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SmI_2-Mediated Cross-Coupling of Nitrones with β-Silyl Acrylates: Synthesis of (+)-Australine

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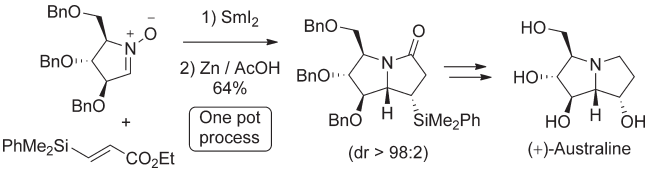
ABSTRACT



The SmI_2-mediated cross-coupling of nitrones with β-silyl-α,β-unsaturated esters, followed by zinc reduction, allows an efficient and highly diastereoselective preparation of β-silyl lactams, which are precursors of β-hydroxy lactams through Tamao–Fleming oxidation. By applying the method to a cyclic, carbohydrate-derived nitrone, a new synthesis of (+)-australine has been realized in only 11 steps and in 21% overall yield from L-xylose.

Since its introduction in 1977, samarium diiodide has become a useful reagent for the reduction of a wide range of organic functions and for stereoselective formation of carbon–carbon bonds.[1] A few years ago, the SmI_2-mediated cross-coupling of nitrones with α,β-unsaturated esters was reported[2] and has since proved useful for elaboration of the bicyclic skeleton of pyrrolizidine iminosugars, such as (+)-hyacinthacine A_2.[3] Recently, we have become interested in designing syntheses of other naturally occurring pyrrolizidines, especially those bearing hydroxyl groups in position 6 and/or 7 (Figure 1).

The introduction of a hydroxyl group in position 7 of pyrrolizidines was first attempted through reductive cross-coupling of nitrone **1** with α,β-unsaturated esters bearing an oxygen atom in the β position. However, treatment of

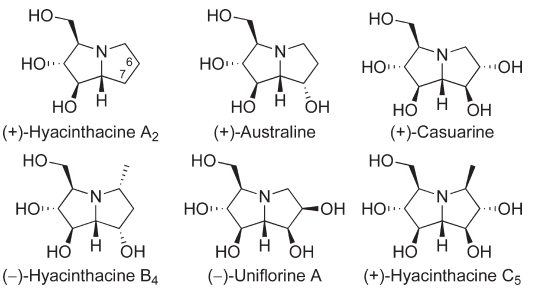


Figure 1. Natural polyhydroxylated pyrrolizidines.

nitrone **1** and ethyl (*E*)-3-trimethylsilyloxypropenoate[4] (**2**) with SmI_2 in the presence of water[3a] did not provide the expected cross-coupled product, but *N*-hydroxy-pyrrolidine **3**, resulting from the reduction of the starting nitrone (Scheme 1).

Although alkoxy-substituted captodative olefins have been used as Michael acceptors for the synthesis of β-hydroxy-γ-lactones through SmI_2-mediated cross-coupling with ketones[5] and aldehydes,[6] the yields are often

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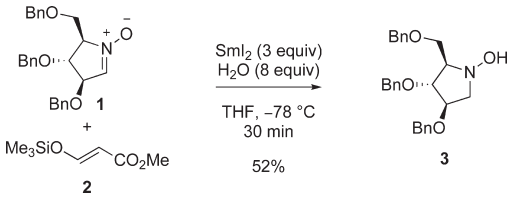
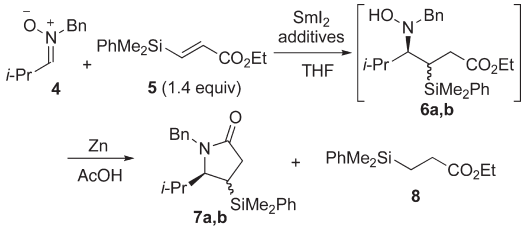
Scheme 1. Attempted Cross-Coupling of Nitrone **1** and Acrylate **2**



moderate in the case of *intermolecular* reactions. Probably due to electronic effects, β-alkoxy-esters are poor acceptors for nitrone conjugate addition reactions. In contrast, the SmI_2-mediated cross-coupling of nitrones with alkyl β-substituted α,β-unsaturated esters, such as methyl crotonate, afforded the expected coupling product in good yields and with excellent stereoselectivities.[2a,c] Carbon and silicon, being in the same column of the periodic table, present similar electronic properties.[7] We thus thought that the SmI_2-mediated cross-coupling of nitrones with β-silyl-substituted α,β-unsaturated esters could be more successful than with the alkoxy esters. The silyl group would then serve as a masked hydroxyl group, to be later revealed by Tamao−Fleming oxidation.[8] β-Silyl acrylates or acrylamides have already been used in conjugate addition reactions[9] but, to the best of our knowledge, never in a SmI_2-mediated cross-coupling reaction.[10] Here, we report the SmI_2-mediated cross-coupling of nitrones with a β-silyl acrylate and its application to the synthesis of (+)-australine.

In a preliminary assay, nitrone **4**[11] and ethyl (*E*)-3-(dimethylphenylsilyl)propenoate (**5**)[12] in the presence of water (8 equiv) at −78 °C were treated with SmI_2. Through coordination to SmI_2, water forms a more reactive species, often allowing faster reactions and better yields.[13] Under these conditions, the desired *N*-hydroxylamines **6a,b** were obtained, but proved to be relatively unstable in air. Fortunately, a direct, single-pot reduction of the reaction product using Zn/AcOH[14] afforded the lactams **7a,b** in 51% yield and in a 90/10 *cis*/*trans*[15] ratio (Table 1, entry 1), accompanied by the β-silylpropanoate **8**,[16] arising from reduction of **5** (35%).

Table 1. SmI_2-Mediated Cross-Coupling of Nitrone **4** and Acrylate **5**



entry	SmI_2 (equiv)	additives (equiv)	temp (°C)	time (h)	**7a,b** (yield %)	*cis*/*trans*[a]
1	3	H_2O (8)	−78	28	51	90/10
2	4	H_2O (8)	−78 to −30	0.1	53	90/10
3	4	H_2O/LiBr (8/12)	−78 to −30	0.1	84	>98/2

[a] Ratio determined by ^1H analysis of the crude reaction mixture.

Next, the same reagents were mixed at −78 °C and the cooling bath was removed at the end of SmI_2 addition. At a temperature of −30 °C (reached after 5 min), the starting nitrone was completely consumed. However, after zinc reduction of the intermediate *N*-hydroxylamines **6a,b**, lactams **7a,b** (90/10 *cis*/*trans* ratio) were isolated in a similar 53% yield (Table 1, entry 2). The introduction into the reaction mixture of LiBr[17] proved to be more rewarding. Indeed, with a combination of SmI_2 and H_2O/LiBr additives, only the *cis* lactam **7a** was formed and in an improved yield of 84% (Table 1, entry 3). Flowers has demonstrated that the addition of 12 equiv of LiBr to solutions of SmI_2 in THF provides a system with an oxidation potential of −1.98 V as compared with −1.33 V for SmI_2 alone vs the $Ag/AgNO_3$ reference electrode.[18] The increase in the reducing ability of the system may well account for the improvement in the reaction efficiency. Furthermore, introduction of the lithium cation seems to favor the formation of the *cis* lactam.

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(14) See Supporting Information.

(15) Relative configuration was determined by NOESY experiments. See Supporting Information.

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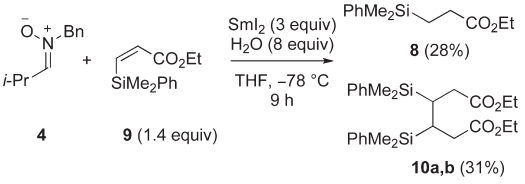
(18) Fuchs, J. R.; Mitchell, M. L.; Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 8157.

The cross-coupling of nitrone **4** was also considered with ethyl (*Z*)-3-(dimethylphenylsilyl)propenoate (**9**).[19] Surprisingly, at −78 °C and in the presence of water, no trace of *N*-hydroxyamino esters **6a,b** was detected (Scheme 2). The starting nitrone was mostly recovered (74%), while acrylate **9** was reduced to propanoate **8** (28%) and dimerized adipic acid derivatives **10a,b** (31%). These results suggest that acrylate **9** is reduced by SmI_2 faster than nitrone **4** (and than its *E*-isomer, **5**). This reduction competing with the formation of a (ketyl-type) radical anion from **4**[20] would thus hamper conjugate addition onto the unsaturated ester.[21]

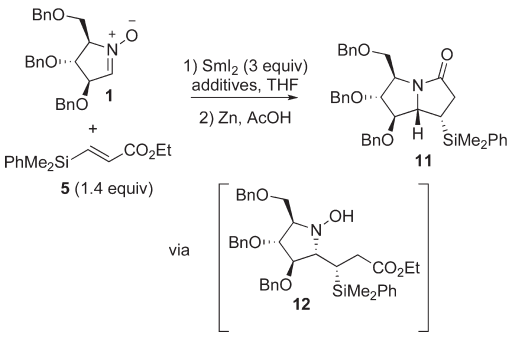
Scheme 2. Attempted Reaction of Nitrone **4** with *Z*-Acrylate **9**



Having in hand suitable reaction conditions for the coupling of nitrone **4** with **5**, we next turned to studying the reaction of this β-silyl acrylate with nitrone **1**,[3a] which exhibits an appropriate substitution pattern for the synthesis of the different alkaloids represented in Figure 1. When nitrone **1** was treated with acrylate **5** under the same conditions (Table 1, entry 3), lactam **11** was isolated in 49% yield as a single diastereomer (Table 2, entry 1). The intermediate *N*-hydroxypyrrolidine **12** could also be isolated in 49% yield and as a single diastereomer when the zinc reduction step was omitted.

With the aim of improving the efficiency of the reductive coupling step, various alternative proton sources were investigated, with a particular focus on the effect of their acidity. Indeed, the rate of SmI_2-mediated reduction of acetophenone has been shown to be proportional to the acidity of the proton source used as an additive.[22] The groups of Procter[23] and Nicolaou[24] have also demonstrated the role of the acidity of additives on the efficiency of C−C bond formation induced by SmI_2. In the presence of phenol (pK_a 9.9) or 2,4,6-trichlorophenol (pK_a 6.2), the yields of the expected lactam **11** were lower (or similar) than with water (Table 2, entries 2 and 3). On the other hand, use of the noncoordinating hexafluoroisopropanol (HFIP, pK_a 9.3) as the additive afforded improved efficiency in the coupling, with **11** being isolated in 64% yield (Table 2, entry 4). It is not clear how to rationalize the effect of HFIP, its pK_a being intermediate between those of the two phenols tested. Although the role of proton sources in such reactions has been extensively investigated, it is still not fully understood and acidity is certainly not the only parameter to consider.[25]

Table 2. Direct Preparation of Lactam **11**



entry	additives (equiv)	temp (°C)	time (h)	**11** (%)	dr[a]
1	H_2O/LiBr (8/12)	−78 to −30	0.1	49	>98/2
2	PhOH/LiBr (8/12)	−78 to −30	0.1	32	>98/2
3	2,4,6-triCl-PhOH/LiBr (8/12)	−78 to −30	0.1	50	>98/2
4	HFIP/LiBr (8/12)	−78 to −30	0.1	64	>98/2

[a] Only one diastereomer was detected by ^1H NMR analysis of the crude reaction mixture.

The configuration of the new stereocenters in **11** was determined to be S at both C-7 and C-7a from NOESY correlations.[14] The approach of the β-silyl acrylate by the *Re* face of nitrone **1** is directed by the substituents of the nitrone (at C-1 and C-3 in the product).[3a] Remarkably, the configuration of the silylated stereocenter is also completely controlled in this SmI_2-mediated cross-coupling reaction. Such control may be explained by a favored chelated transition state **A**, similar to those proposed in Heathcock's model for conjugate addition of *E*-enolates on β-substituted acrylic esters (Scheme 3).[26]

Pyrrolizidinone **11** is thus a possible precursor of (+)-australine, a polyhydroxylated pyrrolizidine isolated from

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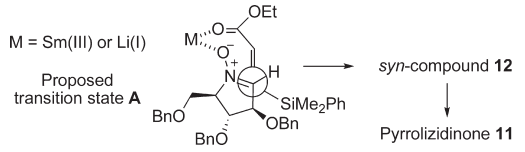
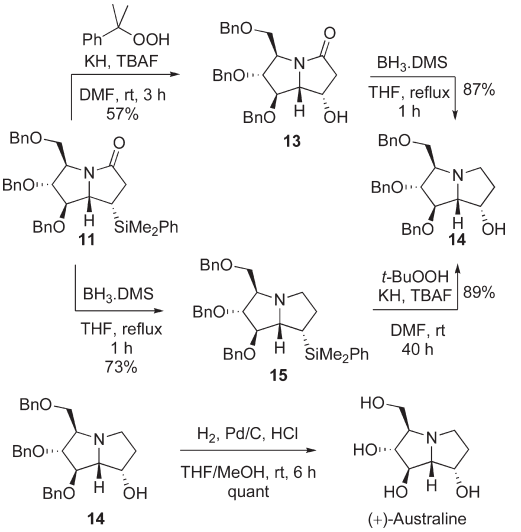
Scheme 3. Possible Transition State for the SmI_2-Promoted Reductive Coupling of Nitrone **1** and Acrylate **5**



the seeds of *Castanospermum australe*.[27] This natural product has attracted the interest of chemists because it not only alters amyloglucosidase activity[28] but also possesses a structure exhibiting five contiguous stereogenic centers, which represents a synthetic challenge.[29]

When the Tamao−Fleming oxidation of pyrrolizidinone **11** was first carried out under acidic (HBF_4•OEt_2 in DCM, then H_2O_2, KF in DMF) or electrophilic (Br_2 and AcO_2H) conditions, decomposition of the starting material was observed. The protocol reported by Woerpel for silyl group oxidation under basic conditions was proved more successful:[30] pyrrolizidinone **11** was treated with potassium hydride, TBAF, and cumene hydroperoxide. Pyrrolizidinone **13**, obtained in moderate yield (57%), was reduced by a BH_3•DMS complex to give pyrrolizidine **14** (Scheme 4).[31] The use of cumene hydroperoxide, instead of *tert*-butyl hydroperoxide, reportly avoids desilylation.[32] Finally, it was found that reduction of pyrrolizidinone **11** to pyrrolizidine **15** prior to Tamao−Fleming oxidation gave a better overall yield (65% vs 50% for the first sequence). Deprotection of the hydroxyl groups was then accomplished by hydrogenolysis to afford quantitatively (+)-australine. The spectroscopic data and optical rotation of our synthetic sample of (+)-australine were in accordance with those previously reported for the natural substance ($[\alpha]^{20}_D$ = 17.1 (*c* 2.9, MeOH); lit.: $[\alpha]^{20}_D$ = 18.6 (*c* 2.5, MeOH)).[29b]

Scheme 4. Synthesis of (+)-Australine



In conclusion, we have shown that the β-silyl acrylate **5** is an excellent partner for the SmI_2-mediated *intermolecular* cross-coupling of nitrones, one that is capable of yielding β-silyl γ-amino acid derivatives or β-silyl γ-lactams with nearly complete diastereoselection. Through the use of this new cross-coupling, (+)-australine could be obtained in 11 steps and with an overall yield of 21% from L-xylose. This methodology should be useful for the synthesis of other polyhydroxylated pyrrolizidines.

Acknowledgment. P.G. is grateful to the Ministère de l'Enseignement Supérieur et de la Recherche for a doctoral fellowship.

Supporting Information Available. Characterization data, full experimental procedures, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.