Copper Catalyzed C–H Sulfonylation of Benzylamines with a Catalytic Transient Directing Group

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ABSTRACT: Transient C–H functionalization involves the dynamic in situ generation of a directing group to allow directed C–H activation/cyclometallation and subsequent functionalization steps. To date most examples involve precious metal catalysis, commonly using palladium. Here we report the first example of copper catalysed C(sp^2)–H functionalization of benzylamines using a transient directing group (TDG), also employed catalytically. A dual catalytic system with copper(II) acetate and 2-hydroxynicotinaldehyde enabled effective sulfonylation of numerous benzylamines *via* a transiently formed imine directing group. Manganese(IV) oxide was identified as an effective terminal oxidant and base for this transformation, enabling a diverse array of sulfinate salts and benzylamines to be coupled in good yields. Computational DFT investigations suggest a turnover limiting C–H activation step with a facile combination of the cupracycle with an RSO_2 radical. The TDG is shown promote the reaction by lowering the energy barrier for an acetate mediated concerted metalation deprotonation in comparison to a potential free amine directed process.

Developments in the functionalization of C–H bonds continue to streamline synthetic routes to valuable compounds.[1] The development of transient C–H functionalization, whereby a directing group is formed in situ from common functionality, presents additional opportunities for efficient synthesis (Figure 1a).[2] In particular, the formation of transient imines to direct cyclometallation combines directing group installation, C–H functionalization and directing group removal into a single step. Pioneering work by Jun[3] and Yu[4] established the potential for aldehydic C–H and benzylic C–H functionalization respectively. Subsequent developments have enabled the palladium catalyzed functionalization of benzaldehydes and aliphatic aldehydes,[5] with fewer examples on amines.[6–13] These transient approaches directly reveal the useful aldehyde or amine functionality for further derivatization reactions. However, it is notable that almost exclusively palladium or other precious metal catalysis have been employed. Given the increasing price and undesirable toxicity profile of Pd, the development of new methods which rely on cheap and readily available base metals is crucial to sustainable synthesis. Very recently, we reported the first example of copper mediated transient C–H functionalization, in the sulfonylation of benzaldehydes with sulfinate salts using β-alanine as a catalytic transient directing group (TDG), albeit using 2.5 equivalents of copper salts (Figure 1b).[14]

Amine functionalities feature in countless pharmaceutically active compounds and in fine chemicals.[15] Amines present challenging substrates for C–H functionalization due to the coordination of the strongly Lewis basic lone pair of electrons that can deactivate metal catalysts. Furthermore, they can be vulnerable to β-hydride elimination, and chemoselectivity issues as both N–H and C–H functionalization are possible. Though there are a few reports of free amine directed C(sp^2)–H functionalization,[16] robust amide and sulfonamide directing groups have been used most commonly.[17,18] For a pertinent example, Samanta reported the palladium catalyzed C–H sulfonylation of benzylamines with sulfinate salts using picolinamide as a directing group.[19]

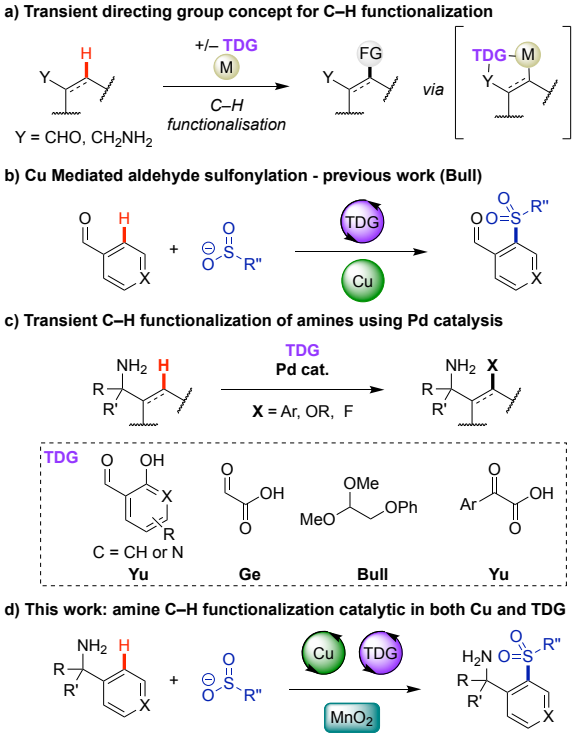


Figure 1. C–H functionalization of transient directing groups

To date the use of transient directing groups with amines has involved exclusively palladium catalysis (Figure 1c).[2] Notably, Yu developed 2-hydroxynicotinaldehyde as a powerful TDG for the Pd-catalyzed C(sp^3)–H arylation,[6] oxygenation,[7] and fluorination[8] of amines. The use of this TDG for Pd-catalyzed C–H arylation of amines was also described by Kameneka for

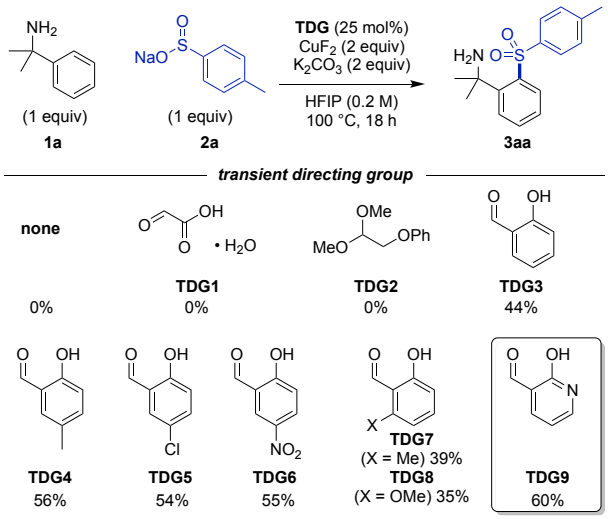
alkyl and benzylamines.[9] Other TDGs for amine functionalization include glyoxylic acid developed by Ge,[10] aryl keto-acids for δ-arylation,[11] and acetal-ethers.[12]

Given the value of sulfones in medicinal chemistry,[20] we envisaged that the direct C–H functionalization of amine precursors to form amino-sulfones would provide valuable building blocks. Specifically, we aimed to avoid using precious metals. Furthermore, a primary goal was to render the reaction catalytic both the transient directing group and the copper species.

Here, we report a dual copper/transient directing group catalyzed C(sp^2)–H functionalization of benzylamines with sulfinate salts, using manganese (IV) oxide as the terminal oxidant. This represents the first C–S bond forming transient C–H functionalization methodology for amines, and the first example of sub-stoichiometric copper salt being used with a transient directing group. Computational studies by DFT provide insights into the mechanism of the reaction.

We first examined different aldehyde additives to function as the transient directing group, employing a catalytic amount (25 mol% TDG) along with a stoichiometric quantity of copper fluoride (ie 2 equiv, as required by the expected oxidative mechanism). HFIP was used as solvent at 100 ºC in the presence of K_2CO_3, with 1 equiv of toluene sodium sulfinate. No reaction was observed in the absence of a TDG nor using glyoxalic acid **TDG1** or 2-phenoxyacetaldehyde dimethyl acetal **TDG2**. Pleasingly, salicaldehyde (**TDG3**) was effective under these conditions, affording 44% yield of sulfone **3aa**. 5-Substituted salicaldehydes (**TDG4–6)** gave very similar improved yields (54–56%), whereas 6-substituted derivatives were less effective (**TDG7–8**). 2-Hydroxynicotinaldehyde (**TDG9**) was identified as an effective TDG, affording the sulfonylated product in 60% yield, and was selected for further optimization.

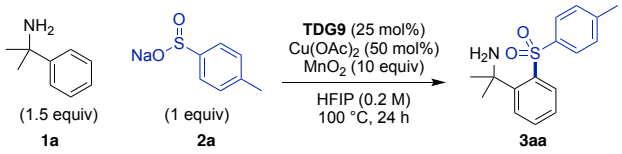
Scheme 1. Optimization of transient directing group[a]



[a] Reactions performed on 0.2 mmol scale. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Encouraged by the results, the effect of using different copper source, co-oxidant, TDG loading, concentration and base were investigated in order to develop a catalytic process.[21] Key findings were that inexpensive and readily available copper(II) acetate in combination with MnO_2 was an effective catalyst system. Furthermore, the addition of a base was no longer required as the MnO_2 could fulfill this role in deprotonating the acetic acid formed in situ while reoxidising Cu^I to Cu^{II}. Under these optimized conditions, the desired sulfonyl amine **3aa** was isolated in 68% yield (Table 1, entry 1).

Table 1 – Control reactions describing deviation from standard conditions.



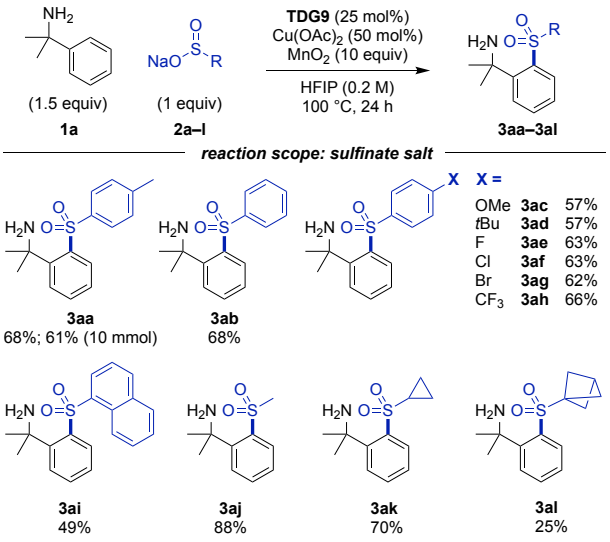
entry	deviation from standard conditions	**3aa** (%)[a]
1	None	67 (68)
2	No [Cu]	0
3	No MnO_2	17
4	No TDG	15
5	Using **TDG1**	5
6	Using **TDG2**	0
7	Using **TDG3**	43
8	$K_2S_2O_8$ as oxidant (2–10 equiv)	11–21
9	+K_2CO_3 (2 equiv)	70 (68)
10	+ TEMPO (1 equiv)	0

Reactions performed on 0.2 mmol scale with respect to the sulfinate salt. [a]Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield in parenthesis. The starting material is volatile so recovered starting material was not reliably determined.

Control reactions established that the copper(II) acetate was critical to the coupling, and about 1 turnover was achieved in the absence of oxidant (Entries 2,3).[22] In the absence of **TDG9** a low, but non-zero yield was obtained (Entry 4). Testing other TDG under the catalytic conditions showed the same trend as using stoichiometric copper (Entries 5-7). Changing the oxidant from MnO_2 to $K_2S_2O_8$ was detrimental for the reaction (Entry 8). The addition of K_2CO_3 gave no change in the isolated yield (Entry 10). The addition of TEMPO as radical trap fully suppressed the reaction, suggesting a radical reaction pathway is in operation (Entry 9). Notably, the formation of sulfonamide was never observed despite the potential for direct coupling with the amine moiety.[23]

The reaction scope varying the sulfinate salt was then investigated (Scheme 2). Sulfonyl amine **3aa** was obtained in 68% yield, which could be scaled to gram scale (10 mmol), affording the product in 61% (1.76 g). Aryl sulfinates bearing electron neutral (H), electron rich (OMe, *t*Bu), or electron poor substituents (CF_3, halogens) all gave good yields with a slight preference for the electron poor sulfinate salts (**3ab-3ah**). A lower yield was observed for the more sterically hindered naphthyl substituted example **3ai**. Methyl and cyclopropyl sulfinate salts were both highly effective, affording the sulfones **3aj** and **3ak** in 88% and 70% respectively. The reaction with BCP sulfinate salt was also successful in generating sulfone **3al**, the BCP motif being of interest as a phenyl isostere.

Scheme 2. Reaction scope varying the sulfinate salt[a]

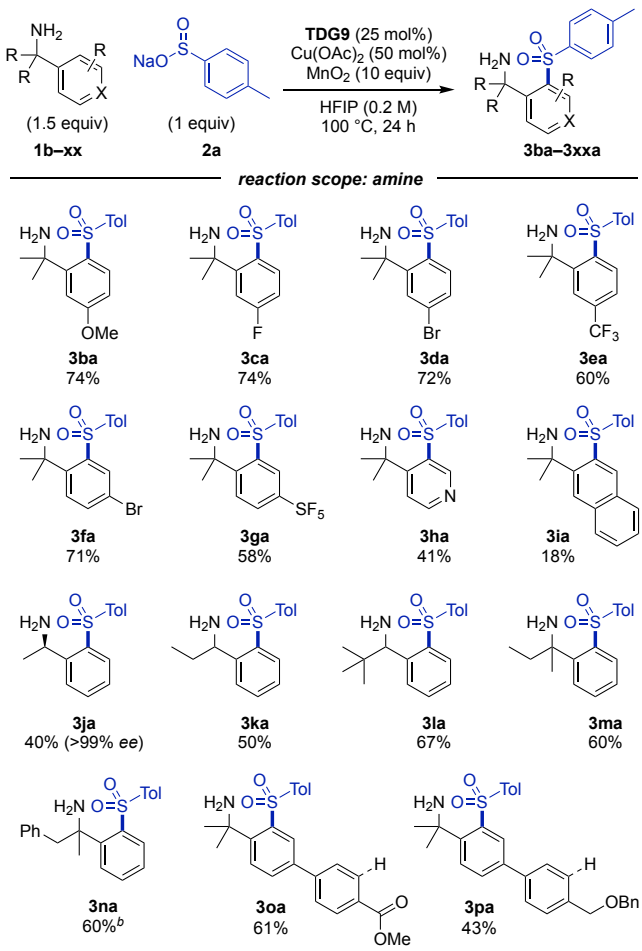


[a] Reactions performed on 0.2 mmol scale. Isolated yields reported.

We next explored the tolerance of the reaction to changes in the benzylamine component (Scheme 3). Initially, we varied the substituent in the 3-position (*para* to the C–H bond being functionalized) and found substrates with electron rich and electron poor substituents reacted effectively (**3ba-3ea**), with slightly improved yields for the 3-OMe (**3ba**) and 3-F-phenyl (**3ca**) derivatives. Changing the bromo substituent from the 3- to 4-position gave sulfonyl amine **3fa** in 71%. The pentafluorosulfanyl (SF_5) group is increasingly of interest in medicinal chemistry, and a SF_5 substituted benzylamine was sulfonylated effectively to give amine **3ga** in 58% yield. The functionalization of more challenging pyridyl containing substrate **3ha** was also realized despite the presence of the additional coordinating moiety. 2-Napthyl derivative **3ia** was formed with selective reaction at the 3-position. A range of α-alkylbenzylamines were also converted to the sulfonylated products **3ja**, **3ka** and **3la** in good yields. Sulfonylation of enantioenriched amine retained the chirality of the starting amine (>99% *ee*). However, unsubstituted benzylamines were unsuccessful. Ethyl and benzyl substituted amines were sulfonylated exclusively at the *ortho*-position to give sulfones **3ma** and **3na** both in 60% yield. In the benzyl substituted example, no sulfonylation of the more distal aryl group was observed. Biaryl substrates **3on** and **3po** possessing functional groups capable of directing *ortho*-metalation were sulfonylated exclusively at the *ortho* position to the amine without any sulfonylation adjacent to either the ester or ether functionality. Furthermore, both the methyl ester and benzyl groups remained intact under these conditions.

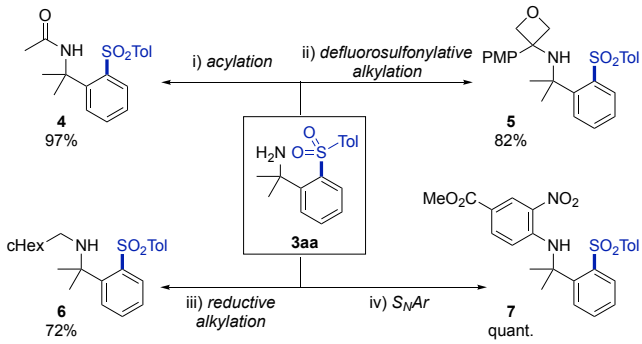
The amine products generated in this transient process were directly available for further derivatization (Scheme 4). To illustrate this, sulfone **3aa** was readily acetylated with acetyl chloride to form amide **4**, and was converted to aminooxetane **5** using an oxetane sulfonyl fluoride reagent in a defluorosulfonylative process.[24] Reductive alkylation and nucleophilic aromatic substitution (S_NAr) reactions as commonly employed in medicinal chemistry programs were also readily demonstrated to provide alkyl amine **6** and aryl amine **7**.

Scheme 3. Reaction scope varying the amine[a]



[a] Reactions performed on 0.2 mmol scale. Isolated yields reported.
[b] Contains 6% inseparable starting material.

Scheme 4. Derivatization of the amine functionality[a]



[a] Reactions performed on 0.20 mmol scale. Isolated yields reported. Reaction conditions: i) AcCl, NEt_3, CH_2Cl_2, r.t., 18 h. ii) 3-(4-Methoxyphenyl)-3-oxetanesulfonyl fluoride, K_2CO_3, MeCN, 80 °C, 1 h. iii) Cyclohexanecarboxaldehyde, $NaBH(OAc)_3$, DCE, r.t., 24 h. iv) Methyl 4-fluoro-3-nitrobenzoate, *i*PrOH, 100 °C, 4 h.

To provide insight to the mechanism of the reaction, a competition KIE gave preferential reaction of the protic substrate [H:D 3.88]. Similarly, H/D exchange was not observed in the product or recovered starting materials, when running the reaction either with a deuterated substrate, or with the protic substrate in d_2-HFIP.[25] These results were suggestive of an irreversible C–H

functionalization process under the reaction conditions, that is the turnover limiting step.

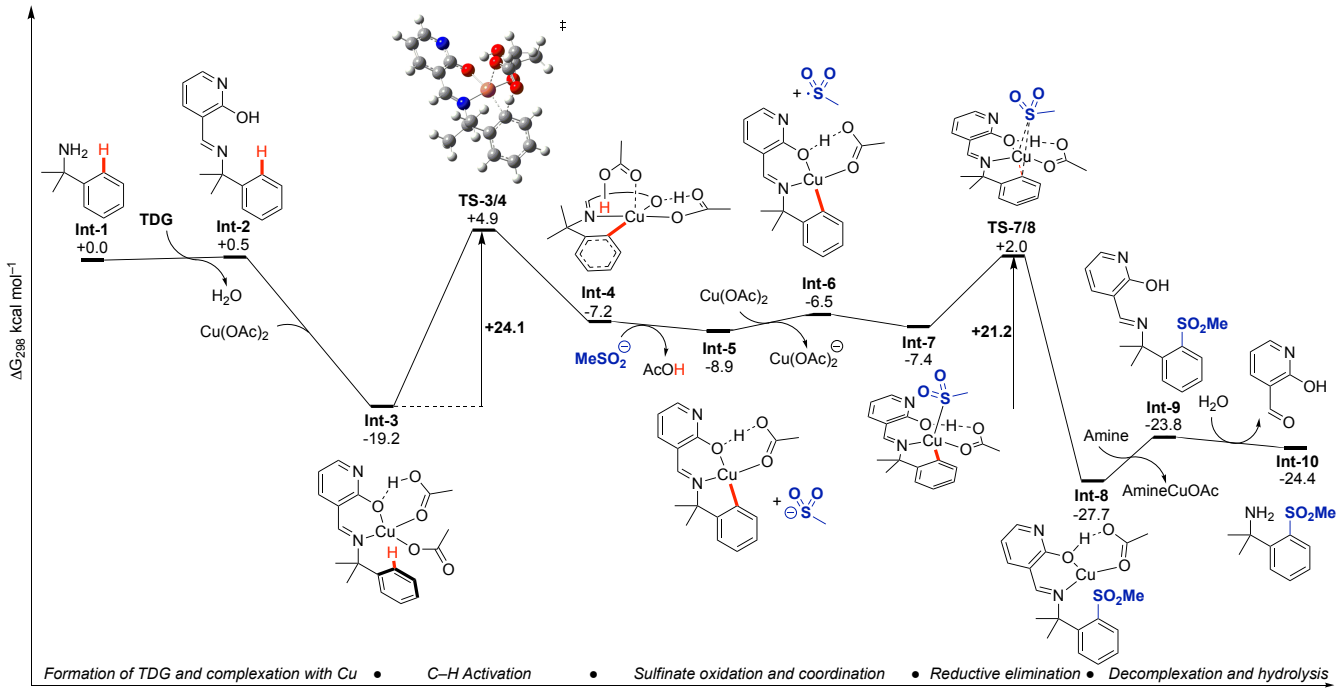


Figure 2 Calculated free energy profile for imine directed C–H sulfonylation of cumylamine via CMD. Dotted lines included to show bonds involved in the transition states.

To further understand the reaction mechanism, we employed DFT calculations using gaussian 16 (Figure 2).[26-29] The mechanism of reoxidation by MnO_2 is poorly understood, and is likely a heterogeneous oxidant, therefore only a single turnover of Cu was considered to examine the elementary steps. Imine formation between **Int-1** and 2-hydroxynicotinaldehyde was slightly endergonic, followed by an exergonic complexation with copper acetate to give **Int-3** as the lowest energy intermediate prior to the turnover limiting C–H activation step. The C–H activation is calculated to proceed *via* a 5-coordinate inner sphere transition state (**TS-3/4**) in which an axial acetate ligand mediates C–H activation, with a barrier of 24.1 kcalmol^{-1}. This CDM process leads to the formation of cupracycle **Int-4** which is converted to **Int-5** by release of acetic acid.

Oxidation of the sulfinate salt is calculated to occur readily by an SET process, mediated by copper acetate. CV studies indicate the sulfinate salt can be oxidized in the redox window of the reaction (CVs in HFIP vs Fc/Fc*: $MeSO_2Na$, E_{pa} = +1.02V; $TolSO_2Na$ E_{pa} = +1.06V). Association of the sulfinyl radical to the copper center occurs a barrierless process converting **Int-5** to **Int-7**.[30] Reductive elimination *via* **TS-7/8** forms the C–S bond and a Cu^I species, with a barrier of +21.2 kcal mol^{-1}. The de-coordination of copper from **Int-8** is slightly uphill in energy, releasing the product imine which can then be hydrolyzed to produce the product sulfonyl amine **Int-10**.

The free amine directed pathway was also calculated with an additional acetate bound to Cu in place of the TDG, to indicate the influence of the TDG. Noticeably the energy barrier of the CMD process is significantly lowered in the presence of the TDG when compared to the free amine directed process (TDG: +24.1 kcalmol^{-1}; free amine: +32.2 kcalmol^{-1}, see supporting information).

Our previous mechanistic studies of the copper mediated transient C–H functionalization of aldehydes was indictive of a Wheland-like transition state for C–H activation.[14] Here NBO analysis of **TS-3/4** revealed a similar charge distribution to that of an arenium ion, in addition to a significant stabilizing effect from donation from the C–Cπ system into empty orbitals on Cu. The similarities in geometry between **TS-3/4** and an arenium ion also support C–H activation by a Wheland-like intermediate in the benzylamine functionalization.[21]

In summary, the catalytic C–H sulfonylation of benzylamines has been achieved using both catalytic copper acetate and a catalytic aldehyde transient directing group. Earth abundant and cheap manganese dioxide was used as a stoichiometric oxidant. The efficacy of this oxidative C–H coupling was demonstrated on a broad range of sulfinate salts and amines allowing rapid construction of γ-sulfonyl amines. Mechanistic experiments and computational investigations indicate this reaction proceeds through a turnover limiting C–H activation step involving a Wheland type intermediate. A significant role of the TDG is to lower the barrier for C–H activation. We expect these findings to unlock further possibilities in the use of transient directing groups with copper catalysis.

Supporting Information

Optimization reactions; deuteration experiments, K.I.E. experiments; Details of computational studies; experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We gratefully acknowledge The Royal Society [University Research Fellowship, UF140161 and URF\R\201019 (to J.A.B.), URF Appointed Grant RG150444 and URF Enhancement Grant RGF\EA\180031]. We gratefully acknowledge Dr. Andreas Phanopoulos for guidance in DFT computational methods.

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(21) See supporting information for more information. For the optimisation of reaction parameters, see S.I. pages **S5–12**. For more details on the computational investigations into the nature of C–H activation, see SI pages **S17–24**.

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(30) An alternative pathway with coordination of the sulfinate anion to the copper center followed by oxidation was also computationally a low energy pathway. The formation of the radical intermediates is consistent with the observed TEMPO inhibition.