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Metal-Free Mediated Meerwein-Type Reaction: A Radical Cascade Arylation/Aryl Migration/Desulfonylation of Conjugated Alkenes

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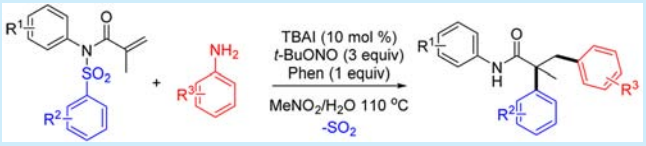
Supporting Information

ABSTRACT: A metal-free cascade arylation/aryl migration/desulfonylation of *N*-phenyl-*N*-(phenylsulfonyl)methacrylamide is described. The in situ generated diazonium salts from anilines and *t*-BuONO are used as aryl precursors. This process provides an efficient strategy for the synthesis of α-all-carbon quaternary stereocenters amides. A radical mechanism was proposed for this transformation.

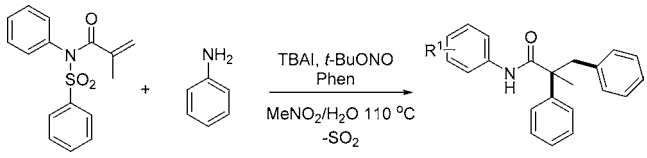


Alkenes are of great importance in organic synthesis because of their potential for the introduction of various functional groups to the C=C bond. Numerous endeavors have been paid to the development of novel difunctionalization of alkenes since it can introduce two functional groups in a single step.[1−7] On the other hand, though cascade reactions are considered as efficient synthetic strategies, the desired product can be obtained directly without the separation of reaction intermediates.[8] It has been widely used in the synthesis of heterocyclic compounds. Recently, cascade reactions based on phenylsulfonyl acrylamide have received increasing attention. Nevado's group first developed a novel radical cascade aryltrifluoromethylation/aryl migration/desulfonylation of phenylsulfonyl acrylamide.[9a] Encouraged by Nevado's pioneering work, arylphosphonylation, arylazidation, arylalkylation, and aryltrifluoromethylation of phenylsulfonyl acrylamide have been developed by several groups.[9] To the best of our knowledge, the diarylation of phenylsulfonyl acrylamide has not been investigated.

Diazonium salts, which can be synthesized from commercial available aniline, have proven to be good aryl radical providers. Diazonium salts are prone to undergo a homolytic dediazoniation to provide aryl radicals, and the in situ generated aryl radicals can be trapped by other reactive species to form the desired products. Various reactions based on the in situ generated aryl radical from diazonium salts have been established, such as Sandmeyer-type reactions[10] and Meerwein-type reactions.[11] Recently, we developed a new approach for the synthesis of 3,3-disubstituted oxindoles from anilines nitrosated in situ.[12] We also realized the C(Sp^3)−H bond activation of acetonitrile using the in situ generated diazonium salts as radical promoter.[13] To further our investigation of the in situ generated diazonium salts, a radical cascade reaction using in situ generated diazonium salts and conjugated alkenes was designed. In this communication, we describe a metal-free cascade arylation/aryl migration/desulfonylation reaction of phenylsulfonyl acrylamide (Scheme 1).

Our study commenced with the reaction of *N*-phenyl-*N*-(phenylsulfonyl)methacrylamide **1a** and *p*-chloroaniline **2a**.

Scheme 1. Cascade Arylation/Aryl Migration/Desulfonylation of *N*-Phenyl-*N*-(phenylsulfonyl)methacrylamide



The results are summarized in Table 1. In the presence of *tert*-butyl nitrite (3.5 equiv), tetrabutylammonium iodide (TBAI) (10 mol %), and NaOAc (1 equiv), the target product **3a** could be obtained with 31% yield (entry 1). The structure of **3a** was confirmed by MS and NMR spectra. In order to increase the yield, several different kinds of bases were screened in this reaction, and the yield was improved (entries 2−5). Among the bases tried, phenanthroline (Phen) gave the best result with 55% yield (entry 5). When the reaction was performed in the absence of Phen, the yield of the target product decreased to 39% (entry 6). Subsequently, the effects of solvent were investigated, and several different solvents were used instead of $MeNO_2$ (entries 7−10), while the results indicated that $MeNO_2$ was the most suitable solvent for this reaction. Benzotrifluoride (BTF) had been used in arylative cyclization of isocyanobiphenyls with anilines by Zhu.[14] However, the target product could be only isolated with 15% yield in our reaction (entry 10). Then, two different nitrosating agents were tested. When isoamyl nitrite was used instead of *tert*-butyl nitrite, the target product could be obtained with 51% yield, which is slightly lower than that with *tert*-butyl nitrite (entry 11). Sodium nitrite was inefficient for this transformation; no product could be isolated (entry 12). If the reaction was performed without the addition of H_2O, the yield would decrease to 45% (entry 13). Further optimization focused on

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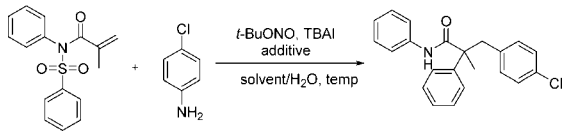
Table 1. Optimization of Reaction Conditions[a]



entry	additive	solvent	temp (°C)	yield[b] (%)
1	NaOAc	$MeNO_2$	110	31
2	Na_2CO_3	$MeNO_2$	110	48
3	HMPA	$MeNO_2$	110	45
4	$NaHSO_3$	$MeNO_2$	110	40
5	Phen	$MeNO_2$	110	55
6		$MeNO_2$	110	39
7	Phen	DMSO	110	46
8	Phen	DMF	110	33
9	Phen	toluene	110	15
10	Phen	BTF	110	20
11[c]	Phen	$MeNO_2$	110	51
12[d]	Phen	$MeNO_2$	110	trace
13[e]	Phen	$MeNO_2$	110	45
14	Phen	$MeNO_2$	100	48
15	Phen	$MeNO_2$	120	52
16[f]	Phen	$MeNO_2$	110	43

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (3 equiv), *t*-BuONO (3.5 equiv), TBAI (10 mol %), additive (1 equiv), solvent (1 mL), H_2O (50 μL), N_2, 10 h. [b]Isolated yield. [c]Isoamyl nitrite instead of *tert*-butyl nitrite was used. [d]sodium nitrite instead of *tert*-butyl nitrite was used. [e]Without the addition of H_2O. [f]$MeNO_2$ (2 mL).

the reaction temperature and concentration of the reactants. The yield could not be improved when the reaction was performed in either a higher or lower temperature (entries 14 and 15). The concentration of the reactants had an obvious influence in this reaction. Increasing the volume of $MeNO_2$ resulted in the decrease of the target product yield (entry 16).

With the optimized reaction conditions in hand, we then set out to explore the substrate scopes of this radical cascade reaction. *N*-Phenyl-*N*-(phenylsulfonyl)methacrylamide **1a** was reacted with various aryl amines **2a**−**k** to give the corresponding products **3a**−**k** with moderate yields (Figure 1). In this transformation, the electron-withdrawing substituents on anilines gave slightly higher yields than the electron-donating ones (**3a**−**f**), which might be because the electron-withdrawing substituents on the aromatic ring would favor homolytic dediazoniations. Fortunately, chloro and bromo groups were inert under these reaction conditions and would allow further functionalization of the products. When the aniline was substituted with a nitro group, which behaves as a strong electron-withdrawing substituent, the yield of the corresponding product decreased to 25% (**3i**). The effects of the substituted position were also investigated. The steric hindrance had obvious effects on this transformation. 3-Chloroaniline **2j** and 2-chloroaniline **2k** only afforded the desired products with 48% and 35% yields, which are lower than that of 4-chloroaniline (**3j**, **3k**).

A series of *N*-phenyl-*N*-(phenylsulfonyl)methacrylamides were also investigated (Figure 2). First, the substituent effects on the phenyl ring were investigated. When the phenyl ring was substituted on the *para*-position, the electron-donating substituents clearly gave higher yields than the electron-withdrawing ones (**3l**−**q**). Then, the effects of steric hindrance were studied. As anticipated, the steric hindrance had a

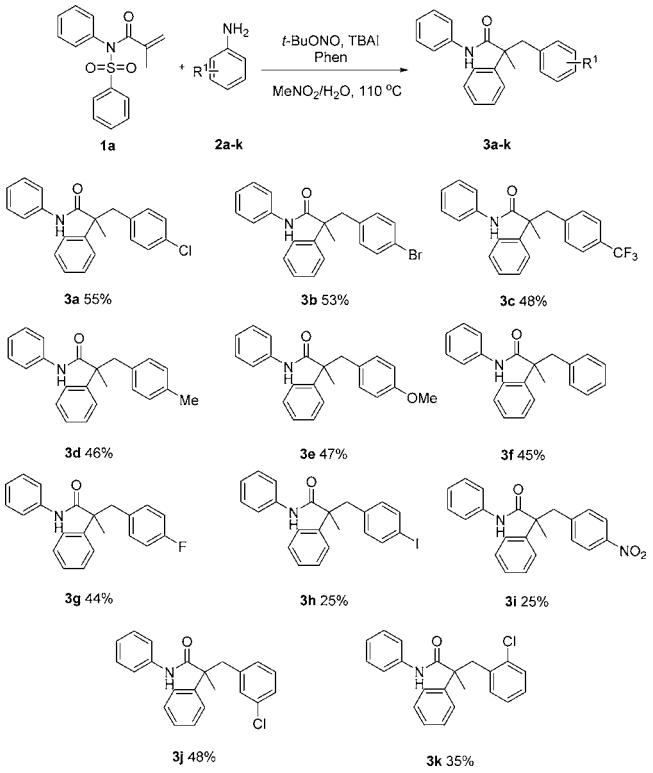


Figure 1. Scope of aryl amines.

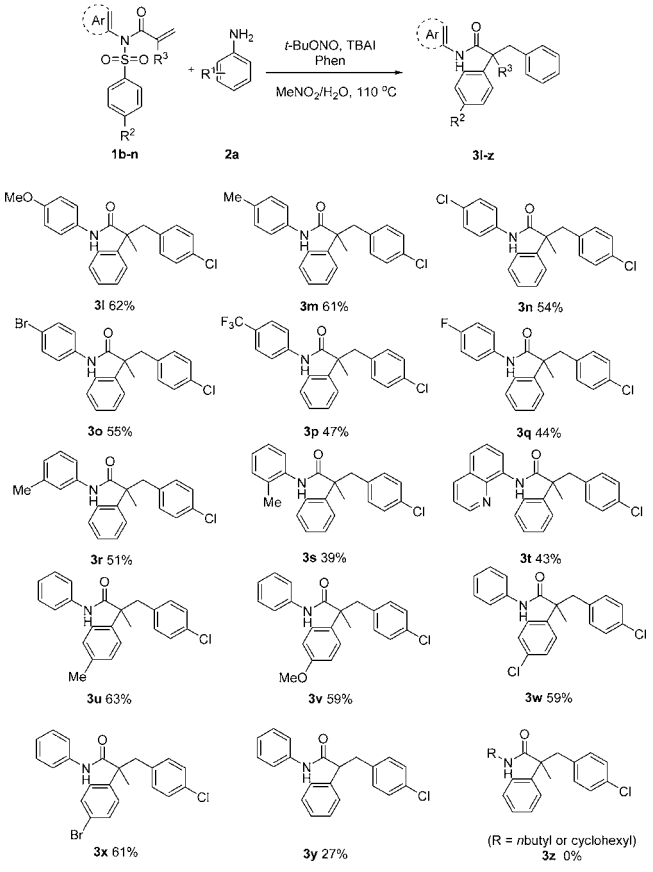


Figure 2. Scope of *N*-phenyl-*N*-(phenylsulfonyl)methacrylamides.

significant influence on this transformation. When the methyl group substituted at the *ortho*- or *meta*-position instead of the

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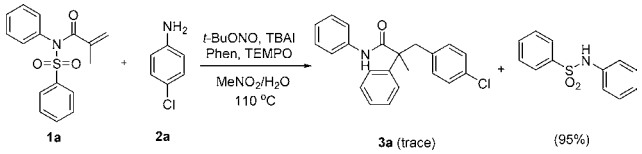
para-position, the yield of corresponding product decreased to 39% or 51% (**3r**, **3s**). We also tried to apply this strategy to heteroaromatic ring substrate. When *N*-(phenylsulfonyl)-*N*-(quinolin-8-yl)methacrylamide was used in this reaction, the target product could be obtained with 43% yield (**3t**). Subsequently, the substituted effects on the phenysulfonyl ring were investigated. The results implied that the electron-withdrawing or -donating substituents had little effect on the yield; instead, the target products could all be obtained with moderate yields (**3u**–**x**). Fortunately, chloro and bromo groups on either phenyl ring or phenylsulfonyl ring could be tolerated and allow for further functionalization reactions. In addition, the reaction could still proceed when R^3 = H, although only 27% of the target product could be obtained (**3y**). Unfortunately, when *N*-butyl-*N*-(phenylsulfonyl)methacrylamide or *N*-cyclohexyl-*N*-(phenylsulfonyl)methacrylamide was used in this reaction, the target products could not be obtained (**3z**).

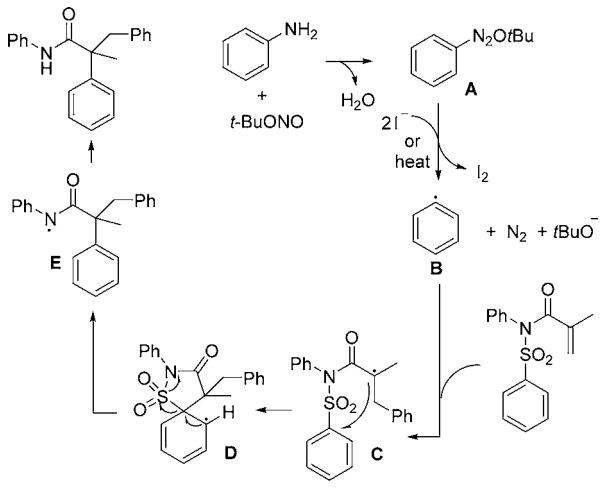
To investigate the mechanism of this cascade reaction, the control experiment was performed (Scheme 2). The 2,2,6,6-tetramethylpiperidin-1-oxyl radical (TEMPO), which has been widely used as radical scavenger, was added to the reaction system. We found that the target product could not be obtained and the starting material decomposed. We speculated the reaction might undergo a radical process.

Scheme 2. Control Experiment



Based on the above-mentioned observations and previous studies,[9,15] we propose a tentative mechanism for this transformation (Scheme 3). Aniline reacts with *t*-BuONO to yield the diazonium salt **A**. The formation of aryl radical **B** may follow two different paths. In the presence of TBAI, aryl radical **B**, nitrogen, and *tert*-butoxy anion are generated. On the other hand, aryl radical **C**, nitrogen, and *tert*-butoxy radical can be generated from diazonium salts under heat. Then the in situ generated aryl radical **B** adds to the C=C bond to afford radical intermediate **C**. The 5-ipso-cyclization on the aromatic ring generates intermediate **D**, and a rapid desulfonylation affords the key amidyl radical **E**. Finally, radical intermediate **E** abstracts a hydrogen atom to give the desired product.

Scheme 3. Proposed Mechanism



In conclusion, we have developed a novel radical cascade arylation/aryl migration/desulfonylation of *N*-phenyl-*N*-(phenylsulfonyl)methacrylamide. The anilines could react with *t*-BuONO to form diazonium salts, and the in situ generated aryl radical from diazonium salts could add to the C=C bond. Through 5-ipso-cyclization and rapid desulfonylation, α-all-carbon quaternary stereocenters amides could be obtained with moderate yield. This process provides a new procedure for the synthesis of α-all-carbon quaternary stereocenter amides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01041.

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

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Notes

The authors declare no competing financial interest.

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