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Trisubstituted Aziridine Ring-Opening by Phenol Derivatives: Stereo- and Regioselective Formation of Chiral Tertiary Alkyl-Aryl Ethers

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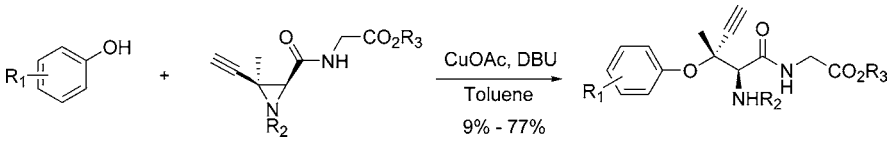
ABSTRACT



An unprecedented stereo- and regioselective trisubstituted aziridine ring-opening by phenol derivatives was discovered. The reaction features very mild reaction conditions and broad functional group compatibility, which provides a good method for the stereoselective formation of tertiary alkyl-aryl ethers in highly functionalized systems.

Aziridines are versatile building blocks in organic synthesis by virtue of their highly strained ring system.[1] Nucleophilic ring-opening reactions are particularly useful in exploiting this reactivity, but trisubstituted and tetrasubstituted aziridines exhibit diminished reactivity due to increased steric hindrance. Regioselectivity can be problematic because both carbons of the aziridine are susceptible to nucleophilic attack. However, acceptable levels of regioselectivity can often be achieved by controlling the steric and electronic effects exerted by the substituents of the two carbon atoms. Few investigations report the generation of a new quaternary carbon center through an aziridine ring-opening reaction.[2] Although useful for the formation of amino ethers, ring-openings by oxygen nucleophiles are limited.[3]

Alkyl-aryl ethers are important constituents of pharmacologically interesting molecules. As a result, their synthesis has been well investigated. The Mitsunobu reaction[4] and transition-metal-catalyzed C−O bond formation[5] are widely used for this operation. However, formation of tertiary alkyl-aryl ethers remains a challenging transformation. In general, tertiary alkoxides are poor nucleophiles in transition-metal-catalyzed C−O bond formation and S_NAr reactions with aryl halides. Alternatively, tertiary alkyl species with a leaving group are not optimal as electrophiles because S_N1 and E1 processes are competitive with the desired S_N2 reaction. The integrity of the stereogenic carbon of the tertiary alkyl group is often not maintained during the substitution. Consequently, most tertiary alkyl-aryl ether formation reactions are limited to aryl *tert*-butyl etherification. Few reports have appeared in the literature to form chiral tertiary alkyl ethers stereoselectively.[6]

During the investigation of the total synthesis of ustiloxin and phomopsin natural products, it was evident that a mild

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reaction for the stereoselective formation of chiral tertiary alkyl-aryl ethers with a vicinal amino group was critical for a convergent synthesis. However, our investigation using existing methods was of limited success because of either harsh reaction conditions or low stereo- and regioselectivity. A regioselective ring-opening reaction of an enantiomerically pure aziridine by phenol derivatives was attractive because it could afford a chiral alkyl-aryl ether with an adjacent stereogenic carbon bearing a nitrogen functionality. However, investigation of traditional Lewis acid promoted ring-opening of a trisubstituted aziridine-2-carboxamide did not provide satisfactory results mainly due to the steric hindrance of the disubstituted carbon center. Reports of copper-catalyzed etherification of 1,1-dimethylpropargylic halides (or carbonates or esters) with phenols provided tertiary alkyl-aryl ethers efficiently even in a sterically congested environment.[7] These reports led us to use an ethynyl aziridine in expectation of forming the desired chiral tertiary alkyl-aryl ether. Pleasantly, the reaction between isovanillin (**1**) and ethynyl aziridine (**2**) afforded chiral tertiary alkyl-aryl ether **3** as a single diastereomeric product (Scheme 1). No stereo- or regioisomer

Scheme 1. Ring-Opening of Trisubstituted Aziridine **2** by Isovanillin

was isolated from the reaction mixture. To the best of our knowledge, this reaction is the first stereo- and regioselective ring-opening reaction of a trisubstituted aziridine and the first nucleophilic substitution reaction occurring on the propargylic site (S_NP) of an ethynyl aziridine.[8]

Moreover, this new reaction seemed to be compatible with many functionalities due to its mild conditions. Changing the protecting group on the aziridine nitrogen from tosyl to the more readily cleaved nosyl or Boc groups had little effect on the yield (Scheme 2). A Cbz-protected aziridine exhibited similar reactivity. The carbamate protecting groups are particularly interesting because carbamates generally are not considered to be sufficiently activating for aziridine ring-opening reactions because of their weak electron-withdrawing ability.

The fact that only one single product was isolated led to the speculation that the C-3 carbon center had undergone

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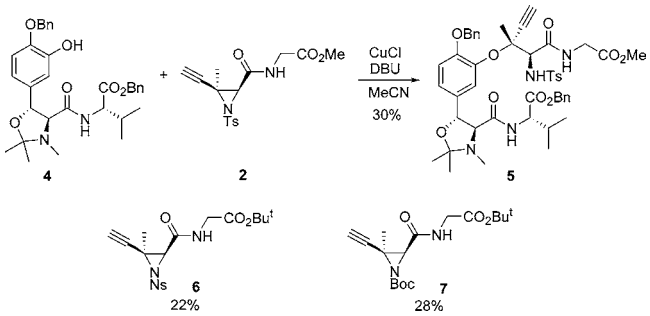
Scheme 2. Effects of Protecting Groups on the Aziridine Nitrogen



inversion. It was therefore critical to confirm the absolute configuration. After many attempts, a crystal of compound **3** that cocrystallized with CH_2Cl_2 was obtained. The X-ray structure showed that the oxygen nucleophile had approached anti to the aziridine nitrogen, to provide the correct stereochemistry of the tertiary alkyl-aryl ether and the vicinal carbon center in ustiloxins and phomopsins (Figure 1).

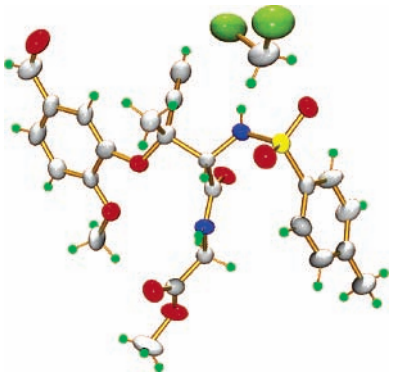
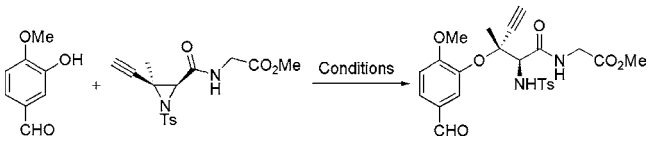


Figure 1. X-ray structure of compound **3**.

Although the ethynyl aziridine ring-opening reaction was very interesting and had the potential to be useful for the formation of tertiary alkyl-aryl ethers, the reaction needed to be optimized as the yield was only moderate. A number of conditions, including different copper species, bases, solvents, and reaction temperatures, were screened (Table 1).

It was found that the solvent had the most significant influence on the reaction. When changing from polar solvents (MeCN, entry 1) to nonpolar solvents (CH_2Cl_2 or toluene, entries 3 and 4), the yield was improved from 15% to 59% and 50%, respectively. Toluene was chosen as the optimal solvent because the reaction was cleaner in this solvent than in CH_2Cl_2, which resulted in easier product purification. Through the screening of different copper sources, CuOAc provided the best reaction with the combination of DBU as the base. The tertiary alkyl-aryl ether **3** was isolated in 60% yield after 24 h at room temperature (entry 7).

Table 1. Optimization of Ethynyl Aziridine Ring-Opening by Isovanillin



copper catalyst	CuCl	$CuCl_2$	$CuCl_2$	$CuCl_2$	$CuCl_2$	CuCl	CuOAc
base	DBU	DBU	DBU	DBU	DBU	DBU/ Cs_2CO_3	DBU
solvent	MeCN	THF	CH_2Cl_2	toluene	toluene	toluene	toluene
temp	rt	0 °C to rt	0 °C to rt	0 °C to rt	rt	rt	rt
yield	15%	41%	59%	50%	47%	44%	60%

The electronic effect of the substituents on the phenol nucleophile was examined. In this study, only para-substituted phenols were screened for easier comparison. A saturated solution of CuOAc in toluene was used to ensure consistent copper catalyst loadings in the reactions. The results of phenols with aziridines **2** and **6** are shown in Table 2. The reaction of tosyl aziridine **2** took longer to complete than that of nosyl aziridine **6** (24 vs 2 h) and proved more difficult to isolate resulting in lower yields with this series.[9] Strong and weak electron-donating groups (OMe and Me) and a weak electron-withdrawing group (Br) provided results similar to those for phenol. When a phenol with a stronger electron-withdrawing group was tested, mixed results were obtained. The reactions of 4-cyanophenol and 4-hydroxybenzaldehyde with tosyl-protected aziridine **2** provided low yields of the desired tertiary alkyl-aryl ethers, whereas good yields were obtained when reacted with nosyl-protected aziridine **6** (entries 5 and 6). This observation could result from the combination of a less-reactive aziridine substrate, weaker nucleophilicity of the phenols, and poor solubility in toluene of these two phenols.

Although the exact mechanism of the ethynyl aziridine ring-opening reaction is under investigation, the reaction was successfully applied to a concise, convergent, and stereoselective synthesis of ustiloxin D due to its mild reaction conditions and broad functionality tolerance. Steric effects were not problematic as excellent yields were obtained even with considerably bulky ortho- and meta-substituted phenols.[10]

In conclusion, an unprecedented stereo- and regioselective ethynyl aziridine ring-opening reaction by phenols was discovered. It is the first nucleophilic trisubstituted aziridine ring-opening occurring at the more hindered position to form a quaternary carbon center. Further investigation of this reaction, specifically toward understanding the role of copper, is ongoing.

(9) A reviewer brought to our attention that nosyl aziridines have been studied extensively and have been found to be more reactive than their tosyl counterparts with excellent regioselectivity with monosubstituted aziridines. However, to the best of our knowledge, phenols and phenolates were not tested as nucleophiles in these systems. Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253.

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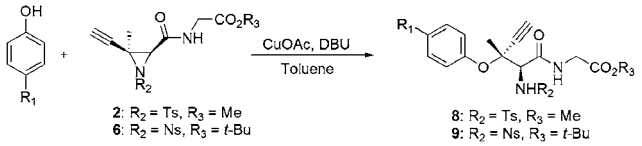
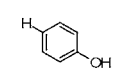
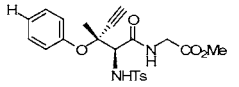
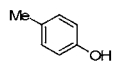
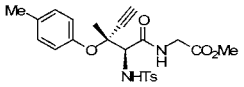
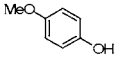
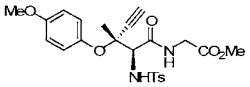
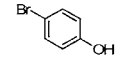
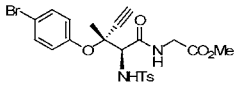
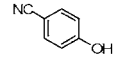
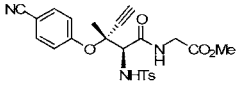
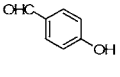
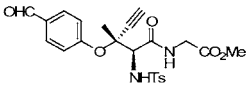
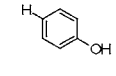
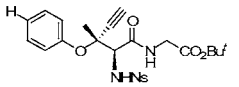
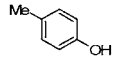
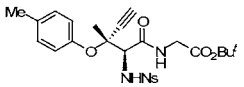
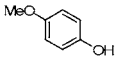
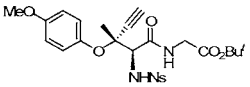
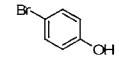
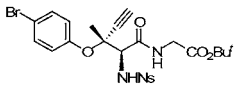
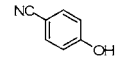
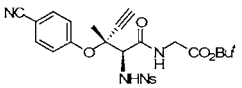
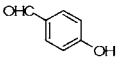
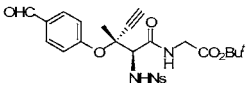
Table 2. Screening of Different Phenols in the Ethynyl Aziridine Ring-Opening Reaction



phenol	aziridine	product	yield
	**2**		41%
	**2**		42%
	**2**		39%
	**2**		39%
	**2**		9%
	**2**		10%
	**6**		64%
	**6**		55%
	**6**		59%
	**6**		77%
	**6**		60%
	**6**		71%

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Supporting Information Available: Experimental procedures and characterization data of aziridines **2** and **6** and tertiary alkyl-aryl ether products. This material is available free of charge via the Internet at http://pubs.acs.org.

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