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Communications

Generation and Alkylation of Carbanions α to the Nitrogen of Amines by a New Metalation Procedure

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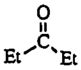
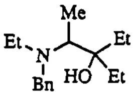
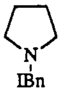
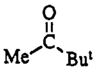
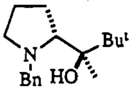
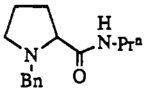
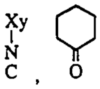
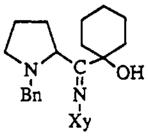
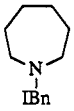
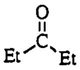
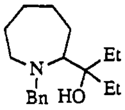
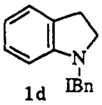
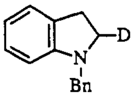
Summary: Treatment of a tertiary amine having a pendent *o*-iodobenzyl group on nitrogen with SmI_2 generates α-amino organosamarium, which reacts with electrophiles giving the corresponding C–C bond formation products in good yield.

The formation of C–C bonds at the α-position of the nitrogen of amines is of great importance for the synthesis of nitrogen-containing natural products. Unlike the sulfur and oxygen analogues, however, methods for the generation of α-amino carbanions are limited.[1] Whereas amines having a stabilizing or an electron-withdrawing group on the nitrogen can be lithiated with a strong base such as an alkyllithium, the carbanions of simple tertiary amines are not accessible by deprotonation. We now report a new method for the generation of a carbanion α to an amino nitrogen and subsequent in situ C–C bond formation.

Tertiary amines **1** having a pendent *o*-iodobenzyl group on the nitrogen[2] were treated with SmI_2 (3 equiv) in the presence of electrophiles in tetrahydropyran (THP)[3]–HMPA. As listed in Table I, cyclic and acyclic amines could be coupled at the α-position of the amine with various electrophiles including enolizable ketones, isocyanates, and isocyanides[4] to give the corresponding C–C bond formation products in good yield. Noteworthy is the observation that a single diastereomer was produced in the reaction of **1b** with 3,3-dimethyl-2-butanone (run 2).

Table I. SmI_2-Mediated Reactions of 1 with Electrophiles[a]

run	1	E	5	(yield, %)
1	 1a			5a (74)
2	 1b			5b (87)
3	1b	OCN–Pr^n		5c (67)
4	1b			5d (70)
5	 1c			5e (88)
6	 1d	MeOD		5f (93)

[a] Key: IBn, *o*-iodobenzyl; Xy, 2,6-dimethylphenyl.

When a cyclic amine **1d** was treated with SmI_2 in the presence of MeOD, deuterium was incorporated in the ring at the α-position (D-/H-**5f** = 92/8, run 6), not ortho to the benzyl group. In addition, the intermolecular version of this reaction (i.e., the SmI_2-mediated reaction of 1-

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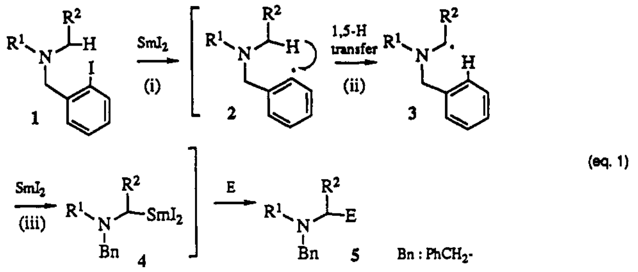
[1] (a) Ager, D. J. In *Umpoled Synthons*; Hase, T. A., Ed.; Wiley: New York, 1987; p 101. For nucleophilic introduction of substituents at the α-position of amines, see: (b) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471. (c) Naota, T.; Nakato, T.; Murahashi, S. *Tetrahedron Lett.* **1990**, *31*, 7475. (d) Shono, T.; Fujita, T.; Matsumura, Y. *Chem. Lett.* **1991**, 81. (e) Tsunoda, T.; Fujiwara, K.; Yamamoto, Y.; Ito, S. *Tetrahedron Lett.* **1991**, *32*, 1975 and references cited therein.

[2] Tertiary amines **1** were easily prepared in high yield by treatment of the parent secondary amines with *o*-iodobenzyl bromide at rt in THF–aq K_2CO_3.

[3] THP as solvent gave **5** in slightly better yield than when THF was used. In the case of THF, some intermolecular hydrogen abstraction by the aryl radical took place.

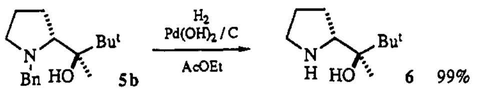
[4] Murakami, M.; Kawano, T.; Ito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2437.

benzylpyrrolidine with iodobenzene and an electrophile) did not afford any C–C bond product. These preliminary mechanistic observations are in accord with a reaction path involving α-amino organosamarium species 4 as a transient intermediate[5] (eq 1). The sequence probably involves the following: (i) deiodination of *o*-iodobenzyl group by SmI_2 giving the corresponding aryl radical 2; (ii) an intramolecular 1,5-hydrogen atom transfer[6,7] producing the α-amino radical 3; and (iii) one-electron transfer from SmI_2 to 3 giving 4. Because of the instability of 4, electrophiles must be present in the reaction medium during its formation.



(eq. 1)

It should be noted that the pendent benzyl group in the product 5 can be removed by hydrogenation to give the secondary amine.[8] Therefore, the reaction provides a useful method for the synthesis of a variety of nitrogen containing compounds including β-amino alcohols and α-amino acid derivatives.



(eq. 2)

Metalation by hydrogen–metal exchange has usually been carried out by abstraction of a proton under strongly basic conditions using an alkyllithium or lithium amide.[1] The present reaction, which constitutes translocation of radical center from the pendent benzyl group to the α-position of an amine and a subsequent one-electron transfer, offers new methodology for amine metalation and subsequent C–C bond formation.

Acknowledgment. This work was supported in part by the Ministry of Education, Science and Culture, Japan (Grant-in-Aid for General Scientific Research (01430017)).

Supplementary Material Available: Experimental details for the synthesis and characterization of 5a–e, 6, and 7 and ^{13}C NMR spectra for 5b–d, 6, and 7 (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(5) Recently, the evidence for the intermediacy of organosamarium species in SmI_2-promoted synthetic reactions has been reported: (a) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236. (b) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171. (c) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* **1990**, 773. (d) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439. (e) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112.

(6) Intramolecular 1,5-hydrogen atom transfer, followed by radical cyclization, has been utilized for synthesis of five- and six-membered carbo- and heterocycles. (a) Bennete, S. M.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 878. (b) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81. (c) Borthwick, A. D.; Caddick, S.; Parsons, P. J. *Tetrahedron Lett.* **1990**, *31*, 6911. (d) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896. (e) Curran, D. P.; Abraham, A. C.; Liu, H. *J. Org. Chem.* **1991**, *56*, 4335 and references cited therein.

(7) It has been reported that reduction of aryl radicals by SmI_2 is slower than intermolecular hydrogen atom abstraction from solvent THF. (a) Matsukawa, M.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 5877. (b) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485.

(8) The stereochemistry of 6 was determined by a ^1H NMR NOE experiment on the corresponding cyclic urethane 7, which is derived from the treatment of 6 with trichloromethyl chloroformate.

Stereoselective Synthesis of Both (*E*)- and (*Z*)-1,2,4-Heptatrien-6-ynes. Formation of an α,3-Dehydrotoluene Biradical, Trapping by an Intramolecular Carbon–Carbon Double Bond, and Decay of the Resulting New Biradical via an Intramolecular Route[†]

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Summary: Condensation between conjugated allenic aldehydes 3 and γ-(trimethylsilyl)allenylboranes 2 followed by the Peterson olefination reaction afforded enyne–allenes 7 and 8. On heating, 8c underwent a sequence of intramolecular transformations through biradical intermediates.

Recently, simple acyclic (*Z*)-1,2,4-heptatrien-6-ynes were reported to undergo facile cycloaromatization reactions at ambient or even subambient temperatures to produce reactive α,3-dehydrotoluene biradicals,[1] which could mimic the DNA-cleaving mechanisms and properties of the new class of very potent antitumor antibiotics calicheamicins,[2] esperamicins,[3] neocarzinostatin,[4] and dynemicins.[5] The synthetic routes to these conjugated enyne–allenes generally involved acetylene to allene transformation of the corresponding enediyne propargylic alcohols. We report

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[†] Dedicated to Professor Herbert C. Brown on the occasion of his 80th birthday.

(1) (a) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057–8059. (b) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130–9132. (c) Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 4995–4998. (d) Nagata, R.; Yamanaka, H.; Murahashi, E.; Saito, I. *Tetrahedron Lett.* **1990**, *31*, 2907–2910. (e) Nicolaou, K. C.; Maligres, P.; Shin, J.; de Leon, E.; Rideout, D. *J. Am. Chem. Soc.* **1990**, *112*, 7825–7826.

(2) (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464–3466. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466–3468. (c) Lee, M. D.; Manning, J. K.; Williams, D. R.; Kuck, N. A.; Testa, R. T.; Borders, D. B. *J. Antibiot.* **1989**, *42*, 1070–1087.

(3) (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461–3462. (b) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462–3464.

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