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Samarium diiodide-promoted electrophilic amination of ketone enolates: efficient synthesis of quaternary carbon-containing α-aminated ketones

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ABSTRACT

An efficient and practical electrophilic amination method that allows the preparation of useful quaternary carbon-containing α-aminoketones was developed. The reaction proceeds regiospecifically via a samarium enolate intermediate at room temperature in the presence of mild reducing agent SmI_2. Unlike the most reported lithium enolate cases, this new amination method does not require the use of strong base such as BuLi or LDA.

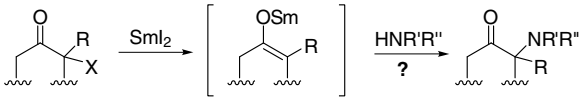
The electrophilic amination of carbanionic species is an important C–N bond formation approach that allows the preparation of a wide range of aminated compounds.[1] Over the past years, many electrophilic aminating reagents have been employed, including sulfonylazides,[2] sulfonyloxycarbamates,[3] hydroxylamine derivatives,[4] azodicarboxylates,[5] oxaziridines,[6] 1-chloro-1-nitroso compounds,[7] and arylazo tosylate.[8] Among them, di-*tert*-butylazodicarboxylate (DTBAD) appears one of the most general and practical electrophilic NH_2^+ equivalents owing to its commercial availability, high stability, and remarkable reactivity.

α-Aminoketones are versatile precursors of many physiologically important compounds and useful intermediates for organic synthesis.[9] These importances have stimulated the effort to develop new and improved synthetic strategies; asymmetric synthesis of optically active α-aminoketones is of particular interest in recent years.[10] Among the methods developed, electrophilic amination of enolates is one of the most important and general way, and many examples of amination of lithium enolates,[11] enamines,[12] and enolsilanes[13] have been documented. To the best of our knowledge, there has been no report concerning the electrophilic amination of samarium enolates. In the last two decades, SmI_2 has played an important role in organic synthesis.[14] Our interest in SmI_2-mediated reactions[15] led us to explore the possibility of the electrophilic amination of samarium enolates.

Previously, Molander[16] and Takeuchi[17] have demonstrated that samarium enolates of ketones could be formed regiospecifically from the corresponding α-heterosubstituted ketones by the SmI_2-mediated reaction. Thus, we envisioned if the mild electrophilic α-amination of α-heterosubstituted ketones could be carried out using appropriate aminating agent in the presence of SmI_2, leading to useful α-aminated ketones. Moreover, quaternary carbon-containing α-aminoketones may also be constructed by this way (Scheme 1). Herein, we report our results. This is also the first example of SmI_2-promoted electrophilic amination of ketone enolate.

First, we examined the reaction of 2-methoxy-2-phenyl-cyclohexanone (**1a**) with di-*tert*-butylazodicarboxylate (DTBAD) in the presence of SmI_2 (Scheme 2). A procedure similar to that reported by Molander[16] and Takeuchi[17] was applied to check the potential of our consideration. To our delight, when the reaction was performed at 0 °C in THF for 15 min, formation of the desired α-amination product **2a** was indeed found, but the yield was very low (23%, Table 1, entry 1). A similar yield was obtained when the reaction time was prolonged to 1 h (entry 2). The reduction product of 2-methoxy-2-phenyl-cyclohexanone (**1a**) was obtained as major product in about 75% yield in both cases.

To find appropriate conditions, more reaction factors were considered and investigated. When the reaction substrate **1a** was first stirred with SmI_2 for an hour before the addition of the aminating reagent DTBAD, the reaction gave good yield of 80% (entry 3). This result suggests the samarium enolate formation is the key to increase the reaction yield. As the reaction temperature increased to room temperature, the yield further increased (84%, entry 4). Gratifyingly, a dramatic improvement of the yield (94%) was achieved by employing 2 equiv of HMPA as additive[18] (entry 5).



R = aromatic or aliphatic HNR'R'' = aminating reagent
X = OMe, OTs, OTMS, Br, Cl,

Scheme 1. Reaction proposal.

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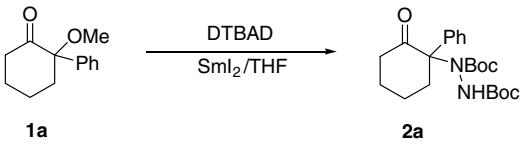


1a 2a

Scheme 2. Amination of substrate **1a** with DTBAD.

Table 1
Initial examination of the amination conditions

Entry	Procedure[a]	Temp	Time	Yield[c] (%)
1	A	0 °C	15 min	23
2	A	0 °C	1 h	25
3	B	0 °C	1 h	80
4	B	rt	1 h	84
5[b]	B	rt	1 h	94

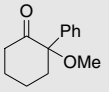
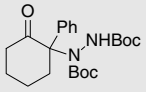
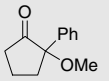
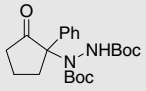
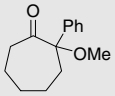
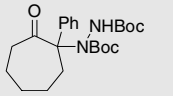
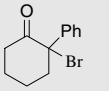
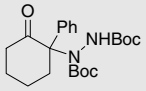
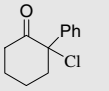
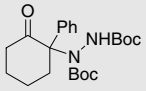
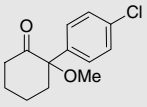
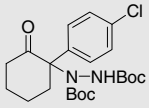
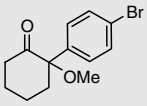
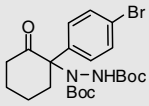
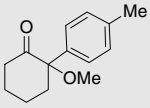
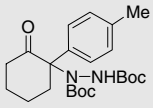
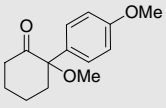
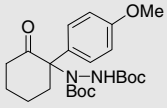
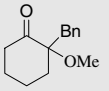
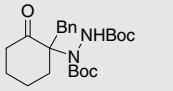
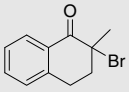
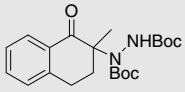
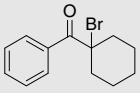
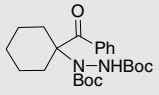
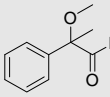
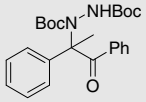
[a] Procedure A: a solution of ketone **1a** and DTBAD in THF was added to the solution of SmI_2. Procedure B: a solution of ketone **1a** was first added to the solution of SmI_2, the mixture was stirred for 30 min, and then DTBAD was added.
[b] Two equivalents of HMPA were added as additive.
[c] Isolated yield.

The detailed experimental procedure used in entry 5 of Table 1 is described below. Under nitrogen, to a solution of freshly made SmI_2 (1 mmol) in THF (5 mL) was added HMPA (0.17 mL, 1 mmol). After the mixture was stirred at room temperature for 15 min, substrate **1a** (102 mg, 0.5 mmol) in freshly distilled THF (3 mL) was added and the stirring continued for an additional 30 min. DTBAD (138 mg, 0.6 mmol) in THF (2 mL) was then added, and the reaction mixture was stirred for 1 h. Subsequently, the reaction mixture was quenched with saturated $Na_2S_2O_3$ aqueous solution. The aqueous layer was separated and extracted with ether. The combined organic layer was washed successively with water, brine, and dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel to give aminated ketone **2a** in 94% yield.

Following the optimal reaction conditions, a variety of α-heterosubstituted ketone substrates were tested for the α-amination. The experimental results are summarized in Table 2. As expected, the reaction was found very effective for a wide range of substrates including both cyclic and acyclic α-substituted ketones. In most cases, the α-amination products could be obtained cleanly in satisfactory yields.[19] In addition to six membered α-methoxy-cyclohexanone substrates, α-methoxy substituted cyclopentanone and cycloheptanone are also successfully aminated (entries 1–3). Moreover, the reactions can be performed smoothly when α-halo-substituted substrates are used (entries 4, 5, 11 and 12). In entries 6-9, 2-methoxy-2-phenyl-cyclohexanone (**1a**) derivatives having both electron-withdrawing and electron-donating substituents on the benzene ring gave the corresponding products in excellent yields. When substrates **1j** was employed, lower yield (67%) was observed (entry 10). This result indicates that an aromatic substituent such as phenyl group at the α-position of carbonyl is very useful but not necessary for the reaction. For acyclic substrates, as shown in entries 12–13, it was found that α-heterosubstituted ketones **1l–m** could be easily aminated and gave amination products **2l–m** in over 90% yields, indicating a mild and readily preparation of structurally interesting quaternary carbon-containing α-aminoketone analogues.

In summary, we have developed an efficient and practical electrophilic amination approach for the preparation of useful quaternary carbon-containing α-aminoketones. The reaction can be performed under very simple and mild reaction conditions. It proceeds regiospecifically via a samarium enolate intermediate in the presence of mild reducing agent SmI_2; unlike the most reported lithium enolate cases, this new method does not require the use of strong base such as BuLi or LDA. Attempts toward the asymmetric version of the reaction as well as the extension of this method are currently underway.

Table 2
Electrophilic amination of α-heterosubstituted ketones with DTBAD[a]

Entry	Substrate		Product		Yield[b] (%)
1		**1a**		**2a**	94
2		**1b**		**2b**	87
3		**1c**		**2c**	83
4		**1d**		**2a**	92
5		**1e**		**2a**	89
6		**1f**		**2f**	95
7		**1g**		**2g**	93
8		**1h**		**2h**	98
9		**1i**		**2i**	85
10		**1j**		**2j**	67
11		**1k**		**2k**	94
12		**1l**		**2l**	91
13		**1m**		**2m**	93

[a] All reactions were carried out in THF using the optimized conditions.
[b] Isolated yield.

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19. *Characterization data for products* **2a**–**m**: Compound **2a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (br s, 9H), 1.48 (br s, 9H), 1.26–1.83 (m, 2H), 2.06–2.19 (m, 2H), 2.38–2.47 (m, 2H), 2.83–3.08 (m, 2H), 5.92 (s, 1H), 7.27–7.41 (m 5H) ppm; FT-IR (KBr) ν 3278, 1724, 1368, 1245, 1161, 698, 581 cm^{-1}; ESI-MS: 427.1 (M^++Na), HRMS (ESI) calcd for $C_{22}H_{32}N_2O_5Na$: 427.2203; found, 427.2201; Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.32; H, 7.97; N, 6.93. Found: C, 65.09; H, 8.03; N, 6.70. *Compound* **2b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (br s, 9H), 1.49 (br s, 9H), 1.36–2.64 (m, 6H), 5. 91 (6.09) (s, 1H), 7.24–7.51 (m, 5H) ppm; FT-IR (KBr) ν 3340, 1750, 1730, 1715, 1496, 1366, 1257, 1181, 1150, 754 cm^{-1}; ESI-MS: 413.2 (M^++Na); Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found: C, 64.70; H, 7.90; N, 7.05. *Compound* **2c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (br s, 9H), 1.49 (br s, 9H), 1.33–2.64 (m, 10H), 5.95 (6.11, 6.16) (s, 1H), 7.34–7.61 (m 5H) ppm; FT-IR (KBr) ν 3301, 2980, 2935, 1715, 2865, 1722, 1368, 1162, 749, 700 cm^{-1}; ESI-MS: 441.2 (M^++Na); HRMS (ESI) calcd for $C_{23}H_{34}N_2O_5Na$: 441.2385; found, 441.2359. *Compound* **2f**: ^{1}H NMR (300 MHz, CDCl $_3$) δ 1.43 (br s, 9H), 1.45 (br s, 9H), 1.43-2.97 (m, 8H), 5.91 (6.08, 6.46) (s, 1H), 7.11–7.44 (m, 4H) ppm; FT-IR (KBr) ν 3238, 3161, 2981, 1715, 1701, 1496, 1160, 1016, 829, 806 cm^{-1}; ESI-MS: 427.1(M^++Na); HRMS (ESI) Calcd for $C_{22}H_{31}N_2O_5ClNa$: 461.1818; found, 461.1814; Anal. Calcd for $C_{23}H_{31}N_2ClO_5$: C, 60.20; H, 7.12; N, 6.38. Found: C, 60.48; H 7.18; N 6.27. *Compound* **2g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (br s, 18H), 1.40–2.98 (m, 8H), 5.94 (6.11, 6.49) (s, 1H), 7.13 (d, 2H, J = 6.9 Hz), 7.34–7.45 (m, 2H) ppm; ESI-MS: 441.2(M^++Na), HRMS (ESI) calcd for $C_{22}H_{31}BrN_2O_5Na$: 505.1309; found, 505.1309. Anal. Calcd for $C_{22}H_{31}BrN_2O_5$: C, 54.66; H, 6.46; N, 5.80; Br, 16.53. Found: C, 55.24; H, 6.58; N, 5.54; Br, 16.19. *Compound* **2h**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (br s, 9H), 1.47 (br s, 9H), 1.26–2.04 (m, 6H), 2.34 (s, 3H), 3.25 (d, 2H, J = 9.0 Hz), 7.19 (m, 4H) ppm; FT-IR (KBr) ν3240, 3163, 2980, 2944, 2870, 1715, 1702, 1016, 790, 613 cm^{-1}; ESI-MS: 441.2(M^++Na); HRMS (ESI) calcd for $C_{23}H_{34}N_2O_5Na$: 441.2354; found, 457.2360; Anal. Calcd for $C_{23}H_{34}N_2O_5$: C, 66.00; H, 8.19; N, 6.69. Found: C, 65.90; H, 8.18; N, 6.61. *Compound* **2i**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.47 (s, 9H), 1.75–2.99 (m, 8H), 3.09 (s, 3H) , 5.99 (6.14, 6.21) (s, 1H), 6.73 (d, 2H, J = 8.8 Hz), 7.19 (d, 2H, J = 8.8 Hz) ppm; FT-IR (KBr) ν 3349, 3065, 2996, 2929, 2859, 2832, 1763, 1454, 1434, 1333, 1284 , 1080, 1061, 1035, 996, 829, 806 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{34}N_2O_6Na$: 457.2379; found, 457.2363. *Compound* **2j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.45 (s, 9H), 1.75–2.98 (m, 10H), 5.99 (6.16) (s, 1H), 7.01–7.387 (m, 5H) ppm; FT-IR (KBr) ν 3359, 2979, 2938, 1751, 1724, 1603, 1368, 758, 705 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{34}N_2O_5Na$: 441.2374; found, 441.2360. *Compound* **2k**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.49 (s, 9H), 1.25–1.38 (m, 4H), 2.95–3.09 (s, 3H), 6.57 (6.63) (s, 1H), 7.18–7.35 (m, 3H), 7.42–7.47 (m, 1H) ppm; FT-IR (KBr) ν 3324, 2978, 2939, 1738, 1703, 1685, 1602, 1505, 1367, 741, 601 cm^{-1}; ESI-MS: 413.2 (M^++Na); HRMS (ESI) calcd for $C_{21}H_{30}N_2O_5Na$: 413.2068; found, 413.2047; Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found: C, 64.85; H, 7.76; N, 7.12. *Compound* **2l**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21–1.49 (m, 4H), 1.50 (s, 18H), 1.53–1.66 (m, 2H), 2.03–2.28 (m, 4H), 5.93 (6.09, 6.13) (s, 1H), 7.39–7.55 (m, 3H), 8.05–8.10 (br s, 2H) ppm; FT-IR (KBr) ν 3356, 3065, 2973, 2938, 1745, 1685, 1503, 1159, 882, 705 cm^{-1}; ESI-MS: 441.2 (M^++Na); HRMS (ESI) calcd for $C_{23}H_{34}N_2O_5Na$: 441.2347; found, 441.2360; Anal. Calcd for $C_{23}H_{34}N_2O_5$: C, 66.00; H, 8.19; N, 6.69. Found: C, 66.21; H, 8.14; N, 6.54. *Compound* **2m**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44–1.49 (br, 18H), 2.10 (s, 3H), 6.12 (s, 1H), 7.22–7.48 (m, 8H), 8.17 (d, J = 10.0 Hz, 2H) ppm; FT-IR (KBr) ν 3316, 3065, 2981, 2934, 1712, 1598, 1369, 1156, 962, 699 cm^{-1}; ESI-MS: 463.2 (M^++Na); HRMS (ESI) calcd for $C_{25}H_{32}N_2O_5Na$: 463.2185; found, 463.2203; Anal. Calcd for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36. Found: C, 68.09; H, 7.40; N, 6.31.