

Copper Mediated C(sp²)-H Sulfonylation of Aldehydes using a Catalytic Transient Imine Directing Group

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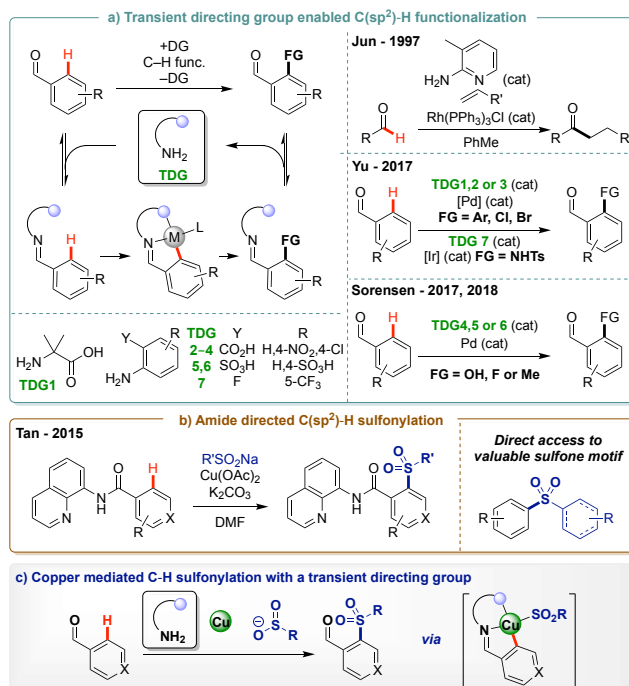
ABSTRACT: The copper mediated β -C(sp²)-H sulfonylation of benzaldehydes with sulfinate salts is accomplished using β -alanine as a catalytic transient directing group. A broad range of sulfonylated benzaldehydes are prepared using copper fluoride as both copper source and oxidant. Both β -(*ortho*) and γ -(*peri*)-sulfonylation are demonstrated. Mechanistic studies indicate the turnover limiting step to be a concerted asynchronous C-H cleavage *via* a Wheland-type transition state.

Strategies for step-efficient C-H functionalization offer the potential for powerful and improved processes in the synthesis of valuable organic compounds.¹ Removable directing groups have provided a means to control site-selectivity in C-H functionalization, between numerous similar C-H bonds, by correctly locating a transition metal and promoting proximity driven C-H activation.² However, the discrete steps required to install and remove directing groups provides an intrinsic efficiency limitation. Transient directing groups (TDGs) have emerged as a powerful solution, whereby the directing group is formed and removed within the C-H functionalization reaction by taking advantage of common valuable functional groups.³ Imine transient directing groups have afforded considerable success in selectively functionalizing either aldehyde or amine components. A TDG approach was first described by Jun for the alkylation of aldehydic C-H bonds (Scheme 1a).⁴ In 2016, Yu reignited interest in this field by demonstrating benzylic and sp³ C-H functionalization of aldehydes and ketones using co-catalytic palladium acetate and glycine to form a transient coordinating imine.⁵ In 2017, Yu reported the palladium catalyzed transient *ortho*-C-H functionalization of benzaldehydes, achieving arylation, bromination and chlorination with imines derived from anilines.⁶ Sorensen developed C(sp²)-H hydroxylation, fluorination and methylation processes.⁷ Noticeably there are no examples of C-S bond formation using transient C-H functionalization.^{8,9} Furthermore, the majority of TDGs use precious metal catalysis, mainly palladium, but also rhodium, ruthenium and iridium.³ The move towards more sustainable earth abundant metals presents a notable challenge in C-H functionalization.^{10,11} To date only 2 reports of 3d metals being used for C-H functionalization in combination with TDGs in cobalt catalyzed amidation.¹² Specifically there are no examples of copper mediated C-H functionalization with TDGs.

Sulfones feature heavily in active pharmaceutical ingredients,¹³ and C-H functionalization processes offer attractive

strategies for their incorporation and for late-stage diversification.¹⁴ Copper has been used stoichiometrically and catalytically to form sulfones through C-H functionalization with an amide directing group, using bench stable sulfinate salts (Scheme 1b).¹⁵

Scheme 1. C(sp²)-H functionalization with transient directing groups and copper mediated sulfonylation

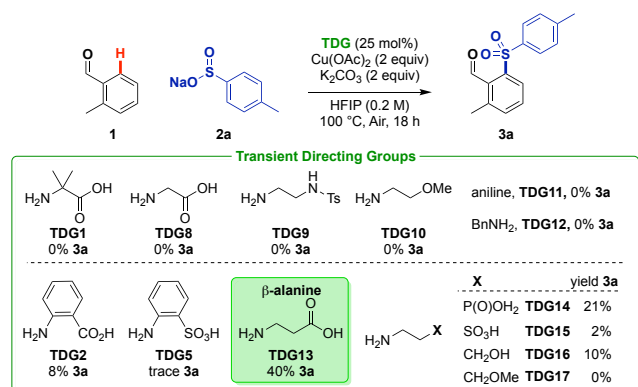


Here we report the first copper mediated, catalytic transient directing group enabled C-H functionalization. This also represents the first C-S bond forming transient C-H functionalization process, enabling the rapid and step-efficient construction of sulfones (Scheme 1c). Kinetics and deuteration studies have provided insight into the reaction

mechanism of this complex process which is catalytic in amine TDG.

Initially, we aimed to establish whether copper mediated C–H functionalization reactions were possible with a catalytic TDG. Studies focused on C–H sulfonylation of benzaldehyde and *o*-tolualdehyde by assessing the potential of different classes of amines as TDGs. Copper (II) acetate was selected for early studies to effect both a putative concerted metalation deprotonation (CMD) process and subsequent functionalization steps, as well as to provide an inexpensive and non-toxic stoichiometric oxidant. Potassium carbonate base and HFIP,¹⁶ used previously in Pd-mediated transient processes, were employed to screen for successful *ortho*-sulfonylation using 25 mol% of the transient directing groups (Scheme 2).

Scheme 2. Assessing transient directing groups in copper mediated C(sp²)-H sulfonylation



Yield determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Bidentate transient directing groups **TDG1**, and **TDG8**–**TDG10** previously reported with Pd in C(sp²)-H functionalization were ineffective, as were monodentate aniline and benzylamine. Pleasingly, reactivity was observed when using anthranilic acid (**TDG2**), forming a presumed [5,6] cupracyclic intermediate, but related orthanilic acid was ineffective. More flexible β-alanine (**TDG13**) was more effective, giving 40% yield of **3a**. Changing the acidic secondary binding site (P(O)(OH)₂, SO₃H, OH or OMe; **TDG14**–**TDG17**) gave lower yield, so **TDG13** was selected for further study.

We next investigated reaction variables including: copper sources, solvents, base, TDG loading, and other additives.¹⁷ CuF₂ was the most effective copper source, and the yield could be further improved with carboxylate additives. Using 0.5 equiv of Cu(OAc) along with 1.5 equiv CuF₂ was most effective. Further investigation confirmed K₂CO₃ and HFIP as the most effective base and solvent respectively. A design of experiment (DoE) optimization focused on CuF₂ equivalents, aldehyde equivalents and reaction concentration identified a key positive interaction between increasing equivalents of aldehyde and CuF₂.^{17a} Using catalytic TDG, the aldehyde in excess and 2 equiv of readily available CuF₂, aldehyde **3a** was isolated in 86% yield (Table 1, entry 1). Importantly, no reaction was observed in the absence of the TDG (Entry 2). Reduced reactivity was observed when

either of the copper salts were omitted (Entries 3 and 4), and when no copper salts were present there was no observable reaction (Entry 5). Using only Cu(OAc)₂ (2.5 equiv) in place of CuF₂ remained effective but with reduced yield (Entry 6). Low yield was observed in the absence of K₂CO₃ (Entry 7). Interestingly, in the absence of the sulfinate salt, ether (**4**) was formed in 33% yield based on the aldehyde, with solvent acting as the coupling partner (Entry 8).¹⁸ We observed complete suppression of sulfone formation on addition of the radical trap TEMPO (Entry 9). The reaction was sensitive to increased water and oxygen as assessed by the Glorius protocol.^{17b,19}

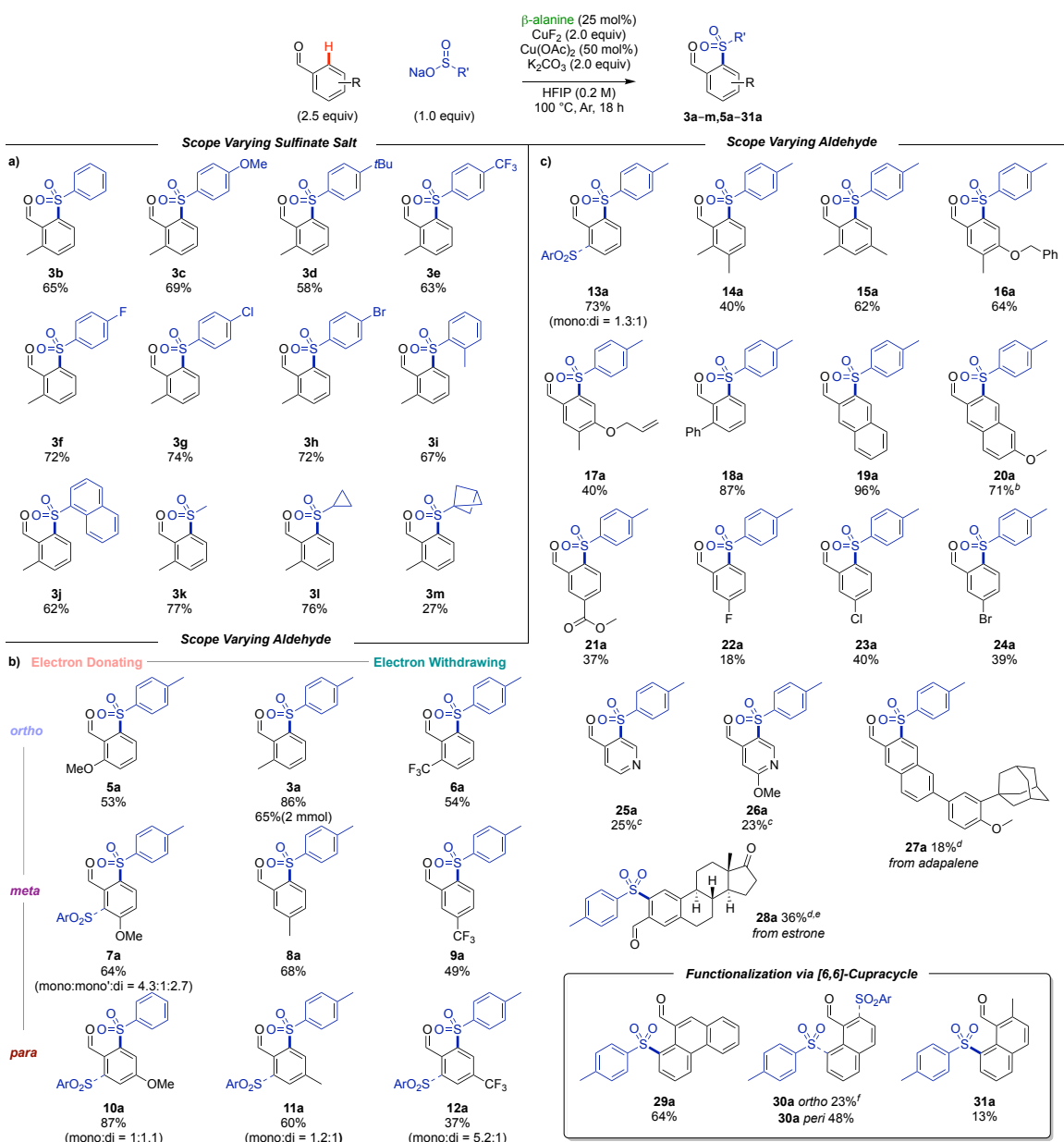
Table 1: Control reactions describing deviation from the optimized conditions

Entry	Deviation from standard conditions	Yield(%) ^a		
		3a	4	1
1	None	93 (86)	0	153
2	No TDG	0	0	102
3	No CuF ₂	20	0	227
4	No Cu(OAc) ₂	82	0	165
5	No CuF ₂ or Cu(OAc) ₂	0	0	250
6	Cu(OAc) ₂ (2.5 equiv)	75	0	150
7	No K ₂ CO ₃	18	0	202
8	No Sulfinate	0	33 ^b (19%) ^c	61 ^b
9	+ TEMPO (1 equiv)	0	trace	178

Reactions performed using 0.2 mmol sulfinate salt. ^aYield determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield in parenthesis. 1 refers to recovered excess aldehyde. ^bYield based on aldehyde as limiting reagent. ^c Yield on 0.5 mmol scale of aldehyde. Note **4** is volatile.

With these optimized conditions, a wide range of electronically and sterically diverse sulfinate salts were effectively coupled to give sulfones in good to excellent yields (Scheme 3a). Sulfinate salts with electronically neutral or electron donating substituents were well tolerated. Sulfinate salts bearing arenes with inductively electron withdrawing groups (*p*-CF₃,*p*-halides) were particularly effective giving yields of 63–74% (**3e**–**3h**). More sterically encumbered *ortho*-substituted sulfonates such as 1-naphthyl and *o*-tolyl derivatives were successful. Methyl and cyclopropyl sulfinate salts were both highly effective in this oxidative coupling reacting in 77% and 76% yield respectively. Additionally, bicyclo[1.1.1]pentane (BCP) sulfinate was used to introduce a BCP moiety. No obvious trend between the oxidation potential of the sulfinate salts and the yield of the coupling was observed,²⁰ indicating direct oxidation of the salt to a sulfonyl radical was likely not a mechanistically significant step.

Scheme 3. Reaction scope varying the sulfinate salt and aldehyde^a



^a Reactions performed on 0.2 mmol scale. Isolated yields reported. ^b 22h reaction time. ^c NaHCO₃ (sat. aq) workup was used. ^d 1 equiv aldehyde and 1.25 equiv sulfinate salt. ^e 91% purity. ^f 87% purity

Next the scope of the aldehyde component was investigated. Electron donating (OMe), neutral (Me) and withdrawing (CF₃) substituents were probed at *ortho*-, *meta*- and *para*-positions in a 3×3 array (Scheme 3b), revealing electron rich substrates tended to be most reactive. Symmetrical 4-methoxybenzaldehyde gave an 87% combined yield of mono and di-functionalization (1:1.1 mono/di). Substrates with the methoxy group in the *meta*- and *ortho*-positions gave decreased yields. This contrasts with the Me and CF₃ substituted systems, where increased yield was observed with *ortho*-substitution. Electron poor derivatives gave lower overall yields and reduced di-functionalization. A broader range of aldehydes was then investigated (Scheme 3c). Benzaldehyde itself gave good yield of combined mono and di-functionalized products (73% **13a**,

mono:di 1.3:1). 2,3-Dimethyl and 2,4-dimethyl benzaldehydes reacted to give **14a** and **15a** in moderate to good yields. Benzyl protected phenol was tolerated as was an O-allyl substituent, a challenging substrate in a palladium mediated process due to allylic activation. 2-Phenylbenzaldehyde, 2-naphthaldehyde and 6-methoxy-2-naphthaldehyde were particularly effective, giving **18a**, **19a** and **20a** in 87%, 96% and 71% yield respectively. Electron poor ester and halogen functionalities were tolerated without hydrolysis or cross-coupling occurring. The Cu-mediated conditions also gave sulfonated pyridine-4-carboxaldehyde and 2-methoxypyridine-4-carboxaldehyde (**25a**, **26a**). Aldehydes derived from adapalene and estrone underwent sulfonation (**27a** and **28a**) using the aldehyde as the limiting reagent.²¹ The reaction of 9-phenanthrene

carboxaldehyde gave *peri*-sulfonylated product **29a** exclusively, favoring the required [6,6]-cupracyclic intermediate over the potential *ortho*-sulfonylation. In the case of 1-naphthaldehyde, *peri*-functionalization was again the major product in a 2:1 ratio with the less hindered *ortho*-product. On blocking the *ortho*-position with a methyl group, reduced *peri*-reactivity was observed.

In depth mechanistic investigations of copper mediated C–H activation reactions remain rare. Cupracyclic intermediates are relatively unstable and only a handful of stable organocuprates have been reported.²² Our attempts at direct investigation of the potential organocuprate intermediate were unsuccessful. Therefore, to interrogate the reaction mechanism kinetic and deuteration experiments were undertaken. Visual comparison methods developed by Blackmond (RPKA)²³ and Burés (VTNA)²⁴ were used to investigate the catalytic performance of the TDG and the orders of all reagents.^{17c} Initially, same-excess experiments uncovered a product inhibition effect. Studying imine formation by ¹H NMR in the absence of copper indicated a preference for the formation of the starting material imine in a competition between product and starting aldehydes.^{17d} Therefore, we hypothesize that inhibition results from the product imine being a more effective ligand for copper, so the TDG is temporarily removed from the catalytic cycle.

Variable time normalization analysis (VTNA) was used to estimate the order in reagents and catalysts. We identified an order of 1 in aldehyde, transient directing group and K₂CO₃. Fractional orders were observed for both the sulfinate and CuF₂ (0.75 and 0.5 respectively), and a zero order in Cu(OAc)₂. Together with the optimization studies is clear that sulfinate has a competing inhibitory effect on the reaction presumably by blocking copper coordination sites.²⁵

No obvious deuteration was observed when performing the reaction in HFIP-d₂, implying that C–H activation is irreversible under the reaction conditions. A significant primary kinetic isotope effect was observed in both parallel (KIE_{parallel} = 2.42) and competition experiments (KIE_{competition} = 3.25) which indicates C–H bond cleavage is intimately linked to the turnover limiting step (Figure 1a).²⁶ Further investigation into the electronics of this step by Hammett analysis revealed a negative correlation (Figure 1b). This implies a buildup of positive charge in the turnover limiting step and therefore an unusual turnover limiting electrophilic mechanism of C–H activation.²⁷ Studies on bases with comparable pK_a showed that those capable of bidentate coordination were more effective, suggestive of an inner sphere deprotonation.^{17e} Considering these findings together, we propose a concerted asynchronous formation of C–Cu bond and cleavage of the C–H bond which involves nucleophilic attack from the aryl π-system and partial Wheland-type transition state.

Overall, we propose the following as a plausible mechanism (Figure 1c). Catalytic amino acid **A** condenses with the aldehyde to form imine **B**. Copper and sulfinate coordinate to form intermediate **C**. Coordination of additional sulfinate (**C'**) may result in inhibition of the reaction. Otherwise, coordination of carbonate to **C** would form intermediate **D** which undergoes a concerted irreversible and

turnover-limiting C–H activation to form **E**. Loss of carbonate leads to cupracycle **E**. Oxidation by Cu(II) leads to formal Cu metallocycle **F** which would undergo reductive elimination to give copper-ligated product imine **G**. This imine must then undergo hydrolysis to release the product aldehyde and regenerate the amino acid catalyst. The equilibrium favoring **G** is likely to be the origin of product inhibition trapping the directing group at high concentration of product.

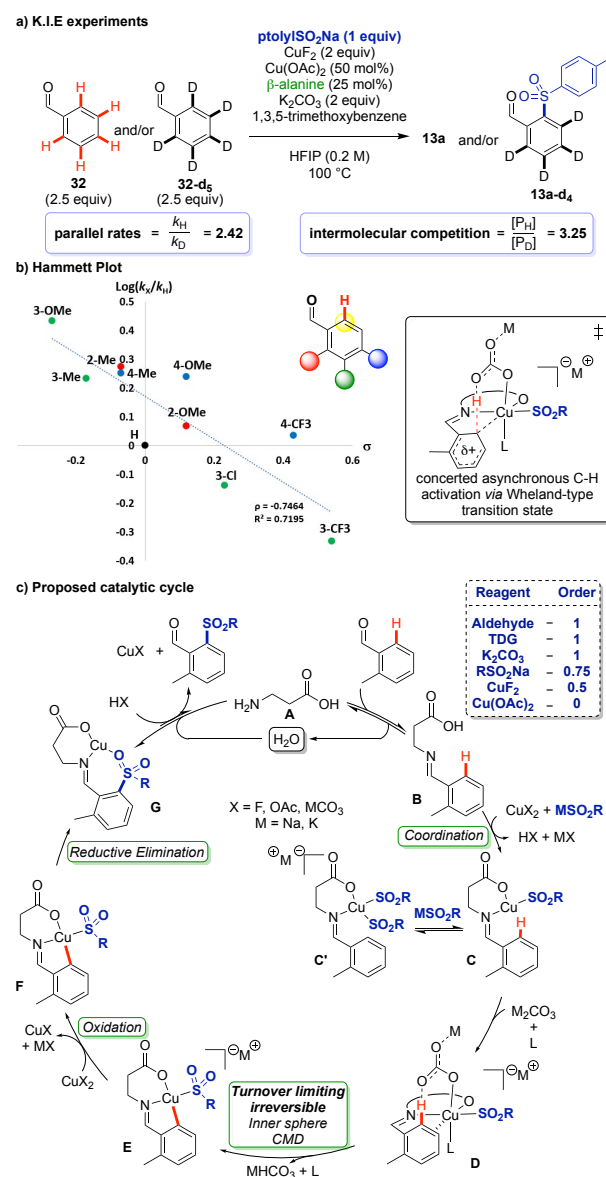


Figure 1: a) K.I.E. experiments. b) Hammett plot of varying substituents with proposed electrophilic mode of C–H activation. c) Proposed mechanism of transient C–H sulfonylation.

In summary, the copper mediated C(sp²)-H sulfonylation of benzaldehydes was achieved using a catalytic β-alanine transient directing group. This demonstrates for the first time the potential to use a transient directing group with copper to promote C–H functionalization. The conditions were applied to a wide range of sulfinate salts and aromatic aldehydes including heteroaromatic aldehydes to effect

ortho- or *peri*-functionalization. Kinetic and mechanistic investigations highlighted an unusual turnover limiting electrophilic C–H activation. We expect these results will open further possibilities for the use of copper species for C–H functionalization processes, particularly in combination with transient directing groups, as well as contribute to improved understanding of copper mediated C–H functionalization processes.

ASSOCIATED CONTENT

Supporting Information

Optimization reactions; details of DoE study; sensitivity screen; deuteration experiments, K.I.E. experiments; kinetic experiments (same excess, different excess, Hammett analysis), experimental procedures and characterization data (PDF)

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