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Allylic Tantalums as Highly Imine-Selective Reagents

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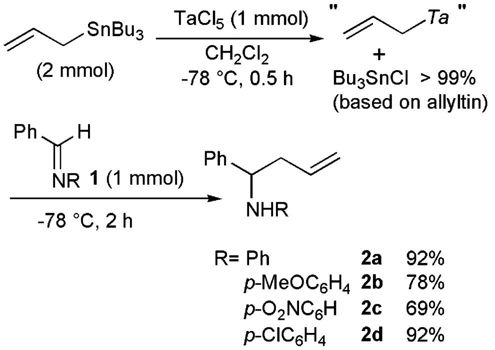
Abstract: A pratical method for the allylation of low electrophilic *N*-aliphatic imines was established by allylic tantalum. This is a superior methodology compared with conventional ones in terms of wide applicability to imines.

Although the allylation of imines is a representative method to give homoallylic amines,[1] there are still limitations in the method. First, the scope of application to imines is still narrow because of their stability. The three-component reaction in which aldehydes, amines, and allylating reagents are treated in one portion is assumed as the method of choice to generate labile imines in situ, in which allylating reagents must bear high imine-selectivity over carbonyls.[2] However, most of the reported three-component reactions include the limitation of the use of aromatic aldehydes as starting substrates. In particular, the reaction using aliphatic aldehydes having α-protones incurs severe side reactions that decrease the yields in the allylation of imines,[1] and such examples of three-compornent reactions have scarcely been reported.[2a,e] Second, imines are less reactive compared with the corresponding carbonyl compounds because of their low electrophilicity. Most allylations of imines are performed on *N*-aromatic imines. In particular, no effective methods of the allylation of imines derived from aliphatic aldehydes and *N*-aliphatic amines have been reported so far. Recently, we have reported the first preparation of active allylic tantalum reagents by the transmetalation between allylic tri-*n*-butyltin with tantalum(V) chloride[3] and the application to selective addition to enones.[4] Herein we report the characteristic reactivity of allylic tantalums toward imines.[5] Thus, high imine-selectivity over carbonyls was observed, and the allylation of low electrophilic imines was established.

SCHEME 1. Allylation of *N*-Aromatic Imines



Initially, as shown in Scheme 1, we performed the allylation of benzylidene *N*-aromatic amines **1** in CH_2Cl_2 at −78 °C for 2 h by using allyltantalum generated by the transmetalation between allyltri-*n*-butyltin and pentachlorotantalum ($TaCl_5$) at −78 °C for 0.5 h.[6] As a result, homoallylamines **2a** was obtained in 92% yield. It was confirmed that complete transmetalation occurred at −78 °C for 0.5 h to form a quantitative yield of tri-*n*-butyltin chloride ($n$$Bu_3SnCl$), which was measured by GLC and ^{119}Sn NMR.

The generated allyltantalum reacted with other *N*-aromatic imines. Imines having electron-donating (p-$MeOC_6H_4$) and -withdrawing (p-$O_2NC_6H_4$) nitrogen sub-

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

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

[3] Allyltri-*n*-butyltin is a good precursor of active allylic metals such as titanium,[3a] boron,[3b] tin,[3c] and indium.[3d] (a) Keck, G. E.; Abbott, D. E.; Borden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927−3930. Marshall, J. A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 863−872. Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Organomet. Chem.* **1985**, *292*, 311−318. Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778−7786. Yamamoto, Y.; Maeda, N.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1429−1431. Hoppe, D. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1996; Vol. 3, Chapter 1.3.3.8, pp 1551−1583. (b) Tanigawa, Y.; Moritani, I.; Nishida, S. *J. Organomet. Chem.* **1971**, *28*, 73−79. Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954−4961. Marton, D.; Tagliavini, G.; Zordan, M.; Wardell, J. L. *J. Organomet. Chem.* **1990**, *390*, 127−138. Harston, P.; Wardell, J. L.; Marton, D.; Tagliavini, G.; Smith, P. J. *Inorg. Chim. Acta* **1989**, *162*, 245−250. Corey, E. J.; Kim, S. S. *Tetrahedron Lett.* **1990**, *31*, 3715−3718. (c) Keck, G. E.; Abott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883−1886. Denmark, S. E.; Wilson, T. M.; Willson, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 984−986. Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M. *Tetrahedron* **1989**, *45*, 1053−1065. Keck, G. E.; Andrus, M. B.; Castellino, S. *J. Am. Chem. Soc.* **1989**, *111*, 8136−8141. (d) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920−1921. Miyai, T.; Inoue, K.; Yasuda, M.; Baba, A. *Synlett* **1997**, 699−700.

[4] Shibata, I.; Kano, T.; Kanazawa, N.; Fukuoka, S.; Baba, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1389−1392.

[5] Generation and synthetic use of tantalum reagents[5a] have scarcely been reported so far, although moderate reactivity of the Ta-carbon bonds to electorophiles is revealed.[5b,c] (a) For example, see: Labinger, J. A. In *Comprehensive Organometallic Chemistry*; Willkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 3, pp 705−782. (b) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973−1981. Kataoka, Y.; Tezuka, M.; Takai, K.; Utimoto, K. *Tetrahedron* **1992**, *48*, 3495−3502. Kataoka, Y.; Oguchi, Y.; Yoshizumi, K.; Miwatashi, S.; Takai, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1543−1549. (c) Yasuda, H.; Arai, T.; Okamoto, T.; Nakamura, A. *J. Organomet. Chem.* **1989**, *361*, 161−171.

[6] The use of 2 equiv of allyltin to $TaCl_5$ gave superior results compared to the case using 1 equiv of allyltin; the yield of **2a** was decreased to 57% when 1 equiv of allyltin was used. As we have already reported, 2 equiv of allyltin was consumed in the reaction with $TaCl_5$. Thus, the generation of diallyltantalum species can be considered.[4]

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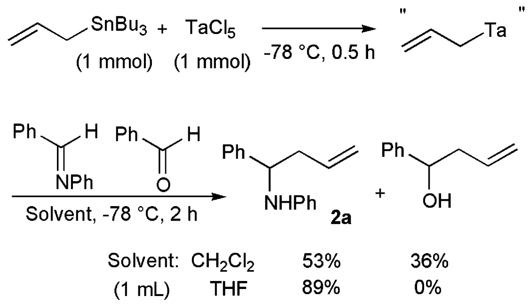
SCHEME 2. Imine-Selective Allylation

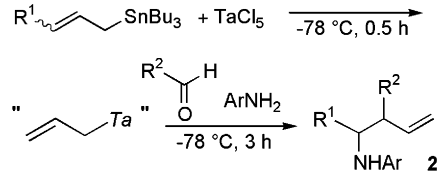


stituents were reactive to give homoallylic amines **2b**−**d** in good to excellent yields. The imine-selectivity of allylic tantalum was investigated in a competitive reaction (Scheme 2). Thus, homoallylamine **2a** was obtained predominantly even in the presence of benzaldehyde in CH_2Cl_2. To achieve complete imine-selectivity, THF was chosen as a solvent, in which case only homoallylamine **2a** was obtained and benzaldehyde was recovered quantitatively. It is assumed that THF coordinates to allylic tantalum to prevent activation of the aldehyde functionality.

To confirm the imine-selectivity of the tantalum species, $TaCl_5$ was treated with an equimolar *N*-benzylideneaniline and benzaldehyde. Because of the efficient solubility of $TaCl_5$ in nitrile solvents, the measurements were performed in CD_3CN. ^{13}C NMR analysis indicated a lower field shift of the aldimine carbon at δ 166.34, ($\Delta\delta$ +4.5 ppm) by the comparison with free *N*-benzylidene aniline (δ 161.84), whereas little shift was observed (from δ 193.94 to δ 193.97, $\Delta\delta$ +0.03 ppm) at the carbonyl carbon of benzaldehyde. This result indicates that the tantalum reagent activates imines selectively over aldehydes.

The presented imine-selectivity could be effectively applied to the three-component reactions of allylic tantalums, aldehydes, and amines, in particular when the steady formation of imines is sluggish. Table 1 summarizes the combinations of aliphatic aldehydes and aromatic amines[7] in the three-component reactions. The results are notable because it is known that severe side reactions occur that decrease yields in the reactions of imines having α-protons in the Lewis acid catalyzed reactions.[1,8] Aliphatic aldehydes, especially nonbranched ones, reacted smoothly with allyltantalum to afford homoallylic amines **2e**−**h** in high yields (entries 1−4). Allylic tantalum only activated imines without inducing any other side reactions. Besides allylation, crotylic tantalum added to imines in high yields. The reaction proceeded regioselectively at the γ-carbon of crotyltantalum to give **2l**−**n** (entries 8−10). In addition, high diastereoselectivities were obtained.[9]

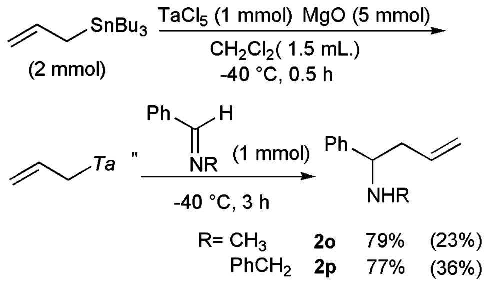
TABLE 1. One-Pot Allylation To Form Homoallylamines[a]



entry	R^1	R^2	Ar	product	yield, %
1	H	$PhCH_2CH_2$	Ph	**2e**	99
2	H	$PhCH_2CH_2$	*p*-$MeOC_6H_4$	**2f**	63
3	H	$PhCH_2CH_2$	*p*-$NO_2C_6H_4$	**2g**	70
4	H	*n*-C_5H_{11}	Ph	**2h**	90
5	H	*c*-C_6H_{11}	Ph	**2i**	96
6	H	*c*-C_6H_{11}	*p*-$MeOC_6H_4$	**2j**	60
7	H	*i*-C_3H_7	Ph	**2k**	90
8	CH_3	$PhCH_2CH_2$	Ph	**2l**	96[b]
9	CH_3	*n*-C_5H_{11}	Ph	**2m**	84[c]
10	CH_3	*c*-C_6H_{11}	Ph	**2n**	76[d]

[a] Allylic tantalum was prepared from $TaCl_5$ (1 mmol), and allyltin (2 mmol); aldehyde (1 mmol), amine (1 mmol), THF (1 mL). [b] *syn*:*anti* = 91:9. [c] *syn*:*anti* = 86:14. [d] *syn*:*anti* = 85:15.

SCHEME 3. Allylation of *N*-Aliphatic Imines



Yields without MgO were in parenthesis.

Compared with *N*-aromatic imines, *N*-aliphatic imines are stable and easy to isolate; however, the electrophilicity of *N*-aliphatic imines is low. In the next stage, we tried to solve the remaining problem of the low reactivity of *N*-aliphatic imines. As shown in Scheme 3, the allylation of benzylidene *N*-methylimine gave *N*-methyl homoallylamine **2o** in only 23% yield under the same conditions as the allylation of *N*-aromatic imines. Higher reaction temperature at −40 °C and prolonged reaction time could not increase the yield at all. The low yield of **2o** is because of the low electrophilicity of *N*-aliphatic imines. However, we found that the addition of magnesium oxide (MgO) increased the yield of *N*-aliphatic homoallylamines. Thus, *N*-methyl and *N*-benzyl homoallylamines, **2o** and **2p**, were obtained in 79% and 77% yields, respectively.

Moreover, as shown in Table 2, the one-pot treatment was achieved in which imines were formed in situ in the presence of MS-4Å prior to the addition of allyltantalum. The use of aliphatic aldehydes was not a problem to afford homoallylic amines **2s**−**u**. These results are noteworthy because no effective methods for the allylation of imines derived from aliphatic aldehydes and *N*-aliphatic amines have been reported so far. Although the exact reason MgO works well is not clear yet,[10] this method is

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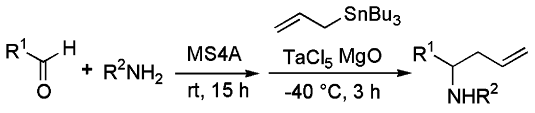
(7) The reaction using anisidine has an advantage because the *p*-methoxyphenyl group of products can be removed.[2c]

(8) Allylaton of isolated *N*-aromatic imines of aliphatic aldehydes was reported: Nakamura, H.; lwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641−6647.

(9) We consider that *syn*-selectivity was obtained through a six-membered chairlike transition state from (*E*)-crotyltantalum, alhough the correct tantalum species could not be confirmed. Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 9493−9499.

(10) The addition of MgO was not effective for the reaction using aromatic amines. As MgO has the ability to trap HCl, there is a possibility that MgO prevents the formation of ammonium salts from aliphatic amines and in situ presented HCl. Mukaiyama, T.; Nakano, M.; Kikuchi, W.; Matsuo, J. *Chem. Lett.* **2000**, 1010−1011.

TABLE 2. One-Pot Allylation To Form *N*-Aliphatic Homoallylamines[a]



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entry	R^1	R^2	product	yield, %
1	Ph	*n*-C$_3$H$_7$	**2q**	71
2	Ph	PhCHMe	**2r**	79[b]
3	*c*-C$_6$H$_{11}$	*n*-C$_3$H$_7$	**2s**	52
4	PhCHMe	*n*-C$_3$H$_7$	**2t**	59[c]
5	*n*-C$_5$H$_{11}$	*n*-C$_3$H$_7$	**2u**	60[d]

[a] Allylic tantalum was prepared from TaCl$_5$ (1 mmol), and allyltin (2 mmol); aldehyde (1 mmol), amine (1 mmol), MgO (5 mmol), MS-4Å (0.3 g), CH$_2$Cl$_2$ (3 mL). [b] dr = 81:19. [c] dr = 84:16 [d] At −20 °C

effective and practical to achieve the allylation of *N*-aliphatic imines.

In summary, allylic tantalums showed high affinity toward imines. Although imine allylation reactions, including asymmetric ones, have been shown so far, almost all examples have been limited to *N*-aromatic imines. The presented method enabled the preparation of the widest range of homoallylic amines, including those unavailable by the conventional agents.

Experimental Section

Representative Procedure for Allylation of *N*-Aromatic Imines. To a dry nitrogen-filled 10-mL round-bottomed flask containing TaCl$_5$ (0.358 g, 1 mmol) in CH$_2$Cl$_2$ (1 mL) was added allyltri-*n*-butyltin (0.662 g, 2 mmol) at −78 °C. TaCl$_5$ was partly insoluble. After the mixture stirred at −78 °C for 30 min, benzylideneaniline (**1a**) (0.181 g, 1 mmol) was added to the resulting solution. As the reaction proceeded, the mixture gradually turned homogeneous. During the reaction, the solution indicated a slight pale yellow color. After the mixture stirred at −78 °C for 2 h, it was quenched by saturated NaHCO$_3$ (2 mL). To the mixture were added saturated NH$_4$F (2 mL) and ether (10 mL). After 30 min of stirring at room temperature, the precipitated Bu$_3$SnF was filtered off, and the filtrate was extracted with ether (15 mL × 3), dried over MgSO$_4$, and filtered. Volatiles were removed under reduced pressure. The residue was chromatographed on a silica gel column (FL100-DX (Fuji silysia)), eluting with hexane/EtOAc (99/1) to give homoallylamine **2a** (0.205 g, 92%).

Representative Procedure for One-Pot Allylation using *N*-Aromatic Amines. To a dry nitrogen-filled 10-mL round-bottomed flask containing TaCl$_5$ (0.358 g, 1 mmol) in THF (1 mL) was added allyltri-*n*-butyltin (0.331 g, 1 mmol) at −78 °C. After 30 min, aniline (0.093 g) and 3-phenylpropionaldehyde (0.134 g, 1 mmol) were added, and the mixture was stirred at −78 °C for 3 h. The reaction mixture was quenched by saturated NaHCO$_3$ (2 mL). To the mixture were added saturated NH$_4$F (2 mL) and ether (10 mL). After 30 min of stirring at room temperature, the precipitated Bu$_3$SnF was filtered off, and the filtrate was extracted with ether (15 mL × 3), dried over MgSO$_4$, and filtered. Volatiles were removed under reduced pressure. The residue was chromatographed on a silica gel column (FL100-DX (Fuji silysia)) eluting with hexane/EtOAc (99/1) to give homoallylamine **2e** (0.249 g, 99%).

Representative Procedure for Allylation of *N*-Aliphatic Imines. To a dry nitrogen-filled 10-mL round-bottomed flask containing TaCl$_5$ (0.358 g, 1 mmol) in CH$_2$Cl$_2$ (1 mL) was added MgO (0.201 g, 5 mmol) at room temperature, and the mixture was stirred for 1 h. The solution was cooled to −40 °C, and allyltri-*n*-butyltin (0.662 g, 2 mmol) was added. After 30 min of stirring, benzylide *N*-methylamine (0.119 g, 1 mmol) was added to the resulting solution. After the mixture was stirred at −40 °C for 3 h, it was quenched by saturated NaHCO$_3$ (2 mL). To the mixture were added saturated NH$_4$F (2 mL) and ether (10 mL). After stirring at room temperature for 30 min, the precipitated Bu$_3$SnF was filtered off, and the filtrate was extracted with ether (15 mL × 3). The organic layer was extracted with aqueous 0.5 M HCl (15 mL × 3), and products were transferred to a water layer as quaternary ammonium salts. To the water layer was added saturated NaHCO$_3$ (10 mL) slowly. The product was extracted with ether (20 mL × 3), dried over MgSO$_4$, and filtered. Volatiles were removed under reduced pressure. The residue was purified by bulb-to-bulb distillation to give **2n** (0.127 g, 79%).

Representative Procedure for One-Pot Allylation using *N*-Aliphatic Amines. To a dry nitrogen-filled 10-mL round-bottomed flask containing *n*-propylamine (0.059 g, 1 mmol) and benzaldehyde (0.106 g, 1 mmol) was added MS-4Å (0.3 g). To prepare the corresponding imine in situ, the mixture was stirred at room temperature for 15 h. Allyltri-*n*-butyltin (0.662 g, 2 mmol) and MgO (0.201 g, 5 mmol) were added, and the solution was cooled to −40 °C. To the resulting solution was added TaCl$_5$ (0.358 g, 1 mmol). After stirring for 3 h, the reaction mixture was quenched by saturated NaHCO$_3$ (2 mL). Saturated NH$_4$F (2 mL) and ether (10 mL) were added. After stirring at room temperature for 30 min, the precipitated Bu$_3$SnF was filtered off, and the filtrate was extracted with ether (15 mL × 3). The organic layer was extracted with 0.5 M HCl (15 mL × 3), when products were transferred to the water layer as quaternary ammonium salts. To the water layer was added saturated NaHCO$_3$ (10 mL) slowly. The product was extracted with ether (20 mL x 3), dried over MgSO$_4$, and filtered. Volatiles were removed under reduced pressure. The residue was purified by bulb-to bulb distillation to give **2p** (0.134 g, 71%).

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Supporting Information Available: Experimental procedures and IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra for **2a**−**e**, **2g**, **2i**, **2k**, and **2l**−**u**. This material is available free of charge via the Internet at http://pubs.acs.org.

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