One-pot cross-coupling of *N*-acyl *N,O*-acetals with α,β-unsaturated compounds†

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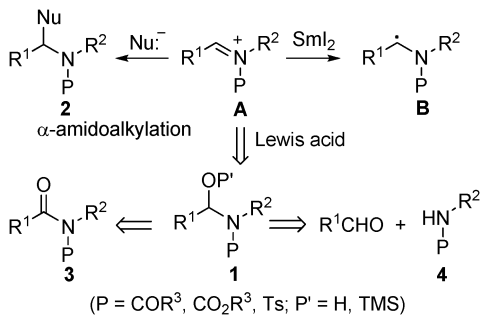
The synergistic action of $BF_3{\cdot}OEt_2$ and SmI_2 allowed a series of intermolecular cross-couplings of readily available *N*-acyl *N,O*-acetals with α,β-unsaturated compounds to be performed in high yields, which was applied to the stereoselective synthesis of pyrrolizidine alkaloid (+)-xenovenine.

After the Mannich reaction,[1] the *N*-acyliminium ion (**A**)-based α-amidoalkylation reaction[2] is probably the most powerful methodology for carbon–carbon bond formation at the *N*-α-carbon[3,4] (Scheme 1, **A** to **2**). The versatility of this methodology is due to both the high reactivity and ready availability of a variety of *N*-acyliminium ions from *N*-acyl *N,O*-acetal precursors **1**. The latter are, in turn, readily available by a number of methods,[2] such as the partial reduction of imides **3**,[5] condensation of carbonyl compounds with carbamates/amides **4**,[6a,b] and so on.[6c] One of the most recent developments in these areas is the one-pot C–C bond formation starting from amines[7] or carbamates.[8] In the light of these developments, we assumed that *N*-acyl *N,O*-acetals **1** could serve as versatile precursors of acylaminoalkyl radicals[9] **B**, *via* *N*-acyliminium ions **A**, for one-pot C–C bond formation (Scheme 1). In connection with our research on the development of synthetic methodologies based on the use of *N*-acyliminium ions,[10] *N*-α-carbanions,[11] and SmI_2,[12] we have undertaken



Scheme 1 *N*-Acyl *N,O*-acetal initiated C–C formation methods.

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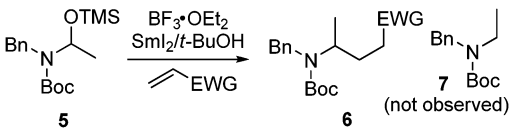
Table 1 SmI_2-mediated reductive coupling of *N,O*-acetal TMS ether **5** with α,β-unsaturated compounds



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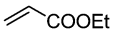
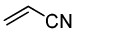
Entry	α,β-Unsaturated compound	Product (% yield)[a]
1		**6a** (72)
2		**6b** (78)
3		**6c** (73)

[a] Isolated yield.

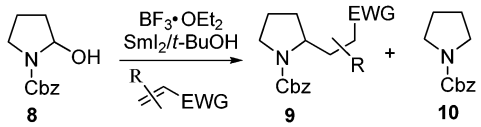
a study on the one-pot Lewis acid and SmI_2-mediated cross-coupling of *N*-acyl *N,O*-acetals with α,β-unsaturated compounds, and wish to report the results herein.

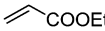
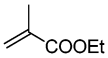
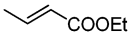
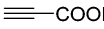
Our initial efforts were focused on exploring $BF_3{\cdot}OEt_2$ and samarium(II) diiodide-mediated[13] reductive coupling of the known and readily-available *N*-carbamoyl *N,O*-acetal TMS ether **5**,[5a] with ethyl acrylate (Table 1). After extensive investigations, we found that treatment of a mixture of ethyl acrylate (2 equiv.), *N,O*-acetal TMS ether **5** (1 equiv.) and $BF_3{\cdot}OEt_2$ (2 equiv.) with a freshly prepared *t*-BuOH-containing (4 equiv.) SmI_2 solution (4 molar equiv.) in THF at −40 °C, followed by stirring at −40 °C for 5 min, afforded the desired coupling product **6a** in 72% yield (Table 1, entry 1).[14] No reduced product **7** was observed. The reaction with α,β-unsaturated compounds such as *t*-butyl acrylate and acrylonitrile also produced the corresponding coupled products **6b** and **6c** in similar yield (Table 1, entries 2 and 3).

Encouraged by these results, the cross-coupling reaction of *N*-benzyloxycarbonyl-2-hydroxypyrrolidine **8** was investigated. Under the above mentioned optimized conditions, the reaction of ethyl acrylate (2 equiv.) with **8** afforded the desired coupling product **9a** in 76% yield (Table 2, entry 1). The reaction was extended to a variety of α,β-unsaturated compounds and similar results were obtained, displayed in Table 2.

To confirm the formation of the α-acylaminoalkyl radical intermediate,[8] the reaction of *N*-carbamoyl *N,O*-acetal **8** was performed in the absence of an α,β-unsaturated compound. As anticipated, the homo-coupling product **11** (Fig. 1) was obtained as a mixture of diastereomers in 24% yield, along with 74% of the reduction product **10** (Table 2, entry 7).

Table 2 SmI_2-mediated cross-coupling of *N*,*O*-acetal **8** with α,β-unsaturated compounds



Entry	α,β-Unsaturated compound	Product **9** (% yield) (d.r.) and **10** (% yield)[a]
1		**9a** (76)
2		**9b** (67)
3		**9c** (79)
4		**9d** (84) (70:30)[b]
5		**9e** (52) (51:49);[b] **10** (19)
6		**9f** (88) (*Z*:*E* = 58:42)
7	none	**11** (24) (50:50); **10** (74)

[a] Isolated yield. [b] Determined by HPLC.

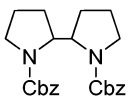


Fig. 1 Homo-coupling product **11**.

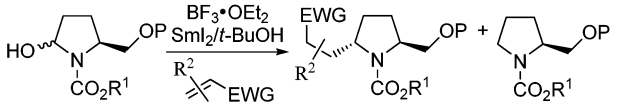
Subsequently, we examined the cross-coupling of *N*-carbamoyl *N*,*O*-acetals **12a–c**, derived from (*S*)-pyroglutamic acid, with α,β-unsaturated compounds, with results summarized in Table 3. As can be seen, the coupling reactions proceeded smoothly, with both the *N*- and *O*-protecting groups showing an effect on the diastereoselectivity of the reaction. The use of more sterically hindered TBDPS as the *O*-protecting group gave excellent *trans*-diastereoselectivities (Table 3, entries, 3–8).

With the dual aim of confirming the stereoselectivity of the reaction and demonstrating the synthetic value of the method, we undertook the synthesis of pyrrolizidine alkaloid (+)-xenovenine[15] (**22**) (Scheme 2). The diastereomeric mixture **16b** was treated with TBAF to give the desilylated product **17** and its diastereomer. To our delight, the two diastereomeric products were separable by flash chromatography. Iodination of the major diastereomer **17** (I_2, Ph_3P, imidazole) gave the desired iodide **18**, which was reduced (H_2, 10% Pd/C) to afford the pyrrolidine **19**. Conversion of ester **19** into the Weinreb amide **20** (Me_3Al, HN(OMe)Me·HCl)[16] followed by treatment with *n*-heptyl magnesium bromide led to the formation of (2*S*,5*R*)-**21**. Finally successive *N*-deprotection and intramolecular reductive amination yielded (+)-xenovenine (**22**).[15] These results confirmed that the cross-coupling reaction (Table 3) is 2,5-*trans*-diastereoselective.

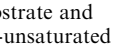
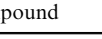
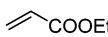
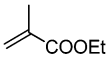
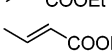
In summary, we have demonstrated that the one-pot reductive cross coupling of *N*-carbamoyl *N*,*O*-acetals **5**, **8**, and **12** with α,β-unsaturated compounds can be conveniently and efficiently achieved by synergistic action of both Lewis acid BF_3·OEt_2 and SmI_2*via* *N*-acyliminium ion and α-acylamino-alkyl radical intermediates. The ready availability of the *N*-acyl *N*,*O*-acetals renders this C–C bond formation method both efficient and versatile for the synthesis of a variety of cyclic and alicyclic *N*-containing compounds in either a racemic or enantioselective manner. The reaction of the pyroglutamic acid derived *N*-carbamoyl *N*,*O*-acetal **12c** exhibited excellent 2,5-*trans*-diastereoselectivity, which was applied to the total synthesis of the ant venom alkaloid (+)-xenovenine. Extension of this method to one-pot coupling of *N*-acyl *N*,*O*-acetals with other electrophiles such as aldehydes is in progress in our laboratory, and will be reported in due course.

The authors are grateful to the NSF of China (20402012; 20832005), the National Basic Research Program (973 Program) of China (Grant No. 2010CB833206), and the Program for New Century Excellent Talents in Xiamen University for financial support.

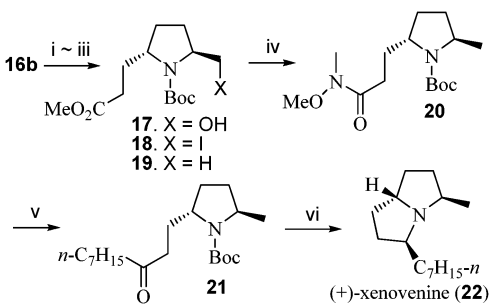
Table 3 SmI_2-mediated cross-coupling of *N*,*O*-acetals **12a–c** with α,β-unsaturated compounds



12a. P = TBS; R^1 = *t*-Bu
12b. P = TBS; R^1 = Bn
12c. P = TBDPS; R^1 = *t*-Bu

Entry	Substrate and α,β-unsaturated compound	Product (% yield) (*trans* : *cis* ratio and/or d.r.) and **14** (% yield)
1	**12a**, 	**13** (67) (69 : 31):[a] **14a** (5)
2	**12b**, 	**15** (62) (90 : 10)[b]
3	**12c**, 	**16a** (73) (91 : 9)[b]
4	**12c**, 	**16b** (74) (91 : 9)[ab]
5	**12c**, 	**16c** (74) (91 : 6 : 3)[b]
6	**12c**, 	**16d** (48) (67 : 33);[c] **14c** (20)
7	**12c**, 	**16e** (73)[d]
8	**12c**, 	**16f** (53) (92 : 8)[b]; **14c** (12)

[a] Ratio determined on the desilylated product. [b] Ratio determined by HPLC. [c] Ratio determined by ^1H NMR at variant temperatures. [d] Only one isomer was detected by HPLC and ^1H NMR at variant temperatures.



Scheme 2 Reagents and conditions: i. TBAF, THF, 77%; ii. I_2, Ph_3P, imidazole, THF, 86%; iii. 10% Pd/C, H_2, Et_3N, MeOH, 97%; iv. $AlMe_3$, NH(OMe)Me·HCl, CH_2Cl_2, 0 °C, 3 h, 81%; v. *n*-$C_7H_{15}MgBr$, THF, 50 °C, 80%; vi. (1) 2 N HCl, AcOEt; (2) MeONa, MeOH; (3) 10% Pd/C, H_2, MeOH, 42% for three steps.

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