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Yb/TMS-Br Promoted Homocoupling Reactions of Aliphatic Ketones and α,β-Unsaturated Ketones

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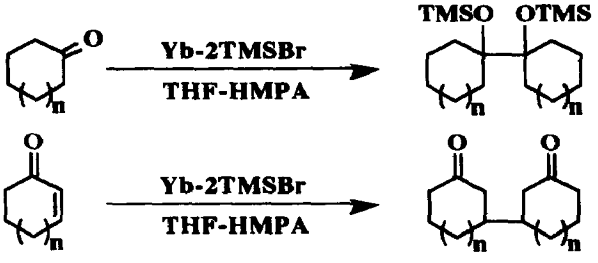
Abstract: *Ytterbium metal reacts with trimethylsilyl bromide (TMS-Br) to give divalent* $YbBr_2$. $YbBr_2$ *thus formed in situ, causes coupling reactions of aliphatic ketones and α,β-unsaturated ketones to give bissilylated 1,2-diols and 1,6-ketones, respectively, in good yields.*

Lanthanide mediated reaction has played an important role in organic synthesis.[1] Particularly, low-valent lanthanide reagents such as samarium diiodide (SmI_2) have been widely used to the organic reactions as one electron reductant. We have developed some lanthanide mediated reactions of carbonyl compounds.[2] In continuing studies on exploring lanthanide mediated reactions, we have investigated the coupling reactions of aliphatic ketones and α,β-unsaturated ketones using a novel reducing agent, Yb/TMS-Br.

Pinacol coupling at the 1-position of ketones using low-valent transition metals such as samarium(II) has been extensively studied and proved to be efficient for a C-C bond formation.[3] Oxidative homocoupling at the 2-position of ketones can be achieved by nickel peroxide.[4] On the contrary, reductive homocoupling reaction at the 3-position of ketones was achieved with electrochemically[5] or some reducing reagents such as Hg(Na),[6a] Li,[6b] organomanganese,[6c] and Bu_3SnH[6d] using α,β-unsaturated ketones. We report here that the Yb/TMS-Br reagent promoted coupling reactions of cyclic ketones and α,β-unsaturated ketones in THF:HMPA (4:1) to give bissilylated 1,2-diols and 1,6-diketones, respectively, in good yields (Eqs. 1 and 2).



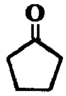
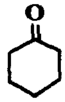
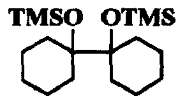
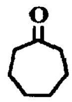
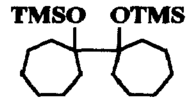
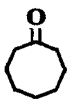
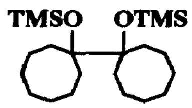
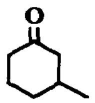
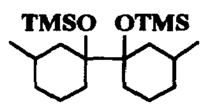
(1)

(2)

The representative results for the homocoupling reaction of cyclic ketones by Yb/TMS-Br are summarized in Table 1. In this reaction, bissilylated diols were selectively obtained without the formation of 1,2-diol.

The preparation of trimethylsilyl 1-(1'-trimethylsilyloxycyclohexyl)cyclohexyl ether is a typical example (entry 2, Table 1): Ytterbium metal (2 mmol, 0.346 mg) was placed in a 20-mL 2-necked flask equipped with a 3-way stopcock and a rubber septa. The flask was replaced with argon. To this flask, THF (4 mL), HMPA (1 mL), cyclohexanone (198 µL, 2 mmol), and then trimethylsilyl bromide (396 µL, 4 mmol) were added by a syringe successively. The mixture was degassed through repetition of three freeze-pump-thaw cycles. The mixture was stirred at room temperature for 5 h. Usual work-up followed by column chromatography (SiO_2, hexane) gave trimethylsilyl 1-(1'-trimethylsilyloxycyclohexyl)cyclohexyl ether (308 mg, 89%), which gives satisfactory IR, NMR, Mass spectral data and elemental analysis. Trimethylsilyl bromide is the best reagent for these coupling reactions; silyl chlorides and iodides are not effective. In addition, these reactions do not occur with ytterbium metal alone. The mixed solvent (THF:HMPA=4:1) gives the best result, but THF or HMPA alone is not effective. The reaction of 3-methylcyclohexanone affords two diastereomers (*dl:meso*) in the ratio of 5.2:1 according to the ^{13}C NMR analysis (entry 5, Table 1). Sterically hindered bulky ketones such as adamantanone and menthone are not reactive.

Table 1. Yb/TMS-Br Promoted Coupling of Cyclic Ketones[a]

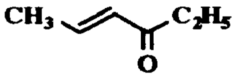
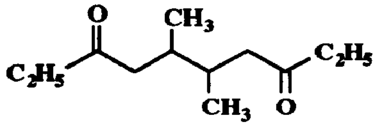
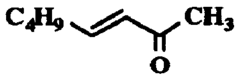
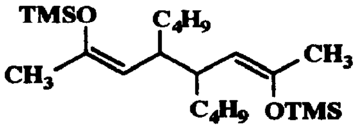
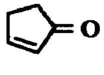
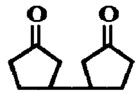
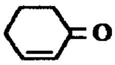
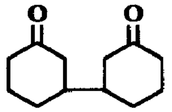
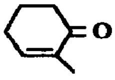
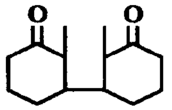
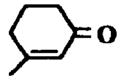
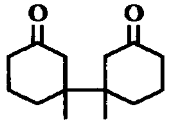
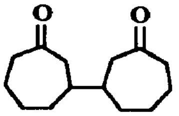
entry	ketone	product	yield/%[b]
1			62[c]
2			89
3			31[c]
4			39
5			57 (5.2:1)[d]

a) Ketone (2mmol), Yb (2mmol), TMSBr (3mmol), THF (4mL)-HMPA (1mL), rt, 5 h. b) Isolated yield based on the ketone. c) Reaction time 15 h. d) Diastereomer ratio was determined by ^{13}C NMR.

There are many reports on inter- and intramolecular reductive coupling reactions at the 3-position of α,β-unsaturated carbonyl compounds. Calas et al. reported that the reaction of α,β-unsaturated ketone with Mg-TMSCl in HMPA gave Michael adducts of silyl anion along with the 3,3'-coupling adducts.[7] Furthermore, Larson and White depicted a formation of the 3,3'-coupling adducts in the reaction of benzylideneacetone with Yb(II)/NH_3 in a lower yield.[8] We also detected the 3,3'-coupling adducts as a minor product in the reaction of chalcone with ytterbium metal.[9] In the case of α,β-unsaturated esters, cerium(IV) assisted electrochemical reduction[10] and samarium iodide promoted homocoupling reaction[11] are reported. We have found that Yb/TMS-Br can cause the 3,3'-coupling reaction of α,β-unsaturated ketones to give 1,6-diketones (Eq. 2). The representative results are listed in Table 2. Both cyclic and acyclic enones undergo coupling. Coupling of

2-methyl- or 3-methyl-2-cyclohexenones gives a single diastereomer (entries 5 and 6, Table 2), but, the reaction of other enones is not stereoselective and gives two diastereomers (*dl*:*meso*=1:1). Electrochemical reaction of enol acetates is reported to be non-stereoselective to give a *dl*:*meso* 1:1 mixture.[12] In the reaction, small amounts of saturated ketones were also formed along with 1,6-diketones (entries 1 and 5, Table 2).

Table 2. Yb/TMS-Br Promoted Coupling of α,β-Unsaturated Ketones[a]

entry	ketone	condition[b], (time/h)	product	yield/%[c]
1		A(72)		67[d,e]
2		A(10)		52[e,f]
3		A(40) B (4)		45[e] 68[e]
4		A(17) B (3)		92[e] 90[e]
5		B (8)		92[g]
6		A(17) B(17)		68 (30)[h] 32 (60)[h]
7		A (6) B(12)		46[e] 46[e]

a) Ketone (1 mmol), Yb (1 mmol), TMS-Br (2 mmol). b) Condition A; THF (2.4 mL)-HMPA (0.6 mL), rt. Condition B; THF (3 mL), reflux. c) GLC yield based on ketones. d) 3-Hexanone (25%) was also formed. e) The *dl*:*meso* ratio (1:1) was determined by ^{13}C NMR. f) (*2E,6E*)- and (*2Z,6E*)-adducts (3:1) were formed. g) 2-Methylcyclohexanone (6%) was also formed. h) The yield in parentheses is of 3-(5'-methylcyclohexa-1',5'-dienyl)-3-methylcyclohexanone.

In order to clarify the active species of the present Yb/TMS-Br reagent, the reaction of triethylsilyl bromide with ytterbium metal in THF was carried out. The reaction gave a green suspension as is the case of the reaction of trimethylsilyl bromide (TMS-Br). The quantitative formation of triethylsilane, which is formed by the abstraction of H• radical from THF by silyl radical ($R_3Si•$), was recognized in a mother solution of this suspension, and any hexaethyldisilane, the coupling product was not detected. (Eq. 3). X-ray analysis of the residual powder separated from this suspension were in fair agreement with the authentic $YbBr_2$ prepared from the reaction of $HgBr_2$ with Yb.[13] In addition, the reaction of the powder with 2-methyl-2-cyclohexenone gave the 1,6-diketone in 92% yield. These results show that the Yb/TMS-Br reagent generates $YbBr_2$ *in situ* and $YbBr_2$ thus formed, acts as a single electron reductant for these coupling reactions.

$$\mathrm{Yb} \quad + \quad 2\ \mathrm{Et_3SiBr} \xrightarrow{\text{THF-HMPA}} \mathrm{YbBr_2} \quad + \quad 2\ \mathrm{Et_3SiH} \qquad (3)$$

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