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SmI_2-mediated hetero-coupling reaction of lactams with aldehydes; synthesis of indolizidine alkaloids, (−)-δ-coniceine, (+)-5-epiindolizidine 167B and (+)-lentiginosine

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Abstract—Treatment of alicyclic and aromatic lactams with several aldehydes in the presence of samarium(II) diiodide was found to undergo a novel nitrogen–carbon (hetero) coupling reaction to generate *N*-α-hydroxyalkylated lactams in high yield. The chiral lactams with an aldehyde-side chain incorporating the L-pyroglutamic acid- or L-tartaric acid-derived skeleton also reacted intramolecularly under the same conditions to afford the corresponding bicyclic coupling products, which were further applied to the convenient syntheses of (−)-δ-coniceine, (+)-5-epiindolizidine 167B and (+)-lentiginosine, respectively.

Samarium(II) diiodide has been extensively investigated as a powerful electron donor able to promote a wide range of reductions and coupling reactions.[1] Its use in synthesis has been especially advantageous for ring closure reactions and C–C bond formation such as hydroxyl-directed conjugate addition and stereocontrolled intramolecular pinacol reactions involving a variety of carbonyl compounds.[2] The reactions of acid chlorides and acid anhydrides with this reagent have also been researched[3] in addition to intramolecular and intermolecular Grignard-type reactions.[4]

Towards the carbonyl group of imides, on the other hand, two reactions, i.e. an intramolecular Barbier-type reaction of some *N*-iodoalkyl cyclic imides[5] and a coupling reaction of acyclic imides such as *N*-acyllactams with carbonyl compounds[6] are known. In this connection we have also recently reported the first pinacolic cross-coupling reaction between phthalimides and carbonyl compounds and its application to the complete stereoselective deoxygenation.[7] However, the lack of studies concerning the reactivity of samarium(II) compounds towards simple amides is surprising except in some special cases.[8] This should be attributed to their low reactivity. Herein we wish to describe the first nitrogen–carbon (hetero) coupling reaction between lactams and aldehydes mediated by SmI_2 to provide *N*-α-hydroxyalkylated lactams and its application to the short synthesis of biologically active indolizidine alkaloids, (−)-δ-coniceine, (+)-5-epiindolizidine 167B and (+)-lentiginosine.

Initial experiments have been performed on a cross-coupling reaction mediated by SmI_2 (2 equiv.) between *N*-alkoxycarbonyl lactams (**1a**–**1c**) and heptanal as shown in Table 1 (entries 1–3), which gave unexpectedly the decarboxylated nitrogen–carbon (hetero) coupling product **2a** in low yields instead of the desired pinacolic-type adduct. Enhancement of the yield was not observed even in the case of employing simple 2-pyrrolidinone (**1d**), however, the use of excess SmI_2 (3 equiv.) remarkably brought about **2a** in 90% isolated yield (entry 5).[9] Although it became apparent that this procedure was not applicable for the reaction of *N*-H lactams with ketones, the beneficial results was again obtained in intramolecular reactions (entries 8 and 9)[10] and in reactions employing an aromatic *N*-H lactam (**1g**) (entries 10–12). It is reasonable to assume that the reaction may proceed by a radical mechanism since the reaction with Bu_3SnH (1.5 equiv.) and cat. AIBN in toluene at 90°C afforded the same coupling product **2a** in 75% yield. However, the ionic simple acetalization involving a samarium(III) chelated six-membered ring structure of **2** obtained from nucleophilic attack of the lactam-anion to the aldehyde should be also considered. Additional studies on the precise mechanistic aspect are in progress.

Keywords: coupling reaction; samarium(II) diiodide; lactam; indolizidine alkaloid; lentiginosine.

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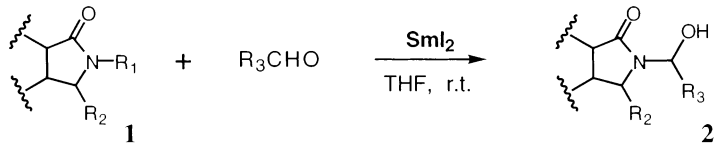
Table 1. Hetero-coupling reaction of lactams (**1**) with aldehydes mediated by SmI_2



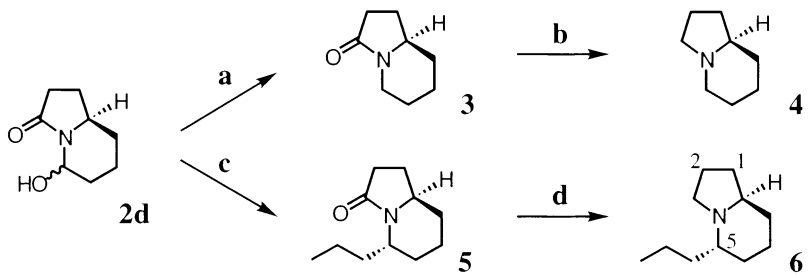
1 **2**

entry	lactam (**1**) R_1	R_2	R_3 [a]	SmI_2 (equiv.)	yield of (**2**) (%) [b,c]
1	COOMe	H (**1a**)	C_6H_{13}	2	7 (**2a**)
2	COOEt	H (**1b**)	C_6H_{13}	2	36 (**2a**)
3	COO^{t}Bu	H (**1c**)	C_6H_{13}	2	5 (**2a**)
4	H	H (**1d**)	C_6H_{13}	2	48 (**2a**)
5	H	H (**1d**)	C_6H_{13}	3	90 (**2a**)
6	H	H (**1d**)	C_3H_7	3	67 (**2b**)
7	H	H (**1d**)	$Ph(CH_2)_2$	3	72 (**2c**)
8	H	(*R*)-$(CH_2)_3$CHO (**1e**)	---	3	65 (**2d**)
9	H	(*R*)-$(CH_2)_4$CHO (**1f**)	---	3	48 (**2e**)
10	H	H (**1g**)	C_6H_{13}	3	84 (**2f**)
11	H	H (**1g**)	C_3H_7	3	67 (**2g**)
12	H	H (**1g**)	$Ph(CH_2)_2$	3	69 (**2h**)

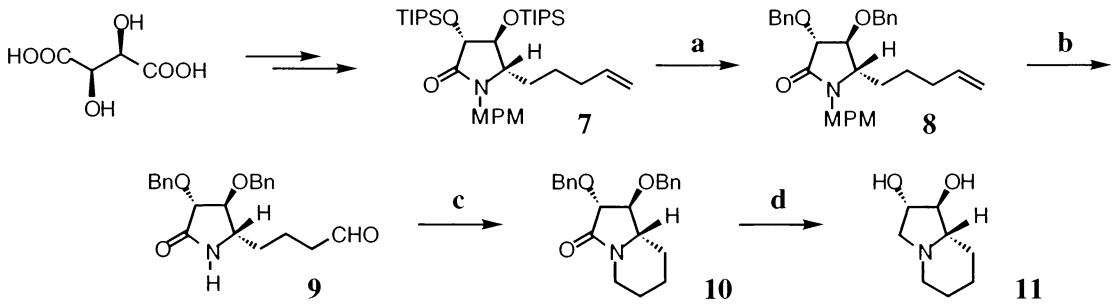
a) 2~5 equiv. of carbonyl compounds were used. b) Isolated yield and unreacted **1d** and **1g** were recovered in each case. c) All products were stable under silica-gel chromatographic conditions.

In light of the above outcome, we turned our attention to the short and convenient synthesis of some biologically active indolizidine alkaloids, such as (−)-δ-coniceine, (+)-5-epiindolizidine 167B and (+)-lentiginosine. To begin with, treatment of **2d** obtained from the intramolecular hetero-coupling reaction with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ easily afforded the deoxgenated compound **3** in high yield, which was in turn reduced with $LiAlH_4$ to give the known product, (−)-δ-coniceine (**4**) ($[\alpha]_D^{23.5}$ −4.02° (*c* 2.12, EtOH)).[12] On the other hand, **2d** was effected by $BF_3{\cdot}OEt_2$-induced allylation[13] with allyltrimethylsilane and hydrogenation followed by reduction under the same conditions as noted above, leading to the alkaloid, 5-epiindolizidine 167B (**6**), $[\alpha]_D^{23.8}$ +9.59° (*c* 0.75, CH_2Cl_2)[14] as a single stereoisomer[15] (determined by ^{13}C NMR and HPLC analysis) in 62% overall yield from **2d** (Scheme 1). These two compounds have properties identical to those reported in the literature, respectively.

The same approach was also applicable to the short synthesis of the least hydroxylated indolizidine alkaloid, (+)-lentiginosine (**11**), which was found to be ca. twice as potent as castanospermine known to inhibit replication of human immunodeficiency virus (HIV), as follows; the *trans*-substituted homochiral lactam **7** (>99% d.e.) obtained from L-tartaric acid based on our reported method[17] was cleavaged via dihydroxylation after exchange of TIPS-protecting groups to benzylethers, providing the aldehyde **9** in high yield. This was subjected to the SmI_2-mediated coupling reaction followed by deoxgenation with Et_3SiH to lead to the indolizidine lactam **10** in 78% 2 steps yield. Deprotection and reduction of **10** finally accomplished the total synthesis of (+)-**11** (Scheme 2), $[\alpha]_D^{25}$ +3.20° (*c* 0.60, MeOH) (lit.[18a] $[\alpha]_D^{27}$ +3.20° (*c* 1.07, MeOH)), whose spectral data were completely identical to those of the natural[19] and previously synthesized product in this laboratory.[18]



Scheme 1. *Reagents and conditions*: (a) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20°C; quant.; (b) $LiAlH_4$, ether, rt; quant.; (c) 1, allyltrimethylsilane, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 to −50°C; 69%; 2, H_2, Pd/C, EtOH; 90%; (d) $LiAlH_4$, ether, rt; quant.



Scheme 2. *Reagents and conditions*: (a) 1, Bu_4NF, THF; quant.; 2, BnBr, Ag_2O, CH_3COOEt; 63%; (b) 1, CAN, CH_3CN–H_2O (9:1); 75%; 2, OsO_4, NMO, acetone–H_2O (1:1); 95%; 3, $NaIO_4$, H_2O–Et_2O (1:); quant.; (c) 1, SmI_2 (3 equiv.), THF; 85%; 2, Et_3SiH, BF_3·OEt, CH_2Cl, −20°C; 92%; (d) 1, Pd(black), 4.4% HCOOH–MeOH; 90%; 2, $LiAlH_4$, THF, reflux; quant.

In summary we have disclosed herein the first example of SmI_2-mediated N-C (hetero) coupling reaction between *N*-unsubstituted lactams and aldehydes. This procedure found application in the shortest synthesis of three types of biologically important indolizidine alkaloids and will be widely applicable to the synthesis of other fused alkaloidal natural products.

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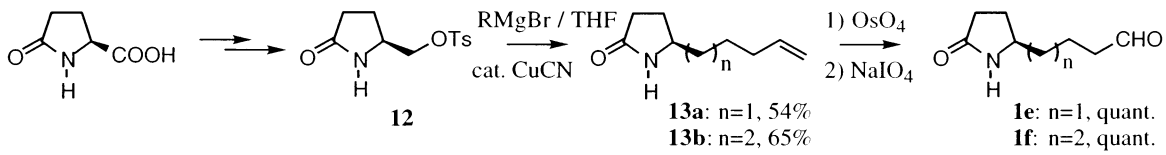
References

1. (a) Girard, P.; Kagan, H. B.; Namy, J.-L. *J. Am. Chem. Soc.* **1980**, *102*, 2693; (b) Namy, J.-L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5; (c) Kagan, H. B. *New J. Chem.* **1990**, *14*, 453.
2. For recent reviews and examples, see: (a) Kagan, H. B.; Namy, J.-L. *Tetrahedron* **1986**, *42*, 6573; (b) Kagan, H. B.; Sasaki, M.; Collin, J. *Pure Appl. Chem.* **1988**, *60*, 1725; (c) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29; (d) Matsuda, F. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 65; (e) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307; (f) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321; (g) Molander, G. A.; Sono, M. *Tetrahedron* **1998**, *54*, 9289; (h) Mochrouhi, F.; Namy, J.-L. *Tetrahedron* **1998**, *54*, 11111; (i) Nishiyama, Y.; Sakaguchi, S.; Ishii, Y. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 129; (j) Riber, D.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *65*, 5382.
3. (a) Souppe, J.; Namy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 2869; (b) Mochrouhi, F.; Namy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1997**, *38*, 7183; (c) Mochrouhi, F.; Pârlea, E.; Namy, J.-L. *Eur. J. Org. Chem.* **1998**, 2431.
4. (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216; (b) Mochrouhi, F.; Namy, J.-L.; Kagan, H. B. *Synlett* **1996**, 633.
5. Ha, D.-C.; Yun, C.-S.; Yu, E. *Tetrahedron Lett.* **1996**, *37*, 2577.
6. Farcas, S.; Namy, J.-L. *Tetrahedron Lett.* **2000**, *41*, 7299.
7. Yoda, H.; Matsuda, K.; Nomura, H.; Takabe, K. *Tetrahedron Lett.* **2000**, *41*, 1775.
8. (a) Ogawa, A.; Takami, N.; Nanke, T.; Ohya, S.; Hirao, T. *Tetrahedron* **1997**, *53*, 12895; (b) Kikukawa, T.; Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1999**, *40*, 7497; (c) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453.
9. Typical experimental conditions: To a deep-blue THF (3 mL) solution prepared from samarium metal powder (0.54 g, 3.60 mmol) and diiodomethane (0.95 g, 3.53 mmol) under Ar was added a solution of 2-pyrrolidine (0.10 g, 1.18 mmol) and heptanal (0.40 g, 3.56 mmol) in THF (3 mL) at 0°C. After the mixture was stirred for 3 h at room temperature, it was poured into a dilute HCl and extracted with ethyl acetate. The product was chromatographed (eluted with ethyl acetate) to give **2a** (0.21 g, 1.06 mmol) in 90% yield.
10. The starting lactams with an aldehyde-containg side chain were easily prepared from L-pyroglutamic acid as shown below.[11] This is, to our knowledge, the best way for the construction of simple lactams with a variety of γ-alkyl side chain.



11. (a) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717; (b) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.
12. Although (−)-δ-coniceine is not a true alkaloid (i.e. not naturally occurring), it has been derived from the poison hemlock alkaloid coniine by chemical transformation, and has held considerable interest as a simple synthetic target. For recent examples, see: (a) Groaning, M. D.; Meyers, A. I. *Chem. Commun.* **2000**, 1027; (b) Sibi, M. P.; Christensen, J. W. *J. Org. Chem.* **1999**, *64*, 6434; (c) Pearson, W. H.; Lin, K.-C. *Tetrahedron Lett.* **1990**, *31*, 7571; (d) Ringdahl, B.; Pinder, A. R.; Pereira, W. E.;

Oppenheimer Jr., N. J.; Craig, J. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1. The spectral data of the synthetic **4** were completely identical to those of the reported compound except for the value of the specific rotation (lit.[12d] $[\alpha]_D^{23}$ −10.2±0.6° (*c* 1.76, EtOH)). The reason for such a difference is not clear at present.

13. Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett*. **2000**, *41*, 275.
14. Natural (−)-indolizidine 167B (also named gephyrotoxin 167B) is a dendrobatid alkaloid found in the toxic skin secretions of certain species of neotropical frogs. For recent syntheses, see: (a) Ma, D.; Sun, H. *Org. Lett*. **2000**, *2*, 2503; (b) Yamazaki, N.; Ito, T.; Kibayashi, C. *Org. Lett*. **2000**, *2*, 465; (c) Back, T. G.; Nakajima, K. *Org. Lett*. **1999**, *1*, 261.
15. The absolute configuration was easily assigned according to the following references in addition to Ref. 12 and the observed stereochemical outcome is documented based on a pseudo 1,3-allylic strain from the lactam carbonyl function forcing the pendant alkyl group to be axial.[15b,16]; (a) Edwards, O. E.; Greaves, A. M.; Sy, W. W. *Can. J. Chem*. **1988**, *66*, 1163; (b) Hart, D. J.; Tsai, Y.-M. *J. Org. Chem*. **1982**, *47*, 4403.
16. Hoffmann, R. W. *Chem. Rev*. **1989**, *89*, 1841.
17. (a) Yoda, H.; Shimojo, T.; Takabe, K. *Tetrahedron Lett*. **1999**, *40*, 1335; (b) Yoda, H.; Nakajima, T.; Takabe, K. *Synlett* **1997**, 911; (c) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1451.
18. (a) Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137; (b) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1455.
19. (a) Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886; (b) Molyneux, R. J. *J. Nat. Prod*. **1990**, *53*, 609.