

## Ketone Coupling with Alkyl Iodides, Bromides, and Chlorides Using Thulium Diodide: A More Powerful Version of $\text{SmI}_2(\text{THF})_x/\text{HMPA}$

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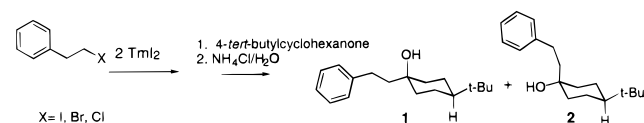
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Since Kagan's seminal studies in 1977,<sup>1</sup> samarium diiodide has become a popular reducing agent in organic synthesis.<sup>2,3</sup> It is used under a variety of conditions to accomplish a wide range of transformations. In many cases, reactivity is enhanced by adding hexamethylphosphoramide (HMPA) to  $\text{SmI}_2(\text{THF})_x$ .<sup>4</sup> Unfortunately, this most effective and popular additive is highly carcinogenic<sup>5</sup> and alternatives are highly desirable.<sup>6</sup> Several other methods for increasing  $\text{SmI}_2$  reactivity have been reported and include the addition of transition metal salts<sup>7</sup> or samarium metal,<sup>8</sup> photolysis,<sup>9</sup> and the design of intramolecular reactions.<sup>10</sup>

Recently, in collaboration with the Bochkarev group, we reported the synthesis and structure of the first molecular Tm(II) complex,  $\text{TmI}_2(\text{DME})_3$ .<sup>11</sup> This complex was found to be structurally analogous to samarium diiodide in DME,<sup>12</sup> but it is much more reactive since  $4f^{13}$  Tm(II) has a much greater reduction potential than  $4f^6$  Sm(II).<sup>13</sup> Preliminary studies indicated that this compound was so reactive<sup>12</sup> that it was uncertain if it would be useful as a reagent like  $\text{SmI}_2(\text{THF})_x$  in organic transformations.

### Scheme 1. The Reaction of 2-Phenethyl Halides with 4-*tert*-Butylcyclohexanone



To determine if  $\text{TmI}_2(\text{DME})_x$ <sup>14</sup> was viable as a reagent and if it had utility as an alternative for  $\text{SmI}_2(\text{THF})_x/\text{HMPA}$ , we have examined its reactivity in the coupling of 4-*tert*-butylcyclohexanone with alkyl halides, Scheme 1. This reaction was used as an assay, since it has been thoroughly studied with samarium diiodide.<sup>15,16</sup> Reactions were carried out<sup>17</sup> in accordance with the samarium Grignard procedure introduced by Curran<sup>16</sup> in which 2 equiv of the lanthanide reagent are added to the alkyl halide and the ketone is added subsequently. Reactions using  $\text{SmI}_2(\text{THF})_x/\text{HMPA}$  were conducted to ensure that Sm/Tm comparisons could be made under one uniform set of conditions.

As shown in Table 1,  $\text{SmI}_2(\text{THF})_x/\text{HMPA}$  gives yields and selectivities for the reaction of phenethyl iodide with 4-*tert*-butylcyclohexanone under our conditions which are consistent with the literature (entry 1).  $\text{TmI}_2(\text{DME})_x$  in DME matched these results (entry 2), *but without any HMPA present*. In contrast,  $\text{SmI}_2(\text{THF})_x$  without HMPA is reported to reduce iodides only after extended reaction times in refluxing THF.<sup>2a</sup>

After establishing that HMPA-free  $\text{TmI}_2(\text{DME})_x$  was at least equivalent to  $\text{SmI}_2(\text{THF})_x/\text{HMPA}$ , less reactive halides<sup>3d</sup> were examined. In our control reactions with 2-phenethyl bromide (entry 3),  $\text{SmI}_2(\text{THF})_x/\text{HMPA}$  required 15 min to change color from the deep purple of Sm(II) to an orange-yellow characteristic of Sm(III). After the addition of 4-*tert*-butylcyclohexanone, a 65% conversion to **1** and **2** in a 77:23 ratio was found. In contrast, when 2-phenethyl bromide was added to  $\text{TmI}_2(\text{DME})_x$  (entry 4), the color changed immediately from the emerald green Tm(II) solution to bright yellow. A white/gray precipitate formed

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







(14)  $\text{TmI}_2(\text{DME})_x$  has  $x = 3$  when obtained as single crystals from DME<sup>11</sup> and  $x = 2$  as a powder.<sup>12</sup> Cf.  $\text{SmI}_2(\text{THF})_x$ ;  $x = 5$  as single crystals,  $x = 2$  as a powder. See: Evans, W. J.; Gummersheimer, T. S.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 8999.  $\text{TmI}_2(\text{DME})_2$  can be produced by reduction of a suspension of  $\text{TmI}_3(\text{DME})_2$  (2.5 g, 3.4 mmol) in 50 mL of oxygen-free, dry DME with Tm powder (0.65 g, 3.86 mmol). The reaction is heated to reflux under nitrogen for 40 min and filtered to remove unreacted Tm metal. Removal of the solvent under vacuum leads to quantitative conversion to  $\text{TmI}_2(\text{DME})_2$  (3.07 g, 5.1 mmol) as an emerald green powder.

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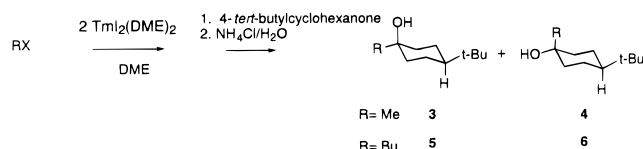
(17) (a) The procedures for reactions using isolated  $\text{TmI}_2(\text{DME})_x$  and for complexometric analysis of the stock solutions are given in the Supporting Information. (b) Procedure using  $\text{TmI}_2(\text{DME})_x$  generated in situ. To a Schlenk flask containing Tm powder (0.80 g, 4.7 mmol) and 90 mL of dry, oxygen-free DME was added iodine (1.20 g, 4.7 mmol) under a  $\text{N}_2$  purge to generate a dark brown-red solution. The solution was heated to reflux with rapid stirring. After about 2 h the solution changed to white. Shortly thereafter (10 min) the color changed to emerald green. Heating continued until white insoluble materials were replaced by dark green product. After about 1 h, no more white precipitate was observable and dark green  $\text{TmI}_2(\text{DME})_x$  was present as a precipitate from the saturated solution. An aliquot of the saturated solution [0.05 M (determined by complexometric titration<sup>17a</sup>), 10 mL, 5 mmol] was then added via syringe to a solution of 0.25 mmol of the organic halide in ca. 5 mL of DME in a septum-covered flask under nitrogen. Once an orange-yellow solution was formed, 0.25 mmol of the ketone was injected through the septum resulting in a clear solution with a white precipitate. The reaction was then quenched with an aqueous solution saturated with  $\text{NH}_4\text{Cl}$  and extracted with ether/pentane (1:1). The organic extracts were washed with  $\text{H}_2\text{O}$  ( $2 \times 5$  mL) and dried over  $\text{MgSO}_4$ . The crude product was analyzed by GC. Isolation of the products by flash chromatography gave a white crystalline product whose spectra were consistent with the literature values.<sup>16</sup> (c) Procedure using  $\text{TmI}_2(\text{THF})_x$  generated in situ in THF. To a Schlenk flask containing Tm powder (1.0 g, 5.9 mmol) and 50 mL of dry, oxygen-free THF was added  $\text{I}_2$  (1.4 g, 5.5 mmol) under a  $\text{N}_2$  purge to generate a dark brown-red solution. The solution was heated to reflux with rapid stirring. After about 20 min the solution changed to white. Shortly thereafter (10 min) the color changed to emerald green. Heating continued until white insoluble materials were replaced by dark green product. After about 1 h, no more white precipitate was observable and dark green  $\text{TmI}_2(\text{THF})_x$  was present as a precipitate from the saturated solution. An aliquot of the saturated solution [0.1 M (determined by complexometric titration<sup>17a</sup>), 5 mL, 5 mmol] was then added via syringe to a solution of 0.25 mmol of the organic halide in ca. 5 mL of THF in a septum-covered flask under nitrogen. Once an orange-yellow solution was formed, 0.25 mmol of the ketone was injected through the septum resulting in a clear solution with a white precipitate. The reaction was then quenched as described in (b).

**Table 1.** Comparison of Reactivity of  $\text{TmI}_2(\text{DME})_x$  and  $\text{SmI}_2(\text{THF})_x/\text{HMPA}$  at 25 °C

Reagent	Alkyl halide	Solvent	Time <sup>a</sup>	Yield <sup>b</sup> (ax:eq <sup>c</sup> )
1. $\text{SmI}_2(\text{THF})_x/\text{HMPA}$		THF	< 1 min	92 % (77:23)
2. $\text{TmI}_2(\text{DME})_x$		DME	< 1 min	99% (79:21) <sup>d</sup>
3. $\text{SmI}_2(\text{THF})_x/\text{HMPA}$		THF	15 min	65 % (77:23)
4. $\text{TmI}_2(\text{DME})_x$		DME	< 1 min	92% (79:21) <sup>d</sup>
5. $\text{SmI}_2(\text{THF})_x/\text{HMPA}$		THF	18 h	(no reaction)
6. $\text{TmI}_2(\text{DME})_x$		DME	3 min	95 % (79:21) <sup>d</sup>
7. $\text{TmI}_2(\text{DME})_x$		THF	< 1 min	99% (79:21)
8. $\text{SmI}_2(\text{THF})_x/\text{HMPA}$		DME	< 1 min	0 %

<sup>a</sup> Time elapsed until color change from characteristic Ln(II) to Ln(III); in each case the Ln(III) color changed immediately to white upon addition of the ketone. <sup>b</sup> Determined by GC/MS based on unreacted ketone. <sup>c</sup> Isomer ratio was determined by GC/MS. <sup>d</sup> Isolated yields were obtained for entries 2 (97%), 4 (97%), and 6 (95%).

**Scheme 2.** The Reaction of Methyl Iodide and *n*-Butyl Halides with 4-*tert*-Butylcyclohexanone (RX = MeI, *n*-BuI, *n*-BuBr, *n*-BuCl)







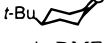
















concurrently which is consistent with the formation of  $\text{TmI}_3$ . After addition of the ketone, a 92% conversion to **1** and **2** in a 79:21 ratio was observed.

The difference between the Tm and Sm diiodide reagents was even more pronounced with 2-phenethyl chloride. When  $\text{SmI}_2(\text{THF})_x/\text{HMPA}$  (entry 5) was employed, little color change was observed, even after 18 h at 25 °C. After addition of the ketone, no product was formed. This is consistent with literature reports that unactivated chlorides<sup>18</sup> are not very reactive with samarium diiodide unless some type of enhancement is employed, e.g. the addition of catalytic amounts of  $\text{NiX}_2$ ,<sup>7</sup> reaction in the presence of samarium metal at 67 °C for 20 h,<sup>8</sup> photolysis for 3–9 h at 25–40 °C,<sup>9</sup> or an intramolecular reaction.<sup>10</sup> However,  $\text{TmI}_2(\text{DME})_x$  in DME (entry 6) reacted to give a yellow solution in 3 min, which after addition of the ketone resulted in a 79:21 ratio of **1** and **2** in 88% yield.

Since THF is typically used for  $\text{SmI}_2$  reactions and since solvent effects can be influential in  $\text{SmI}_2(\text{THF})_x$  reductions,<sup>6a</sup> the reaction with 2-phenethyl iodide was carried out in THF with  $\text{TmI}_2(\text{DME})_x$  (entry 7). The results showed comparable yields and identical selectivities to reactions conducted in DME (entry 2). However, the reaction of  $\text{SmI}_2(\text{THF})_x/\text{HMPA}$  in DME gave ethylbenzene as the only product by GC (entry 8). This is consistent with the report of Molander that DME is an unacceptable solvent for organosamarium reactions.<sup>19</sup>

Reactions of  $\text{TmI}_2(\text{DME})_x$  with other alkyl halides were also investigated, Scheme 2 (Table 2). The reaction of MeI with 2 equiv of  $\text{TmI}_2(\text{DME})_x$  in DME led to 99% conversion to products with a ratio of axial **3** to equatorial **4** of 64:36 (entry a). The reaction of *n*-butyl iodide (entry b) gave a 99% conversion with an axial **5**:equatorial **6** ratio of 74:26. **5** and **6** can also be obtained from *n*-butyl bromide and chloride in yields of 96% and 97%, respectively (entries c and d). The product ratios are the same as for the *n*-butyl iodide reaction. Reactions using the Barbier procedure (entry e) in which  $\text{TmI}_2(\text{DME})_x$  is added to a mixture

**Table 2.** Additional  $\text{TmI}_2$  Reactivity: Other Substrates, Low Temperature Reactions, and  $\text{TmI}_2(\text{THF})_x$  Reactions in THF

Alkyl halide	Electrophile	Temp	Time <sup>a</sup>	GC Yield (ax:eq <sup>c</sup> )	Isolated Yield
Reactions in DME using isolated $\text{TmI}_2(\text{DME})_x$					
a) MeI		25°C	< 1 min	99% (64:36)	-
b) <i>n</i> -BuI		25°C	< 1 min	99% (74:26)	85%
c) <i>n</i> -BuBr		25°C	< 1 min	96% (74:26)	97%
d) <i>n</i> -BuCl		25°C	5 min	97% (74:26)	95%
e) MeI <sup>d</sup>		25°C	< 1 min	36% <sup>d</sup> (68:32)	-
Reactions in DME using $\text{TmI}_2(\text{DME})_x$ generated <i>in situ</i>					
f) 		-22°C	10 min	93%	87%
g) 		0°C	20 min	96%	90%
h) 		-22°C	60 min	94%	94%
i) 		25°C	3 min	98%	95%
j) 		0°C	1 h	90%	85%
Reactions using $\text{TmI}_2(\text{THF})_x$ generated <i>in situ</i>					
k) 		-45°C	40 min	83%	80%
l) 		-25°C	45 min	87%	83%
m) 		25°C	10 min	90%	85%

<sup>a-c</sup> See Table 1. <sup>d</sup> Barbier conditions.

of the ketone and the alkyl halide gave significantly lower yields of coupled products and generated 4-*tert*-butylcyclohexanol, due to reduction of the ketone. This is consistent with the expected high reactivity of Tm(II) compared to Sm(II) with ketones.

Since  $\text{TmI}_2(\text{DME})_x$  exhibited such high reactivity at room temperature, its viability at reduced temperature was examined. In these reactions,  $\text{TmI}_2(\text{DME})_x$  was added as a DME solution by syringe using a saturated stock solution generated *in situ* from Tm and  $\text{I}_2$ .<sup>17b</sup> Phenethyl iodide reacted smoothly with cyclohexanone at -22 °C in 10 min to form phenethylcyclohexanol in 96% yield (entry f). Phenethyl bromide reacts at 0 °C in 20 min (entry g), while reaction at -22 °C gave a 94% yield in 60 min (entry h). Phenethyl chloride reacted at 0 °C to give a 90% yield after 1 h (entry j). This variation of reaction time as a function of temperature could be used to control regiochemistry in sequenced reactions.<sup>10</sup>

Encouraged by these results, we examined the possibility of accomplishing this  $\text{TmI}_2$  reactivity exclusively in THF, since it may be desirable to avoid DME in some situations. As shown in entries k–m,  $\text{TmI}_2(\text{THF})_x$  generated conveniently *in situ* in THF as a stock solution on a Schlenk line from Tm and  $\text{I}_2$ <sup>17c</sup> gave excellent results as well.

On the basis of these results,  $\text{TmI}_2$  has the potential to be an effective replacement for  $\text{SmI}_2(\text{THF})_x$  when HMPA is to be avoided, when the  $\text{SmI}_2(\text{THF})_x/\text{HMPA}$  system is too weak a reductant to accomplish a reaction, when subambient reaction temperatures are desirable, and when reactions faster than those achievable via  $\text{MX}_2$ <sup>7</sup> and samarium addition<sup>8</sup> and photolysis<sup>9</sup> are needed. The higher reactivity of  $\text{TmI}_2$  may limit its functional group tolerance in some applications, but it is possible that this can be overcome by developing the appropriate protocols.

**Acknowledgment.** We thank the National Science Foundation for support for this research.

**Supporting Information Available:** Experimental procedures (PDF). These materials are available free of charge via the Internet at <http://pubs.acs.org>.

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