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Generation of Prenylhafnium and α-Selective Addition to Imines

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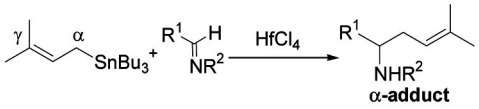
Keywords: Allylation / Regioselectivity / Hafnium / Tin / Transmetalation / Imines

Allylhafnium compounds were generated by transmetalation between allyl-$SnBu_3$ and $HfCl_4$ in EtCN. A highly α-selective addition reaction of prenyltributyltin to imines was observed.

Introduction

Allylation of imines is a representative method to give homoallylic amines,[1] but limitations of the method remain to be resolved. First, the scope of application to imines is still narrow due to the instability of the starting material. Second, the regioselectivity is difficult to control. In most cases, allylation to imines has been performed via γ-addition. In particular, no effective methods for the α-allylation of imines derived from aliphatic aldehydes have thus far been reported. Allyltin compounds are often used in combination with another acidic metal for the allylation of carbonyls and imines.[2] Herein, we report the generation of allylhafnium compounds via the allyltin/$HfCl_4$ system, and their characteristic reactivity toward imines. High α-selectivity for the prenylation reaction of various imines was achieved (Scheme 1).

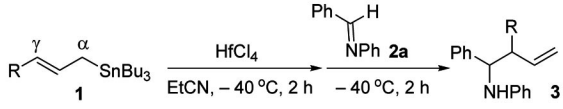


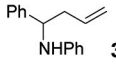
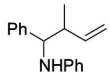
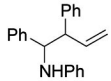
Scheme 1. Prenylation to imines.

Results and Discussion

Table 1 shows the results of the allylation of benzylideneaniline (**2a**) by the allyltributyltin (**1a**)-hafnium tetrachloride ($HfCl_4$) system. In propionitrile as solvent the allylation of the C=N group of **2a** proceeds effectively to give the homoallylamine **3a** (entry 1). In particular, the use of 2 equiv. of allyltin/$HfCl_4$ affords **3a** in quantitative yield (entry 2). γ-Substituted allyltin compounds like crotyl- and cinnamyl$SnBu_3$ (**1b** and **1c**) react with the γ-carbon of allyl-Sn compounds to give homoallylic amines **3b** and **3c**, respectively (entries 3 and 4).

Table 1. Allylation of benzylideneaniline (**2a**).[a]



Entry	R (**1**) (equiv.)	$HfCl_4$ (equiv.)	Product **3**	% Yield
1	H (**1a**) (1)	1	 **3a**	26
2	H (**1a**) (2)	2	**3a**	99
3	Me (**1b**) (2)	2	 **3b**	63[b]
4	Ph (**1c**) (2)	2	 **3c**	89[c]

[a] Reduction was performed by the reaction of **2a** (1 mmol) with **1**/$HfCl_4$ in EtCN at –40 °C for 2 h. [b] *dr* = 64:36. [c] *dr* = 79:21.

Next, we focused on the prenylation of imines starting from prenyl$SnBu_3$ (**1d**) (Table 2). We have already reported that the allyltantalum system (allyl$SnBu_3$/$TaCl_5$) exhibits efficient reactivity toward imines.[3b] However, the system could not be applied to prenyl$SnBu_3$ (**1d**) because no reaction occurs with imines. This can be attributed to steric hindrance at the nucleophilic carbon of the generated prenyltantalum species. By contrast, the presented reaction with prenyl$SnBu_3$ (**1d**)/$HfCl_4$ proceeds well. The regioselectivity of the reaction is noteworthy. When benzylideneaniline (**2a**)

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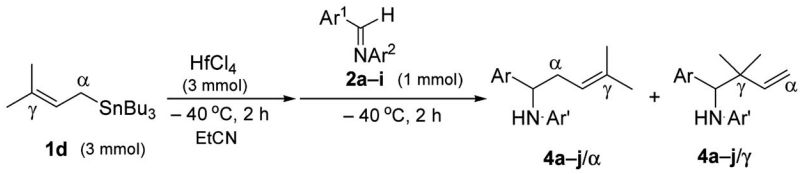
Table 2. Prenylation to imines.[a]



Entry	Ar^1 (**2**)	Ar^2 (**2**)		% Yield of **4**	**α/γ**
1	Ph	Ph	**a**	92	100:0
2	Ph	Ph	**a**	87[b]	100:0
3	Ph	Ph	**a**	46[c]	24:76
4	Ph	*p*-ClC_6H_5	**b**	70	100:0
5	Ph	*p*-FC_6H_5	**c**	60	100:0
6	Ph	*p*-$MeOC_6H_5$	**d**	51	100:0
7	Ph	*p*-$NO_2C_6H_5$	**e**	98	0:100
8	Ph	SO_2Ph	**f**	70	0:100
9	*p*-ClC_6H_5	Ph	**g**	77	100:0
10	*p*-FC_6H_5	Ph	**h**	60	100:0
11	*p*-$MeOC_6H_5$	Ph	**i**	(traces)	
12	*p*-$NO_2C_6H_5$	Ph	**j**	55	0:100

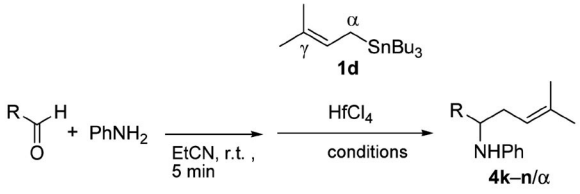
[a] Reduction was performed by the reaction of **2** (1 mmol), with allyl$SnBu_3$/$HfCl_4$ (3 mmol) in EtCN at –40 °C for 2 h. [b] –78 °C. [c] CH_2Cl_2.

is treated with 3 equiv. of prenyl$SnBu_3$ (**1d**)/$HfCl_4$ in propionitrile, the addition to the imine proceeds at the α-carbon of **1d** (Table 2, entry 1). α-Allylation takes place at low temperature (–78 °C, entry 2). To the best of our knowledge, only the prenylbarium reagent shows α-selectivity.[4] The influence of solvents on the regioselectivity is drastic. In CH_2Cl_2, the γ adduct **4a** is obtained predominantly (entry 3). When the reaction is performed in CH_2Cl_2, the addition of EtCN solvent to the reaction mixture does not change the regioselectivity. Hence, it can be concluded that the α adduct is obtained directly rather than by a rearrangement of the γ adduct.

Table 2 shows the prenylation to various imines and a summarizing of the role of the substituents on the nitrogen atom. The halogen and methoxy groups[5] on the *N*-aromatic rings induced α-selective addition to **4b**–**4d/α** (entries 4–6). By contrast, highly electrophilic groups such as *N*-*p*-nitrophenyl- and *N*-phenylsulfonyl (**2e** and **2f**) selectively afforded γ adducts **4e/γ** and **4f/γ** (entries 7 and 8). As to imines **2g**–**2j**, aromatic substituents bonded to acyl carbon also affected the α/γ-selectivity. Haloaryl-substituted groups such as **2g** and **2h** gave α adducts **4g/α** and **4h/α**, respectively (entries 9 and 10). In the case of *p*-methoxyphenyl-substituted imine **2i**, no reaction proceeded due to its low electrophilicity (entry 11). The reaction of imine **2j**, a strong electrophile, selectively gave γ adduct **4j/γ** (entry 12).

The three-component reaction in which aldehyde, amine, and allylating reagents are treated in one portion is accepted as the method of choice to generate labile imines in situ, in which the allylating reagents should indicate high imine selectivity and must tolerate the generated water.[6] The reaction using aliphatic aldehydes having α-protones incurs severe side reactions to decrease the yields in the Lewis acid-catalyzed reactions,[1,7] and such examples of three-component reactions have only scarcely been reported.[6a,6e] Table 3 summarizes the three-component reactions, including the combination of aliphatic aldehyde and aniline. In the hafnium chloride-mediated prenylation using aliphatic aldehydes, including nonbranched ones, the reaction proceeds smoothly in the α-addition way to afford homoallylic amines **4k/α**–**4n/α** in moderate yields. These results are noteworthy because no effective methods have thus far been reported for the α-allylation of imines derived from aliphatic aldehydes.

Table 3. Prenylation to imines by three component reactions.[a]



Entry	R	Conditions	Product	% Yield
1	$PhCH_2CH_2$	–40 °C, 9 h	**4k/α**	47
2	*n*-C_5H_{11}	–78 °C to room temp., 14 h	**4l/α**	58
3	*c*-C_6H_{11}	–40 °C, 2 h	**4m/α**	62
4	*i*-C_3H_7	–40 °C, 2 h	**4n/α**	27

[a] Reduction was performed by the reaction of aldehyde (1 mmol), amine (1 mmol) with allyl$SnBu_3$/$HfCl_4$ (1 mmol) in EtCN.

The assumption of a transmetalation reaction between the highly reactive allyltin species and $HfCl_4$ is supported by the detection of Bu_3SnCl after quenching the reaction mixture. When prenyl$SnBu_3$ (**1d**) is treated with $HfCl_4$ at –40 °C for 2 h in EtCN, Bu_3SnCl is obtained in 63% yield (GLC analysis). At the initial stage (30 min at –40 °C), Bu_3SnCl is observed only in 5% yield. When the measurement is performed at room temp., Bu_3SnCl can be detected in quantitative yield. In CH_2Cl_2, only small amounts of

Bu_3SnCl are detected. In our previously reported allyl$SnBu_3$/$TaCl_5$ system, Bu_3SnCl was obtained quantitatively even at –78 °C for 5 min.[3] This result indicates that the Sn–Hf exchange proceeds at a relatively slow rate compared with the Sn–Ta exchange. When the EtCN solution of prenyl$SnBu_3$ (**1d**)/$HfCl_4$ was measured at –40 °C by ^{119}Sn NMR, the formation of Bu_3SnCl was detected, but the original prenyltin **1d** was also observed as a major peak (Figure 1).

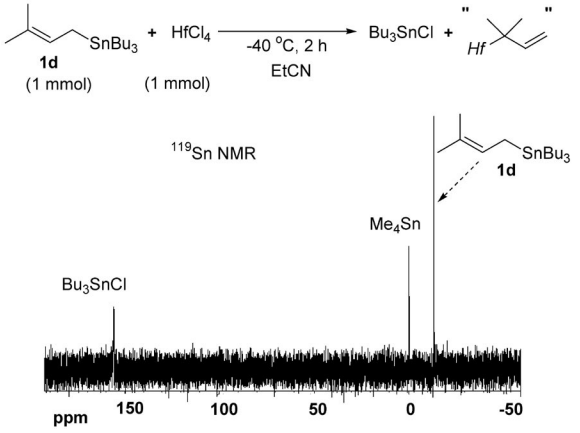
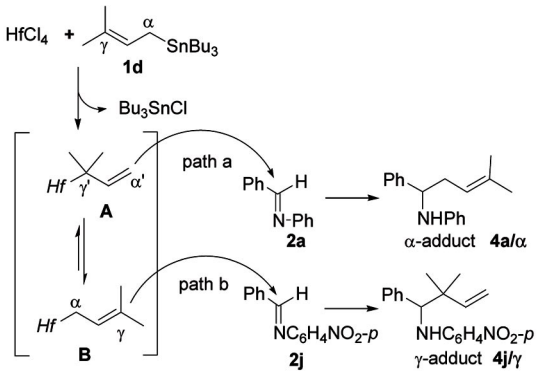


Figure 1. Transmetalation between prenyl$SnBu_3$ and $HfCl_4$.

According to the results obtained in the present study, the α-selective addition of prenyl$SnBu_3$ (**1d**) can be explained as shown in Scheme 2. Initially, the Sn–Hf exchange occurs to generate the (dimethylallyl)hafnium species **A** which reacts at the α′-C atom with imine **2** to give the α adduct **4a/α** (path a). Generally, transmetalation of γ-substituted allyltin compounds quickly results in a similar type of stable γ-substituted allylic metals **B**.[2] Thus, the (dimethylallyl)metal species **A** is regarded as a transient intermediate in the isomerization to **B**. Hence, the trapping of an intermediate like **A** is generally difficult except for the crotyl$SnBu_3$/Bu_2SnX_2 system.[8] In the case of the Sn–Hf exchange, the rate to **A** is so slow that the initially formed (dimethylallyl)hafnium **A** can react with imine **2** (path a). An excess amount of reagents is required to obtain good yields because of the slow generation of the reactive allylic hafnium species. Of course, rapid isomerization from **A** would generate the prenylhafnium species **B** at a higher concentration than **A**. However, reagent **B** bears a sterically hindered nucleophic γ-carbon. The less reactive **2a** cannot react with **B**, and therefore can only react with **A** to provide the product **4a/α**. More reactive imines such as **2j** can react with either complex. Since the major complex in solution is **B**, the major product is compound **4j/γ** (path b).[9]



Scheme 2. Change of regioselectivity.

Conclusions

α-Addition of prenyl$SnBu_3$ to imines was established in the presence of $HfCl_4$. A variety of aldimines were applicable including in situ generated ones. As active species for forming α adducts, (dimethylallyl)hafnium was generated by transmetalation between prenyl$SnBu_3$ and $HfCl_4$.

Experimental Section

General Procedure for the Preparation of *N*-Aromatic Imines: (Table 2, entry 1). To a dry nitrogen-filled 10 mL round-bottomed flask containing $HfCl_4$ (0.96 g, 3 mmol) in EtCN (3 mL) was added prenyltributyltin (**1d**) (1.08 g, 3 mmol) at –40 °C. After stirring at –40 °C for 2 h, to the resulting solution was added benzylideneaniline (**2a**) (0.181 g, 1 mmol). As the reaction proceeded, the mixture gradually turned homogeneous. During the reaction, the solution indicated a slight pale yellow color. After stirring the mixture at –40 °C for 2 h, the reaction mixture was quenched by saturated $NaHCO_3$ (2 mL). To the mixture were added saturated NH_4F (2 mL) and ether (10 mL). After stirring at room temp. for 30 min, the precipitated Bu_3SnF was filtered off and the filtrate was extracted with diethyl ether (3 × 15 mL), dried with $MgSO_4$ and filtered. Volatile components were removed under reduced pressure. The residue was chromatographed on silica-gel column [FL100-DX (Fuji Silysia Chemical Ltd.)], eluting with hexane/EtOAc (99:5, v/v) to give homoallylamine **4a** (0.231 g, 92%).

Supporting Information (see also the footnote on the first page of this article): Experimental and characterization data of all new compounds.

Acknowledgments

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[1] For the allylation of imines, see for example a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1992**, *93*, 2207–2293; b) R. Bloch, *Chem. Rev.* **1998**, *98*, 1407–1438; c) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094.

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[4] A. Yanagisawa, K. Ogasawara, K. Yasue, H. Yamamoto, *Chem. Commun.* **1996**, 367–368.

[5] The reaction using anisidine is expedient because the *p*-methoxyphenyl group of the products can be removed.[6c]

[6] The three-component synthesis of homoallylic amines has been carried out by using aromatic amines: a) S. Kobayashi, T. Busujima, S. Nagayama, *Chem. Commun.* **1998**, 19–20; b) T. Akiyama, J. Iwai, *Synlett* **1998**, 273–274; c) H. C. Aspinall, J. S. Bissett, N. Greeves, D. Levin, *Tetrahedron Lett.* **2002**, *43*, 323–325; d) B. M. Choudary, S. Chidara, C. V. R. Sekhar, *Synlett* **2002**, 1694–1696; e) J. S. Yadav, B. V. S. Reddy, P. S. R. Reddy, M. S. Rao, *Tetrahedron Lett.* **2002**, *43*, 6245–6247; f) J. S. Yadav, B. V. S. Reddy, A. Krishnam Raju, *Synthesis* **2003**, *43*, 883–886.

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[8] In the crotyl$SnBu_3$/Bu_2SnX_2 system, net retention occurred in the crotylation to carbonyl groups to generate α adducts. Thus, α-substituted allyltin compounds like **A** were formed as reactive species: I. Shibata, H. Kato, N. Kanazawa, M. Yasuda, A. Baba, *J. Am. Chem. Soc.* **2004**, *126*, 466–467.

[9] In CH_2Cl_2 as solvent, $HfCl_4$ acts as Lewis acid and activates the imine (Table 2, entry 3). Thus, free **1d** reacts with the imine to give the γ adduct.

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