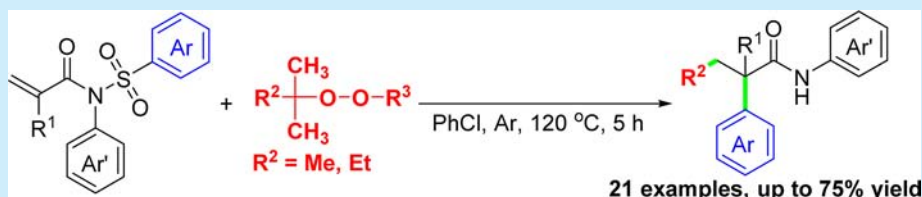


Metal-Free Oxidative 1,2-Arylmethylation Cascades of *N*-(Arylsulfonyl)acrylamides Using Peroxides as the Methyl ResourceFang-Lin Tan,[†] Ren-Jie Song,^{*,‡} Ming Hu,[†] and Jin-Heng Li^{*,†,‡}[†]State Key Laboratory of Chemo/Biosensing and Chemometrics, Hunan University, Changsha 410082, China[‡]Key Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China

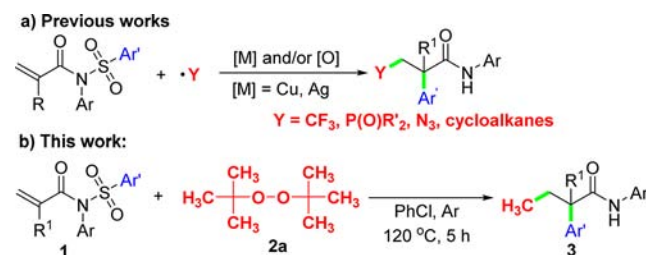
Supporting Information



ABSTRACT: A new, metal-free oxidative 1,2-arylmethylation cascades of *N*-(arylsulfonyl)acrylamides for the assembly of 2,2-disubstituted-*N*-arylbutanamides containing an all-carbon quaternary center is presented. This reaction enables the one-step formation of two new C–C bonds through a sequence of methylation/1,4-aryl migration/desulfonylation using an organic peroxide as the methyl resource with a broad substrate scope and excellent functional group tolerance.

Difunctionalization of alkenes is one of the most important methods for increasing molecular complexity in synthesis, which can simultaneously construct two new chemical bonds in one-step.^{1,2} As a result, considerable efforts have been devoted to develop new efficient strategies for the alkene difunctionalization.³ Among them, oxidative dicarbo-functionalization are particularly appealing, which enable the formation of two new C–C bonds in a single reaction.⁴ However, approaches for the oxidative 1,2-arylalkylation of alkenes are less abundant, and the majority are restricted to transformations of *N*-arylacrylamides to oxindoles and related heterocycles via a sequence of intramolecular C(sp²)–H functionalization and cyclization.⁵ Recently, attention has been attracted on the difunctionalization of *N*-(arylsulfonyl)acrylamides, which proceeded involving aryl migration and desulfonylation.⁶ In 2013, Nevado and co-workers first reported a copper-catalyzed 1,2-aryltrifluoromethylation of the alkene moieties in *N*-(arylsulfonyl)acrylamides via a radical-mediated trifluoromethylation, aryl migration/desulfonylation tandem process^{6b} leading to α -aryl- β -trifluoromethyl amides.⁷ Subsequently, some new radical-mediated strategies, including 1,2-arylphosphonylation,^{6a} 1,2-arylazidation,^{6g} and 1,2-arylalkylation,^{6c} for the transformations of *N*-(arylsulfonyl)acrylamides have been developed (Scheme 1a). Although the oxidative 1,2-arylalkylation of *N*-(arylsulfonyl)acrylamides has been described by the group of Zhu, it was limited to the use of cycloalkanes as the alkyl resources. Further, to our knowledge, methods for the 1,2-arylmethylation cascades of *N*-(arylsulfonyl)acrylamides have never been reported, despite the obvious synthetic utility of the methylation reaction in chemistry, especially in medicinal chemistry.^{8–10}

Herein, we report a new metal-free oxidative 1,2-arylmethylation cascade of *N*-(arylsulfonyl)acrylamides with peroxides for

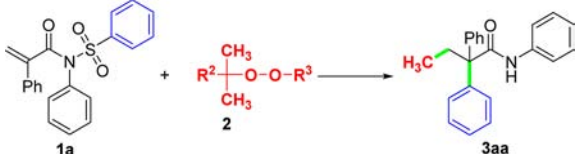
Scheme 1. Difunctionalization Cascades of *N*-(Arylsulfonyl)acrylamides

the synthesis of 2,2-disubstituted-*N*-arylbutanamides containing an all-carbon quaternary center. This radical-mediated reaction employs peroxides as the methyl resource, thus enabling the one-step formation of two C–C bonds through a sequence of methylation, aryl migration, and desulfonylation (Scheme 1b).

We began our studies by examining the 1,2-arylmethylation cascades of *N*,2-diphenyl-*N*-(phenylsulfonyl)acrylamide (**1a**) with peroxides (Table 1). Pleasingly, treatment of acrylamide **1a** with di-*tert*-butyl peroxide (DTBP; **2a**) in PhCl under argon atmosphere at 120 °C for 5 h afforded the desired product **3aa** in 72% yield (entry 1). Encouraged by the results, a series of other peroxides, including dicumylperoxide **2b** (DCP), *tert*-butyl peroxybenzoate **2c** (TBPB), *tert*-butyl hydroperoxide **2d** (TBHP; in decane), and aqueous TBHP **2e**, was examined (entries 2–5): each of which could serve as the methyl resource for the reaction but was less reactive than DTBP in terms of yields. Notably, the use of DCP **2b** exclusively resulted in the

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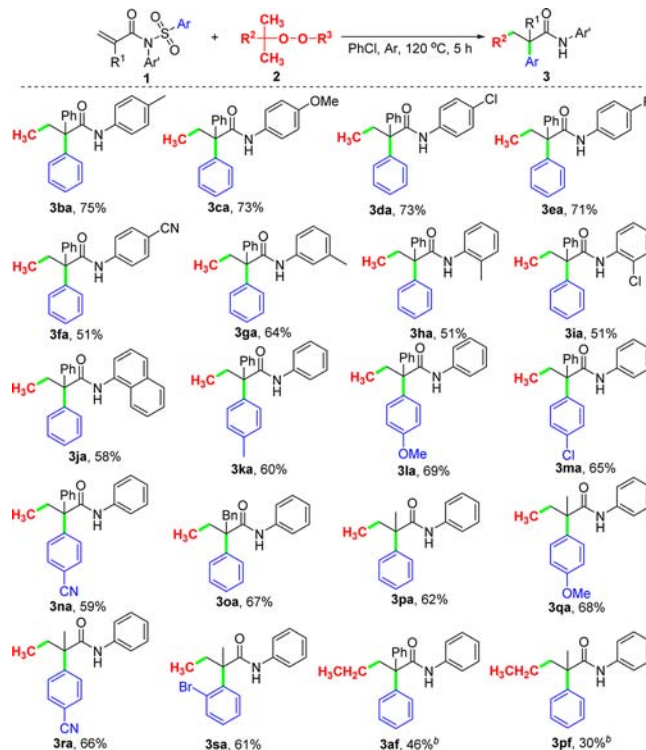
Table 1. Screening of Optimal Conditions^a


entry	peroxide (equiv)	solvent	<i>t</i> (°C)	yield (%) ^b
1	DTBP 2a (3)	PhCl	120	72
2	DCP 2b (3)	PhCl	120	67
3	TBPB 2c (3)	PhCl	120	38
4 ^c	TBHP 2d (3)	PhCl	120	15
5 ^d	TBHP 2e (3)	PhCl	120	14
6	DTBP 2a (4)	PhCl	120	70
7	DTBP 2a (2)	PhCl	120	52
8 ^e	DTBP 2a (3)	MeCN	120	38
9 ^f	DTBP 2a (3)	toluene	120	29
10	DTBP 2a (3)	DMF	120	21
11	DTBP 2a (3)	PhCF ₃	120	64
12	DTBP 2a (3)	<i>t</i> -BuOH	120	trace
13	DTBP 2a (3)	PhCl	130	68
14	DTBP 2a (3)	PhCl	110	24
15 ^g	DTBP 2a (3)	PhCl	120	65

^aReaction conditions: **1a** (0.2 mmol), **2**, solvent (2 mL), argon, and 5 h. ^bIsolated yield. ^cTBHP (anhydrous, 5 M in decane). ^dTBHP (70% in water). ^eA trace amount of cyano-containing product was detected by GC–MS analysis. ^fA trace amount of 1,2-benzylmethylation product was detected by GC–MS analysis. ^g**1a** (726 mg, 2 mmol) for 8 h.

formation of the 1,2-phenylmethylation product **3aa**, not the 1,2-phenylphenylation product (entry 2). A screen of the amount of DTBP **2a** revealed 3 equiv of DTBP as the best choice (entries 6 and 7). Among the effect of solvent examined, the use of PhCl solvent turned out to be the most effective than the other solvents, such as MeCN, toluene, DMF, PhCF₃, and *t*-BuOH (entries 8–12). Further screening on the reaction temperature proved that the reaction at 120 °C gave the best yield (entries 1, 13, and 14). Gratifyingly, the scale of acrylamide **1a** up to 2 mmol was also viable for the synthesis of **3aa** in moderate yield (entry 15).

With the optimized reactions in hand, we set out to explore the scope of this oxidative 1,2-arylmethylation cascades protocol with respect to the *N*-(arylsulfonyl)acrylamides **1**, and the results are summarized in Scheme 2. The optimal conditions were compatible with a variety of *N*-aryl-*N*-(arylsulfonyl)acrylamides **1**, providing the corresponding products **3ba–sa** in moderate yields. Importantly, several substituents, namely, Me, OMe, Cl, F, and CN, on the aromatic ring of the *N*-aryl moiety were well-tolerated, and the reactive order of the substituents was *para* > *meta* > *ortho* in terms of yields (products **3ba–ia**). While *para*-Me-substituted substrate **1b** gave **3ba** in 75% yield, *meta*-Me-substituted substrate **1g** or *ortho*-Me-substituted substrate **1h** delivered the corresponding products **3ga** and **3ha**, respectively, in lower yields. Notably, *N*-(naphthalen-1-yl)-substituted substrate **1j** was also proved to be viable for furnishing **3ja**. Subsequently, the substitution effect on the aromatic ring of the *N*-(arylsulfonyl) moiety was investigated. Substrates **1k–n**, bearing a Me, a OMe, a Cl, or a CN group on the aryl ring of the *N*-(arylsulfonyl) moiety, were efficiently converted to the corresponding products **3ka–na** in moderate to good yields. Using substrates **1o** or **1p** with benzyl or methyl group at the 2 position of the acrylamides moiety smoothly assembled products

Scheme 2. Variation of the Acryl Sulfonamides (**1**)^a

^aReaction conditions: **1a** (0.2 mmol), **2** (3 equiv), PhCl (2 mL), argon, 120 °C, and 5 h. ^b2-Hydroperoxy-2-methylbutane (**2f**) (0.4 mmol) was used as ethyl source.

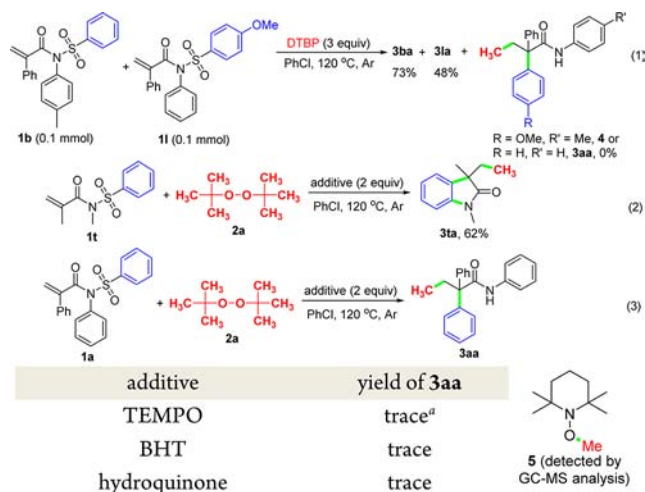
3oa and **3pa**, respectively. In the case of *N*-(arylsulfonyl)-methacrylamides **1q–s**, the reaction were successfully performed, giving **3qa–sa** in moderate yield. Notably, Cl, F, and Br groups could also survive, thereby facilitating additional modifications at the halogenated position (products **3da–ea**, **3ia**, **3ma**, and **3sa**).

Gratifyingly, the optimal conditions were applicable to 1,2-arylethylation cascades of *N*-(arylsulfonyl)acrylamides (products **3af** and **3pf**). For example, substrate **1a** treated with 2-hydroperoxy-2-methylbutane (**2f**) exclusively afforded the 1,2-phenylethylation product **3af** in 46% yield.

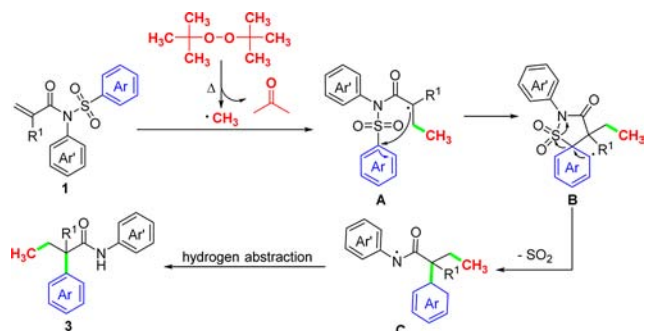
To understand the mechanism, some control experiments were designed (Scheme 3). A mixture of two different acryl sulfonamides **1b** and **1l** was reacted with DTBP (**2a**) under the optimal conditions; no cross aryl-migrating products were obtained (eq 1). The results demonstrate that 1,4-aryl migration proceeds via an intramolecular process. To our surprise, *N*-alkyl substrate **1t** afford a cyclization product 3-ethyl-1,3-dimethylindolin-2-one (**3ta**), in 62% yield (eq 2). Notably, the reaction of *N*,2-diphenyl-*N*-(phenylsulfonyl)acrylamide (**1a**) with DTBP **2a** was completely inhibited when using a stoichiometric amount of radical scavengers, including TEMPO, 2,6-di-*tert*-butyl-4-methylphenol (BHT), and hydroquinone. Moreover, 1-methoxy-2,2,6,6-tetramethylpiperidine **5** was in situ detected by GC–MS analysis. These results suggest that the reaction may involve a radical process (eq 3).

The plausible mechanism of this metal-free oxidative 1,2-arylmethylation cascades was proposed (Scheme 4).^{3,6–10} DTBP readily generates methyl radical and acetone under heating. Addition of the methyl radical across the C–C double bond in *N*-(arylsulfonyl)acrylamides **1** affords the radical intermediate **A**,

Scheme 3. Control Experiments



Scheme 4. Possible Mechanism



followed by intramolecular 5-*is*po-cyclization, which forms the intermediate **B**. The intermediate **B** then transforms into the amidyl radical intermediate **C** via desulfonation. Finally, hydrogen abstraction of the intermediate **C** gives the desired product **3**.

In summary, we have developed new, metal-free oxidative 1,2-arylmethylation cascades of *N*-(arylsulfonyl)acrylamides using organic peroxides as the methyl source through a sequence of methylation/aryl migration/desulfonation. This reaction provides a simple and facile route to the straightforward synthesis of 2,2-disubstituted-*N*-arylbutanamides with a quaternary stereocenter with excellent functional group tolerance.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01419.

Descriptions of experimental procedures for compounds and analytical characterization (PDF)

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Notes

The authors declare no competing financial interest.

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