J|A|C|S COMMUNICATIONS

Published on Web 09/24/2009

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

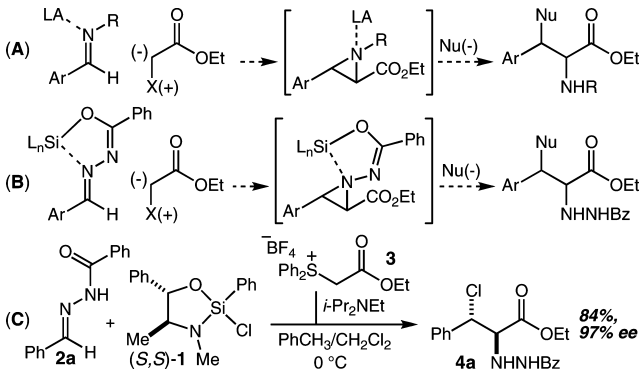
S. Corey Valdez and James L. Leighton*

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

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

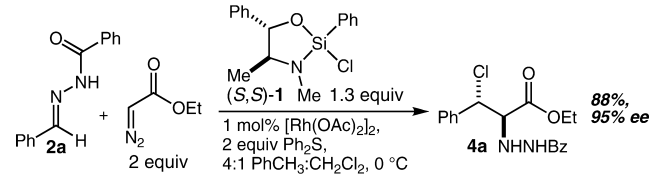
The asymmetric synthesis of aziridines has received a significant amount of attention,[1] primarily because of their utility in ring-opening reactions.[2] These two processes are typically staged sequentially, and we wondered whether they might instead be orchestrated in an efficient and step-economical 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 **3**[6] 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 (≥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



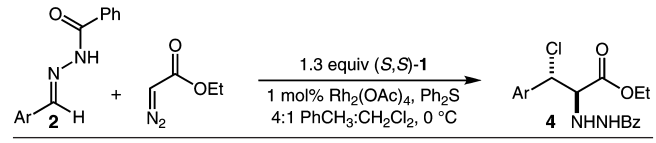
The synthesis of sulfonium salt **3** requires the use of stoichiometric amounts of $AgBF_4$ and takes several days. We therefore investigated whether it might be possible to adapt the procedure of Aggarwal whereby the ylide is generated in situ by the rhodium-catalyzed reaction of a sulfide with a diazo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



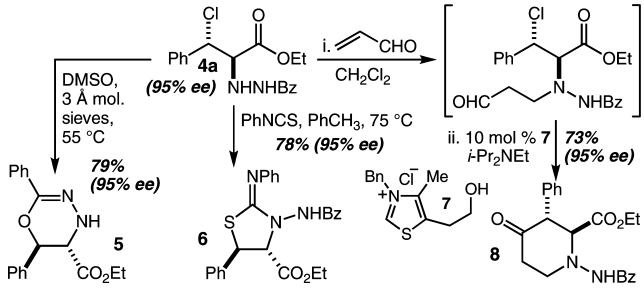
entry	Ar	yield (%)	rr	ee (%)
1	Ph (**a**)	88	≥20:1	95
2	*p*-Br-C_6H_4 (**b**)	85	17:1	91
3	*p*-F-C_6H_4 (**c**)	81	11:1	92
4	*p*-NO_2-C_6H_4 (**d**)	82	6:1	94
5	*p*-CF_3-C_6H_4 (**e**)	83	9:1	97
6	*p*-CH_3-C_6H_4 (**f**)	76	≥20:1	94
7	*o*-Br-C_6H_4 (**g**)	81	6:1	86
8	*o*-CH_3-C_6H_4 (**h**)	84	10:1	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

10.1021/ja9066354 CCC: $40.75

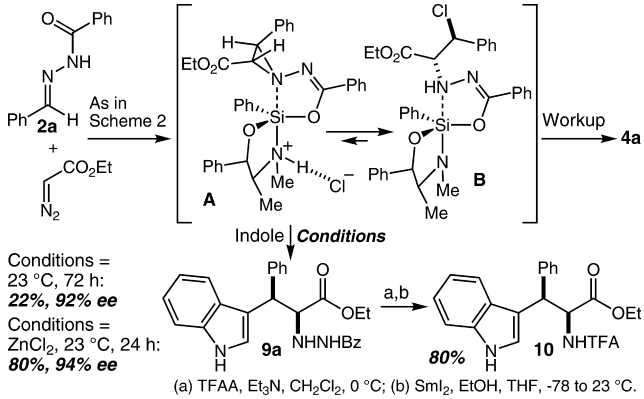
with acrolein followed by 10 mol % thiazolium salt **7** and Hunig's base. This one-pot procedure produced piperidone derivative **8** in 73% yield.[9] Compounds **5**, **6**, and **8**, representing a diverse set of densely functionalized heterocycles, are thus readily accessible in just two straightforward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

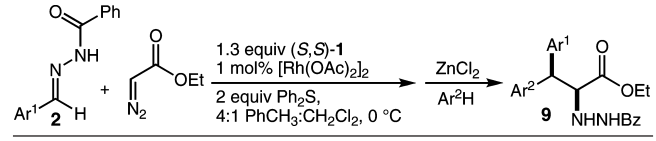
Scheme 4



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	*p*-Me_2N-C_6H_4 (**d**)	65	92
5	Ph	2-MeO-4-Me_2N-C_6H_3 (**e**)	50	92
6	*p*-CF_3-C_6H_4	3-indolyl (**f**)	56	91

Acknowledgment. This work was supported by a grant (CHE-0809659) from the National Science Foundation. S.C.V. is a National Science Foundation Graduate Research Fellow. We thank Prof. G. F. R. Parkin and Mr. Kevin Yurkerwich for X-ray structure analyses (see the Supporting Information), and the National Science Foundation (CHE-06-19638) is thanked for the acquisition of an X-ray diffractometer.

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.

References

(1) (a) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 607. (b) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

(2) (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (c) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (d) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (e) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (f) Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979.

(3) For the chiral Lewis acid-catalyzed addition of diazo esters to imines, see: (a) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099. (b) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518. (c) Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7185. (d) Zhang, Y.; Desai, A.; Lu, Z.; Hu, G.; Ding, Z.; Wulff, W. D. *Chem.—Eur. J.* **2008**, *14*, 3785.

(4) For the chiral Brønsted acid-catalyzed addition of diazo amides to imines, see: Hashimoto, T.; Uchiyama, N.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 14380.

(5) (a) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686. (b) Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858. (c) Shirakawa, S.; Lombardi, P. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 9974. (d) Notte, G. T.; Leighton, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 6676.

(6) (a) Nozaki, H.; Tunemoto, D.; Matubara, S.; Konda, K. *Tetrahedron* **1967**, *23*, 545. (b) Müller, P.; Fernandez, D.; Nury, P.; Rossier, J.-C. *Helv. Chim. Acta* **1999**, *82*, 935.

(7) For asymmetric (chiral-auxiliary-controlled) alkene aminohalogenation reactions, see: (a) Xu, X.; Kotti, S. R. S. S.; Liu, J.; Cannon, J. F.; Headley, A. D.; Li, G. *Org. Lett.* **2004**, *6*, 4881. (b) Wang, Y.-N.; Kattuboina, A.; Ai, T.; Banerjee, D.; Li, G. *Tetrahedron Lett.* **2007**, *48*, 7894.

(8) (a) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368. (b) Aggarwal, V. K.; Ferrara, M.; O'Brien, C. J.; Thompson, A.; Jones, R. V. H.; Fieldhouse, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1635.

(9) This reaction appears to be the first example of N-heterocyclic carbene (NHC)-catalyzed alkylation with a secondary electrophile (and thus the first with stereochemical consequences). For a report on an NHC-catalyzed alkylation reaction with primary alkyl tosylates, see: He, J.; Zheng, J.; Liu, J.; She, X.; Pan, X. *Org. Lett.* **2006**, *8*, 4637.

(10) Lin, J.; Liao, S.; Hruby, V. J. *J. Pept. Res.* **2005**, *65*, 105.

(11) For examples of the Lewis acid-promoted opening of aziridines with electron-rich arenes, see: (a) Sato, K.; Kozikowski, A. P. *Tetrahedron Lett.* **1989**, *30*, 4073. (b) Dubois, L.; Mehta, A.; Tourette, E.; Dodd, R. H. *J. Org. Chem.* **1994**, *59*, 434. (c) Bennani, Y. L.; Zhu, G.-D.; Freeman, J. C. *Synlett* **1998**, 754. (d) Nishikawa, T.; Kajii, S.; Wada, K.; Ishikawa, M.; Isobe, M. *Synthesis* **2002**, 1658. (e) Manaka, T.; Nagayama, S.-I.; Desadee, W.; Yajima, N.; Kumamoto, T.; Watanabe, T.; Ishikawa, T.; Kawahata, M.; Yamaguchi, K. *Helv. Chim. Acta* **2007**, *90*, 128.

(12) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637.

JA9066354