Copper-Catalyzed Sulfimidations of Benzylic C(sp3)-H Bonds

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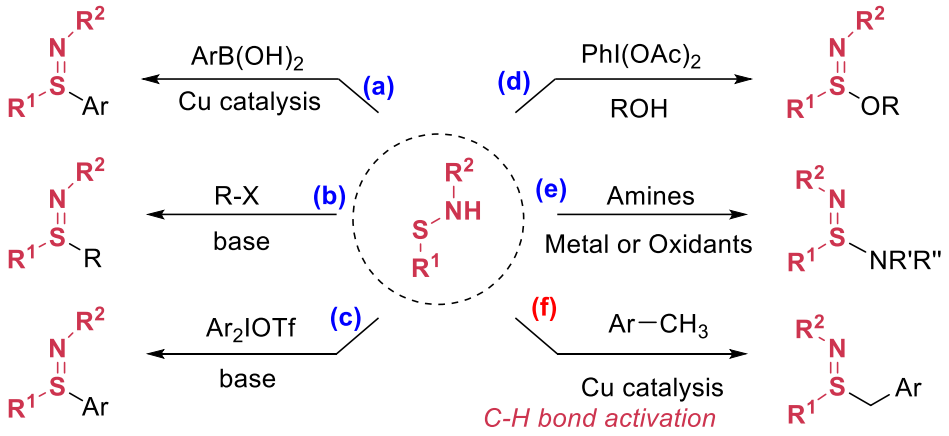
In this study, we elucidate a novel strategy for benzylic C(sp3)-H activation, enabling the construction of C-S bonds through a copper-catalyzed sulfimidation process. Leveraging readily available methylarenes as substrates, our methodology offers an economically efficient and highly viable approach. The scalability of the reaction, its applicability to a broad range of substrates, and significant application value underscore its potential and transformative impact in the realm of synthetic organic chemistry.

C-H activation, a critical process in organic synthesis, allows for the selective transformation of pervasive yet inert C-H bonds into functional sites. Despite the inherent challenges of activating these bonds, it's increasingly leveraged in chemical processes due to its potential to enhance synthetic efficiency and sustainability by bypassing the need for protective groups and pre-functionalized materials.[1] Methylarenes, sourced abundantly and inexpensively from petroleum, are stable substrates that allow for safe handling and storage. Their inherent benzylic reactivity enables selective C-H activation even under mild conditions, while their structural diversity offers a broad array of potential products. Utilizing methylarenes also aligns with the principles of sustainable chemistry, making them ideal candidates for C-H activation. The realm of catalyzed benzylic C-H activation has been extensively probed for C-C[2], C-N[3], C-Si,[4] and C-B[5] bond formations, reflecting the significant research interest in these areas. However, the crucial aspect of harnessing C-H activation for the construction of C-S bonds is a more recent discovery and is currently

at the forefront of nascent investigations in this domain.[6] Recognizing the remarkable utility of sulfilimines as fundamental components in organic synthesis,[7] chiral auxiliaries, and ligands [8] in transition-metal-catalyzed reactions, coupled with their diverse applications as active constituents in pharmaceuticals,[9] we've prioritized the development of a sulfilimines synthesis route. This approach hinges on the formation of C(sp3)-S bonds via C-H activation—an innovative concept that we explore and illustrate in this work. Sulfenamides, with their notable sulfur activity, have been increasingly utilized as pivotal intermediates in organic synthesis. This trend has been underscored by a surge in research exploring these compounds. Illustrative examples include This research encompasses Ellman's work using a Rh(II) catalyst for the S-alkylation of carbenes with sulfenamides[10] and, in a separate line of exploration, the successful accomplishment of S-alkylation under metal-free conditions by Li [11], our group[12] and Ellman[13], employing the concept of sulfinimidoyl anions. (Scheme 1a and 1b) Simultaneously, our group and others have made strides in reporting on the S-arylation of sulfenamides. (Scheme 1c)[14] Additionally, we have unveiled methodologies involving hypervalent iodine-mediated S-esterification and S-amination of sulfenamides. (Scheme 1d and 1e)[15] Progress in the synthesis of sulfinamidines has also been significant, with Li [16]and our group[17] respectively revealing NBS-mediated and Cu-catalyzed aerobic S-amination of sulfenamides (Scheme 1d). Most recently, Ellman has added to the body of knowledge with the sulfur-arylation of sulfenamides via Ullmann-Type coupling with (hetero)aryl iodides(Scheme 1e).[18] While the existing coupling partners are primarily functionalized entities, reactions between sulfenamides and hydrocarbons remain largely uncharted. In an effort to fill this void, we've pioneered a copper-catalyzed process, enabling the synthesis of sulfilimines via coupling of in situ-generated sulfinimidoyl anions with oxidatively activated methylarenes (Scheme 1f).

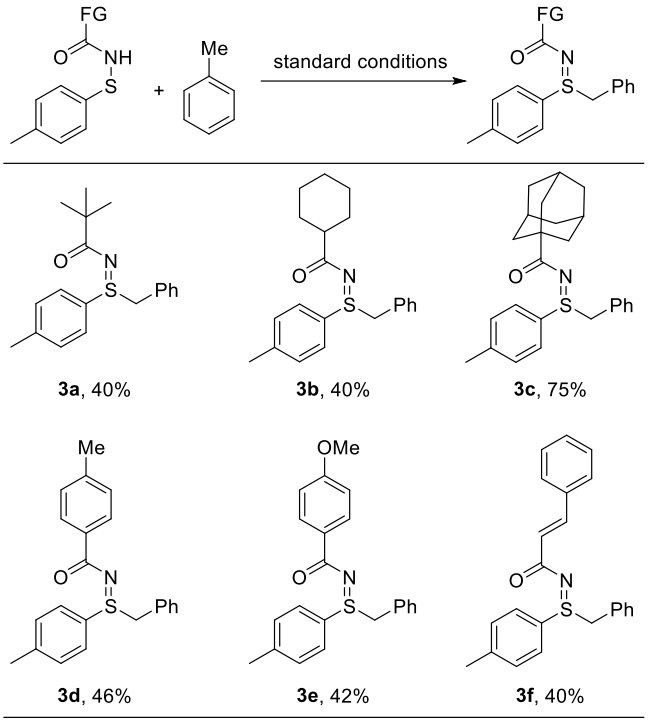


Scheme 1. Prior works and this work

In the preliminary stage of our investigation, we opted for N-(p-tolylthio)pivalamide **1a** and toluene (**2a**) as model substrates (Table S1, see the Supporting Information for more details). We employed toluene in a considerably higher proportion (63-fold), attributing to its dual functionality as both a solvent and reactant. Upon incorporating a base of moderate strength, Cs_2CO_3, we anticipated that β-elimination of **1a** would transpire under elevated temperature conditions, thereby yielding the corresponding sulfinimidoyl anion. This anion, in turn, was projected to engage with the benzyl radical derived from the copper-catalyzed oxidation of **2a**, mediated by peroxide. This interaction was expected to yield sulfilimines (**3a**). Following an exhaustive assessment of various catalysts and oxidants, CuBr and BzO_2tBu emerged as demonstrating enhanced catalytic and oxidative activities (entries 1-8). However, in scenarios devoid of ligand involvement or where the reaction was subject to air exposure, the reaction performance significantly deteriorated (entries 4 and 5). Subsequent to this, we undertook a meticulous examination of various ligands. It was found that 1,10-phen emerged as the most effective, facilitating the production of **3a** with a yield of 71% after 12 hours. (entries 9-12). Interestingly, the use of a stronger base, sodium tert-butoxide, proved detrimental to the reaction, while the milder base, potassium carbonate, had minimal impact on reactivity (entries 13 and 14). Further evaluations, including those related to catalyst loading and temperature, were conducted, with details available in the Supporting Information (SI). Employing the optimal reaction conditions, we demonstrated that the reaction could be successfully scaled up, albeit with a moderate yield outcome

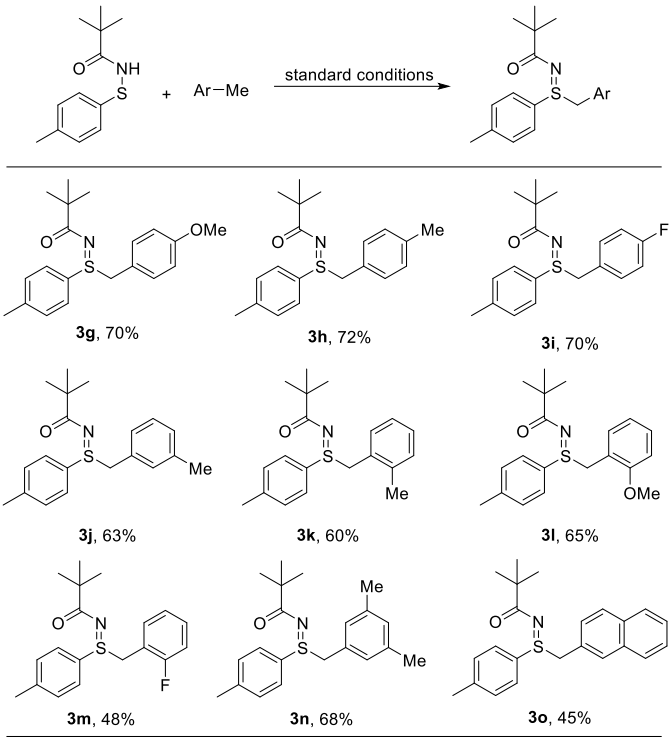
(entry12).

Scheme 2. Substrate scope of *N*-substituent groups of sulfenamides



Upon establishing the optimal reaction conditions, we initiated an exploration into the tolerance of various amide-derived sulfenamides under the established conditions(Scheme 2). Our findings suggested that amides with less steric hindrance exhibited poor reactivity. However, sulfenamides derived from sterically hindered alkane cyclohexanecarboxamide and adamantanecarboxamide resulted in considerably higher yields of the target products **3b** and **3c**, at 40% and 75%, respectively. This suggests that enhancing steric hindrance can indeed benefit the reaction. We also investigated arylamide-derived sulfenamides, but these resulted in only moderate yields (**3d** and **3e**). Pleasingly, alkenes demonstrated good tolerance under standard conditions without any observed oxidation of alkene by-products (**3f**).

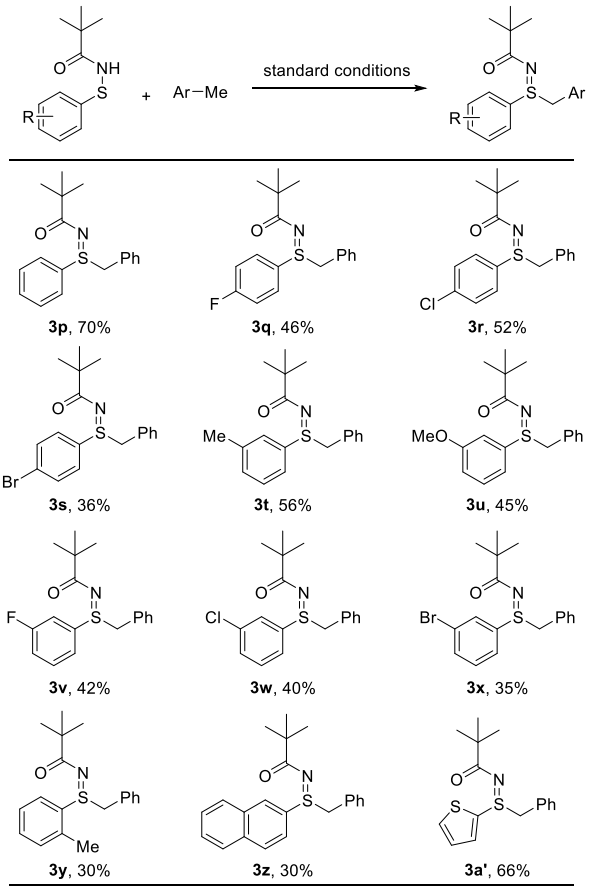
Scheme 3. Substrate scope of methyl arenes



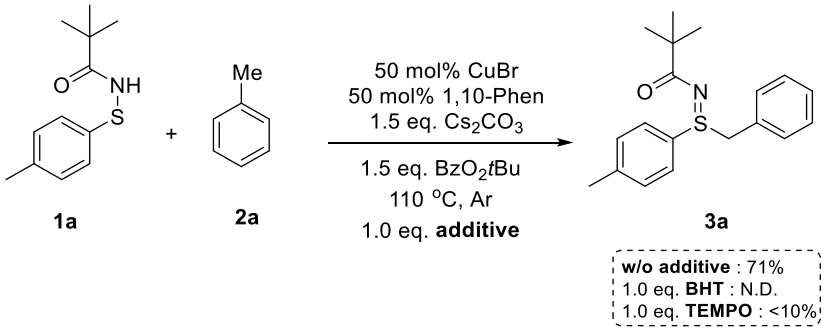
Following the initial findings, we further delved into the scope of benzylic C-H bond sulfimidations with a range of methyl arenes(Scheme 3). Our observations revealed that when electron-donating groups (methoxy or methyl) or electron-withdrawing groups (fluorine) were present at the para-position, the reaction showed commendable activity. This led to the efficient generation of the intended product, with yields peaking at an impressive 72%. Interestingly, the yield seemed largely unaffected by the para-electron effect. Equivalently, the presence of electron-donating groups at the meta or ortho positions showcased similar reactivity, suggesting a minor role of arene steric effects. Contrastingly, the introduction of fluorine at the ortho-position culminated in a significant yield drop to 42%, indicating a strong influence of the ortho-electron effect on the reaction's activity.

Intriguingly, when we turned to polysubstituted aromatic hydrocarbons and 2-methylnaphthalene under the standardized reaction conditions, the synthesis of the corresponding target products was successful, with yields amounting to 68% and 45%, respectively.

Scheme 4. Sulfenamide substrates derived from various thiophenols



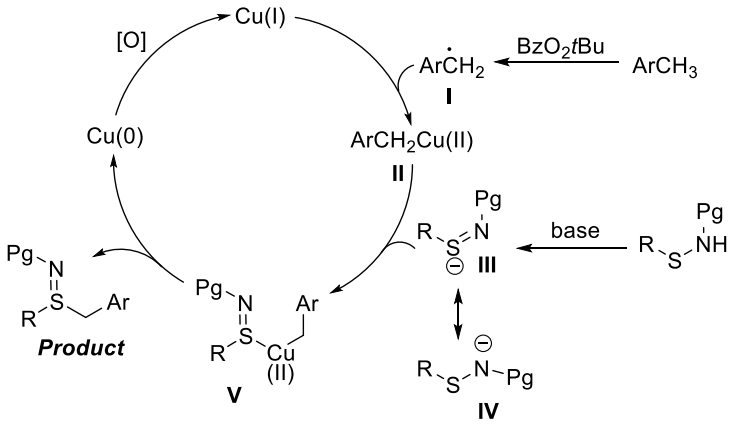
Ultimately, we assessed the suitability of sulfenamides derived from variously substituted arylthiols in forming sulfilimines via Cu-catalyzed benzylic C(sp3)–H sulfimidations of toluene(Scheme 4). Sulfenamide derived from unsubstituted thiophenol demonstrated notable reactivity, procuring the target product 3p in 70% yield. However, the introduction of substituents at the para, meta, and ortho positions of the benzene ring in the sulfenamide structure significantly influenced the reactivity (3q-3y). In particular, when a halogen atom (F, Cl, Br) was positioned at the para-location, a significant reduction in yield was observed—with bromine at the para-position leading to a yield of merely 36%. The presence of an electron-donating group at the meta-position of the benzene ring led to a noticeably higher yield compared to when a halogen atom occupied the meta-position, although the yield difference was not substantial, implying a minor role of the electron effect at the meta-position. Contrastingly, introducing a methyl group—an electron-donating entity—at the ortho-position markedly impeded the yield. This decrease is likely attributed to the considerable steric hindrance at the ortho-position. Sulfenamides derived from naphthol also displayed subpar reactivity under standard conditions, leading to a scanty 30% of the target product. Despite the varying reactivity observed in our investigations, the promising potential of thiophene-derived sulfenamides, coupled with the notable yield of 66% under Cu-catalyzed oxidation conditions, inspires optimism for future breakthroughs in this field of benzylic C-H bond sulfimidations.



Scheme 5. Mechanism investigation

Through straightforward control experiments, we endeavored to elucidate the reaction mechanism (Scheme 5). The significant suppression of yield under standard conditions upon the introduction of radical scavengers (BHT and TEMPO) indicates a radical pathway as the likely mechanistic course for this reaction.

Scheme 6. Proposed possible mechanism



A potential mechanism inferred from the above results and previous literature is depicted in Scheme 6.[19] Initially, the radical I is produced from the methyl arene through hydrogen abstraction involving the tert-butoxide radical, leading to the formation of intermediate II via oxidative coupling with the catalyst. Concurrently, the sulfinimidoyl anion III is generated from the corresponding sulfenamides, which deprotonate under basic conditions. Subsequently, a ligand exchange event occurs between the sulfinimidoyl anion III and copper intermediate II, resulting in the formation of intermediate V. This intermediate then undergoes reductive elimination to generate the desired product and a copper species in a lower oxidation state. The catalytic cycle is closed by the reoxidation of this copper species, restoring the initial copper complex.

In sunmmary, this research delivers a novel methodology for the selective C-H activation of benzylic C(sp3)-H bonds, setting the stage for C-S bond construction through copper-catalyzed sulfimidations. The work employs easily accessible methylarenes, offering an economical and efficient synthetic approach. The study uncovers the influence of steric and electronic effects on sulfenamide reactivity, while mechanistic examinations suggest a free radical pathway for the reaction. Despite variable yields, the research represents a significant leap forward in C-H activation, paving the way for new opportunities in the field of synthetic organic chemistry.

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