Cu-Catalyzed Dehydrogenative Olefinsulfonation of Alkyl Arenes

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 β -Elimination happens as an important dehydrogenative event during many organometallic transformations.¹ It plays a vital role as a step or a side reaction toward alkenes, which shapes β elimination in a metal-mediated process into the major synthetic tool for diverse olefin scaffolds.² The most wellknown β -elimination takes place in the Heck reaction and its modified versions.³ They have been extensively employed for the construction of functionalized alkenes in current industrial manufacturing. During such an event, the metal hydride olefin species generates from the metal alkyl complex and subsequently releases modified alkene derivatives (Figure 1a). This reaction pattern has been broadly investigated, and



Figure 1. β -Elimination via metal hydride species for olefin scaffolds.

many elegant methodologies have been developed.⁴ Despite these signs of progress, during the metal-mediated radical process, the metal alkyl complex's generation from the alkanes is still very challenging in synthetic chemistry (Figure 1b). In particular, dehydrogenation of ethylbenzene into styrene has been massively utilized in industrial production. But these manufacturing processes require a harsh temperature of $500-600^{\circ}$ C.⁵ The further optimization of them into a mild and effective synthetic method for the formation of functionalized olefin derivatives is rare. Impressive progress on the dehydrogenation of alkanes was made by Newhouse and coworkers, who revealed arylnickel-catalyzed benzylic dehydrogenation of electron-deficient heteroarenes for the synthesis of 2-alkenyl heteroarenes.^{1e} Huo and co-workers also reported the elegant dehydrogenation of ethylbenzene with glycine derivatives into quinoline-2-carboxylates and demonstrated that the reaction could be applicable in 10 g scale synthesis of a medicinally important motif.⁶ Despite these important contributions, construction of functionalized styrene derivatives through one-pot consecutive dehydrogenation has not been reported yet.⁷

Herein, we disclose a Cu(I)-catalyzed sulfonation of ethylbenzene (EB) **1** with *N*-sulfonylbenzo[*d*]imidazole **2**, which features an unprecedented simultaneous dehydrogenation and functionalization process of ethylbenzene involving two successive metal-mediated β -hydride elimination steps. Vinylsulfone **3** is subsequently delivered in a *trans* form. The catalyzed process can be rationalized in terms of a [Cu-(OTf)]₂-toluene-mediated consecutive dehydrogenation of the benzylic metal species, accompanied by radical addition between the sulfone radical and the in situ generated styrene.⁸ This approach applies to a variety of ethyl arenes and numerous *N*-sulfonylbenzo[d]imidazoles, affording the corresponding vinyl sulfones in good yields under mild conditions.

We began our investigation using ethylbenzene 1a as a model substrate for dehydrogenative transformation. *N*-Sulfonylbenzo[d]imidazole 2a was used as a mild sulfonating reagent, which was different from traditional reagents and new sulfonating reagents developed by other groups such as sulfonyl chloride and tosyl hydrazide.⁹ Key optimization results from the extensive screening (Tables S1–S13, including catalysts, ligands, solvents, additives, molecule sieves, etc.) are shown in Table 1. Several copper catalysts were tested initially

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Table 1. Optimization of the Reaction Conditions⁴

	+	N Cat., L ₁ , DTBP, additives toluene, 120 °C, 36 h, Argon	► C	
	1a	2a	3aa	
entry	catalyst (mol %)	co-catalyst	additive	yield ^b (%)
1	CuCl			trace
2	$Cu(OTf)_2$			trace
3	[Cu(OTf)]₂·toluene			11
4	[Cu(OTf)]₂·toluene		NCS	6
5	[Cu(OTf)] ₂ ·toluene		3 Å MS	trace
6	[Cu(OTf)]2·toluene	TBAB		trace
7^c	[Cu(OTf)]2·toluene	TBAB	NCS + 3 Å MS	34
8 ^d	[Cu(OTf)]2·toluene	KBr	NCS + 3 Å MS	40
9	[Cu(OTf)]2·toluene	LiBr	NCS + 3 Å MS	52
10 ^e	[Cu(OTf)]2·toluene	FeBr ₃	NCS + 3 Å MS	37
11 ^e	[Cu(OTf)]₂·toluene	FeBr ₃ + LiBr	NCS + 3 Å MS	70
12	[Cu(OTf)] ₂ ·toluene	$Fe(ClO_4)_3 \cdot xH_2O + LiBr$	NCS + 3 Å MS	70
13 ^f	[Cu(OTf)] ₂ ·toluene	$Fe(ClO_4)_3 \cdot xH_2O + LiBr$	NCS + 3 Å MS	75
14^{f}	[Cu(OTf)] ₂ ·toluene	$Fe(ClO_4)_3 \cdot xH_2O + LiBr$	3 Å MS	34

^{*a*}Reaction conditions: **1a** (1.4 mmol), **2a** (0.2 mmol), [Cu] (10 mol %), DTBP (0.4 mmol), L1 (6 mol %), NCS (1.2 equiv), Fe(ClO₄)₃·H₂O (10 mol %), LiBr (2 equiv), 3 Å MS (25 mg), toluene (1.0 mL), 120 °C, 36 h, Argon. ^{*b*}Isolated yield. ^{*c*}TBAB (0.5 equiv). ^{*d*}KBr (2 equiv). ^{*c*}FeBr₃ (10 mol %). L₁ = 3,4,7,8-tetramethyl-1,10-phenantholine, TBAB = tetrabutylammonium bromide, NCS = N-chlorosuccinimide. ^{*f*}Li₂CO₃ (2 equiv).

in the presence of di-tert-butyl peroxide (DTBP) in toluene under argon. It was observed that these catalysts could catalyze the transformation, but most of them led to a trace amount of product 3aa, such as CuCl and Cu(OTf)₂ (entries 1 and 2), when using $[Cu(OTf)]_2$ toluene complex as a catalyst, and the desired dehydrogenative olefinsulfonation proceeded to afford the expected product 3aa in 11% isolated yield (entry 3). A decline in the yield of 3aa was observed when Nchlorosuccinimide (NCS) or tetrabutylammonium bromide (TBAB) was used as the additive (entries 4-6), respectively. To our delight, the accidental addition of both NCS and TBAB into the reaction led to a higher yield (20%) (see Table S5, entry 4). Enlightened by this, we added a combination of TBAB, NCS, and 3 Å MS into our present reaction simultaneously, and the product was obtained with a slightly but consistently improved yield (34%, entry 7). These results indicated that suitable bromide salts may be critical reagents for the optimal reaction conditions. Consistent amelioration in the yield of 3aa was achieved when KBr or LiBr was used instead of tetrabutylammonium bromide (TBAB) (entries 8 and 9, Table S9). Afterward, iron salts with LiBr were found to promote the desired transformation more effectively. An obvious improvement in yield was found when the catalytic amount of FeBr₃ or Fe(ClO₄)₃·xH₂O served as the co-catalyst (entries 10–12, Tables S9 and S11). This may be attributed to the fact that combination of iron salts with LiBr could always leave the FeBr₃ species in the reaction system, and FeBr₃ might help generate suitable benzylic radical species during DTBPinitiated reactions (Table S11).¹⁰ This speculation was in accordance with the control experiments that were carried out to figure out the functions of co-catalyst and additives (see entry 14, Tables S1-S13, and Mechanistic Studies in the Supporting Information) for the reaction proceeding and its high yields. However, considering FeBr₃ is sticky and not easy to handle, $Fe(ClO_4)_3$ xH₂O was chosen as the iron source for in situ generation of FeBr₃ in the final reaction conditions. Further reaction optimization found that 75% yield of 3aa could be realized using $[Cu(OTf)]_2$ toluene as a catalyst,

 $Fe(ClO_4)_3$: xH_2O as co-catalyst with a combination of LiBr, NCS, and Li₂CO₃ as additives (entry 13). We also investigated NBS (*N*-bromosuccinimide) instead of the combination of $Fe(ClO_4)_3$: xH_2O , LiBr and NCS; unfortunately, messy results were acquired.

The scope of the dehydrogenative olefinsulfonation of alkyl arenes was summarized in Scheme 1. For substituted ethylbenzenes, both electron-withdrawing groups, such as chloro, bromo, and iodo, and electron-donating groups, such as amyl ether, could be tolerated and proceeded smoothly to



^aReaction conditions: **1a** (1.4 mmol), **2a** (0.2 mmol), $[Cu(OTf)]_2$. toluene (10 mol %), DTBP (0.4 mmol), L1 (6 mol %), NCS (1.2 equiv), Fe(ClO₄)₃·H₂O (10 mol %), LiBr (2 equiv), 3 Å MS (25 mg), Li₂CO₃ (2 equiv), toluene (1.0 mL), 120 °C, 36 h, argon.

afford the desired vinyl sulfones 3aa-3fa in moderate to good yields (54-75%) with exclusive trans-stereoselectivity. Specifically, vinyl sulfone 3aa was successfully prepared on a 1 mmol scale with 60% yield, and the stereochemistry was unambiguously confirmed by X-ray crystallographic analysis of 3ba. Interestingly, 1,4-diethylbenzene underwent exclusive dehydrogenative olefinsulfonation on only one of the ethyl moieties even in the presence of excess N-sulfonylbenzo [d]imidazole to afford 3ea. However, the dehydrogenative olefinsulfonation became inefficient with those substrates bearing trimethylsilyethynyl and allyloxy (3ga and 3ha) groups due to decomposition under the reaction conditions. Using the present method, (E)-1-(2-tosylvinyl)naphthalene 3ia was obtained in good yield by employing ethyl naphthalene as substrate. It was noteworthy that alkyl heteroarenes were also amenable to this methodology, producing vinyl sulfones 3ja and 3la in moderate yields. The dehydrogenative olefinsulfonation can also occur on cycloalkenes. Tetrahydronaphthalene was used to furnish 3-tosyl-1,2-dihydronaphthalene 3ka and 3-(cyclopropylsulfonyl)-1,2-dihydronaphthalene 3kt in good yields with different sulfonation reagents, respectively. However, 4-ethylpyridine failed to participate in the reaction, and no desired product 3ma was observed.

Next, the dehydrogenative olefinsulfonation of 1a with diverse N-sulfonylbenzo[d]imidazoles were examined. A variety of alkyl and aryl N-sulfonylbenzo[d]imidazoles took part in the present reaction to afford the corresponding vinyl sulfones 3ab-3au in moderate to good yields. Evaluation of substituted N-sulfonylbenzo[d]imidazoles revealed that both electron-deficient and electron-rich derivatives were effective in the dehydrogenative olefinsulfonation. This transformation was compatible with fluoro (3ae), chloro (3af, 3am and 3an), bromo (3ag), alkyl (3ad, 3al), alkoxy (3ac, 3ah), trifluoromethyl (3ai), and cyano (3aj) functional groups summarized in Scheme 2. Although both electron-donating and electron-withdrawing groups on N-sulfonylbenzo[d]imidazole could be





^aReaction conditions: **1a** (1.4 mmol), **2a** (0.2 mmol), $[Cu(OTf)]_2$. toluene (10 mol %), DTBP (0.4 mmol), L1 (6 mol %), NCS (1.2 equiv), Fe(ClO₄)₃·H₂O (10 mol %), LiBr (2 equiv), 3 Å MS (25 mg), Li₂CO₃ (2 equiv), toluene (1.0 mL), 120 °C, 36 h, argon.

tolerated, the reaction was not efficient with a bulky substituent (**3ao**, 34%). 1-Naphthyl and 2-naphthyl *N*-sulfonylbenzo[*d*]imidazoles were amenable to our strategy in good yields (**3ap**, 74% and **3aq**, 61%). In addition, heterocyclic substituents behaved differently in our reactions. Sulfonation reagent with pyridyl group led to a very low yield (**3ar**, 10%), while the thiofurylsulfonation reagent could still offer a good yield (**3as**, 56%). This might be due to pyridine's susceptibility to the radical process. Thus, the present reaction pathway was interrupted. We also tested alkyl-substituted *N*-sulfonylbenzo-[*d*]imidazoles such as 1-(cyclopropylsulfonyl)-1*H*-benzo[*d*]imidazole, and olefinsulfonation products **3at** and **3au** were obtained in 70% and 30% yield, respectively.

To gain insight into the present reaction process, a radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added into the reaction systems in Scheme 3a. Although

Scheme 3. Mechanistic Investigation



TEMPO-trapped products were not detected, the formation of **3aa** was suppressed substantially, which was indicated that a single-electron-transfer radical process may be involved. To validate the radical process, another radical scavenger, 2,6-di*tert*-butyl-4-methylphenol (BHT), was added to the reaction under standard reaction conditions in Scheme 3b. No desired product **3aa** was found. To further clarify the reaction pathway of the dehydrogenative olefinsulfonation, experiments with styrene (the proposed intermediate C) instead of ethylbenzene were carried out under the standard conditions in Scheme 3c. Sulfonation product **3aa** was then obtained in 67% isolated yield, which may be indicated that the in situ generated styrene was one of the key intermediates during the dehydrogenative olefinsulfonation process.

On the basis of the above results and previous reports, a possible mechanism was illustrated in Scheme 4, though it might be controversial.¹¹ Initially, *N*-sulfonylbenzo[*d*]-imidazole is reduced by Cu(I) via a single-electron-transfer (SET) process to generate tosyl radical and Cu(II) complex A.¹² While benzylic radical is generated by a radical transfer process initiated by decomposition of DTBP.¹³ Subsequently, metal alkyl complex B is formed via a Cu(II)-mediated SET oxidation process.¹⁴ β -Hydride elimination of intermediate B releases the styrene C and Cu(I) species.^{12b,15} This metal hydride species is then oxidized into the Cu(II) catalyst by *N*-sulfonylbenzo[*d*]imidazole or DTBP to close the first catalytic cycle. The second catalytic circle is continued with the styrene C and the tosyl radical generated before. The in situ generated

Scheme 4. Possible Mechanism for the Dehydrogenative Olefinsulfonation



styrene traps the tosyl radical to form the functionalized intermediate **D**. The final product is delivered via a Cu(II)mediated SET oxidative process followed by a second β hydride elimination step. Cu(I) complex is also formed during this step and then oxidized into Cu(II) catalysis, completing the second catalytic cycle. The addition of Fe(III) species leads to a significant improvement of yield, but this reaction can occur smoothly in moderate yields without Fe(ClO₄)₃·*x*H₂O. We speculate that it might bring some benefits to the generation of benzylic radicals as reported.⁹ Detailed investigations into their roles are shown in the Supporting Information (see Tables S1–S13 and Mechanistic Studies).

In conclusion, we report an efficient copper-catalyzed dehydrogenative coupling reaction of enthylbenzene with *N*-sulfonylbenzo[*d*]imidazole under mild conditions, featuring two successive β -elimination steps along with radical sulfonation. A series of *E*-vinyl sulfones have been prepared in moderate to good yields. Further studies to clearly understand the detailed mechanism as well as applications in natural product synthesis are currently underway.

ASSOCIATED CONTENT

3 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03146.

Experimental procedures, full spectroscopic data, and ¹H and ¹³C NMR spectra of all compounds (PDF)

Accession Codes

CCDC 2033227 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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