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Regioselective Synthesis of Alkylpyrroles from Imines and Nitroalkenes by Lanthanide Compounds

Hiroyuki Shiraishi, Takayuki Nishitani, Tatsuo Nishihara, Satoshi Sakaguchi and Yasutaka Ishii*

Department of Applied Chemistry, Faculty of Engineering & High Technology

Research Center, Kansai University, Suita, Osaka 564-8680, Japan

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Abstract: Various types of substituted alkylpyrroles were synthesized in regioselective manner by the cyclization of nitroalkenes with imines catalyzed by $Sm(O\textit{i}\text{-}Pr)_3$ under mild conditions. Tetrahydroindole derivative was also synthesized in fair yield by the use of cyclic nitroalkene and imine as starting material. This method provides a novel alternative route for the regioselective synthesis of substituted alkylpyrrole derivatives.

Keyword: Pyrroles, Imines, Nitroalkenes, Samarium compounds

Introduction

Pyrroles are important synthetic targets for their application as precursors to many useful classes of organic compounds such as porphyrins and alkaloids.[1] In particular, the biological importance of pyrroles and their derivatives is emphasized, because several natural pigments, such as heme, chlorophyll, or enzymes like the various cytochromes, include the pyrrole nuclei.[2] In addition, amino acids such as proline and hydroxyproline also contain the hydrogenated pyrrole ring, that is a pyrrolidine framework. Although there are a number of potentially useful methods for pyrrole synthesis using various reagents, the Knorr or Paal-Knorr method is frequently used.[3] Roskamp *et al.* reported that the pyrrole synthesis via the coupling of α,β-unsaturated imines with ester or *N,N*-dimethylformamide is achieved by the use of $NbCl_3$ as the catalyst.[4] Recently, we have reported that the three-component coupling reaction of aldehydes, amines, and nitroalkanes is efficiently catalyzed by Sm catalysts to give substituted alkylpyrroles in fair yields.[5] This pyrrole synthesis involves the following reactions: (i) condensation of an aldehyde with amines giving imines; (ii) aldol-type condensation of the imine itself catalyzed by Sm catalysts; (iii) cyclization of the resulting α,β-unsaturated imines with nitroalkanes (eq. 1). In this reaction, the most important step is the formation of α,β-unsaturated imines derived from aldol-type condensation of imines catalyzed by Sm species. The resulting α,β-unsaturated imines are found to react easily with nitroalkanes without any catalyst to produce 1,3,4-alkylpyrroles in reasonable yields. A plausible intermediate [**A**] formed in this step was expected to be formed by the reaction of imines with nitroalkenes. Thus, the reaction of *N*-butylidenebutylamine (**1a**) with *trans*-β-nitrostyrene (**2a**) was examined in the presence of a lanthanide compound

*e-mail: ishii@ipcku.kansai-u.ac.jp

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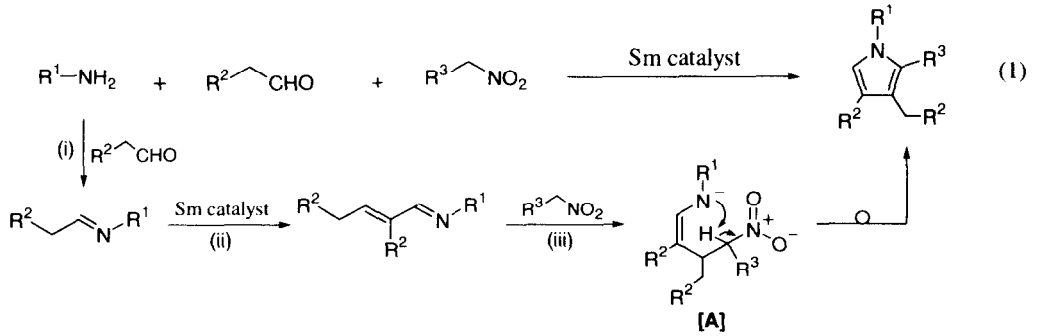
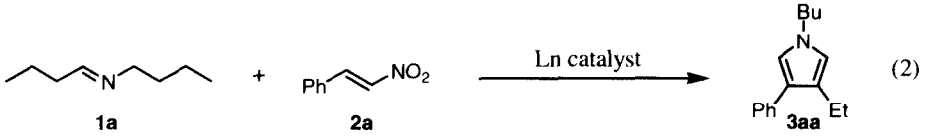




as a catalyst. As expected, the reaction produced *N*-butyl-3-ethyl-4-phenyl pyrrole (**3aa**).

This paper describes facile syntheses of pyrroles as well as fused pyrroles such as indoles[6] through the coupling reaction between imines and nitroalkenes catalyzed by samarium compounds under mild conditions.

Results and Discussion

In the first instance, the reaction of a 1:1 mixture of **1a** (1 mmol) and **2a** (1 mmol) in the presence of $Sm(O\textit{i}\text{-}Pr)_3$ (0.05 mmol) in THF (1 mL) was carried out at 60 °C for 3 h (standard conditions) to give **3aa** in 63% yield (entry 1). Among the samarium catalysts examined, $Sm(O\textit{i}\text{-}Pr)_3$ was found to be the best catalyst. The catalytic activities of SmI_2, $SmCl_3$ and $Sm(OTf)_3$ which act as Lewis acids were found to be less efficient than $Yb(O\textit{i}\text{-}Pr)_3$ and $La(O\textit{i}\text{-}Pr)_3$ as well as $Cp^*Sm(thf)_2$ which serve as Lewis bases[7] (entries 3 to 8). Pyrrole **3aa** was found to be obtained in satisfactory yield by the use of 5 mol% of $Sm(O\textit{i}\text{-}Pr)_3$ with respect to **1a**. The yield of **3aa** decreased to 35% when $Sm(O\textit{i}\text{-}Pr)_3$ was reduced from 5 mol% to 1 mol% (entry 2).

In order to extend the present method to the synthesis of a variety of pyrroles, aldimines and ketimines were allowed to react with several nitroalkenes in the presence of $Sm(O\textit{i}\text{-}Pr)_3$ under the standard conditions. Table 2 shows the results for the synthesis of various pyrroles.

Imine **1a** was reacted with an aliphatic nitroalkene such as 1-nitropent-1-ene (**2b**) to give the corresponding alkylpyrrole, **3ab**, in 51% yield (entry 2). To know the steric effect in the present pyrrole synthesis, some alkyl substituted imines were allowed to react with **2a** under standard conditions. The reaction of *N*-(3-methyl)butylidenebutylamine (**1b**) with **2a** proceeded smoothly to give the corresponding substituted pyrrole,

Table 1. Reaction of *N*-butylidenebutylamine (1a) with *trans*-β-nitrostyrene (2a) by various Ln catalysts[a]

Entry	Catalyst	Yield (%)
1	$Sm(O\textit{i}\text{-}Pr)_3$	63
2[b]	$Sm(O\textit{i}\text{-}Pr)_3$	35
3	$Cp^*_2Sm(thf)_2$	45
4	SmI_2	20
5	$SmCl_3$	12
6	$Sm(OTf)_3$	7
7	$Yb(O\textit{i}\text{-}Pr)_3$	58
8	$La(O\textit{i}\text{-}Pr)_3$	45

[a]A 1 : 1 mixture of **1a** (1 mmol) and **2a** (1 mmol) was reacted in the presence of lanthanoide catalyst (0.05 mmol) in THF (1 mL) at 60 °C for 3 h. [b]$Sm(O\textit{i}\text{-}Pr)_3$ (0.01 mmol) was used.

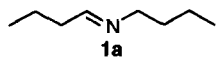
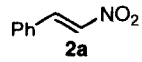
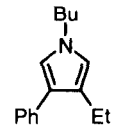
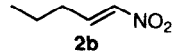
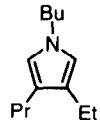
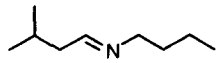
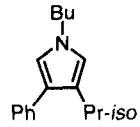
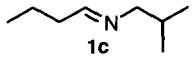
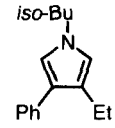
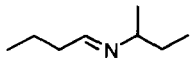
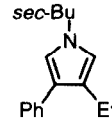
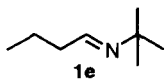
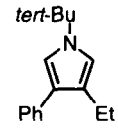
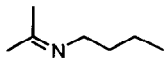
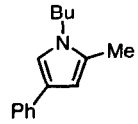
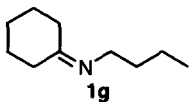
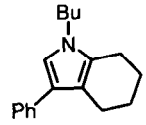
3ba, in 70% yield (entry 3). Similarly, β- and α-substituted *N*-butylidenebutylamines, **1c** and **1d**, reacted with nitroalkene **2a**, giving the corresponding alkyl substituted pyrroles, **3ca** and **3da**, in fair yields (entries 4 and 5). Owing to the *tert*-butyl substituent on the nitrogen atom of imine **1e**, the reaction with **2a** afforded pyrrole **3ea** in low yield (28%) (entry 6). These results show that the yield of pyrrole decreases with increasing bulkiness of the alkyl substituents on the nitrogen atom of imines.

In a previous pyrrole synthesis by the three-component coupling reaction of amines, aldehydes and nitroalkanes by Sm catalysts, α,β-unsaturated imines, resulting from the aldol-type condensation of imines which are derived from amines and aldehydes, react with nitroalkanes to form pyrroles. However, the aldol-type condensation of ketimines derived from amines and ketones was not promoted by $SmCl_3$ or SmI_2, and ketimine was recovered unchanged. As a result, pyrroles were difficult to be synthesized by the coupling reaction of amines, ketones and nitroalkanes. Furthermore, the reaction of ketimine, *N*-(1-methyl)ethylidenebutylamine (**1f**), prepared easily from 3-pentanone and butylamine, with nitroalkene **2a** was found to be efficiently catalyzed by $Sm(O\textit{i}\text{-}Pr)_3$ to afford *N*-butyl-2-methyl-4-phenylpyrrole (**3fa**) in good yield (72%) (entry 7). Thus, pyrroles having alkyl substituents on the 2,4-positions also could be successfully synthesized by using the present methodology. The reaction of *N*-cyclohexylidenebutylamine (**1g**) with **2a** produced *N*-butyl-3-phenyl-4,5,6,7-tetrahydroindole (**3ga**) in high yield (80%).

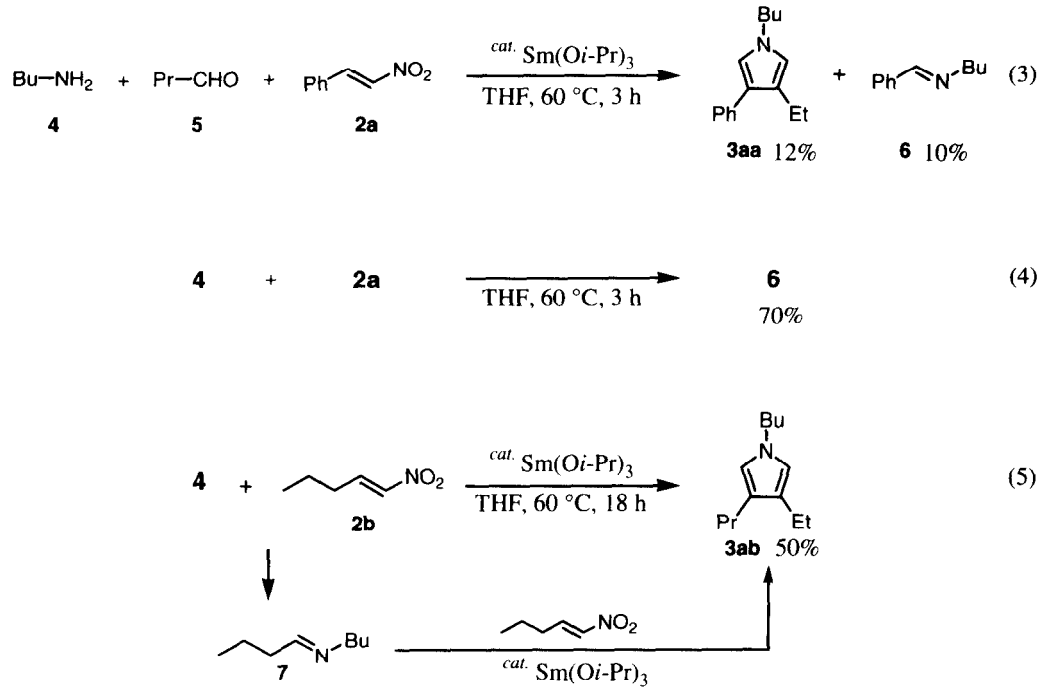
Since imines are derived from amines and aldehydes, we tried the one-pot reaction of butylamine (**4**), butylaldehyde (**5**) and **2a** in the presence of $Sm(O\textit{i}\text{-}Pr)_3$ under standard conditions. However, the desired alkyl pyrrole **3aa** was obtained in unsatisfactory yield (12%). In this reaction *N*-benzylidenebutylimine **6** was obtained as a side-product. It was found that **6** was formed by the reaction of **4** with **2a** in the absence of any catalyst. The reaction seems to proceed via Michael addition of amine to nitroalkene (eq. 4).[8]

Therefore, we tried the reaction of **4** and 1-nitropent-1-ene (**2b**) in the presence of a catalytic amount of $Sm(O\textit{i}\text{-}Pr)_3$. As expected, the reaction gave the corresponding pyrrole derivative (**3ab**) (eq. 5). It is reasonable to assume that the reaction proceeds *via* the formation of *N*-butylidenebutylimine (**7**) from **4** and **2b**, followed by

Table 2. Pyrrole synthesis from imine (1) and nitroalkene (2)[a]

Entry	Imine	Nitroalkene	Product		Yield(%)[b]
1	 **1a**	 **2a**		**3aa**	63
2	**1a**	 **2b**		**3ab**	51
3	 **1b**	**2a**		**3ba**	70
4	 **1c**	**2a**		**3ca**	59
5	 **1d**	**2a**		**3da**	54
6	 **1e**	**2a**		**3ea**	28
7	 **1f**	**2a**		**3fa**	72
8	 **1g**	**2a**		**3ga**	80

[a]Imine (1.0 mmol) was allowed to react with nitroalkene (1.5 mmol) in the presence of $Sm(O\textit{i}\text{-}Pr)_3$ (0.05 mmol) in THF (1 mL) at 60 °C for 3 h. [b] Isolated yield.



the reaction of **7** with **2b** to form **3ab**.

Scheme 1 shows a plausible reaction path for the present pyrrole synthesis from imines and nitroalkenes catalyzed by $Sm(Oi\text{-}Pr)_3$. The samarium complex is considered to act as a base and activates imine **1** to form an intermediate (**B**). The subsequent reaction of the **B** with nitroalkene **2** would form an adduct (**C**), followed by the intramolecular cyclization of the **C** to lead to a pyrrole precursor **D**. The elimination of HNO and H_2O from the **D** results in pyrrole **3**. Previously, we showed that the synthesis of pyrrole from amines, aldehyde, and nitroalkanes catalyzed by SmI_2 follows a reaction path analogous to the present reaction sequence (eq. 1).[5] In the furan synthesis by the reaction of 1,3-dicabonyl compounds and aliphatic nitroalkenes in the presence of KF, Miyashita *et al.* have shown a similar reaction path.[9]

In conclusion, we have developed a facile alternative method for preparing alkyl pyrroles and their derivatives from imines and nitroalkenes catalyzed by $Sm(Oi\text{-}Pr)_3$ under mild conditions.

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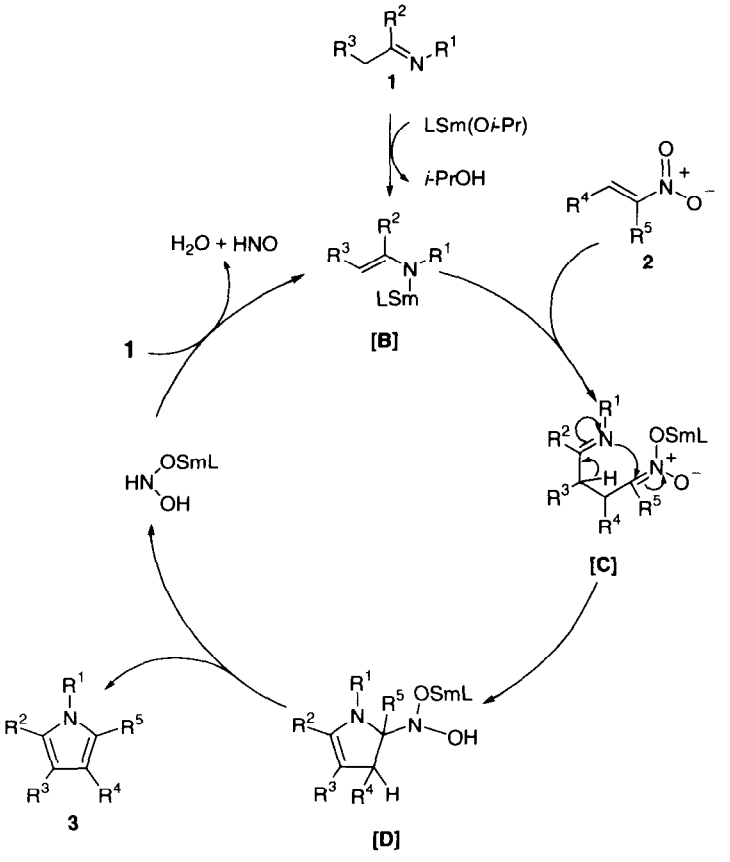

Scheme 1. A possible mechanism for the reaction of imine (1) with nitroalkene (2) by Sm(O*i*-Pr)$_3$

Experimental Section

General Procedure. ^{1}H and ^{13}C NMR measured at 270 and 67.5 MHz, respectively, in $CDCl_3$ with TMS as the internal standard. IR spectra were measured as thin films on NaCl plate. GLC analysis was performed with flame ionization detector using 1 mm × 30 m capillary column (OV-1). Mass spectra were determined at an ionizing voltage of 70 eV.

General Procedure for the Reaction of Imine (1) with Nitroalkene (2) Catalyzed by Samarium Complexes. To a solution of samarium complexes (0.05 mmol) in THF (1 mL) were added imines (**1**) (1.0 mmol), nitroalkene (**2**) (1.5 mmol), and the reaction mixture was stirred at 60 °C for 3 h. After removal of the catalyst by flash column, products were isolated by column chromatography (silica gel, ethyl acetate / hexane=1 / 20 eluent). All products were new compounds and were obtained as liquid. The structures were determined by using ^{1}H and ^{13}C NMR, IR, and GC-MS measurements. Elemental analysis was performed after isolation by column chromatography (silica gel, ethyl acetate / hexane=1 / 20 eluent).

***N*-Butyl-3-ethyl-4-phenylpyrrole (3aa)** : ^{1}H-NMR δ 7.42-7.15 (m, 5H), 6.71 (s, 1H), 6.49 (s, 1H), 3.82 (t, *J* =7.3 Hz, 2H), 2.65, (q, *J* =7.3 Hz, 2H), 1,82-1,71 (m, 2H) 1.39-1.28 (m, 2H), 1.21 (t, *J* =7.4 Hz, 3H), 0.94 (t, *J* =7.3 Hz, 3H); ^{13}C-NMR δ 136.8, 128.2, 127.6, 125.1, 123.6, 123.4, 118.8, 118.5, 49.3, 33.5, 20.0, 19.3, 14.7, 13.6; IR (neat) 2960, 2872, 1602, 1536, 1460, 1368, 1196, 1151, 763, 698 cm^{-1}; MS *m/e* = M$^+$ 227 (100), 184 (99), 156 (46), 92 (51). Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.21; H, 9.38; N, 6.21.

***N*- Butyl-3-ethyl-4-propylpyrrole (3ab)** : ^{1}H-NMR δ 6.28 (s, 2H), 3.67 (t, *J* =7.3 Hz, 2H), 2.39-2.26 (m, 4H), 1.64-1.05 (m, 6H), 0.91-0.85 (m, 9H); ^{13}C-NMR δ 117.8, 117.0, 62.8, 49.1, 33.6, 27.6, 23.6, 22.8, 20.0, 18.4, 14.6, 14.2, 13.6; IR (neat) 2960, 2873, 1643, 1548, 1462, 1260, 1092, 798 cm^{-1}; MS *m/e* = M$^+$ 193 (34), 164 (100), 122 (30), 108 (13).

***N*-Butyl-3-isopropyl-4-phenylpyrrole (3ba)** : ^{1}H-NMR δ 7.41-7.15 (m, 5H), 6.63-6.62 (s, 1H), 6.47 (s, 1H), 3.82-3.77 (t, *J* = 7.3 Hz, 2H), 3.18-3.11 (q, *J* = 6.6 Hz, 1H), 1.80-1.69 (m, 2H), 1.41-1.27 (m, 2H), 1.16 (t, *J* = 6.9 Hz, 6H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR δ 137.1, 129.2, 128.1, 128.0, 125.2, 123.2, 118.9, 116.9, 49.3, 33.4, 24.9, 24.3, 20.0, 13.6; IR (neat) 3026, 2930, 2873, 1530, 1466, 1369, 1314, 1159, 767, 730 cm^{-1}; MS *m/e* = M$^+$ 241 (32), 226 (100), 198 (24), 156 (24). Anal. Calcd for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.35; H, 9.64; N, 5.91.

***N-iso*-Butyl-3-ethyl -4-phenylpyrrole (3ca)** : ^{1}H-NMR δ 7.42-7.17 (m, 5H), 6.68 (s, 1H), 6.44 (s, 1H), 3.61-3.59 (d, *J* = 7.3 Hz, 2H), 2.66-2.63 (m, 2H), 2.10-1.98 (m, 1H), 1.21-1.15 (t, *J* = 7.6 Hz, 3H), 0.92-0.90 (d, *J* = 6.6 Hz, 6H); ^{13}C-NMR δ 136.8, 128.2, 127.5, 125.0, 123.5, 119.3, 57.5, 30.4, 20.1, 19.3, 14.7; IR (neat) 2982, 2977, 2945, 1604, 1530, 1385, 1138, 730, 697 cm^{-1}; MS *m/e* = M$^+$ 227 (73), 184 (100), 156 (77), 128 (37). Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.43; H, 9.39; N, 6.21.

***N-sec*-Butyl-3-ethyl -4-phenylpyrrole (3da)** : ^{1}H-NMR δ 7.43-7.13 (m, 5H), 6.74 (s, 1H), 6.51 (s, 1H), 3.88-3.80 (m, 1H), 2.70-2.62 (q, *J* = 7.4 Hz, 3H), 1.79-1.66 (m, 2H), 1.44-1.42 (d, *J* = 6.6 Hz, 3H), 1.21-1.16 (t, *J* = 7.4 Hz, 3H), 0.86-0.81 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR δ 137.0, 128.1, 127.5, 124.9, 123.1, 122.9, 116.8, 116.5, 56.9, 31.1, 21.6, 19.4, 14.6, 10.8; IR (neat) 3073, 2980, 2973, 2944, 2937, 1603, 1528, 1382, 1142, 763, 697 cm^{-1}; MS *m/e* = M$^+$ 227 (59), 212 (45), 198 (100), 156 (68). Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.38; H, 9.45; N, 6.17.

***N-tert*-Butyl-3-ethyl -4-phenylpyrrole (3ea)** : ^{1}H-NMR δ 7.45-7.18 (m, 5H), 6.89 (s, 1H), 6.67 (s, 1H), 2.73-2.65 (q, *J* = 7.4 Hz, 2H), 1.55 (s, 9H), 1.24-1.19 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR δ 137.0, 128.1, 127.6, 125.0, 123.1, 116.0, 115.5, 54.5, 30.6, 19.4, 14.6; IR (neat) 3053, 2971, 2932, 2870, 1601, 1531, 1460, 1371, 1120, 1071, 1034, 761, 698, 630 cm^{-1}; MS *m/e* = M$^+$ 227 (31), 212 (13), 171 (41), 156 (100). Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.32; H, 9.20; N, 6.05.

***N*-Butyl-2-methyl-4-phenylpyrrole (3fa)** : ^{1}H-NMR δ 7.48-7.08 (m, 5H), 6.86 (d, *J* = 1.7 Hz, 1H), 6.18 (s, 1H), 3.79 (t, *J* = 7.6 Hz, 2H), 2.24 (s, 3H), 1.72 (dt, *J* = 7.2 Hz, 2H), 1.37 (dd, *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR δ 136.1, 129.4, 128.5, 124.9, 124.7, 123.1, 116.6, 104.7, 46.5, 33.4, 20.0, 13.7, 12.0; IR (neat) 2958, 1604, 1530, 1448, 1385, 1365, 1207, 792, 758, 730, 694 cm^{-1}; MS *m/e* = M$^+$ 213 (64), 171 (40), 170(100), 156 (15), 128 (13), 85(9). Anal. Calcd for $C_{15}H_{19}N$: C, 84.46; H, 8.98; N, 6.57. Found: C, 84.16; H, 8.98; N, 6.54.

***N*-Butyl-6-phenyl-2,3,4,5-tetrahydroindole (3ga)** : ^{1}H-NMR δ 7.44-7.13 (m, 5H), 6.73 (s, 1H), 3.74 (t, *J* = 7.3 Hz, 2H), 2.69 (m, 2H), 2.55 (m, 2H), 1.84-1.67 (m, 6H), 1.41-1.32 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR δ 136.7, 128.5, 128.2, 126.6, 124.7, 121.8, 116.5, 115.1, 45.9, 33.3, 23.7, 23.4, 23.0, 22.0, 13.7; IR (neat) 2928, 1704, 1619, 1534, 1459, 1396, 1226, 1168, 1071, 1029, 769, 734, 697 cm^{-1}; MS *m/e* = M$^+$ 253 (82), 224 (21), 211 (100), 105 (47). Anal. Calcd for $C_{18}H_{23}N$: C, 85.32; H, 9.15; N, 5.53. Found: C, 85.24; H, 9.02; N, 5.45.

Procedure for the Reaction of Butylamine (4) with 1-Nitropentene (2b) Catalyzed by Sm(O*i*-Pr)$_3$. To a solution of Sm(O*i*-Pr)$_3$ (0.05 mmol) in THF (1 mL) were added **4** (1.0 mmol) and **2b** (2.0 mmol), and the reaction mixture was stirred at 60 °C for 18 h. The product was isolated as described above.

References and Notes

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