Synthetic Methods

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

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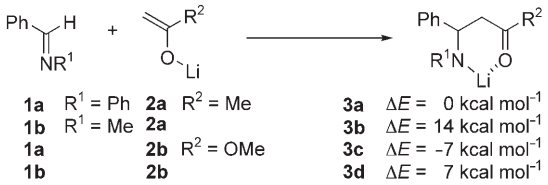
The β-aminoketone is an important structural intermediate in the synthesis of many biologically active compounds.[1,2] Mannich-type reactions provide one of the most efficient approaches to the synthesis of the β-aminoketone skeleton and considerable efforts have been devoted to the improvement of this 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**, $\Delta E = 14$ kcal mol^{-1}) is less favorable than addition of **2a** to *N*-benzylideneaniline (**1a**, $\Delta E = 0$ 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 ($\Delta E = 7$ kcal mol^{-1}) compared with the exothermic formation of *N*-phenyl adduct **3c** ($\Delta E = -7$ kcal mol^{-1}).

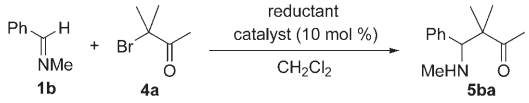


Scheme 1. Mannich-type reactions of the lithium enolate (energy values are calculated values).

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 $SnCl_2$ were ineffective (Table 1, entries 1 and 2), and SmI_2, which is known to be an effective reductant,[10] resulted in poor yields (Table 1, entries 3 and 4). In contrast, $GeCl_2$/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 $TiCl_4$ lowered the yield to 6% (Table 1, entry 6), and $BF_3{\cdot}OEt_2$, $Zn(OTf)_2$, 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	$BF_3{\cdot}OEt_2$	33
8	$GeCl_2$/dioxane	1.5	RT, 2 h	$Zn(OTf)_2$	34
9	$GeCl_2$/dioxane	1.5	RT, 2 h	Me_3SiOTf	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 CH_2Cl_2 (2 mL). [b] Yield determined from ^{1}H NMR spectrum. [c] Run in THF.

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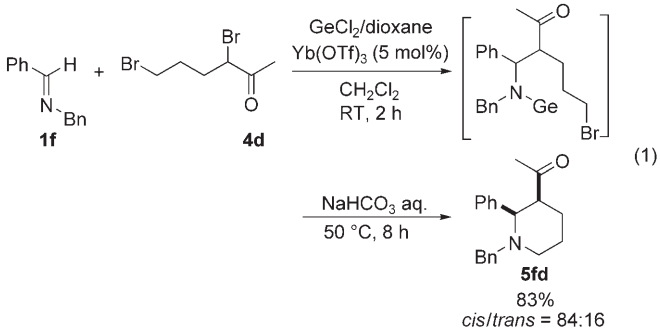
Me_3SiOTf were also found to be poor catalysts (Table 1, entries 7–9). In contrast to these representative Lewis acids, $Bi(OTf)_3$ and $In(OTf)_3$ both increased the yield to approximately 50% (Table 1, entries 10 and 11). The group three metal triflates, $Y(OTf)_3$ and $Sc(OTf)_3$, also increased the 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 formaldimine **1j** gave higher yields than those obtained with $Yb(OTf)_3$ (Table 2, entries 13–16).

The mild and selective reducing ability of $GeCl_2$/dioxane was demonstrated in the Mannich-type reaction by using dibromide **4d** and imine **1f.** Subsequent treatment with aqueous $NaHCO_3$ afforded the substituted piperidine **5fd** in good yield [Eq. (1)]. The 2-arylpiperidine unit is an important



(1)

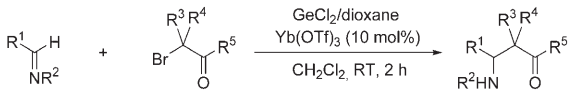
structure found in a number of biologically active compounds.[13] Next, we synthesized the antihypertensive agent, Be-2254, in just a few reaction steps (Scheme 2).[1c] Formaldimine **1k** was prepared in two steps from commercially available tyramine hydrogen chloride **6**. The germanium-mediated Mannich-type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

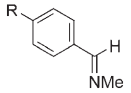
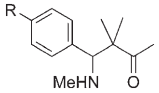
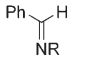
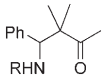
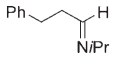
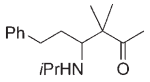
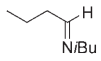
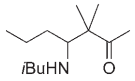
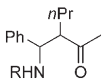
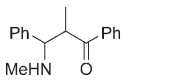
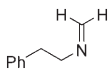
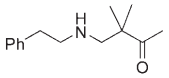
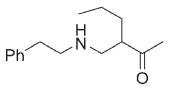
To complement the experimental studies, the thermodynamic parameters of the reaction involving trichlorogermanium enolate **2c**[14] were evaluated (Scheme 3).[8] Notably, results of the theoretical calculations show that the reactions of *N*-phenyl **1a** and *N*-methylimine **1b** are equally exothermic ($\Delta E = -24$ 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.

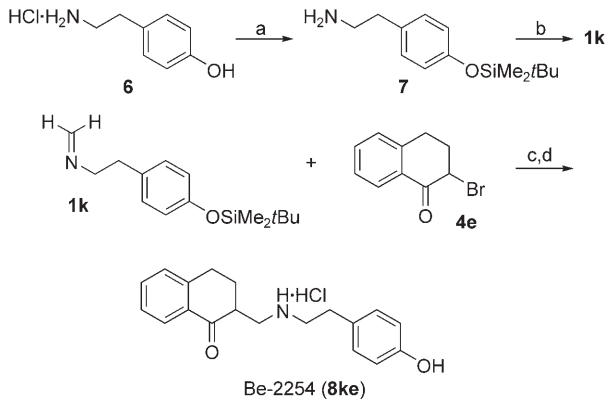
The optimized structures of the lithium–adducts (**3a** and **3b**) are depicted in Figure 1 a–b. The main difference between the structures is the negative charge on the nitrogen atoms (**3a** −0.84498, **3b** −1.00322). In **3a**, a lone pair on the nitrogen atom is in same plane as the phenyl ring (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		**1b** R = H		**4a**		**5ba**	93 (84)
2[c]		**1c** R = NO_2		**4a**		**5ca**	86 (79)
3		**1d** R = OMe		**4a**		**5da**	97 (83)
4[d]		**1e** R = Br		**4a**		**5ea**	89 (84)
5		**1f** R = Bn		**4a**		**5fa**	96 (83)
6		**1g** R = allyl		**4a**		**5ga**	91 (82)
7		**1a** R = Ph		**4a**		**5aa**	93 (81)
8[d]		**1h**		**4a**		**5ha**	66 (40)
9[e]		**1i**		**4a**		**5ia**	65 (44)
10		**1b**		**4b**		**5bb** (R = Me)	71[f] (51)
11		**1g**		**4b**		**5gb** (R = allyl)	80[g] (60)
12		**1b**		**4c**		**5bc**	97[h] (97)
13[i]		**1j**		**4a**		**5ja**	60
14[i,j]		**1j**		**4a**		**5ja**	67 (58)
15[i]		**1j**		**4b**		**5jb**	27
16[i,j]		**1j**		**4b**		**5jb**	52 (44)

[a] Reaction conditions: **1** (0.6 mmol), $GeCl_3$/dioxane (0.9 mmol), **4** (0.9 mmol), $Yb(OTf)_3$ (0.06 mmol), and CH_2Cl_2 (2 mL), unless otherwise stated. [b] Yield determined from ^{1}H 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*BuMe$_2$SiCl, imidazole, CH_2Cl_2, RT, 84%; b) $(CH_2O)_n$, $MgSO_4$, CH_2Cl_2, RT, 96%; c) $GeCl_2$/dioxane, $Bi(OTf)_3$, CH_2Cl_2, 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).

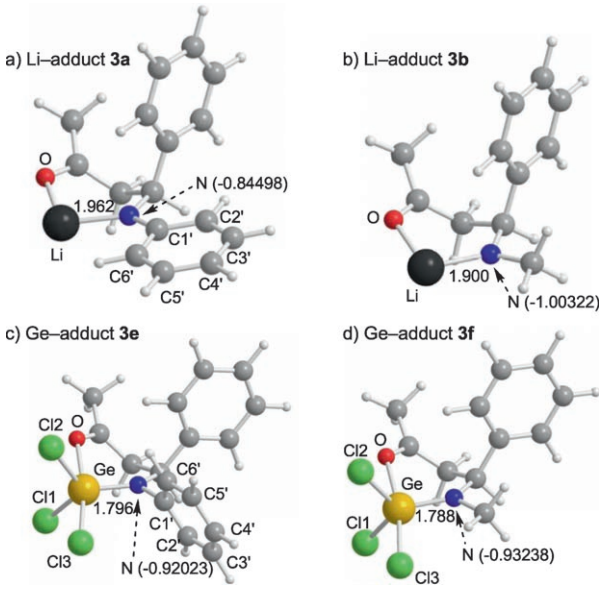


Figure 1. Optimized structures of metal-chelated Mannich adducts: a) **3a**, b) **3b**, c) **3e**, and d) **3f** (bond distances in Å and numbers in parentheses are for natural bond orbitals (NBO) charges).

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 1c–d). In addition, the phenyl ring of **3e** is almost perpendicular to the plane of N, Ge, and C1′ (Ge-N-C1′-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 $GeCl_2$/dioxane (0.9 mmol) in CH_2Cl_2 (2 mL) at room temperature. The mixture was then stirred for 2 h at room temperature, and saturated aq. $NaHCO_3$ (20 mL) was added. The mixture was extracted with Et_2O (10 mL × 3), dried ($MgSO_4$), and evaporated. The crude product was purified by silica gel chromatography to afford aminoketone **5ba** as a colorless solid.

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