Fe-Catalyzed C–H Alkenylation of Dialkyl Anilines with Disulfonylthlenes

Joon Young Hwang, Sang Hyeok Lee, Yuri Kim, Minju Jin, Kyungtae Kang, and Eun Joo Kang

ABSTRACT: The oxidative alkenylation reaction of α-aminoalkyl C(sp³)−H bonds has been investigated with (E)-1,2-bis(sulfonyl)-ethenes. The catalytic process of iron-polypyridyl complexes drives the single-electron oxidation of dialkyl anilines, resulting in the formation of α-aminoalkyl radical species. Subsequent cascades of radical addition and elimination reactions ensue, ultimately leading to the generation of sulfonlated allylic amine products. The utility of these products extends further, enabling the synthesis of multisubstituted heterocycles like pyrroles, pyrazines, and triazoles.

Allylic amines hold significant importance in the realm of organic chemistry due to their pivotal role in advancing synthetic methodology. They are widely recognized for their presence as functional groups in natural products, their versatility as intermediates in medicinal chemistry, and their utility as starting materials for the synthesis of α- and β-amino acids, alkaloids, and carbohydrate derivatives. Notably, sulfonlated allyl amines have emerged as a novel category of small molecule electrophilic inactivators of cysteine proteases, a type of proteolytic enzyme with implications in diseases like cardiovascular, inflammatory, and cancer. These inhibitors form stable thioether adducts through the electrophilic capture of Cys nucleophiles via 1,4-conjugate addition, irreversibly deactivating the enzyme.

The synthesis of sulfonlated allylic amines employs a diverse array of disconnection strategies, as outlined in Scheme 1. To begin, intermolecular Pd(II)-catalyzed 1,2-carboamination of electron-deficient dienes with ureas enables the synthesis of functionalized indolines (Scheme 1, II-a). In a complementary approach, the allylic amines are obtained through the insertion reaction of chromium aminocarbenes into the β-CH bond of the electron-deficient alkenes (II-b). Employing Horner–Emmons–Wadsworth methodologies, oleilation of aldehydes smoothly yields the desired molecules (II-c). Expanding the repertoire, radical hydrosulfonylation of alkynes with sulfonyl chlorides, under photoredox catalysis, delivers vinyl sulfones with moderate Z-selectivity (II-d). Notably, among these synthetic methods, recent research highlights an intriguing avenue: the α-amino C(sp³)−H bond functionalization reaction with SOMOphiles through radical addition–elimination (II-e).

To directly access the α-C(sp³)−H activation of amides, one approach involves generating α-amidoalkyl radical intermediates by abstracting hydrogen from amides, facilitated by M₃S₅O₈ (M = K or NH₄) under elevated temperatures. Alternatively, a distinct line of investigation centers on homolytic activation reactions of the α-amido C(sp³)−H bond, utilizing photosensitizers such as aryl ketones. Further diversification is evident in the exploration of single electron oxidation of α-amido carboxylic acids via Ir or anthracene photoredox catalysis. This innovative strategy presents a platform for the formation of the reactive α-amidoalkyl radical, which effectively engages with electron-deficient radical acceptors, including sulfonyl substituents as proficient leaving groups, ultimately facilitating α-C(sp³)−H alkenylation through addition–elimination reactions.

Building upon our previous investigation into iron-catalyzed α-amino C(sp³)−H bond functionalization of dialkyl anilines via amine radical cation intermediates, we have applied this strategy to the construction of sulfonlated allylic amines, employing diverse sulfonyl alkene acceptors. Notably, our exploration of vinyl sulfone derivatives as radical acceptors has unveiled the substantial influence of various alkene substituents on the outcome of the addition–cyclization versus addition–elimination reactions. For instance, treatments involving 1,2-bis(sulfonyl)ethene and vinyl sulfone with a nitro group primarily yield cycloadducts, whereas reactions with 1,2-bis(sulfonyl)ethene bearing phenyl substituents predominantly yield alkenylation products. This observation underscores the critical role of meticulous design in achieving α-amino C(sp³)−H bond functionalization to α-amidoalkyl radicals, given the inherent versatile reactivity and the potential for competing oxidative pathways, particularly concerning aryl amines.

Received: August 28, 2023
Published: October 3, 2023
Our current research represents a pioneering achievement: the successful demonstration of the first iron-catalyzed α-amino alkenylation of dialkyl anilines employing 1,2-bis-(sulfonyl)ethene derivatives. This transformation yields sulfonyl allyl amines, which not only hold promise as valuable amino alkenylation of dialkyl anilines employing 1,2-bis-(sulfonyl)ethene derivatives but also exhibit potential as efficient 1,3-dipolarophiles in subsequent cycloaddition reactions.

First, optimization of the iron-catalyzed alkenylation reaction conditions was performed with 4,N,N-trimethylaniline 1a and 1,2-bis(phenylsulfonyl)ethene 2a as the model substrates (Table 1). Initial reactions with Fe(phen)$_2$(PF$_6$)$_3$, Fe(phen)$_3$(PF$_6$)$_2$, and other polypyridyl Fe(II) catalysts were carried out in DMSO at 70 °C under aerobic conditions. The alkylated product 3aa was obtained in promising yields (33–54%, entries 1–7), suggesting that the Fe complex acted as a single electron oxidant and selectively oxidized the trimethylaniline to a nucleophilic aminomethyl radical species. While the Fe(phen)$_2$ catalytic cycle was efficiently maintained by O$_2$ as the terminal oxidant in our previous report on the [4 + 2] cycloaddition reaction of aniline 1a, it was necessary to use an additional oxidant. More than an equimolar amount of peroxy oxidants was then examined under the milder conditions in CH$_2$CN at 25 °C. The use of benzyloxyl peroxide, peroxy benzoic acid, and hydrogen peroxyxide was detrimental to the reaction efficiency, with cumene hydroperoxide (CHP, CH$_3$C(CH$_3$)$_3$OOH) emerging as the optimal oxidant to afford the product 3aa in 73% yield (entries 8–11). Performing the reaction with 5 equiv of aniline in CH$_2$CN and DMSO solvent increased the efficiency of the entire reaction in each 90% and 89% yield, similarly (entries 12–13).

The amount of CHP was gradually decreased to check the feasibility of radical chain reaction; 30 mol % of CHP exhibits a prominent effect to give the product in 95% yield (entries 14–15). Control experiments verified the importance of the Fe catalyst and other polypyridyl Fe(II) catalysts were evaluated by X-ray analysis, confirming the (E)-configured isomers. Employing the halogenated phenyl substituents on disulfonylethenes (2h–2j) provided the alkylated products (Scheme 2) in good yields; moreover, the CF$_3$ functional group in 2l was well tolerated under the reaction conditions. Various N,N-dimethylanilines incorporating 4-F, 4-Br, 3-Br, 4-By, and 4-OMe delivered a range of alkylated products in good to high yield. Substrates other than dimethylanilines were more challenging. In the reaction of 1i and 1j having two different N-alkyl groups, aminomethyl...
radicals were exclusively generated and alkenylation took place on the N-methyl carbon. While the secondary radical was more stable than the primary one, we hypothesized that the reaction tended to proceed to the primary position due to fast deprotonation rates after single electron oxidation of amines. The reaction of N-methyl-lacking anilines generated the corresponding products 3ka–3ma in moderate to good yield under CH$_3$CN conditions. When 2-phenyl-3-(phenylsulfonyl)acrylate 2m was used, a roughly 1.5:1 mixture of diastereoisomers (3ma and 3ma') was formed, suggesting that the sulfonyl radical is eliminated after the formation of the α-carbonyl radical intermediate.

Vinyl sulfones are key structures in several bioactive molecules possessing anticancer and antitrypanosomal activity. Due to their vinylogous acceptor reactivity, they readily participate in conjugate additions and cycloadditions. We investigated the synthetic usefulness of the vinyl sulfonyl compounds in 1,3-dipolar cycloaddition for the synthesis of N-heterocycles such as pyrrole, pyrazole, and triazole (Scheme 3). 2,3,4-Multisubstituted pyroles 4a–4d were synthesized under the basic condition reaction with tert-butyl isocyanoacetate in 62–81% yields. The reaction of vinyl sulfones and ethyl diazoacetate afforded the corresponding pyrazole heterocycles 5a–5d in moderate yield. Additionally, several vinyl sulfones were transformed to 4-alkyl-5-aryl-1,2,3-triazoles (6a–6d) under the reaction with sodium azide. This family of compounds is popularized as click chemistry, and several members are reported to have interesting pharmacological properties such as muscarinic anticonvulsant anti-HIV and β-lactamase inhibitory activities.

Mechanistic investigations progressed to prove the iron-catalyzed oxidative alkenylation reaction mechanism (Scheme 4). A radical trapping reagent, TEMPO, markedly suppressed the reaction, suggesting that α-aminoalkyl radicals are significant and responsible for the reactivity in this Fe(III) catalysis (eq 1). As a detection of radical aromatic substitution byproduct in eq 2, 4-methoxy-N,N-dimethyl-2-(phenylsulfonyl)aniline (7) was isolated under standard conditions.

**Scheme 2. Reaction Scope in α-Amino Alkenylation**

\[(R = F; 3a_{bf}, 87\%)
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**Scheme 3. Synthetic Application to 1,3-Dipolar Cycloaddition**

**Scheme 4. Mechanistic Investigation**
reaction conditions for the synthesis of 3ga.18 Moreover, benzenesulfonate species were detected in the D2O layer by ESI-MS analysis (found 156.9697; calculated 156.9695), which is the autoxidation byproduct of sulfonyl radical species (eq 3).19 These results have proven that the sulfonyl radical was generated in the elimination step after the addition of the α-aminoalkyl radical to disulfonylethylene. To check the role of the cumyloxyl radical species, the reaction was treated with dicumyl peroxide without Fe(III) catalyst in eq 4. At ambient temperature, which is the iron catalyst reaction temperature, the hydrogen atom transfer (HAT) reaction by homolysis of dicumyl peroxide does not seem to occur, and the desired product was obtained with a yield of 49% when heated to 120 °C. The AIBN-initiated reaction of 1a did proceed to give alkenylated product 3aa in a 40% yield (eq 5), which supports the HAT reaction of the sulfonyl radical species is likely to occur as a competitive pathway.20 The observation of product 8 with allylic sulfone 2n also strongly proves the reaction mechanism of the sulfonyl radical elimination pathway (eq 6).

The authors have developed a novel iron-catalyzed alkenylation reaction that can promote the HAT reaction by homolysis of dicumyl peroxide. This reaction is driven by the Fe(III)-catalyzed single-electron transfer. The mechanism involves the addition of the Fe(II) catalyst and sulfonyl radical, followed by HAT to form the α-sulfonyl radical intermediate. Deprotonation of this intermediate gives the α-sulfonyl radical intermediate, which can undergo 1,3-dipolar cycloaddition with nucleophiles. The sulfonyl radical is efficiently generated through a Fe(III)-catalyzed single-electron oxidation, allowing for the synthesis of multisubstituted heterocycles under mild conditions. This work has the potential to open up new avenues for the synthesis of complex organic compounds using iron catalysts, which are known to be more sustainable and environmentally friendly compared to other transition metals.