Generation of Hafnium Hydride and its Application to Chemo- and Diastereoselective Reactions

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Abstract: Hafnium hydride was generated by the transmetalation between Bu_3SnH and $HfCl_4$ using either THF or EtCN as the solvent. This process effectively reduced aldehydes, aldimines, ketones, and esters. In the hafnium hydride reduction of α-alkoxyketones, the diastereoselectivity was dependent on whether THF or EtCN was used as the solvent.

Key words: hafnium, hydrides, transmetalation, reduction, selectivity

Hafnium tetrachloride ($HfCl_4$) is a characteristic Lewis acid, which catalyzes both the hydrometalation of alkynes[1] and esterification.[2] Hafnium tetrachloride catalyzes these reactions by activating both the alkynes and the carbonyl functional groups.

By contrast, organotin nucleophiles easily transmetalate with other acidic metals.[3] We previously reported that indium halide (InX_3)[4] or early transition-metal halides, such as tantalum halide ($TaCl_5$)[5], were easily transmetaled with tin compounds, such as tin hydride and allylic tins, to generate active metal species. Thus, an advantage of the organotin-based metal exchange is that the byproducts, such as the trialkyltin halides, are weak Lewis acids that reduce decomposition of the generated active metal species.[4,5]

In the present study, we examined the transmetalation between tri-*n*-butyltin hydride (Bu_3SnH) and $HfCl_4$ (Figure 1). We estimated transmetalation by monitoring the formation of Bu_3SnCl using ^{119}Sn NMR.

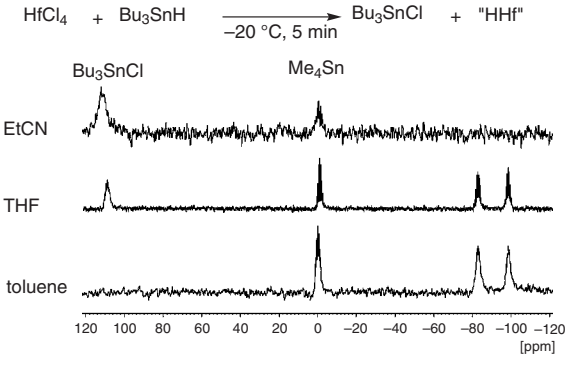

Figure 1 Generation of Bu_3SnCl by transmetalation

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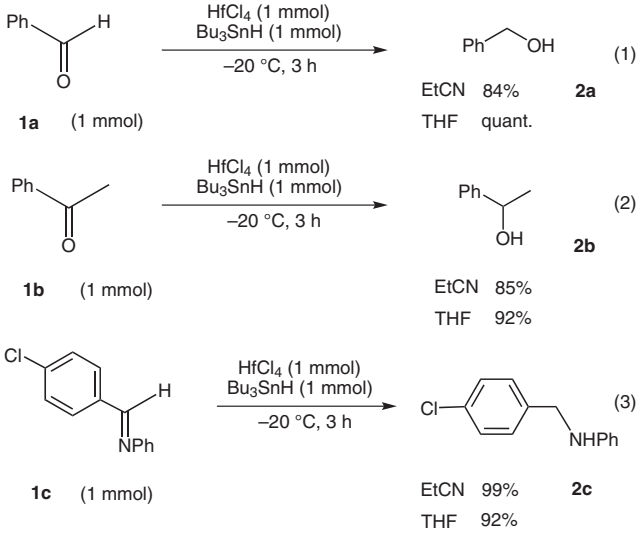
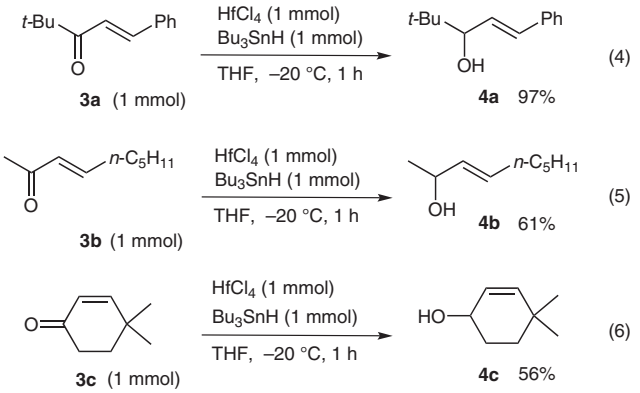
When the mixture of Bu_3SnH and $HfCl_4$ was stirred in toluene at –20 °C, Bu_3SnH first appeared after 5 minutes.[6] When THF was used as the solvent, both Bu_3SnH and Bu_3SnCl were detected. Although the reaction was not quantitative, the formation of Bu_3SnCl indicated that partial transmetalation of Bu_3SnH with $HfCl_4$ had occurred. In addition, when the reaction was performed in EtCN, only Bu_3SnCl was detected.[4] This result indicated that the hafnium hydride species formed immediately in EtCN. At lower reaction temperatures, for example, –40 °C, transmetalation did not occur. The generated hafnium hydride was labile, as evidenced by its decomposition (accompanied by H_2 production) concurrent with the generation of Bu_3SnCl.[7]

In the next stage, the ability of the hafnium hydride formed in situ to react with carbonyl derivatives was investigated. Tri-*n*-butyltin hydride, $HfCl_4$, and substrate **1** were mixed in either EtCN or THF at –20 °C, and the reactions were allowed to proceed for 3 hours. Benzaldehyde (**1a**), acetophenone (**1b**), and aldimine **1c** were effectively reduced to the corresponding alcohols **2a**,**b** and amine **2c**, respectively (Scheme 1, eq 1–3).

Regioselective 1,2-reduction of α-enones **3** gave allylic alcohols **4**. Cyclic and acyclic aliphatic enones were applicable substrates (Scheme 2, eq 4–6). The reaction of aromatic enones, such as chalcone, resulted in complex mixtures.



Scheme 1 Reduction of carbonyl derivatives



Scheme 2 1,2-Reduction of enones

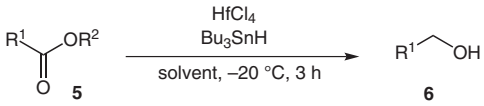
The reducing ability of this system is so high that the ester functional groups **5** were effectively reduced to the corresponding alcohols **6** (Table 1). The use of EtCN as solvent in these reactions gave a greater yield compared with that obtained using THF (entries 1 and 2). Thus, both aliphatic and aromatic alkyl esters were applicable substrates.

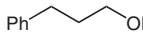
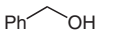
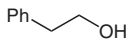
As shown in Scheme 3, the chemoselectivity of the reduction of the α,β-unsaturated ester **7a** was dependent on which solvent was used to induce either of the active hafnium species, hafnium hydride or $HfCl_4$. Thus, the reaction in EtCN afforded predominantly the allylic alcohol **8a** (eq 7). On the other hand, in toluene, the carbon–carbon double bond was reduced to give the saturated ketone **8b** (eq 8). In toluene, $HfCl_4$ acted as a Lewis acid, and no transmetalation occurred.

Finally, we performed the reduction of α-alkoxyketones **9** (Table 2).[8] Interestingly, the diastereoselectivity of the reaction was dependent on whether EtCN or THF was used as the solvent. When the reduction was carried out in EtCN, predominantly *erythro*-alkoxy alcohols **11** were obtained (entries 1 and 3). On the other hand, use of THF as the solvent increased the ratio of *threo*-isomers **10** (entries 2 and 6).[9]

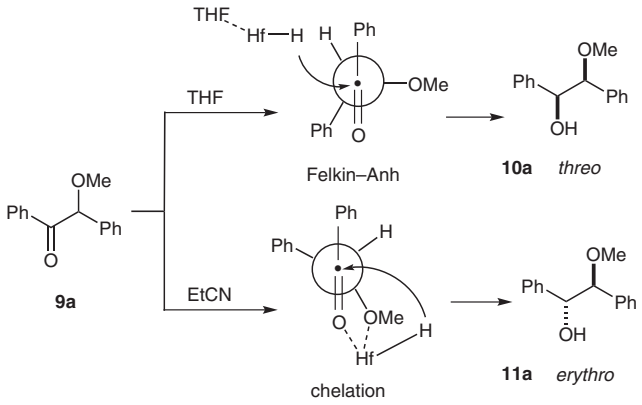
Scheme 4 explains, in terms of the Lewis acidity of the hafnium center, why the diastereoselectivity of the hafnium hydride reduction of **9** varies with the solvent. Tetrahydrofuran coordinates to the hafnium center, and prevents chelation between hafnium and the oxygen substituent of **9**.[10] Hence, the reaction proceeds according to the Felkin–Anh model[11] to give *threo*-alcohol **10**. On the other hand, the ability of EtCN to coordinate with hafnium is poor; hence, the reduction with hafnium hydride results in chelation with the substrate **9** to give the *erythro*-alcohol **11**.[12]

Table 1 Reduction of Esters[a]

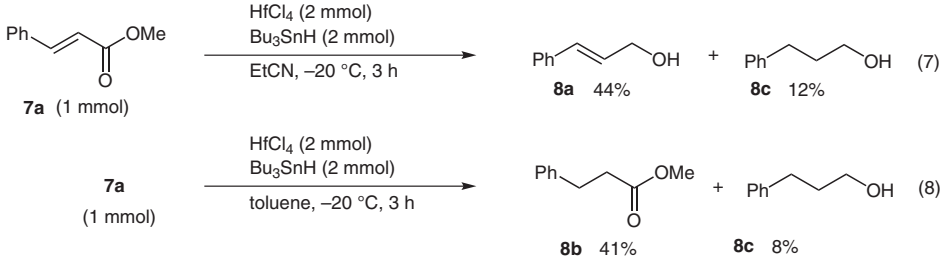


Entry	R^1	R^2	Solvent	Product	Yield (%)
1	$BnCH_2$	Et	EtCN	 **6a**	97
2			THF	**6a**	0 (48)[b]
3	$BnCH_2$	*t*-Bu	EtCN	**6a**	78
4	*n*-C_8H_{17}	Et	EtCN	*n*-$C_9H_{19}OH$ **6b**	83
5	Ph	Et	EtCN	 **6c**	96
6	Bn	Bn	THF	 **6d**	99
				 **6c**	95

[a] Hafnium hydride was generated by the $HfCl_4$/Bu_3SnH system. Reduction was performed by the reaction of **9** (1 mmol) with $HfCl_4$/Bu_3SnH (3 mmol) in EtCN or THF (2 mL) at –20 °C for 3 h.
[b] Room temperature.

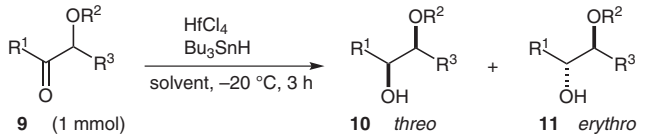


Scheme 4 Control of diastereoselectivity

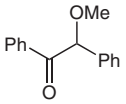
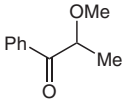
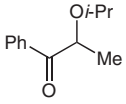


Scheme 3 Reduction of unsaturated esters

Table 2 Reduction of α-Alkoxyketones[a]



9 (1 mmol) **10** *threo* **11** *erythro*

Entry	Substrate **9**	Solvent	Yield (%)	**10/11**
1		EtCN	93	15:85
2		THF	96	77:23
	9a			
3		EtCN	85	10:90
4		THF	77	54:46
	9b			
5		EtCN	100	52:48
6		THF	94	86:14
	9c			

[a] Hafnium hydride was generated by $HfCl_4/Bu_3SnH$ system. Reduction was performed by the reaction of **9** (1 mmol) with $HfCl_4/Bu_3SnH$ (1 mmol) in EtCN or THF (2 mL) at –20 °C for 3 h.

In conclusion, hafnium hydride generated in situ demonstrated consistent reducing ability. In some cases, control of regio- and diastereoselectivity was achieved by varying the solvent.

Acknowledgment

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References and Notes

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(6) Hafnium(IV) chloride and Bu_3SnH were mixed in NMR sample tube under the conditions of –20 °C, and the mixture was immediately introduced NMR instrument and measured. The obtained chart was the one after 5 minutes from mixing.

(7) In transmetalated mixture in EtCN over –20 °C, fast decomposition occurred with quantitative generation of H_2, hence we could not determine exact hafnium species such as $HHfCl_3$ or H_2HfCl_2.

(8) Shibata, I.; Yoshida, T.; Kawakami, T.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 4049.

(9) **Typical Procedure**
A 10 mL round-bottom flask charged with $HfCl_4$ (1.0 mmol) was dried by heating to 110 °C under reduced pressure ($1.33 \cdot 10^{-3}$ bar) for 1 h. After the nitrogen was filled, EtCN (2 mL) was added to dissolve $HfCl_4$, and the solution was cooled to –20 °C. To the mixture was added Bu_3SnH (1.0 mmol) and after 5 minutes benzoin methyl ether (**9a**, 1.0 mmol). After stirring for 3 h, the resulting mixture was quenched by aq MeOH (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layer was treated with NH_4F, and then the precipitate was filtered to remove the tin compound. The organic layer was dried over $MgSO_4$, and then filtered and evaporated. Yield and ratio of **10a/11a** were determined by NMR. Further purification was performed by SiO_2 column chromatography eluting with hexane–EtOAc = 85:15 afforded **10a** and **11a** as a mixture.
***threo*-2-Methoxy-l,2-phenylethanol (10a) and *erythro*-2-Methoxy-l,2-phenylethanol (11a)**
Compound **10a**: Mp 84–87 °C. IR (KBr): 3400, 1030, 1045 cm^{-1}. MS: *m/z* = 228 [M^+]. ^1H NMR (400 MHz, $CDC1_3$): δ = 2.45 (br, 1 H, OH), 3.30 (s, 3 H, OCH_3), 4.12 (d, 1 H, *J* = 8.3 Hz, CHOMe), 4.65 (d, 1 H, *J* = 8.3 Hz, CHOH), 7.11–7.28 (m, 10 H, Ph).
Compound **11a** ^1H NMR (400 MHz, $CDC1_3$): δ = 2.45 (br, 1 H, OH), 3.22 (s, 3 H, OCH_3), 4.34 (d, 1 H, *J* = 5.4 Hz, CHOMe), 4.88 (d, 1 H, *J* = 5.4 Hz, CHOH), 7.11–7.28 (m, 10 H, Ph).

(10) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

(11) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199.

(12) In the reduction of **9a** in MeCN, the addition of ligand such as $Ph_3P=O$ afforded 79% *anti* selectivity. Hence $Ph_3P=O$ coordinates to hafnium center to prevent the chelate formation.