

Tandem Asymmetric Aza-Darzens/Ring-Opening Reactions: Dual Functionality from the Silane Lewis Acid

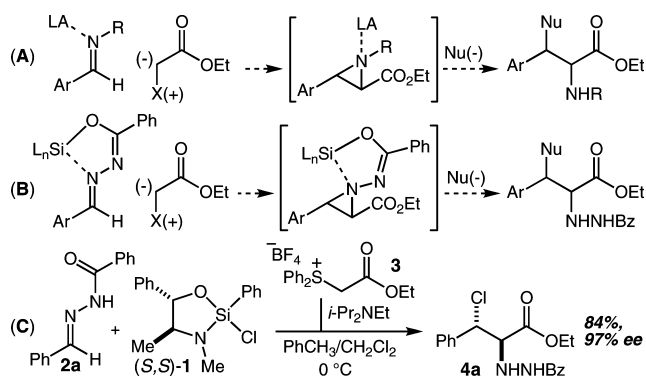
S. Corey Valdez and James L. Leighton*

Department of Chemistry, Columbia University, New York, New York 10027

Received August 5, 2009; E-mail: leighton@chem.columbia.edu

The asymmetric synthesis of aziridines has received a significant amount of attention,¹ primarily because of their utility in ring-opening reactions.² These two processes are typically staged sequentially, and we wondered whether they might instead be orchestrated in an efficient and step-economical tandem reaction sequence. The asymmetric aza-Darzens reaction^{3,4} seemed especially relevant in this regard because it seemed plausible that the Lewis acid (LA) that serves to activate the imine might further serve to activate the aziridine toward ring-opening nucleophilic attack (Scheme 1A). Our chiral silane Lewis acid–acylhydrazone platform has been shown to be effective for a range of nucleophilic addition reactions,⁵ and we speculated that it might also be effective in promoting aza-Darzens reactions and subsequent ring-opening reactions (Scheme 1B). Exploratory reactions were carried out with silane (S,S)-1 and hydrazone 2a. Whereas ethyl diazoacetate was unreactive toward the silane–hydrazone complex, treatment with the stabilized ylide derived from sulfonium salt 3⁶ and Hunig's base led not to the aziridine but rather to ring-opened product 4a (Scheme 1C). Upon optimization, this reaction was quite effective, giving 4a in 84% yield as a single regioisomer and diastereomer ($\geq 20:1$ rr and dr) in 97% ee. The aziridine is thus clearly formed in the reaction, but it is still complexed to and activated by the silane Lewis acid and undergoes a highly regio- and diastereoselective ring-opening reaction in the presence of the chloride ion that is liberated in the silane–hydrazone complexation process. The reaction may thus be considered as a tandem aza-Darzens/ring-opening reaction in which the silane Lewis acid performs two distinct functions as well as a simple synthetic equivalent of and alternative to alkene aminohalogenation reactions.⁷

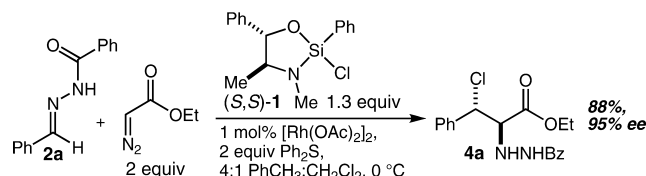
Scheme 1



The synthesis of sulfonium salt 3 requires the use of stoichiometric amounts of AgBF_4 and takes several days. We therefore investigated whether it might be possible to adapt the procedure of Aggarwal whereby the ylide is generated in situ by the rhodium-catalyzed reaction of a sulfide with a diazo ester.⁸ Indeed, the combination of Ph_2S (2 equiv) and ethyl diazoacetate (2 equiv) in the presence of 1 mol % $[\text{Rh}(\text{OAc})_2]_2$ generates the ylide derived from 3 in situ, and this

procedure is fully compatible with the silane–hydrazone complex (Scheme 2). After optimization, the product 4a was obtained in 88% yield and 95% ee. In principle, the sulfide may be used in substoichiometric amounts, but in this case, that procedure led to extensive dimerization of the ethyl diazoacetate. This is nevertheless a simple and reliable procedure that employs inexpensive and readily available starting materials, and we have found it to be preferable to the procedure described in Scheme 1C.

Scheme 2



With optimal conditions identified, an examination of the scope of the reaction was carried out (Table 1). Substituted benzaldehyde-derived hydrazones (2a–i) were employed, and in every case the reactions proceeded smoothly, delivering the products 4a–i in good yield. In some cases, a significant amount of a minor regioisomeric product (α -chloro- β -hydrazido ester) was formed, while in most cases the major product was formed with excellent levels of enantioselectivity.

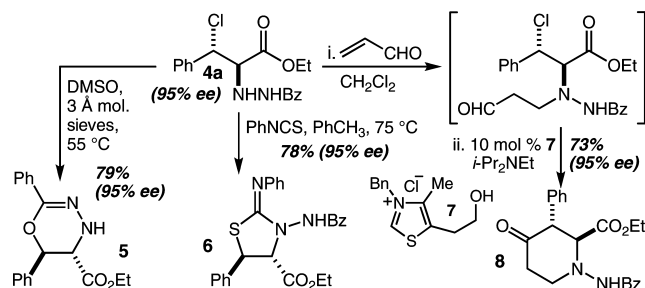
Table 1. One-Pot Aza-Darzens/Ring-Opening Reactions with (S,S)-1

entry	Ar	yield (%)	rr	ee (%)
1	Ph (a)	88	$\geq 20:1$	95
2	<i>p</i> -Br-C ₆ H ₄ (b)	85	17:1	91
3	<i>p</i> -F-C ₆ H ₄ (c)	81	11:1	92
4	<i>p</i> -NO ₂ -C ₆ H ₄ (d)	82	6:1	94
5	<i>p</i> -CF ₃ -C ₆ H ₄ (e)	83	9:1	97
6	<i>p</i> -CH ₃ -C ₆ H ₄ (f)	76	$\geq 20:1$	94
7	<i>o</i> -Br-C ₆ H ₄ (g)	81	6:1	86
8	<i>o</i> -CH ₃ -C ₆ H ₄ (h)	84	10:1	93
9	1-naphthyl (i)	82	7:1	89

β -Chloro- α -hydrazido esters 4 are arguably primarily of interest as an entry into unusual α -amino acid derivatives by way of nucleophilic substitution reactions. For example, simply heating 4a in DMSO at 55 °C led to the isolation of 5, a β -hydroxy- α -hydrazido ester derivative, in 79% yield with complete retention of optical purity (Scheme 3). Similarly, treatment of 4a with phenyl isothiocyanate gave 2-(phenylimino)thiazolidine 6 in 78% yield. While many other versions of processes such as these with heteroatom nucleophiles may be imagined, the use of carbon nucleophiles was of interest as well. Toward that end, 4a was treated

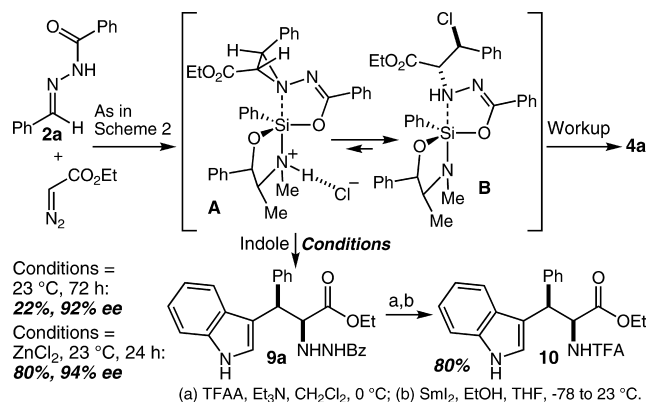
with acrolein followed by 10 mol % thiazolium salt **7** and Hunig's base. This one-pot procedure produced piperidone derivative **8** in 73% yield.⁹ Compounds **5**, **6**, and **8**, representing a diverse set of densely functionalized heterocycles, are thus readily accessible in just two straightforward steps.

Scheme 3



To more fully exploit the ability of the silane Lewis acid to promote both the aza-Darzens reaction and subsequent ring-opening reactions, the addition of electron-rich arenes was investigated in order to develop a single-step synthesis of diarylalanine derivatives.^{10,11} When the reaction shown in Scheme 2 was repeated and indole was then added (and the resulting mixture stirred for 3 days), **9a** was isolated in 22% yield and 92% ee (Scheme 4). Although inefficient, this reaction and its diastereochemical outcome clearly implied that the conversion of aziridine intermediate **A** into initial product **B** is reversible and that the silane is competent to activate the aziridine toward attack of the indole. On the basis of the hypothesis that the conversion of **B** to **A** is rate-limiting, exogenous Lewis acids were screened in the hope of accelerating this process. Eventually, it was found that ZnCl_2 was particularly effective, leading to **9a** in 80% yield and 94% ee. With an effective synthesis of **9a** in hand, its two-step conversion into protected amino acid **10** was demonstrated.¹²

Scheme 4



The results of a brief survey of the scope of this process are compiled in Table 2. Substitution on the indole was tolerated (entries 2 and 3), as was the use of dimethylaniline nucleophiles (entries 4 and 5) and substitution on Ar^1 (entry 6). While the efficiency of these reactions ranged from moderate to good (50–80% yields), in every case the product was obtained as a single regioisomer and diastereomer with excellent enantioselectivity.

We have developed an efficient and highly enantioselective aza-Darzens-like reaction wherein the chiral silane Lewis acid further activates the initially formed aziridine toward ring-opening reactions with either chloride or arene nucleophiles to deliver complex amino acid derivatives in a simple one-pot process. Current efforts are focused on expanding the scope of the process.

Table 2. One-Pot Aza-Darzens/Ring-Opening Reactions with Arenes

entry	Ar^1	Ar^2	yield (%)	ee (%)
1	Ph	3-indolyl (a)	80	94
2	Ph	5-Br-3-indolyl (b)	68	92
3	Ph	5-MeO-3-indolyl (c)	74	92
4	Ph	<i>p</i> -Me ₂ N-C ₆ H ₄ (d)	65	92
5	Ph	2-MeO-4-Me ₂ N-C ₆ H ₃ (e)	50	92
6	<i>p</i> -CF ₃ -C ₆ H ₄	3-indolyl (f)	56	91

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Supporting Information Available: Experimental procedures, characterization data, stereochemical proofs, and CIF files for **4a**, **5**, and **9b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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