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Functionalization of α,*β*-Unsaturated Esters and Ketones: A Facile and Highly Stereoselective One-Pot Approach to N-Protected α,*β*-Dehydroamino Acid Derivatives

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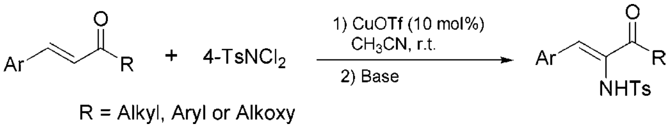
ABSTRACT



A new, facile, and highly stereoselective protocol toward α,*β*-dehydroamino acid derivatives has been developed. The one-pot synthesis was very convenient to perform by using the aminohalogenation reaction of α,*β*-unsaturated esters and ketones followed by treatment with specific bases. Only two [2.2.2] bicyclic organic bases were found to be effective for this transformation. Good yields (58–68%) and excellent *Z*-selectivity were obtained for 12 examples.

The functionalization of olefins has long served as an important tool in organic synthesis and medicinal chemistry.[1−3] Although great progress in this field has been made in the past decade, it continuously provides both academic and technological challenges. The amino functionalization of olefins, particularly the α-vinylic functionalization of α,*β*-unsaturated systems with amine groups, has not been well documented so far.

In the past several years, versatile electrophilic aminohalogenation, aziridination, and imidazolination (diamination) reactions of electron-deficient alkenes have been developed in our and other research groups using 4-TsNCl$_2$, 2-NsNCl$_2$, or related combinations as the electrophilic nitrogen sources.[4−8]

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By changing reaction conditions (catalyst, quenching reagent, temperature, etc.), a variety of building blocks such as diamines **1**,[5] aziridines **2**,[6] and vicinal haloamines **3**[4] can be synthesized stereo- and regioselectively from the same reaction system (Figure 1). In this communication, the application of this versatile reaction system to the synthesis of N-protected α,*β*-dehydroamino acid derivatives is presented. All of these products can serve as very useful precursors for organic synthesis. These reactions do not require the use of expensive reagents, and more importantly, they can be readily performed on a large scale.

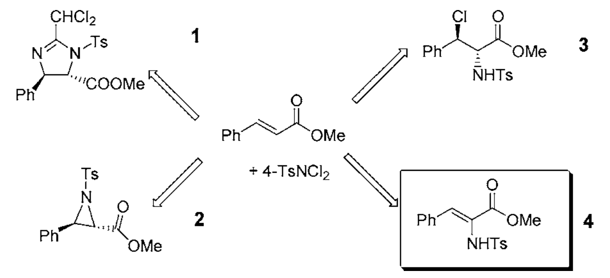
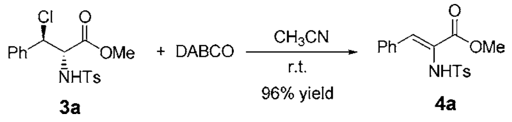


Figure 1. Functionalization of methyl cinnamate.

During the study of aziridine synthesis, we found that only a few common bases such as Et_3N and NH_4OH can efficiently convert vicinal haloamines into aziridines.[6]

Other organic bases were also tested for this system. Interestingly, when a bicyclic organic base, DABCO (1,4-diazobicyclic[2.2.2]octane), was added into the reaction mixture, a major side product was generated predominantly. This product was later determined to be N-protected α,*β*-dehydroamino acid derivative **4a** (Scheme 1), which was formed from elimination. This product was unambiguously determined by X-ray structural analysis and proven to be in *Z*-configuration. The resulting dehydroamino acids are important precursors to natural and unusual amino acids. They also exist in many biologically active natural products. In the past several decades, much work on the asymmetric hydrogenation of these compounds to give enantiomerically pure amino acids has been reported.[9,10]

Scheme 1



Several synthetic approaches to N-protected dehydroamino acids have been developed so far.[11] However, these known methods suffer from one or more of the following drawbacks: multiple-step preparation, harsh conditions, expensive reagents, or unsatisfactory yields. For example, expensive alkynoates and toxic phosphines are often needed for this synthesis (Scheme 2, eq 1).[11a] Vicinal amino alcohols are usually utilized for the two-step synthesis of dehydroamino acids (Scheme 2, eq 2).[11b] In comparison, the present method represents a simple, economic, and highly stereospecfic one-pot synthetic approach to N-protected dehydroamino acid derivatives. Furthermore, the reaction is very convenient to perform under mild conditions, as shown in the reaction procedure.

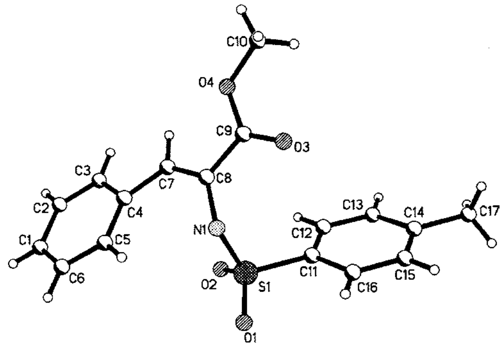
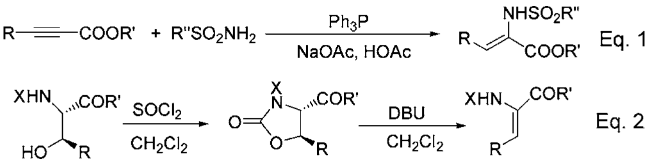


Figure 2. X-ray crystallography for **4a**.

Scheme 2



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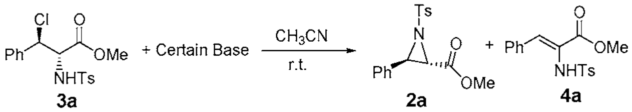
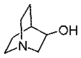
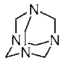
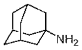
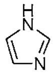
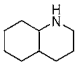
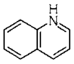
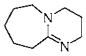
Different bases were tested for their effects on vicinal haloamine **3a**. The results are listed in Table 1.

Table 1. Effects of Bases on Elimination of Vicinal Haloamine **3a**

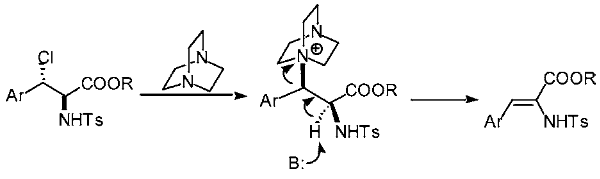


base	product 2a	 4a
	Not observed	Complete conversion
	Not observed	Complete conversion
	Only starting material observed	
	Only starting material observed	
	Only starting material observed	
	Only starting material observed	
	Only starting material observed	
	Complex mixture	
Et_3N	Complete conversion	Not observed
NH_4OH	Complete conversion	Not observed
HN(Pr-*i*)$_2$	Mostly converted	Not observed
NaOH	Only starting material observed	
t-BuOK	Only starting material observed	

As revealed in Table 1, only the two organic bases that have a [2.2.2] bicyclic ring and a bridgehead nitrogen can effectively promote the formation of dehydroamino acid product **4a** (entries 1 and 2, Table 1). Other bases gave either aziridine **2a** or no product at all. It seems that the nucleophilicity and structural characteristics of the [2.2.2] bicyclic amino bases play an important role in controlling the chemoselectivity.

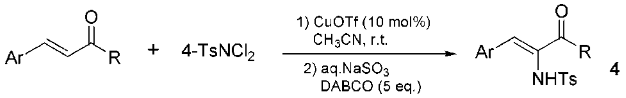
The mechanistic hypothesis is described in Scheme 3. The first step involves a typical S_N2 substitution reaction between the vicinal haloamine and DABCO to give the quaternary amine salt with syn stereoselectivity. The syn diamino intermediate is subjected to the elimination reaction by extra equivalents of base. The syn stereoselectivity of the first step can be explained by the complete control of the geometry of the resulting dehydroamino acid after the E2 elimination (Scheme 3).

Scheme 3



As shown in Scheme 1, nearly quantitative yield was obtained for the preparation of the dehydroamino acid by treating vicinal haloamine with DABCO. We then turned our attention to the more practical one-pot procedure directly starting from α,*β*-unsaturated esters and ketones. However, when we performed the aminochlorination of methyl cinnamate followed by the in situ treatment of the resulting haloamine product with DABCO (2.0 equiv) without quenching with aqueous Na_2SO_3 solution, only a small amount of dehydroamino acid was observed as revealed by the crude ^1H NMR analysis. It was then found that the formation of the dehydroamino acid derivative was increased by quenching with aqueous Na_2SO_3 at first and then by adding the same amount of DABCO (2.0 equiv). Fortunately, when a large excess of DABCO (5.0 equiv) was added into the quenched reaction mixture, this one-pot transformation proceeded to completion within 30 min with the results listed in Table 2.[12]

Table 2. One-Pot Synthesis of Dehydroamino Acid Derivatives



entry	Ar	R	protecting group	product	yield (%)[a]
1	Ph−	−OMe	4-Ts−	**4a**	66
2	Ph−	−OPr-*i*	4-Ts−	**4b**	73
3	Ph−	$-OCH_2Ph$	4-Ts−	**4c**	67
4	4-Cl-Ph−	−OMe	4-Ts−	**4d**	67
5	4-F-Ph−	−OMe	4-Ts−	**4e**	66
6	4-Me-Ph−	−OMe	4-Ts−	**4f**	62
7	4-O_2N-Ph−	−OMe	4-Ts−	**4g**	65[b]
8	Ph−	−OMe	4-Bs−	**4h**	64
9	Ph−	−OMe	2-Ns−	**4i**	68
10	Ph−	−Ph	4-Ts−	**4j**	58
11	Ph−	−Ph-F-4	4-Ts−	**4k**	61
12	Ph−	−Me	4-Ts−	**4l**	66

[a] Isolated yield after column chromatography. [b] After the recovery of remaining staring material.

As shown in Table 2, α,*β*-dehydroamino acid derivatives **4a−l** were obtained with chemical yields ranging from 58

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(12) Typical procedure of the one-pot synthesis of α,*β*-dehydroamino acids: Into a dry, capped vial were added α,*β*-unsaturated substrate (1 mmol), copper(I) trifluoromethanesulfonate (CuOTf) benzene complex (50.3 mg, 0.1 mmol, 10 mol %), 4 Å molecular sieves (500 mg), and freshly distilled CH_3CN 2 mL. 4-$TsNCl_2$ (360 mg, 1.5 mmol) was dissolved in 4 mL of newly distilled CH_3CN, and then the resulting solution was introduced into the reaction vial via a syringe pump over a period of 30 min. The resulting solution was stirred at room temperature and monitored by TLC determination. Upon completion, the reaction was quenched with 1.0 mL of saturated aqueous Na_2SO_3 solution followed by DABCO (5.0 mmol). The resulting system was stirred for 30 min at room temperature. The phase was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine and dried with anhydrous sodium sulfate. Purification by flash chromatography (EtOAc/hexane, v/v, 1/4) provided the pure product.

to 73%. The geometry of the products was completely controlled. In fact, for all cases that were examined, only the (*Z*)-isomers were observed as revealed by the crude ^{1}H NMR analysis. The substitutions on the aromatic rings have no obvious effects on either chemical yields or reaction rates. Other nitrogen sources such as $BsNCl_2$ and 2-$NsNCl_2$ resulted in similar results for two cases examined (entries 8 and 9 in Table 2). Besides α,*β*-unsaturated esters, α,*β*-unsaturated ketones can also be utilized as the substrates for this functionalization to give similar chemical yields and excellent stereoselectivity (entries 10−12).

So far, aliphatic α,*β*-unsaturated esters/ketones have not been successfully employed as the substrate for this synthesis. Further study will be carried out to extend the substrate scope for both alkene substrates and nitrogen sources, including $BnOCNCl_2$, $EtOCONCl_2$, and $AcNCl_2$.

In summary, an economic and convenient procedure for the synthesis of α,*β*-dehydroamino acid derivatives directly from α,*β*-unsaturated esters and ketones has been developed. Good yields and excellent *Z*/*E*-stereoselectivity were achieved under mild conditions. To the best of our knowledge, this is the first practical sulfonylamino functionalization of α,*β*-unsaturated esters. This method is suitable for large-scale synthesis.

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Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR) and X-ray crystallographic data for **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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