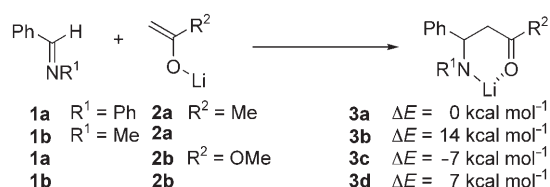


Germanium(II)-Mediated Reductive Mannich-Type Reaction of α -Bromoketones to *N*-Alkylimines**

Shin-ya Tanaka, Nobuo Tagashira, Kouji Chiba, Makoto Yasuda, and Akio Baba*

The β -aminoketone is an important structural intermediate in the synthesis of many biologically active compounds.^[1,2] Mannich-type reactions provide one of the most efficient approaches to the synthesis of the β -aminoketone skeleton and considerable efforts have been devoted to the improvement of this methodology.^[3,4] In particular, Lewis acid catalyzed addition of silicon enolates to imines has been extensively studied and the method is well-established.^[5] In addition, direct organocatalyst-promoted Mannich-type reactions have recently received increasing attention.^[6] Generally, imines bearing aryl groups or electron-withdrawing groups, such as sulfonyl, carbonyl (Boc, Cbz, etc.), or phosphine oxide groups, on the nitrogen atom have been employed. However, no general method that uses an *N*-alkylimine in a Mannich-type reaction with a ketone-derived enolate has been reported because of the poor electrophilicity of *N*-alkylimines.^[7] In addition, Mannich-type reactions between metal enolates and *N*-alkylimines would be less thermodynamically favorable because of the increased basicity of the product (metal amide). In fact, theoretical calculations for the Mannich-type reaction involving ketone-derived lithium enolate **2a** show that the addition to *N*-benzylidenemethylamine (**1b**, $\Delta E = 14 \text{ kcal mol}^{-1}$) is less favorable than addition of **2a** to *N*-benzylideneaniline (**1a**, $\Delta E = 0 \text{ kcal mol}^{-1}$; Scheme 1).^[8] Similar results were calculated for Mannich-type reactions by using ester-derived lithium enolate **2b**. Use of the ester-derived enolate in the Mannich-type reaction, however, is more favorable than use of the corresponding ketone-derived enolate because of the higher reactivity of the ester-derived enolate.^[9] Formation of *N*-methyl adduct **3d** is unfavorable ($\Delta E = 7 \text{ kcal mol}^{-1}$) compared with the exothermic formation of *N*-phenyl adduct **3c** ($\Delta E = -7 \text{ kcal mol}^{-1}$).



Scheme 1. Mannich-type reactions of the lithium enolate (energy values are calculated values).

These results strongly suggest that addition of the ketone-derived enolate to *N*-alkylimines remains a challenge to researchers in the field. Herein, we report the first general and practical reaction system for Mannich-type reactions that employ germanium-enolate species.

First, we tested several low-valent metals in the reductive Mannich-type reaction between α -bromoketone **4a** and *N*-benzylidenemethylamine (**1b**; Table 1). Zn and SnCl₂ were ineffective (Table 1, entries 1 and 2), and SmI₂, which is known to be an effective reductant,^[10] resulted in poor yields (Table 1, entries 3 and 4). In contrast, GeCl₂/dioxane markedly raised the yield of β -aminoketone **5ba** to 32% (Table 1, entry 5).^[11] To increase the yield, we screened various Lewis acids for their catalytic activity in the germanium-mediated system. Addition of TiCl₄ lowered the yield to 6% (Table 1, entry 6), and BF₃·OEt₂, Zn(OTf)₂, and

Table 1: Optimizing the reaction with *N*-methylimine **1b**.^[a]

Entry	Reductant	X (equiv)	Conditions	Catalyst	Yield ^[b] [%]
1 ^[c]	Zn	1.5	68 °C, 2 h	none	< 1
2	SnCl ₂	1.5	RT, 2 h	none	< 1
3 ^[c]	SmI ₂	3.0	−78 °C, 2 h	none	14
4 ^[c]	SmI ₂	3.0	−78 °C to RT, 2 h	none	< 1
5	GeCl ₂ /dioxane	1.5	RT, 2 h	none	32
6	GeCl ₂ /dioxane	1.5	RT, 2 h	TiCl ₄	6
7	GeCl ₂ /dioxane	1.5	RT, 2 h	BF ₃ ·OEt ₂	33
8	GeCl ₂ /dioxane	1.5	RT, 2 h	Zn(OTf) ₂	34
9	GeCl ₂ /dioxane	1.5	RT, 2 h	Me ₃ SiOTf	34
10	GeCl ₂ /dioxane	1.5	RT, 2 h	Bi(OTf) ₃	45
11	GeCl ₂ /dioxane	1.5	RT, 2 h	In(OTf) ₃	52
12	GeCl ₂ /dioxane	1.5	RT, 2 h	Y(OTf) ₃	71
13	GeCl ₂ /dioxane	1.5	RT, 2 h	Sc(OTf) ₃	84
14	GeCl ₂ /dioxane	1.5	RT, 2 h	Yb(OTf) ₃	93

[a] Reaction conditions: **1a** (0.6 mmol), reductant (X equiv), **4a** (0.9 mmol), catalyst (0.06 mmol), and CH₂Cl₂ (2 mL). [b] Yield determined from ¹H NMR spectrum. [c] Run in THF.

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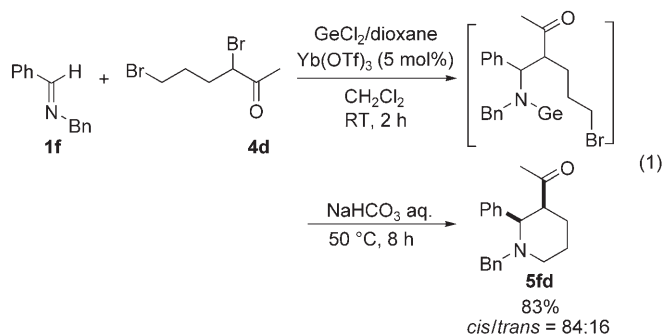
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Me₃SiOTf were also found to be poor catalysts (Table 1, entries 7–9). In contrast to these representative Lewis acids, Bi(OTf)₃ and In(OTf)₃ both increased the yield to approximately 50% (Table 1, entries 10 and 11). The group three metal triflates, Y(OTf)₃ and Sc(OTf)₃, also increased the product yield (Table 1, entries 12 and 13); Yb(OTf)₃ was the most effective catalyst among the Lewis acids screened, producing **5ba** in excellent yield (Table 1, entry 14).^[12]

Because of the effective optimization of the reaction (Table 1), the generality of the method was investigated under optimized conditions (Table 2). High yields were obtained from *N*-methylimines derived from aromatic aldehydes bearing electron-withdrawing or electron-donating groups (Table 2, entries 1–4). *N*-Benzylimine **1f**, *N*-allylimine **1g**, and *N*-phenylimine **1a** also gave their respective products in excellent yields (Table 2, entries 5–7). Even enolizable imines **1h–i** effectively afforded the desired β-aminoketones (Table 2, entries 8–9). Both aliphatic and aromatic secondary α-bromoketones **4b–c** furnished the desired products in modest to high yields. The diastereoselectivities were substrate dependent, ranging from 55 to 83% (Table 2, entries 10–12). The use of a mild catalyst, Bi(OTf)₃, in the reaction with formalimine **1j** gave higher yields than those obtained with Yb(OTf)₃ (Table 2, entries 13–16).

The mild and selective reducing ability of GeCl₂/dioxane was demonstrated in the Mannich-type reaction by using

dibromide **4d** and imine **1f**. Subsequent treatment with aqueous NaHCO₃ afforded the substituted piperidine **5fd** in good yield [Eq. (1)]. The 2-arylpiperidine unit is an important



structure found in a number of biologically active compounds.^[13] Next, we synthesized the antihypertensive agent, Be-2254, in just a few reaction steps (Scheme 2).^[1c] Formalimine **1k** was prepared in two steps from commercially available tyramine hydrogen chloride **6**. The germanium-mediated Mannich-type reaction of **1k** and subsequent treatment with 5*N* HCl afforded Be-2254 (**8ke**) in 15% overall yield.

To complement the experimental studies, the thermodynamic parameters of the reaction involving trichlorogermanium enolate **2c**^[14] were evaluated (Scheme 3).^[8] Notably, results of the theoretical calculations show that the reactions of *N*-phenyl **1a** and *N*-methylimine **1b** are equally exothermic ($\Delta E = -24 \text{ kcal mol}^{-1}$). This result differs considerably from those obtained for the lithium-enolate reactions. The results of the calculations were consistent with the experimental results, which demonstrated that both *N*-aromatic and *N*-alkylimines could be successfully used.

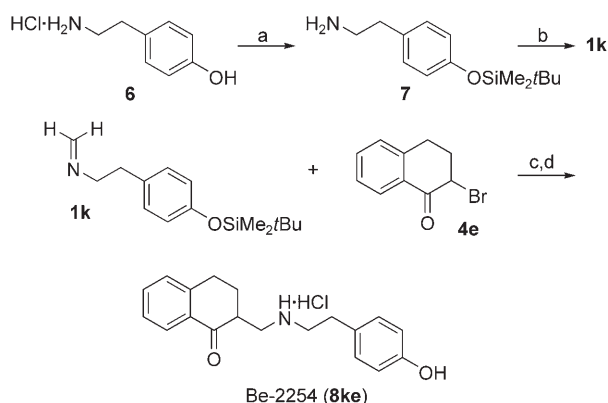
Our next objective was to determine the structural features that contribute to the germanium-mediated Mannich-type reaction. To achieve this goal, we investigated optimized structures of the Mannich adducts by using the lithium enolate and the trichlorogermanium enolate.

The optimized structures of the lithium-adducts (**3a** and **3b**) are depicted in Figure 1 a–b. The main difference between the structures is the negative charge on the nitrogen atoms (**3a** -0.84498 , **3b** -1.00322). In **3a**, a lone pair on the nitrogen atom is in same plane as the phenyl ring (Li–N–C1'–C2' dihedral angle = 174.8°), effec-

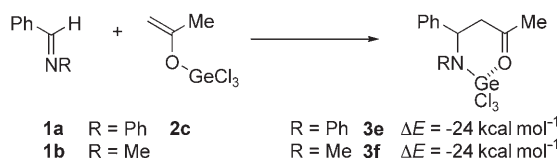
Table 2: Reaction of various imines **1** with α-bromoketones **4**.^[a]

Entry	Imine	α-Bromoketone	Product	Yield ^[b] [%]
1				93 (84)
2 ^[c]				86 (79)
3				97 (83)
4 ^[d]				89 (84)
5				96 (83)
6				91 (82)
7				93 (81)
8 ^[d]				66 (40)
9 ^[e]				65 (44)
10				71 ^[f] (51)
11				80 ^[g] (60)
12				97 ^[h] (97)
13 ^[i]				60
14 ^[i,j]				67 (58)
15 ^[i]				27
16 ^[i,j]				52 (44)

[a] Reaction conditions: **1** (0.6 mmol), GeCl₂/dioxane (0.9 mmol), **4** (0.9 mmol), Yb(OTf)₃ (0.06 mmol), and CH₂Cl₂ (2 mL), unless otherwise stated. [b] Yield determined from ¹H NMR spectrum and values in parentheses are yields of the isolated products. [c] RT, 15 min. [d] RT, 1 h. [e] Used 5 mol % Yb(OTf)₃. [f] *anti/syn* = 73:27. [g] *anti/syn* = 83:17. [h] d.r. = 55:45. [i] RT, 30 min. [j] Bi(OTf)₃ was used instead of Yb(OTf)₃.



Scheme 2. Facile synthesis of Be-2254. Reagents and conditions: a) *t*BuMe₂SiCl, imidazole, CH₂Cl₂, RT, 84 %; b) (CH₂O)_{*n*}, MgSO₄, CH₂Cl₂, RT, 96 %; c) GeCl₂/dioxane, Bi(OTf)₃, CH₂Cl₂, RT, 53 % NMR yield, 30 % yield of isolated product (not optimized); d) 5 N HCl, 100 °C, 64 %.



Scheme 3. Mannich-type reactions of trichlorogermanium enolate (energy values are calculated values).

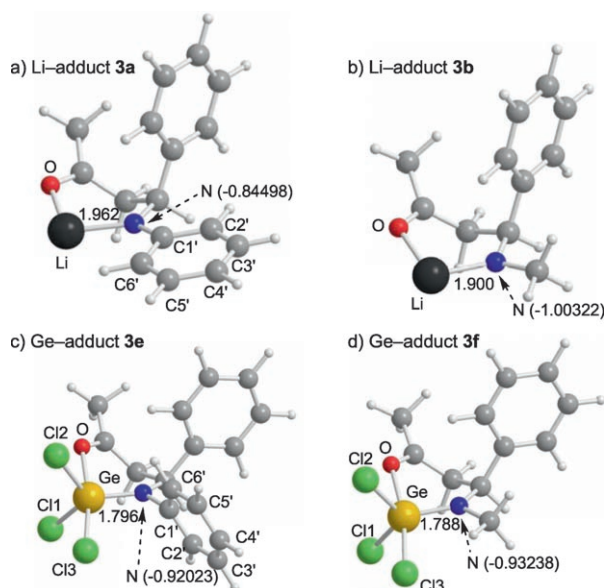


Figure 1. Optimized structures of metal-chelated Mannich adducts: a) **3a**, b) **3b**, c) **3e**, and d) **3f** (bond distances in Å and numbers in parentheses are for natural bond orbitals (NBO) charges).

tively delocalizing the negative charge. In the case of **3b**, loss of the conjugated system significantly increases the negative charge on the nitrogen atom of **3b**. We hypothesized that the increased negative charge makes adduct **3b** highly unstable.

As a result, the reaction pathway for the *N*-alkyl Mannich adduct would be unfavorable, as noted in Scheme 1.

Unlike **3a–b**, the nitrogen atoms of germanium–adducts **3e–f** have similar negative charges (**3e** -0.92023, **3f** -0.93238; Figure 1 c–d). In addition, the phenyl ring of **3e** is almost perpendicular to the plane of N, Ge, and Cl' (Ge–N–Cl'–C2' dihedral angle = 108.7°). Conjugation of the phenyl ring with a lone pair on the nitrogen atom is likely to be sterically unfavorable, thus explaining the difference in the charge. The adducts (**3e–f**) have germanium centers that exhibit a distorted trigonal bipyramidal structure with the nitrogen center in an equatorial position. The Ge–N bond distances are much shorter (**3e** 1.796 Å, **3f** 1.788 Å) than the sum of the covalent radii (1.96 Å)^[15]—possibly because of the effective d or p orbital interaction between germanium and the nitrogen atoms.^[16] The strong bond contributes to the stabilization of adducts **3e** and **3f**, although conjugation with the phenyl group is disturbed. These results strongly suggest that the germanium-mediated reaction takes place regardless of the substituents on the nitrogen atom. The difference in the thermodynamic values between Schemes 1 and 3 provides strong evidence that the pπ–dπ bond in the germanium amide effectively stabilizes the adducts.

In summary, an efficient method for the Mannich-type reaction of α-bromoketones with simple *N*-alkylimines was demonstrated. Germanium is a novel promoter with three roles: 1) reduction of the α-bromoketones, 2) C–C bond formation, and 3) stabilization of the Mannich adducts. Detailed mechanistic studies and additional applications of the system are ongoing.

Experimental Section

3-Bromo-3-methyl-2-butanone (**4a**, 0.9 mmol) was added to a stirred suspension of *N*-benzylidenemethylamine (**1b**, 0.6 mmol), Yb(OTf)₃ (0.06 mmol), and GeCl₂/dioxane (0.9 mmol) in CH₂Cl₂ (2 mL) at room temperature. The mixture was then stirred for 2 h at room temperature, and saturated aq. NaHCO₃ (20 mL) was added. The mixture was extracted with Et₂O (10 mL × 3), dried (MgSO₄), and evaporated. The crude product was purified by silica gel chromatography to afford aminoketone **5ba** as a colorless solid.

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