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Allylation of Aldehydes and Imines: Promoted by Reuseable Polymer-Supported Sulfonamide of *N*-Glycine

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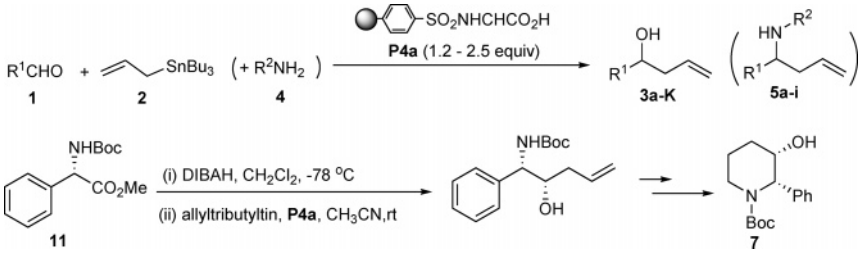
ABSTRACT



A allylation of aldehydes and imines (generated in situ from aldehydes and amines) with allyltributyltin promoted by recoverable and reusable the polymer-supported sulfonamide of *N*-glycine has been developed. Good to high yields were obtained in various cases. Most of the $SnBu_3$ residue can be recovered as Bu_3SnCl. Highly stereoselective synthesis of *N*-Boc-(2*S*,3*S*)-3-hydroxy-2-phenylpiperidine 7 was achieved by using the P4a-mediated allylation of Boc-L-phenylglycinal as a key step.

Allylation of aldehydes and imines with allyltributyltin is a powerful method of forming carbon−carbon bonds and producing useful homoallylic alcohols and homoallylic amines in organic synthesis.[1] Lewis acids, especially metal Lewis acids, or transition metal complexes have been extensively utilized to catalyze or promote these allylations in the past years. However, the traditional methods using Lewis acids such as $Et_2O{\cdot}BF_3$, $TiCl_4$, and $SnCl_4$ must be carried out under strictly anhydrous conditions. Water-tolerant Lewis acids, for example, lanthanide triflates, have been developed as catalysts for the allylation of aldehydes and three-component reactions of the synthesis of homoallylamines in recent years,[2] but they are rather expensive. On the other hand, in the conventional allylation with allytributyltin, the byproduct containing SnR_3 group is unwanted. The removal of SnR_3 residue is time-consuming and unavoidable in order to obtain pure allylation product. Several techniques and reagents have been developed to make the manipulation simple.[3]

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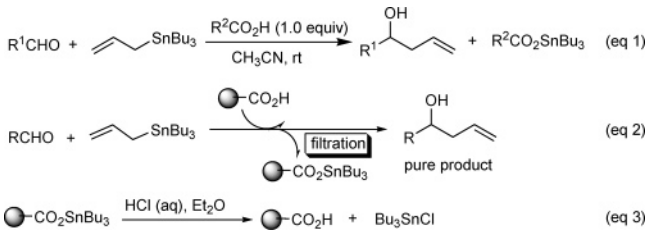
Using polymer-supported reagents and catalysts is a popular tool in modern organic synthesis because the workup of the reaction and the recovery of reagents and catalysts are convenient.[2] Recently, we have found that a series of carboxylic acids are efficient promoters for allylation of aldehydes with allyltributyltin under very mild conditions.[5] In this allylation, the $SnBu_3$ group is transferred to the carboxylic acid, forming the tin ester (eq 1, Scheme 1). On

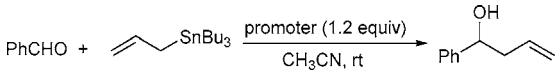
Scheme 1



the basis of these results, we think that if this allylation can be promoted by polymer-supported carboxylic acids with a certain acidic degree, we can allylate cleanly by transferring the $SnBu_3$ group to the polymer promoter (eq 2, Scheme 1). In addition, after the tin ester of the polymer is treated with aqueous HCl, the $SnBu_3$ residue will be recovered as Bu_3SnCl (eq 3, Scheme 1). In this Letter, we would like to describe the results of this protocol.

We are interested in α-amino acids because of two factors: (1) α-Amino acids have a good linking site, NH_2, which makes them convenient for being supported by polymer. (2) The acidity of the N-protected α-amino acid is tunable by using different protective groups, and thus the excess allyltributyltin can be decomposed and removed if polymer-supported α-amino acid was used. Therefore, first, we screened various α-amino acids and their derivatives for this allylation by employing benzaldehyde as a model substrate. The results are summarized in Table 1. The allylation promoted by D-phenylalanine was sluggish (entry 1). When D-phenylalanine was protected with a tosyl group, which effectively enhanced the acidity of the carboxylic acid, a good yield allylation was obtained (entry 2). Further investigation revealed that α-amino acids with a weak electronic-withdrawing protective group (e.g., Cbz) at the amino group (entry 4) and more steric hindrance at the *β*

Table 1. Screening of α-Amino Acid and Their Derivatives as Promoters for the Allylation of Benzaldehydes



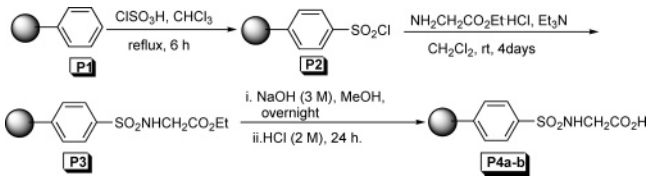
entry	promoter	time, h	yield, % [b]
1	D-phenylalanine	72	5
2	*N*-tosyl-D-phenylalane	23	84
3	*N*-tosyl-L-proline	23	74
4	*N*-Cbz-L-proline	55	51
5	*N*-tosyl-L-valine	23	80
6	*N*-tosyl-L-2-phenylglycine	23	40
7	*N*-tosyl-glycine	23	92

[a] **1a**/**2** = 1.0 equiv (0.5 mmol)/1.2 equiv (0.6 mmol). [b] Isolated yield.

carbon (entries 5 and 6) were less active. The best result was obtained from the simplest *N*-tosylglycine with a yield up to 92% of **3a** at room temperature in acetonitrile (entry 7). In addition, it needs to be noted that the corresponding product of homoallyl alcohol **3a** was racemic, although the reactions used the pure optically active α-amino acid derivatives as promoters (entries 1−6).

The polymer-supported sulfonamide of *N*-glycine (**P4**) was prepared easily in three steps according to a similar method.[3] As shown in Scheme 2, the beads of polystyrene (**P1**, 2%

Scheme 2



divinylbenzene, 200−400 mesh) were treated with excess chlorosulfonic acid to produce chlorosulfonylated polymer (**P2**). The degree of chlorosulfonylation of **P2** determined by elemental analysis was about 4.61 mmol/g Cl and 4.80 mmol/g S. Next glycine ethyl ester was grafted onto **P2** in the presence of Et_3N at room temperature over 4 days. Elemental analysis showed that the percentage of remaining Cl of **P3** was less than 0.5%. Finally, **P3** was saponified in aqueous NaOH (3.0 M)[7] and subsequently acidified under HCl (2.0 M). After 48 h of stirring in distilled water to remove the trace amount of hydrochloric acid and drying in a vacuum (1 mmHg, P_2O_5, 50 °C overnight), the polymer-supported sulfonamide of *N*-glycine (**P4a)** was obtained. The polymer **P4a** was characterized by IR spectroscopy, which

(3) (a) Fouquet, E.; Pereyre, M.; Roulet, T. *J. Chem. Soc., Chem. Commun.* **1995**, 2387. (b) Fouquet, E.; Pereyre, M.; Rodriguez, A. L. *J. Org. Chem.* **1997**, *62*, 5242. (c) Curran, D. P.; Hadida, S.; He, M. *J. Org. Chem.* **1997**, *62*, 6714. (d) Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 4539. (e) Ryu, I.; Niguma, T.; Minakata, S.; Komatsu, M.; Luo, Z.; Curran, D. P. *Tetrahedron Lett.* **1999**, *40*, 2367. (f) Cossy, J.; Rasamison, C.; Pardo, D. G. *J. Org. Chem.* **2001**, *66*, 7195. (g) McCluskey, A.; Muderawan, I. W.; Muntari; Young, D. J. *J. Org. Chem.* **2001**, *66*, 7811. (h) Ryu, I.; Kreimerman, S.; Niguma, T.; Minakata, S.; Komatsu, M.; Luo, Z.; Curran, D. P. *Tetrahedron Lett.* **2001**, *42*, 947. (i) Cossy, J.; Rasamison, C.; Pardo, D. G.; Marshall, J. A. *Synlett* **2001**, 629.

(4) (a) An issue of Chemical Reviews (*Chem. Rev.* **2002**, *102*, 3215) has been devoted to polymer-supported catalysts and reagents. (b) Maurizio, B.; Alessandra, P.; Franco, C. *Chem. Rev.*, **2003**, *103*, 3401.

(5) Li, G.-l.; Zhao, G. *J. Org. Chem.* **2005**, *70*, 4272.

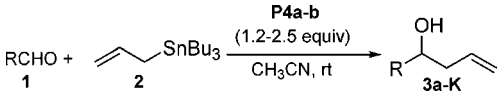
(6) Hu, J.-B.; Zhao, G.; Ding, Z.-D. *Angew. Chem., Int. Ed.* **2001**, *40*, 1109.

(7) The strong IR absorption at 1747 cm^{-1}(C═O of ethyl ester) disappeared and was replaced by another strong band near 1601 cm^{-1} (C═O of sodium salt of the polymer). It suggests that the saponification was completed.

revealed the characteristic absorptions at 3284 (OH and NH), 1732 (C=O), 1324, 1156 cm^{-1} (SO_2), and by elemental analysis, which showed that the loading of N was 3.65 mmol/g. Polymer **P4b** (3.82 mmol/g N) was also prepared from another polystyrene (1% divinylbenzene, 200−400 mesh) according to a similar procedure.

Next, we tested the allylation mediated by polymer **P4** under the same reaction conditions as above. The mixture of aldehydes (**1**, 1.0 equiv), allyltributyltin (**2**, 1.2−2.0 equiv), and **P4** (1.2−2.5 equiv based on the amount of N) was stirred in acetonitrile at room temperature untill the reactions were completed. Pure products (**3a**−**K**) were obtained by filtration and concentration. The purity is determined by ^{1}H NMR, and the unreacted **2** could be removed by reacting with excess **P4a**. As shown in Table 2, polymer **P4a** was more efficient

Table 2. Allylation of Aldehydes Promoted by **P4**



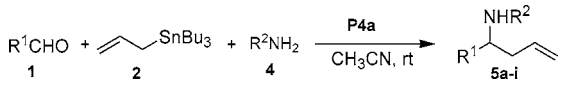
entry	R	P4	3	time, h	yield, %[e]
1[a]	Ph	**P4a**	**3a**	3	96
2[a]	Ph	**P4b**	**3a**	5	90.5
3[a]	*p*-NO_2Ph	**P4a**	**3b**	5	99
4[a]	2,4-Cl_2Ph	**P4a**	**3c**	12	99
5[a]	*p*-F Ph	**P4a**	**3d**	12	84
6[b]	*p*-CH_3O Ph	**P4a**	**3e**	19	92
7[b]	*m*-CH_3O Ph	**P4a**	**3f**	17	99
8[c]	*E*-PhCH=CH	**P4a**	**3g**	17	95
9[c]	2-naphthyl	**P4a**	**3h**	19	90
10[c]	*p*-Br Ph	**P4a**	**3i**	19	95
11[d]	*n*-C_7H_{15}	**P4a**	**3j**	19	85
12[c]	*c*-C_6H_{11}	**P4a**	**3K**	17	87

[a] **1**/**2**/**P4** = 1.0/1.2/1.2 (equiv). [b] **1**/**2**/**P4** = 1.0/2.0/2.5 (equiv). [c] **1**/**2**/**P4** = 1.0/1.2/1.5 (equiv). [d] **1**/**2**/**P4** = 1.0/1.5/1.8(equiv). [e] Isolated yields.

than **P4b** (entry 1 vs 2) and *N*-tosylglycine (Table 1, entry 7). So, we chose **P4a** to conduct the allylation of other aldehydes. The desired homoallylic alcohols were obtained from good to quantitative yields in all cases, although in some examples 1.5−2.5 equiv of **P4a** and prolonged time were needed to complete the reactions and obtain the corresponding pure products through simple filtration.

The three-component (i.e., aldehyde, amine, and allyltributyltin) reaction is a convenient approach to forming synthetically useful homoallylic amines.[1,2f−o] However, the amine and water produced during the formation of imine can deactivate or decompose the traditional Lewis acids.[4] Additionally, the highly selective synthesis of homoallylic amine (no homoallylic acohol produced) is also not so easy. We initially used polymer acid **P4a** (1.5 equiv) as a promoter. Benzaldehyde (1.0 equiv), aniline (1.0 equiv), and allyltributyltin (1.2 equiv) were stirred in acetonitrile. The three-component reaction proceeded rapidly and afforded the desired homoallyllic amine **5a** selectively in a quantitative yield, but in the presence of the amine, the excess allyltributyltin could not be decomposed as completely as the forenamed allylation of aldehydes (entry 1, Table 3). When

Table 3. Three-component Reaction Promoted by **P4a**



entry	R^1	R^2	5	time, h	yield, %[a]
1[b]	Ph	Ph	**5a**	3	100
2[c]	Ph	Ph	**5a**	5	99
3[c]	*p*-NO_2Ph	Ph	**5b**	6	99
4[c]	*m*-CH_3OPh	Ph	**5c**	6	90
5[d]	α-furyl	Ph	**5d**	7	91
6[d]	*c*-C_6H_{11}	Ph	**5e**	7	89
7[d]	*p*-BnOPh	Ph	**5f**	4	94
8[d]	Ph	2-F-5-MePh	**5g**	6	96
9[d]	Ph	3-CF_3Ph	**5h**	6	98
10[d]	Ph	3,4,5-$(MeO)_3$Ph	**5i**	6	84
11[c]	*n*-C_7H_{15}	Ph		6	tr
12[c]	Ph	Bn		12	*e*

[a] Isolated yields and determined by ^{1}H NMR. [b] **1**/**2**/**4**/**P4a** = 1.0/1.0/1.2/1.5 (equiv). [c] **1**/**2**/**4**/**P4a** = 1.0/1.0/1.0/1.2 (equiv). [d] **1**/**2**/**4**/**P4a** = 1.0/1.0/1.0/1.3 (equiv). [e] No desired product was observed.

1.0 equiv of allyltributyltin was used, this reaction resulted in a quantitative yield and the pure product **5a** was obtained after the filtration of the produced polymer **P5a** (entry 2, Table 3). Then under similar reaction conditions, several aldehydes and aromatic amines were examined; these results are presented in Table 3. Various aromatic aldehydes and aromatic amines could proceed smoothly to give the corresponding homoallylic amines **5a**−**i** (only traces of the corresponding homoallylic alcohols were detected by ^{1}H NMR). For the aliphatic aldehyde of Cyclohexyl aldehyde, the three-component reaction also resulted in **5e** in a good yield of 89%. Unluckily, only trace amount of desired products was obtained when other aliphatic aldehydes and aliphatic amines were used as substrates (entries 11 and 12).

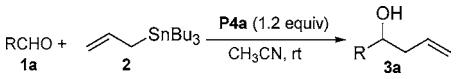
After the allylation reactions were completed, the insoluble polymer tin ester **P5a** [5] was filtrated off and then treated with aqueous HCl (2.0 M), filtered, and washed with Et_2O and distilled water to recover **P4a**. As shown in Table 4, **P4a** was still efficient after being reused at least five times, although the time to complete the allylation needs to be prolonged after it was used for three times (runs 4 and 5). The minor decrease of activity of **P4a** may be due to the fact that the shape of the resin changed after several runs (elemental analysis showed that the content of N of **P4a** did not change after the fifth run).[10] Another prominent merit of this polymer **P4**-mediated allylation is that the expensive and toxic tin reagent could be recovered easily. The filtrate

(8) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773.

(9) **P5a** is characterized by IR spectroscopy (see Supporting Information for details).

(10) Ogawa, C.; Sugiura, M.; Kobayashi, S. *Chem. Commun.* **2003**, 192.

Table 4. Reuse of **P4a** and Recovery of $SnBu_3$ Residue

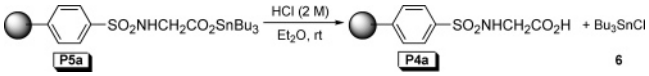


entry	R^1	R^2	**5**	time, h	yield, %[a]
1[b]	Ph	Ph	**5a**	3	100
2[c]	Ph	Ph	**5a**	5	99
3[c]	*p*-NO_2Ph	Ph	**5b**	6	99
4[c]	*m*-CH_3OPh	Ph	**5c**	6	90
5[d]	α-furyl	Ph	**5d**	7	91
6[d]	*c*-C_6H_{11}	Ph	**5e**	7	89
7[d]	*p*-BnOPh	Ph	**5f**	4	94
8[d]	Ph	2-F-5-MePh	**5g**	6	96
9[d]	Ph	3-CF_3Ph	**5h**	6	98
10[d]	Ph	3,4,5-$(MeO)_3$Ph	**5i**	6	84
11[c]	*n*-C_7H_{15}	Ph		6	tr
12[c]	Ph	Bn		12	*e*

[a] Isolated yields. [b] Based on **2**.

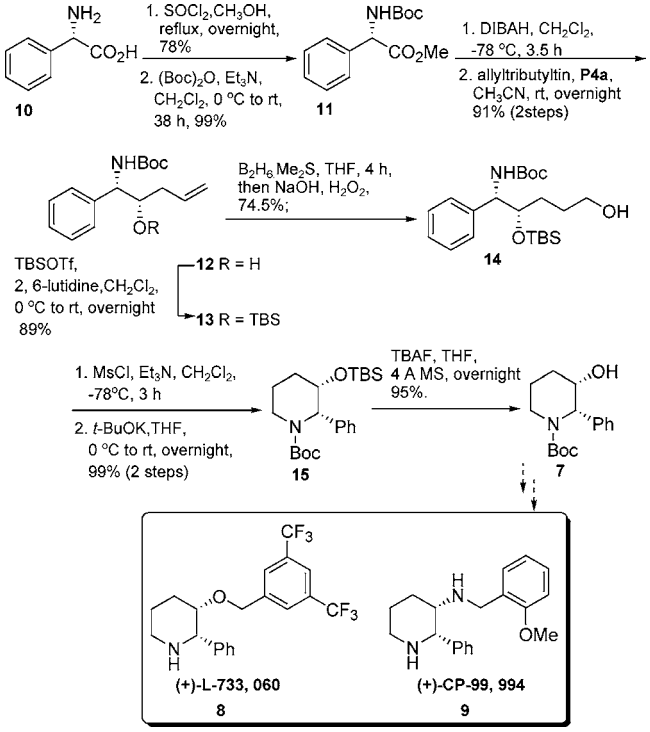
was extracted with Et_2O to recover most of the Bu_3Sn residue as Bu_3SnCl (**6**, Scheme 3; not less than 86%, Table 4, runs 1−5).[11]

Scheme 3 . Recovery of **P4a** and Bu_3SnCl



The piperidine ring is a common moiety found in bioactive natural products, drugs, and drug candidates. In recent years, *N*-Boc-(2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **7** has drawn much attention of organic chemists since it is a valuble precursor for the synthesis of nonpeptide neurokinin NK1 receptor antagonists **8** and **9** (Scheme 4).[12] During our studies of the allylation of chiral α-aminoaldehydes, we found that, using **P4a** as a promoter, the allylation of Boc-L-phenylglycinal afforded 1,2-*syn*-**12** as nearly a single product (*syn*/*anti* 12:1, determined by ^1H NMR)[13] in 91% yield (Scheme 4). This method is much better than using allylmagnesium bromide as a allylation reagent, which gave lower allylation

Scheme 4



yield and diastereoselectivity.[12b,e,f,13] Then, from L-phenylglycine **10**, the target compound **7** was synthesized in high overall yield (43.8%) according to known procedures.[12b,f] The spectroscopic and physical data of **7** ($[\alpha]^{25.7}_D$ +33.18; *c* 0.50, $CHCl_3$) are consistent with the literature values ($[\alpha]^{20}_D$ +35.41; *c* 1.2, $CHCl_3$).[12b]

In summary, a general and clean allylation of aldehydes with allyltributyltin promoted by a recoverable and reusable polymer-supported sulfonamide of *N*-glycine has been developed. Good to quantitative yields are obtained in various cases. Furthermore, the workup of these allylations is quite simple. Using silica gel chromatography purification to get pure products is not needed. Additionally, most of the $SnBu_3$ residue can be recovered as Bu_3SnCl. Using **P4a**-mediated allylation of Boc-L-phenylglycinal as a key step, the high stereoselective synthesis of *N*-Boc-(2*S*,3*S*)-3-hydroxy-2-phenyl- piperidine **7** was accomplished in a high overall yield.

Acknowledgment. Financial support by the Major State of Basic Research Development Program (no. G2000048007), the National Natural Science Foundationof China (nos. 20525208, 20532040, 20390050), QT Program, and Shanghai Natural Science Council is gratefully acknowledged.

Supporting Information Available: General methods and ^1H NMR, IR, MS data, and spectra of the corresponding compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0528235

(11) Curran, D. P.; Hasida, S.; Kim, S.-Y. *Tetrahedron* **1999**, *55*, 8997; The recovered Bu_3SnCl was confirmed by ^1H NMR, IR, EIMS, and GC, which are the same with the standard spectra of Bu_3SnCl.

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(13) (a) Jayasinghe, L. R. *J. Med. Chem*. **1994**, *37*, 2981. (b) The *p*-nitrobenzoic acid mediated allylation of the same aminoaldehyde gave similar diastereoselectivity.