1, the HTE screen encompassed 10,080 reactions across two experiments, representing, to our knowledge, the largest Chan–Lam high-throughput experimentation screen reported to date. Through this extensive optimization campaign, we identified highly efficient, TEMPO-promoted conditions for the direct cross-coupling of primary sulfonamides with arylboronic acids.



B) High-throughput experimentation study design

Parameter	First HTE campaign - Oxidant screen	Second HTE campaign - TEMPO optimization
Reaction scope	5,088	4,992
Substrate scope*	12 primary sulfonamides, 8 boronic acids	12 primary sulfonamides, 8 boronic acids
Oxidant	none, TEMPO, NMO, *p*-benzoquinone, DMP, H_2O_2, *tert*-butyl peroxide, Selectfluor, Ammonium persulfate, Sodium percarbonate, Oxone	none, TEMPO, NMO, *p*-benzoquinone, DMP, 4-hydroxy-TEMPO, 4-oxo-TEMPO, 1,2,2,6,6-pentamethylpiperidine
Oxidant mol %	50%, 100%	5%, 25%, 50%, 100%, 200%
Solvent	DMA, DMA/Dioxane, DMA/Dioxane/Water, DMA/Diglyme	DMA/Diglyme, DMA, DMA/BuOH, DMA/Dioxane, DMA/BuOH/Water, DMA/Diglyme/Water
Base	K_2CO_3, CsF, 2,6-Lutidine	K_2CO_3, K_3PO_4, CsF, Cs_2CO_3, KOAc, KO*t*-Bu, Na_2CO_3, $NaHCO_3$
Catalyst	$Cu(OAc)_2 \cdot H_2O$	$Cu(OAc)_2 \cdot H_2O$, $CuCl_2$, $Cu(OTf)_2$, $Cu(MeCN)_4PF_6$
Catalyst mol %	10%, 20%, 40%	2.5%, 5%, 10%, 20%, 40%

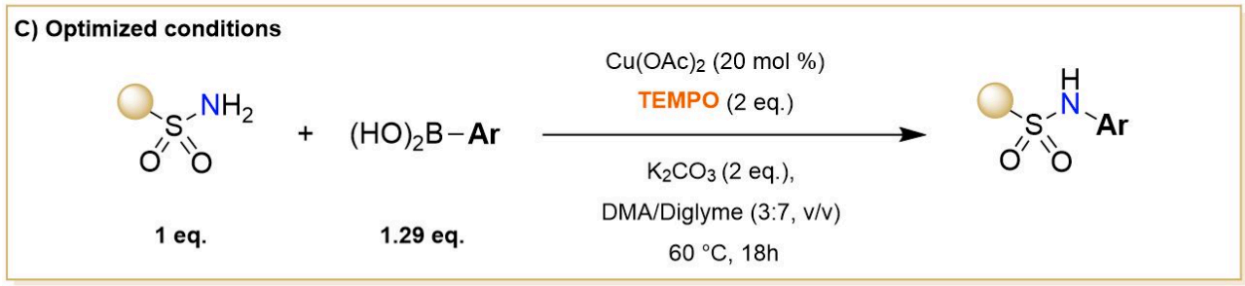


Figure 1. Two-stage microscale HTE optimization of the Chan–Lam coupling of primary sulfonamides with arylboronic acids. A) General reaction scheme and parameters evaluated during optimization. B) Design of the two HTE campaigns: the first screen comprised 5,088 reactions and focused on evaluating oxidant identity under varied solvent, base, and copper-loading conditions; the second screen comprised 4992 reactions and further optimized oxidant loading, temperature, base, copper source, solvent, and catalyst loading, while also evaluating structural variants of TEMPO. C) Optimised TEMPO-promoted conditions identified in the HTE study (for the representative procedure in optimized HTE conditions see SI, 2.2.2A, for the same in conditions applied to milligram-scale see SI, 3.2).
*One boronic acid and two sulfonamides from the first campaign were replaced in the second campaign after the original materials were consumed (See SI, Figure S1).

Our contributions are as follows:

1. **Largest Chan–Lam HTE Campaign:** This work reports the largest Chan–Lam high-throughput screening dataset to date, comprising 10,080 reactions performed at microliter scale.
2. **First Report of TEMPO-Assisted Sulfonamide Coupling:** Stoichiometric TEMPO was identified as an effective additive for improving yields in the Chan–Lam coupling of primary sulfonamides, see Figure 1C. Across the dataset, the mean product yield generally increased with TEMPO loading up to 2 equivalents. To our knowledge, this is the first report demonstrating that TEMPO improves primary sulfonamide Chan–Lam coupling relative to ambient-air oxidation alone.
3. **Suggesting a Novel Role for TEMPO:** The data suggest a previously unreported role for TEMPO in primary sulfonamide Chan–Lam coupling. TEMPO was observed to decrease the mean estimated yield of oxidative deboronation products. These findings indicate that the beneficial effect of TEMPO may arise from the suppression of boronic acid-derived decomposition, though further mechanistic studies are required to confirm this hypothesis.
4. **Potential Industrial Viability and Scalability via TEMPOL:** The beneficial effect of TEMPO was also achieved using 4-hydroxy-TEMPO (TEMPOL), a commercially available analogue widely used at industrial scale in the plastics industry. 4-hydroxy-TEMPO is substantially less expensive than TEMPO, depending on scale. Furthermore, the polar C-4 hydroxyl group on TEMPOL fundamentally alters its partition coefficient; unlike lipophilic TEMPO it can be easily and cleanly washed out of the reaction mixture via simple aqueous extraction. This finding may enable broader application of these results in process chemistry for molecules containing secondary sulfonamide motifs.[14,15]

2. Experimental Description

To systematically evaluate the effect of oxidants on primary sulfonamide Chan–Lam coupling, we designed a high-throughput experimentation campaign around a structurally diverse substrate matrix. Across two HTE campaigns, we performed 10,080 microscale Chan–Lam reactions covering 12 primary sulfonamides and 8 boronic acids, which gave 96 unique substrate-pair combinations in each HTE campaign (Figure 1). The substrate matrix was largely conserved across both HTE campaigns, with one boronic acid and two sulfonamides from the first campaign replaced in the second campaign due to material consumption; complete substrate lists and tested conditions for both campaigns are provided in the SI. The substrate set was selected to represent the structural diversity commonly encountered in medicinal chemistry, including aromatic, heteroaromatic, and aliphatic primary sulfonamides, together with aryl and heteroaryl boronic acids spanning different electronic and steric profiles. This design allowed us to evaluate whether oxidant effects were general across substrate classes or limited to specific coupling partners. Each substrate pair was tested across a range of reaction conditions combinations,

including oxidant identity and loading, copper source and loading, base, solvent, and temperature. This matrix design was intended not only to identify productive conditions, but also to capture substrate-dependent trends in yield, mono-/di-arylation selectivity, and boronic acid side-product formation.

All reactions were performed on a microliter scale in 96-well plates using automated liquid-handling workflows. The reactions were run at a 14 mM concentration and a total reaction volume of 28.6 μL, enabling broad exploration of chemical space while minimizing material consumption. Reaction outcomes were quantified by LC-PDA-MS analysis using an internal standard. Product yields were estimated by integrating product and internal-standard peaks and correcting for DFT-predicted absorption profiles for the corresponding products (see the full experimental procedure in SI).

3. First High-throughput Campaign: Oxidant Screen

The first high-throughput screening was designed to test whether oxidant additives could improve primary sulfonamide Chan–Lam coupling by improving yield while suppressing unproductive deactivation pathways. We evaluated 10 structurally and mechanistically diverse oxidants across 53 distinct condition sets, using reaction parameters inspired by high-performing conditions from literature[17] but deliberately introducing oxidant variation.

Milder, organic, non-peroxide oxidants - including TEMPO, *N*-methylmorpholine *N*-oxide (NMO), *p*-benzoquinone (*p*-BQ) - were tested at a stoichiometric amount (1.0 equivalent), given their clean single-electron transfer (SET) or proton-coupled electron transfer (PCET) pathways, which pose minimal risk of substrate degradation. Conversely, stronger, radical-generating, or peroxide-based oxidants - *tert*-butyl peroxide, Selectfluor, Oxone, hydrogen peroxide (H_2O_2), sodium percarbonate, and ammonium persulfate - were evaluated at reduced loading (0.5 equivalents) to prevent undue oxidative stress.

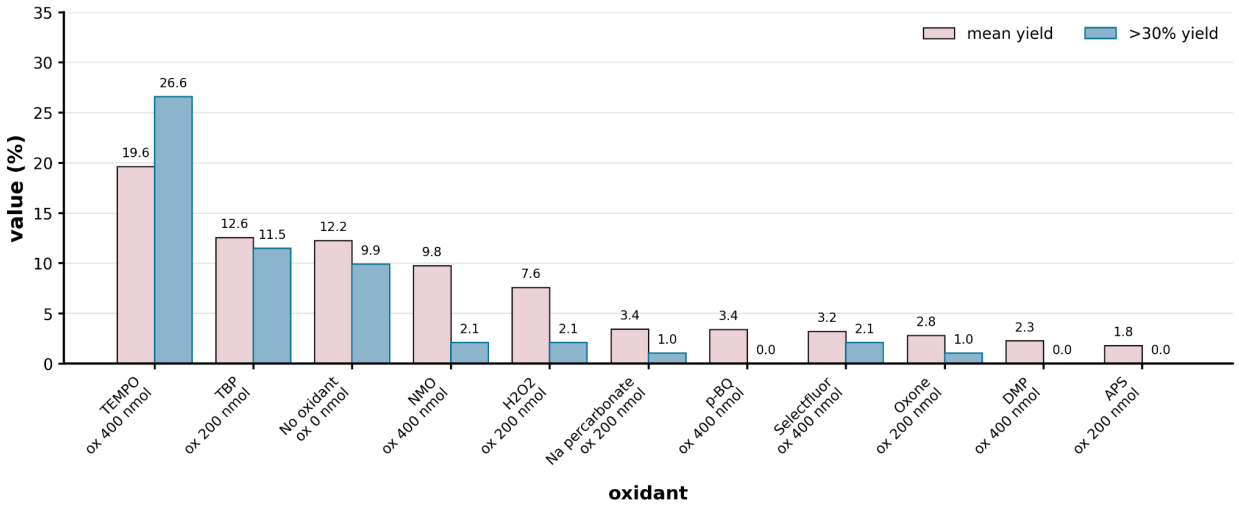
Furthermore, as several of these inorganic and peroxide-based salts (such as Oxone, sodium percarbonate, and persulfates) are highly polar and insoluble in tested organic solvents (DMA, diglyme, *n*-BuOH, dioxane), they were evaluated under conditions containing water as a co-solvent. The complete list of tested variants is provided in the SI.

The overall results are summarized in Figure 2. Rather than selecting conditions solely on the basis of average estimated yield, we prioritized robustness across the substrate set, defined as the fraction of reactions giving >30% estimated yield. By this criterion, the best-performing condition used TEMPO (1 eq.), K_2CO_3 (2 eq.), and DMA/diglyme (3:7, v/v) at 60 °C for 18 h. Diglyme was investigated as the principal reaction solvent; however, DMA was unavoidably present because the substrates were dispensed from DMA stock solutions.

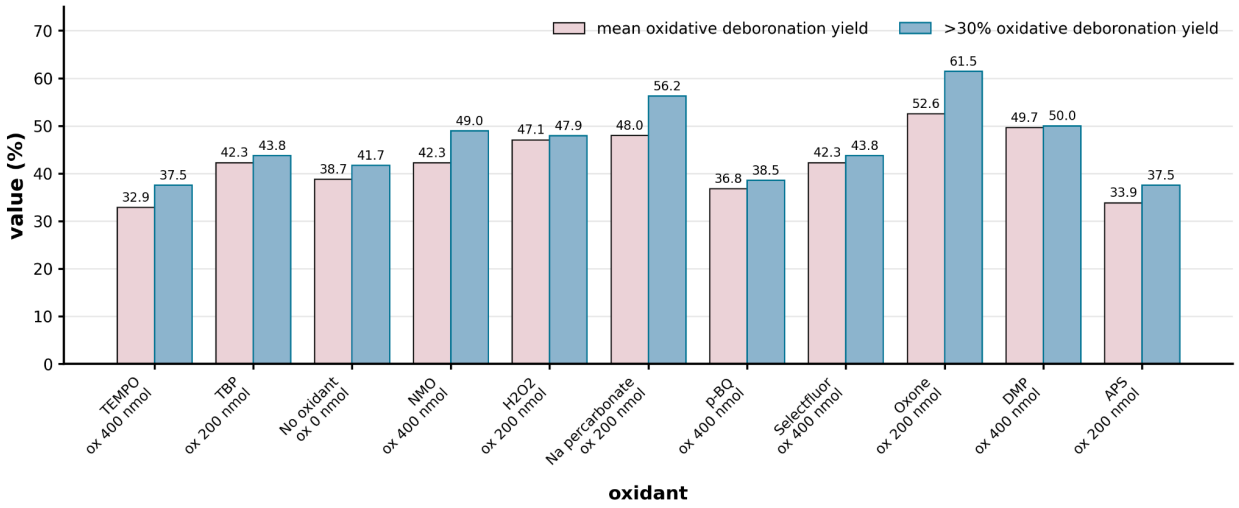
At the same copper loading (10 mol%), the reaction performed without an added oxidant gave only 9.9% of reactions above the 30% yield threshold, with a mean estimated yield of 12.2%. Adding TEMPO improved both metrics, increasing the hit rate to 26.6% and the mean estimated yield to 19.6% (Figure 2A). Although modest in absolute terms, this improvement is meaningful given the breadth of the screen, which included 96 distinct substrate pairs. By contrast, most other oxidants either reduced the overall yield or gave no significant improvement. Importantly,

TEMPO remained the top-performing oxidant even when each oxidant was compared under its own best observed condition from the broader screen, including conditions with higher copper loading (See SI, Figure S2). NMO and *tert*-butyl peroxide gave mean yields comparable to, or slightly higher than, the no-oxidant control, whereas oxidants such as *p*-benzoquinone, H_2O_2, Dess–Martin Periodinane, Selectfluor, sodium percarbonate, Oxone, and ammonium persulfate substantially decreased productive coupling.

Analysis of the side-product profile supports the hypothesis that the beneficial effect of TEMPO is not simply due to the presence of an external oxidant for copper turnover. Strong oxidants often increased oxidative deboronation - likely due to the oxidation of boronic acids to phenols, byproducts which can act as nucleophiles in Chan–Lam *O*-arylation (Figure 2B). In contrast, TEMPO decreased the mean oxidative deboronation estimated yield relative to the no-oxidant control while also improving the desired product yield. These results indicate that productive Chan–Lam performance is highly sensitive to oxidant identity: strongly oxidizing or poorly matched oxidants accelerate boronic acid decomposition, whereas TEMPO appears to favor productive coupling while limiting oxidative deboronation.



A. Mean estimated yield of the main product, and percentage of reactions achieving >30% yield across 96 substrate pairs for each condition at fixed copper loading (10 mol%)



B. Mean estimated yield, and percentage of reactions achieving >30% yield of oxidative deboronation across 96 substrate pairs for each condition at fixed copper loading (10 mol%)

Figure 2. Effect of oxidant on primary sulfonamide Chan–Lam coupling and side-product formation in the first HTE campaign. The average estimated yield (red) and the percentage of reactions achieving >30% yield (blue) for all oxidants under conditions using 10 mol% copper, for the main product (A) and oxidative deboronation (B). A detailed description of the selected conditions, together with additional comparisons of oxidant performance under the best condition identified for each oxidant, is provided in the SI (Figure S2 and Tables S1–S2). This copper loading corresponds to the best-performing condition identified for TEMPO, the top-performing oxidant overall. TEMPO emerges as the only oxidant significantly improving the mean yield across the tested 96 substrate pairs.

In conclusion, adding an oxidant is not sufficient to improve primary sulfonamide Chan–Lam coupling. In fact, some oxidants such as *p*-benzoquinone, H_2O_2, Dess–Martin Periodinane, Selectfluor, sodium percarbonate, Oxone, and ammonium persulfate mainly promote boronic acid degradation and lower product estimated yield. TEMPO behaved differently: it improved C–N bond formation while reducing oxidative deboronation. This suggests that the benefit of TEMPO does not come from stronger oxidation, but from providing a mild aminoxyl-mediated redox environment that supports *N*-arylation without accelerating organoboron decomposition.

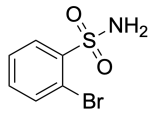
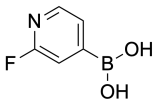
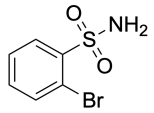
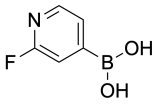
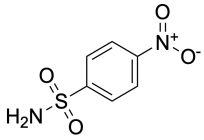
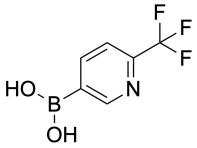
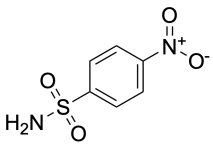
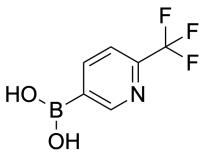
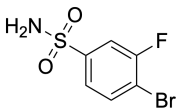
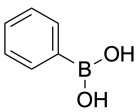
4. Bench-scale validation of TEMPO-promoted conditions compared to optimized copper loading without TEMPO

Four substrate pairs were advanced to bench-scale validation to test the reproducibility of the TEMPO effect observed in the HTE campaign. The reactions were performed at 42 mM, a three-fold higher concentration than used in HTE, to better reflect practical synthetic conditions, as the lower concentration employed in the screening campaign was dictated by format-specific solubility constraints.

Rather than using the same copper loading for all experiments, this parameter was selected based on the best-performing results from the initial HTE screen (10 mol% for TEMPO and 40 mol% for no-oxidant conditions). We chose four substrate pairs that achieved relatively high HTE yields for TEMPO-containing conditions, aiming for each to have distinct sulfonamide and boronic acid.

Aliquots of crude reaction mixtures were analyzed by LC-PDA-MS prior to purification; the relative ratios of reaction products to internal standard (IS) are presented in Table 1. Crude reaction mixtures were then subjected to purification to confirm product identity by ^{1}H NMR (for more details see SI). Product identity was confirmed for all entries.

As shown in Table 1, in three out of four cases, addition of TEMPO significantly increased the product/IS ratio relative to the no-oxidant control, with up to a four-fold improvement. In the remaining case (entries 5 and 6), TEMPO and no-oxidant conditions gave comparable results (product/IS ratio: 2.12 vs. 2.60, respectively). These results support the HTE finding that TEMPO improves primary sulfonamide Chan–Lam coupling.

Entry	**Sulfonamide**	**Boronic Acid**	**Oxidant**	**Product to IS ratio* LC-PDA-MS**	**qNMR yield**
1			None[a]	0.5	10%
2			TEMPO[b]	**1.87**	**33%**
3			None[a]	2.26	27%
4			TEMPO[b]	**7.21**	**59%**
5			None[a]	**2.60**	**49%**

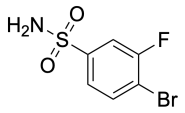
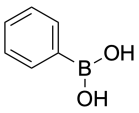
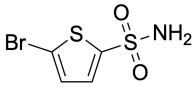
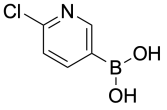
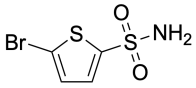
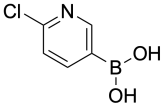
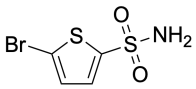
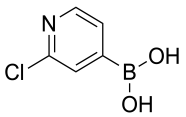
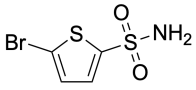
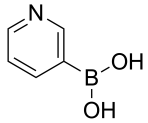
6			TEMPO[b]	2.12	42%
7			None[a]	2.19	36%
8			TEMPO[b]	**6.63**	**99%**

Table 1. Four substrate pairs were advanced to bench-scale validation to test the reproducibility of the TEMPO effect observed in the HTE campaign. The table shows LC-PDA-MS based product/IS (Internal Standard) ratio for milligram scale crude reactions mixtures comparing no-oxidant control conditions with TEMPO-containing conditions. Product identity was confirmed for all entries by ^{1}H NMR. qNMR yields were calculated using ^{1}H NMR measured with suitable standard (see SI 3.6). Conditions: [a] $Cu(OAc)_2 \cdot H_2O$ (40 mol%), no oxidant; [b] $Cu(OAc)_2 \cdot H_2O$ (10 mol%), TEMPO (1.0 eq.); General conditions: sulfonamide (0.225 mmol, 1.0 eq.), boronic acid (0.290 mmol, 1.29 eq.), K_2CO_3 (2.0 eq.), DMA/diglyme (3:7, v/v; 42 mM), 60 °C, 18 h. For the representative procedure see SI 3.1, 3.2.

An additional test intended to more systematically examine the influence of boronic acid identity was performed with 20 mol% copper loading for both variants (Table 2). Nine out of ten selected boronic acids were not used in the high-throughput campaigns and were selected to provide a representative set of substrates encompassing a range of electronic properties, functional groups, and heterocyclic motifs. The benefit of the TEMPO addition was clearly demonstrated for all electron-poor boronic acids (Entries 1-3, 6-8, 10) and one of electron-rich boronic acids (Entry 9), averaging a roughly twofold increase in the measured product amount, while it was not observed in the remaining two or addition of TEMPO even led to lower relative amount of product (Entries 4 and 5).

Entry	**Sulfonamide**	**Boronic Acid**	**Product to IS ratio* LC-PDA-MS**	
			No oxidant[a]	**TEMPO[b]**
1			0.79	**2.17**
2			2.00	**3.23**

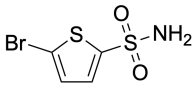
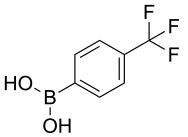
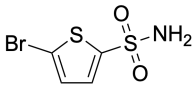
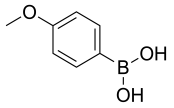
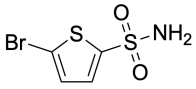
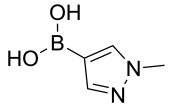
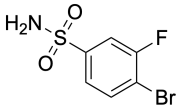
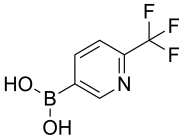
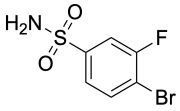
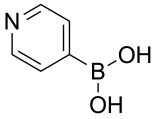
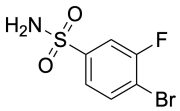
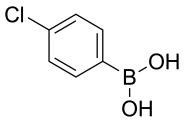
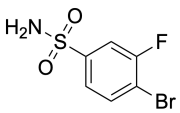
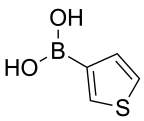
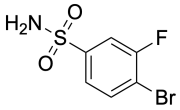
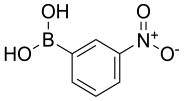
3			2.00	**3.57**
4			**0.51**	0.46
5			**0.56**	0.13
6			1.03	**2.17**
7			1.30	**3.85**
8			0.42	**7.69**
9			7.14	**12.50**
10			1.69	**3.57**

Table 2. Ten boronic acids were tested in milligram scale, each paired with one of the two selected sulfonamides. The table shows LC-PDA-MS based product/IS (Internal Standard) ratio for milligram scale crude reactions mixtures comparing no-oxidant control conditions with TEMPO-containing conditions. Conditions: [a] $Cu(OAc)_2 \cdot H_2O$ (20 mol%), no oxidant; [b] $Cu(OAc)_2 \cdot H_2O$ (20 mol%), TEMPO (2.0 eq.); General conditions: sulfonamide (0.225 mmol, 1.0 eq.), boronic acid (0.290 mmol, 1.29 eq.), K_2CO_3 (2.0 eq.), DMA/diglyme (3:7, v/v; 42 mM), 60 °C, 18 h. For the representative procedure see SI 3.3, 3.4.

5. Second High-throughput Campaign: TEMPO Optimization

With the positive results from the initial oxidant screen in hand, the second high-throughput campaign was designed to optimize the TEMPO-promoted *N*-arylation. Conditions varied in TEMPO loading (from 0.25 to 2 equivalents), copper catalyst source and loading (from 2.5 mol% to 40 mol%), as well as temperature, base and solvent. Detailed description of the 52 tested conditions is provided in SI. We tested all the conditions across the 96 substrate pairs, producing a total of 4992 reactions. Two sulfonamides and one boronic acid were replaced in the second screen because the material was exhausted.

The selected combination used 2 equivalents of TEMPO and 20 mol% $Cu(OAc)_2$, see Figure 1C. We compared this condition with selected no-oxidant controls and with the initial TEMPO-containing condition from the first campaign (Figure 3). The optimized TEMPO-containing condition gave the strongest overall performance, increasing the percentage of reactions achieving >30% yield from 15.6% under the no-oxidant control to 37.5%. Increasing copper loading alone also improved performance, but to a much smaller extent, indicating that the benefit of the optimized condition cannot be explained by copper loading alone (see Figure 5).

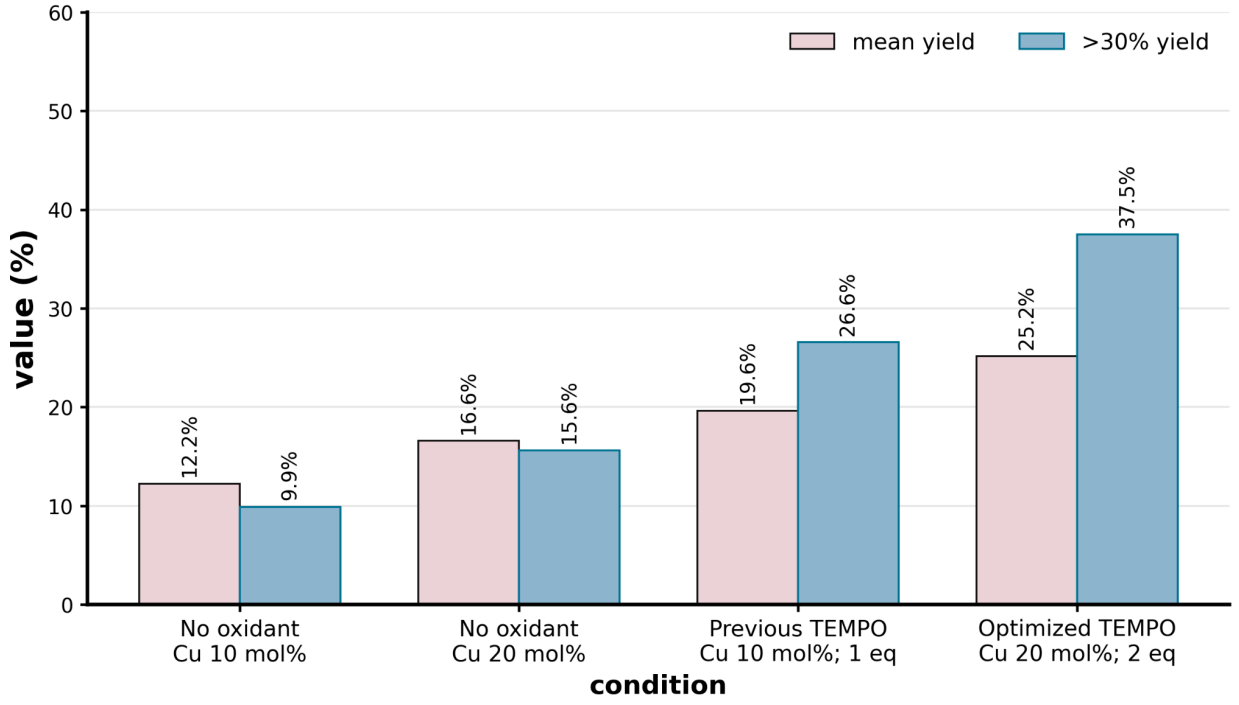
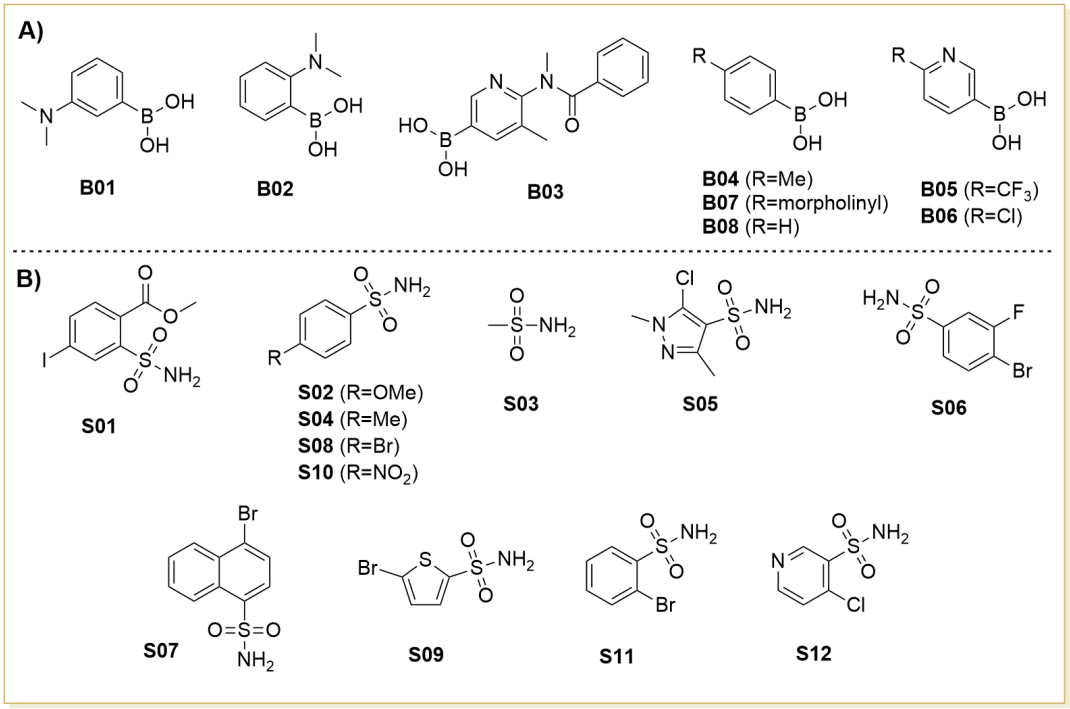


Figure 3. Results of the optimization of TEMPO-containing conditions in the second HTE campaign. Mean estimated product yield (red) and the percentage of reactions achieving >30% yield (blue), for selected control conditions and optimized TEMPO-containing conditions.

The second experimental campaign also included a few condition combinations (see Supporting Information for details) that optimized the base and solvent in the best

TEMPO-containing conditions (1 equivalent and 10 mol% of Cu) from the first campaign. Two condition combinations showed early benefit: (1) changing K2CO3 to K3PO4 and (2) changing the DMA/diglyme co-solvent system to DMA/*n*-BuOH. We decided to keep solvent and base intact in the optimized conditions (Figure 1c) and move a more exhaustive optimization of solvent and base to future work.

Additionally, we were particularly interested in how substrate structure influences reaction outcomes; therefore, we analyzed the mean yield for each substrate (averaged across all conditions), as shown in Figure 4. The substrate library consisted of 12 primary sulfonamides and 8 boronic acids, giving 96 unique substrate pairs. The results demonstrated that addition of TEMPO (blue) improved the mean yield for the majority of substrates (with the exception of **B01** and **S04** that appear slightly worse) compared to no-oxidant control (red). The improvement is seen for a variety of sulfonamides and boronic acids, hence not limited to only one substrate class.



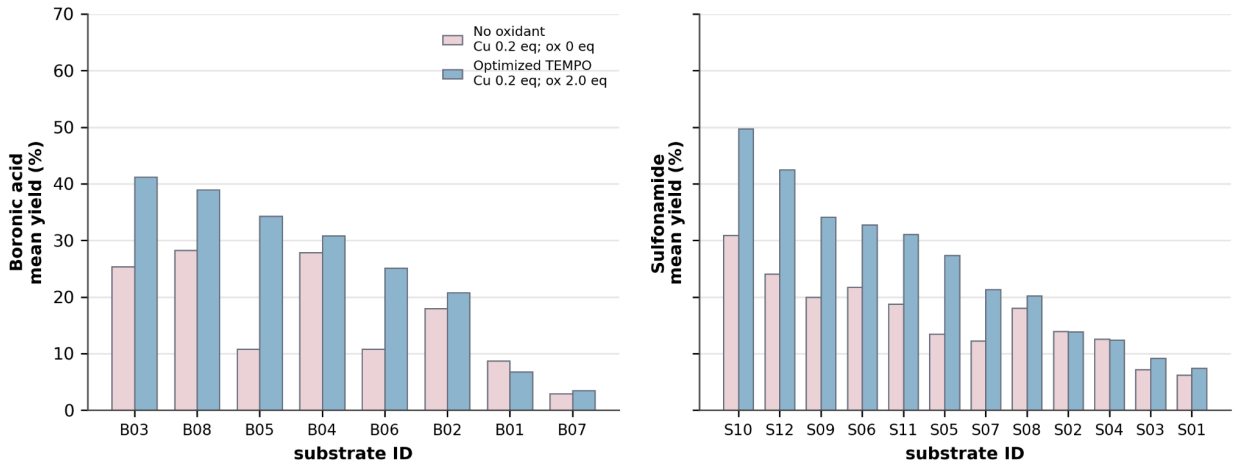


Figure 4. Substrate scope for High-Throughput Experimentation (HTE). A) Representative aryl and heteroaryl boronic acids (**B01–B08**) and B) aromatic, heteroaromatic, and aliphatic primary sulfonamides (**S01–S12**) utilized in the study. The HTE campaign was executed as a full cross-matrix of all substrate pairs, resulting in 96 unique coupling combinations, evaluated across a range of conditions. C) Average yield per substrate, boronic acid (left) and sulfonamide (right), in the second high-throughput campaign for the optimized conditions (Figure 1C) compared to no-oxidant variant.

An investigation into the substrate scope revealed distinct trends dictated by electronic, steric, and coordination effects. Among the primary sulfonamides evaluated, derivatives bearing electron-withdrawing groups (**S06**, **S10**, and **S12**) were among the ones delivering the highest mean yields. Notably, *ortho*-substitution in **S12** was well tolerated under the developed conditions, despite the potential for steric hindrance to inhibit transmetallation and C–N bond formation. Furthermore, the performance of the highly functionalized pyrazole derivative **S05**, giving approximately 28% mean yield, is particularly noteworthy and highlights the compatibility of our protocol with highly substituted five-membered heterocycles.
For the boronic acid substrate, sterically unhindered and electronically favorable variants, such as phenylboronic acid **B08** and the weakly electron-rich 4-tolyl derivative **B04**, performed consistently well which might reflect undergoing smooth transmetallation. Notably, the amide-functionalized pyridine **B03** emerged as the best performer in the tested library, with its structural analog **B05** (R=CF_3) in the third position. Conversely, substrates bearing basic tertiary amines, such as the *meta*-dimethylamino derivative **B01** and the *para*-morpholine analog **B07**, severely suppressed reaction outcomes. These Lewis-basic motifs potentially act as competitive ligands that poison the copper catalyst. In contrast, the *ortho*-dimethylamino analog **B02**; despite its electronic similarities to **B01**, showed improved yields under the optimized TEMPO-containing conditions, with overall mean yield of 21%, which might be due to the ability of the *ortho*-nitrogen to position the catalyst in immediate proximity to the C-B bond. In general, benefits of TEMPO were most pronounced for electron-poor boronic acids, in line with our bench-scale findings (see Table 2).

5.1. Increased TEMPO loading improves product yield and reduces oxidative deboronation

Having identified the optimized TEMPO-containing conditions, we examined whether the improvement reflected a genuine loading-dependent effect of TEMPO. To verify this, we analyzed mean product yield and side-product formation as a function of TEMPO loading across the second HTE campaign (Figure 5).

A strong loading-dependent trend was observed. Across most copper loadings, increasing TEMPO generally improved mean product yield, with the highest value observed at 2 equivalents TEMPO and 20 mol% $Cu(OAc)_2$. This trend is particularly evident at 20 mol% copper loading, where the mean yield increases from 16.7% without TEMPO to 25.3% when paired with 2 equivalents of TEMPO.

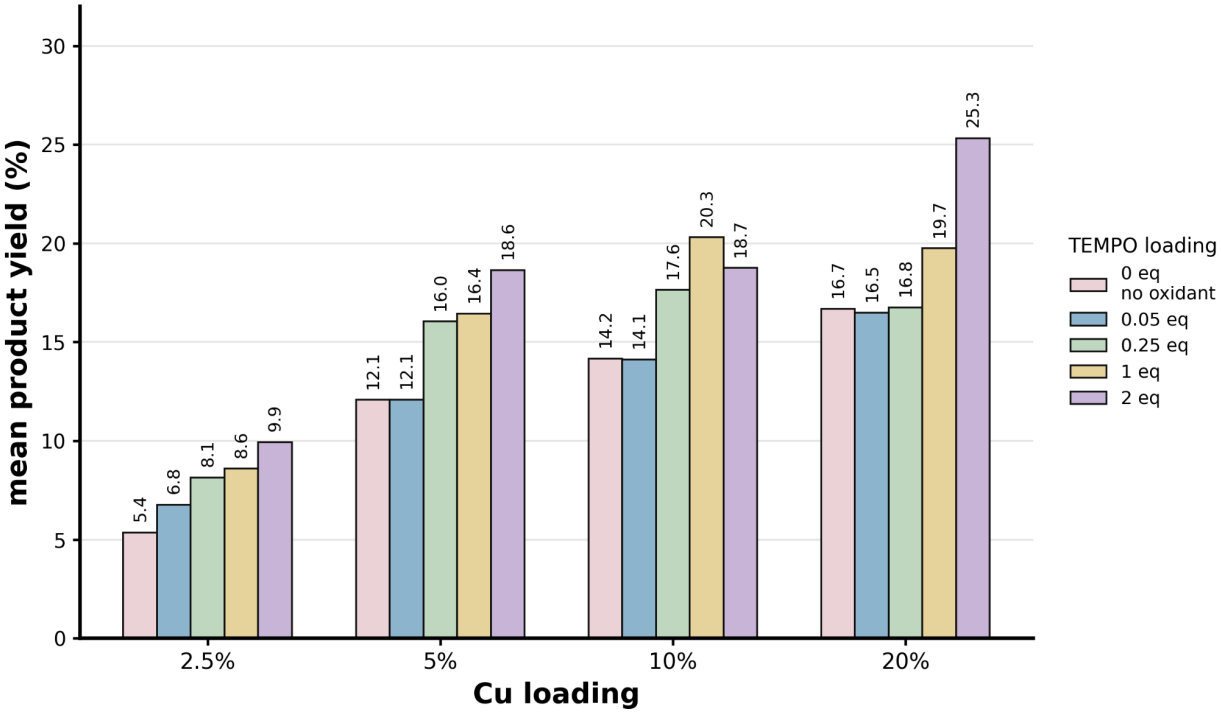


Figure 5. Mean estimated product yield as a function of TEMPO and $Cu(OAc)_2$ loading across the second HTE campaign.

In the next step we examined whether this improvement was accompanied by changes in the side-product profile. At 20 mol% copper loading, increasing the TEMPO concentration reduced oxidative deboronation from 37.3% under oxidant-free conditions down to 30.2% at 2 equivalents of TEMPO (Figure 6). The mean estimated yield of oxidative homocoupling remains small (between 2.2% and 5.9%).

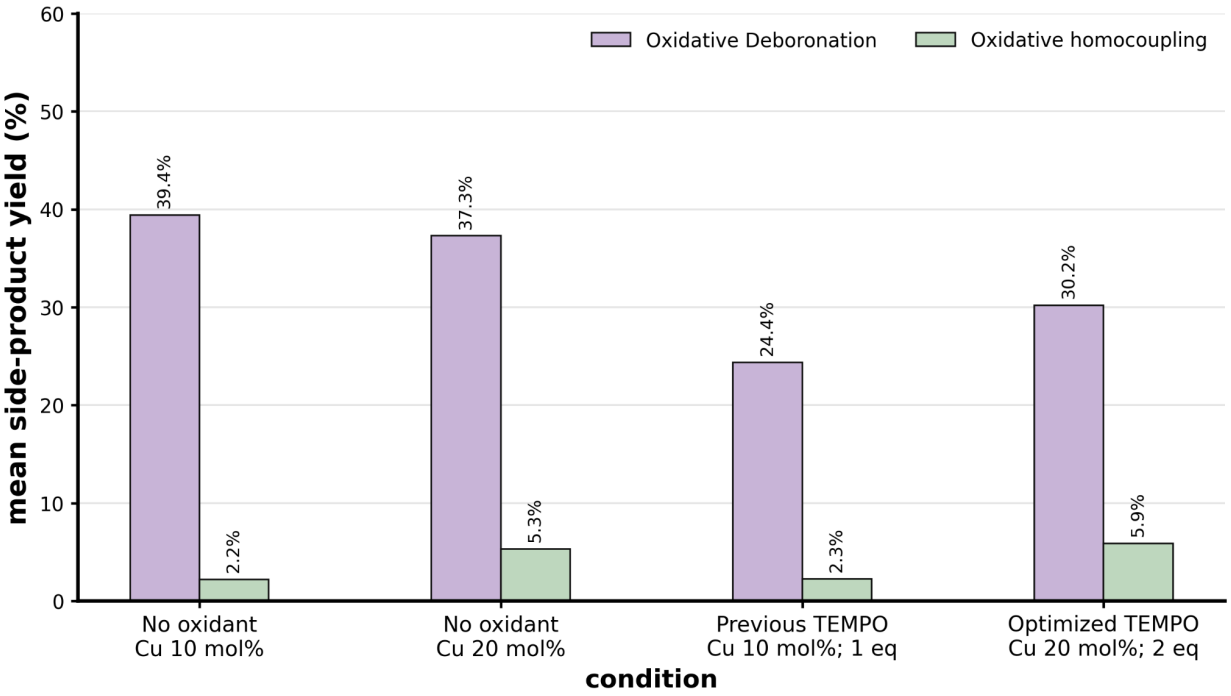


Figure 6. Mean estimated yield of oxidative deboronation and oxidative homocoupling at best TEMPO-conditions identified in each HTE campaign, compared to the no-oxidant control at the same copper loading.

Taken together, these data underscore that the optimized condition identified in Figure 3 is not an isolated high-throughput hit, but part of a systematic response to TEMPO loading: higher TEMPO loading generally favors C–N bond formation and, at 20 mol% Cu, reduces oxidative deboronation.

5.2. Evaluation of TEMPO-Related Additives

The beneficial effect of TEMPO prompted us to investigate whether related aminoxyls could reproduce the observed improvement in primary sulfonamide Chan–Lam coupling. We tested TEMPO, TEMPO-derived aminoxyl radicals: 4-hydroxy-TEMPO, 4-oxo-TEMPO, and 1,2,2,6,6-pentamethylpiperidine (PMP) as a sterically related non-radical piperidine control (Figure 7).

Among the tested additives, only 4-hydroxy-TEMPO maintained performance comparable to TEMPO. This result is synthetically important because 4-hydroxy-TEMPO is significantly less expensive than TEMPO, reflecting its broader availability from polymer and materials applications. In contrast, both 4-oxo-TEMPO and PMP gave significantly worse results (Figure 7). These results suggest that the effect is sensitive to the additive structure and is not simply a consequence of introducing a sterically hindered piperidine scaffold.

4-hydroxy-TEMPO also gave a slightly higher mean level of oxidative deboronation than TEMPO while maintaining comparable coupling performance. In contrast, both 4-oxo-TEMPO and PMP showed substantially higher oxidative deboronation and poorer product formation.

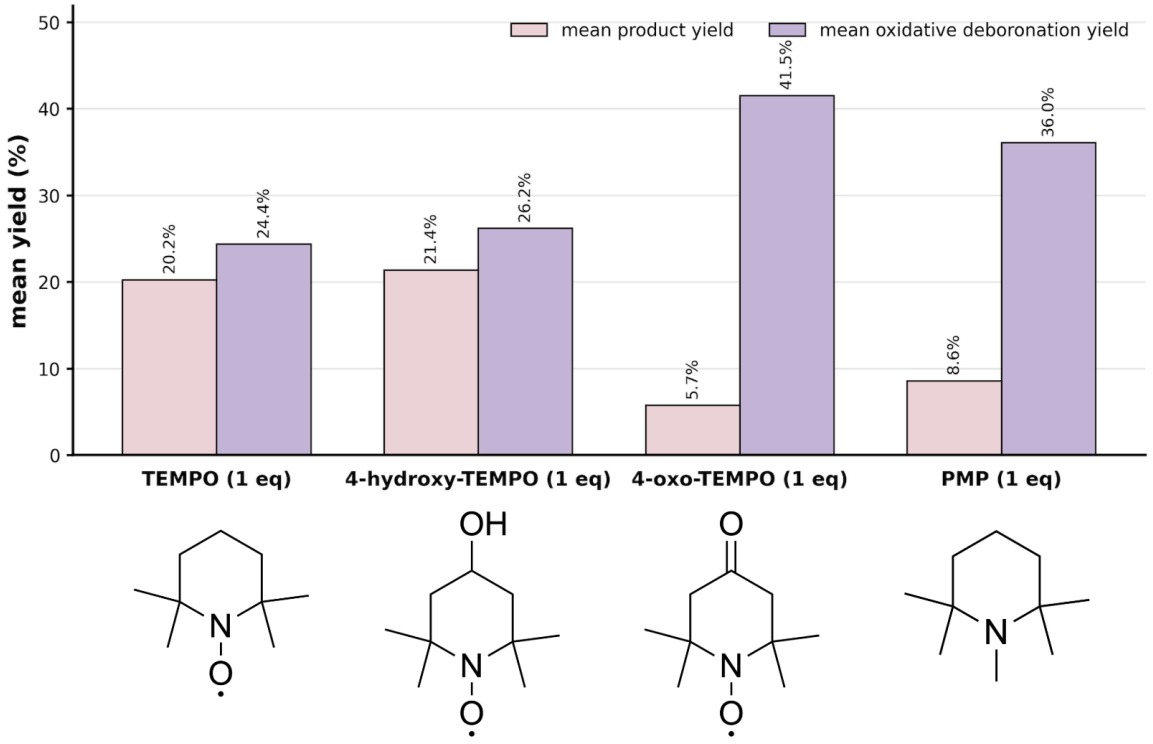


Figure 7. Evaluation of TEMPO and structurally related additives. The mean yield of the main product (red) and mean yield of oxidative deboronation (purple) across 96 substrate pairs using TEMPO, 4-hydroxy-TEMPO, 4-oxo-TEMPO, or 1,2,2,6,6-pentamethylpiperidine (PMP). All additives were tested at 1 equivalent under otherwise identical conditions.

Conclusions

In conclusion, we report the largest high-throughput screening of Chan–Lam coupling of primary sulfonamides, comprising 10,080 microscale reactions across a diverse substrate matrix. The systematic screen identified – among 10 oxidants tested – stoichiometric TEMPO as a surprisingly effective additive for improving primary sulfonamide N-arylation. The optimized condition increases mean product yield from 16.6% to 25.2% and doubles the fraction of reactions exceeding 30% yield relative to the no-oxidant control. Bench-scale validation confirmed the beneficial effect of TEMPO in 11 of 14 representative substrate pairs, with LC-PDA-MS yields improving over twofold in the majority of cases. Notably, we observe consistent gains for electron-poor boronic acids across the high-throughput campaign and the bench-scale validation.

Crucially, profiling across the selected library demonstrated that the optimized conditions are effective across multiple substrate classes, although strongly substrate-dependent. The reaction tolerates a wide array of functional groups, enabling the efficient coupling of polyhalogenated aromatics, sterically hindered *ortho*-substituted compounds, and complex heterocycles.

These data suggest a previously underexplored role for aminoxyl radicals in primary sulfonamide Chan–Lam coupling. High-throughput side-product tracking demonstrated that the addition of TEMPO significantly suppresses the competitive oxidative deboronation pathway. Importantly, Chan–Lam coupling yields generally increased with TEMPO loading, with the best mean yield observed at 2 equivalents TEMPO and 20 mol% $Cu(OAc)_2$.

From a process chemistry perspective, the developed protocol offers attractive avenues for potential industrial implementation. The beneficial effects of TEMPO on reaction yield persist even at reduced copper loadings (2.5 mol% to 10 mol%), underscoring its potential utility in process chemistry settings where minimizing residual transition-metal content is often desirable. Furthermore, we demonstrated that TEMPO can be replaced with comparable performance using 4-hydroxy-TEMPO (TEMPOL) without sacrificing reaction efficiency. Owing to its widespread use in the polymer industry, TEMPOL stands as a substantially less expensive alternative for the synthesis of sulfonamide-containing APIs. Additionally, its highly polar C-4 hydroxyl group grants distinct practical advantages, altering its solubility profile and facilitating clean aqueous extraction during workup and presenting opportunities for immobilization.[18,19]

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ASSOCIATED CONTENT

1. Supporting Information.