

# Asymmetric reactions on polymers: diastereoselective allylation of polymer-supported chiral imines

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Letter

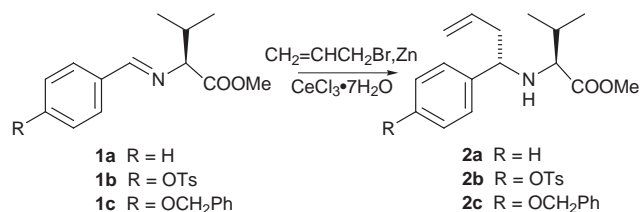
Reaction of allylzinc reagent with enantiopure imine species attached to polystyrene proceeded smoothly with perfect diastereoselectivity and in excellent yield to afford polymer-supported chiral homoallylic amines.

Polymers having chiral pendant groups have been of great interest owing to their applications in enantiomer separation technology and in polymeric chiral catalysts or reagents in asymmetric synthesis.<sup>1</sup> Generally these chiral polymers are prepared by the following two methods.<sup>1d</sup> One involves a chemical modification of preformed reactive polymer with enantiomerically pure compounds. Copolymerization of enantiopure monomers with some achiral monomers is the alternative method. However, rather straightforward methodology is available if an asymmetric reaction can be applied directly to the prochiral pendant functionality of the polymer to create a new stereogenic center on the polymer. This method has not been studied extensively mainly owing to the requirement of a highly stereoselective and quantitative reaction and a suitable analytical method to evaluate the optical purity of the chiral moieties on the polymer.<sup>2</sup> In chemical transformations of polymeric functionality, it is impossible to remove any side product yielded in the polymer. Stereoisomeric impurities also can not be eliminated once the reactions have been completed on the polymer. A highly stereoselective and quantitative reaction is therefore required to achieve this methodology. Another problem pointed out in the literature is that a lowering of the stereoselectivity usually accompanies the polymer reaction compared to the corresponding reaction with the low-molecular-weight counterpart.<sup>3</sup> Recent vigorous developments in asymmetric reactions allowed us to apply some highly stereoselective reactions to the direct asymmetric transformation of polymeric functionalities. For example, Umani-Ronchi and co-workers<sup>4</sup> have developed an excellent methodology for diastereoselective allylation of chiral imines. Here we have chosen this reaction to investigate diastereo-

selectivity on the polymeric substrate and have shown that polystyrene having diastereomerically pure pendant groups can be prepared by this new method.

According to the Umani-Ronchi-Savoia method, benzaldimine **1a** was smoothly converted into (*S,S*)-homoallylamine **2a** in quantitative yield with excellent diastereoselectivity (Table 1, run 1) by using the allylzinc reagent prepared from allyl bromide (3-bromopropene), zinc powder and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  as additive (Scheme 1).<sup>4a</sup> Since we chose a sulfonate (OTs) or a benzyl ether linkage between the chiral ligand and polystyrene, the corresponding model compounds such as **1b** and **1c** were prepared to examine their reactivity and selectivity in the allylation reaction. Table 1 shows that allyl bromide–Zn– $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  reacted with both **1b** and **1c** to give the homoallylic amines **2b** and **2c**, respectively, with almost perfect diastereoselectivities and excellent isolated yields (run 2, 6).<sup>5</sup> Instead of  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ ,  $\text{SnCl}_2$  is another choice of additive in a highly diastereoselective allylation (run 3). The reactions of the prenylzinc reagent formed from prenyl bromide (4-bromo-2-methylbut-2-ene) were also efficient and highly diastereoselective with the same imines (run 4, 5, 7, 8).

The above results encouraged us to apply this reaction to the synthesis of a polymer-supported chiral ligand by using direct transformation of the prochiral functionality in the



Scheme 1 Diastereoselective allylation of chiral imine

Table 1 Diastereoselective allylation of imines<sup>a</sup>

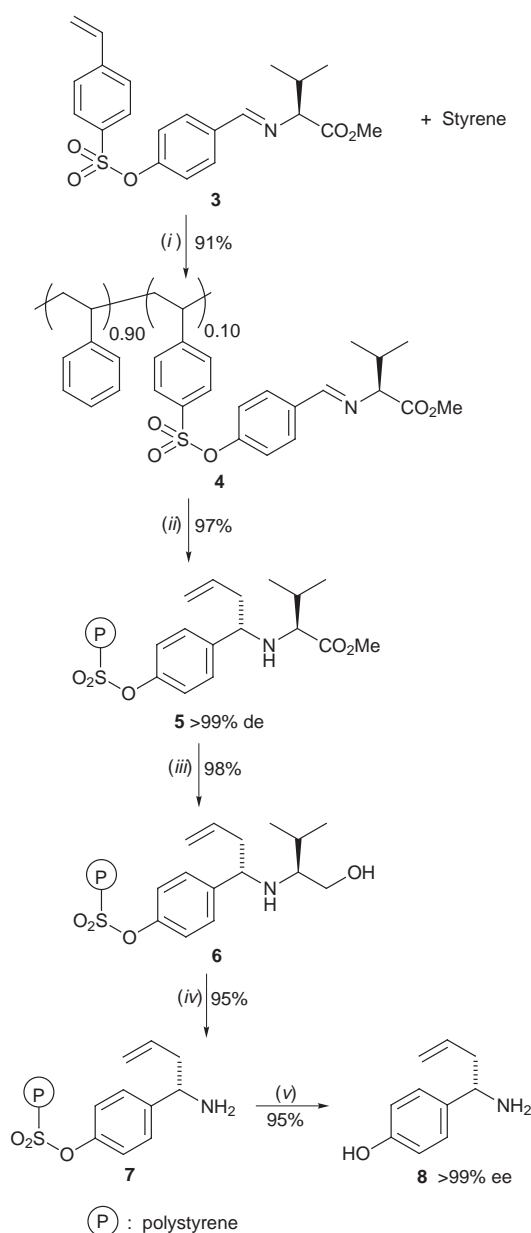
Run	R	Allylating agent	Time/h	Yield/%	Diastereoselectivity (de)/% <sup>b</sup>
1 <sup>c</sup>	H	$\text{CH}_2=\text{CHCH}_2\text{Br}\cdot\text{Zn}\cdot\text{CeCl}_3\cdot 7\text{H}_2\text{O}$	0.5	100 <sup>d</sup>	> 99
2	OTs	$\text{CH}_2=\text{CHCH}_2\text{Br}\cdot\text{Zn}\cdot\text{CeCl}_3\cdot 7\text{H}_2\text{O}$	4	93 <sup>e</sup>	100
3	OTs	$\text{CH}_2=\text{CHCH}_2\text{Br}\cdot\text{Zn}\cdot\text{SnCl}_2$	0.25	96 <sup>e</sup>	100
4	OTs	$\text{Me}_2\text{C}=\text{CHCH}_2\text{Br}\cdot\text{Zn}\cdot\text{CeCl}_3\cdot 7\text{H}_2\text{O}$	2	91 <sup>e</sup>	100
5	OTs	$\text{Me}_2\text{C}=\text{CHCH}_2\text{Br}\cdot\text{Zn}\cdot\text{SnCl}_2$	3	94 <sup>e</sup>	100
6	OCH <sub>2</sub> Ph	$\text{CH}_2=\text{CHCH}_2\text{Br}\cdot\text{Zn}\cdot\text{CeCl}_3\cdot 7\text{H}_2\text{O}$	12	89 <sup>e</sup>	> 99
7	OCH <sub>2</sub> Ph	$\text{Me}_2\text{C}=\text{CHCH}_2\text{Br}\cdot\text{Zn}\cdot\text{CeCl}_3\cdot 7\text{H}_2\text{O}$	2	93 <sup>e</sup>	100
8	OCH <sub>2</sub> Ph	$\text{Me}_2\text{C}=\text{CHCH}_2\text{Br}\cdot\text{Zn}\cdot\text{SnCl}_2$	1	94 <sup>e</sup>	100

<sup>a</sup> Reaction conditions: imine–bromide–Zn–salt = 1.0 : 1.2 : 2.0 : 0.15 (mmol), THF, 25 °C. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis. <sup>c</sup> See ref. 4(a).

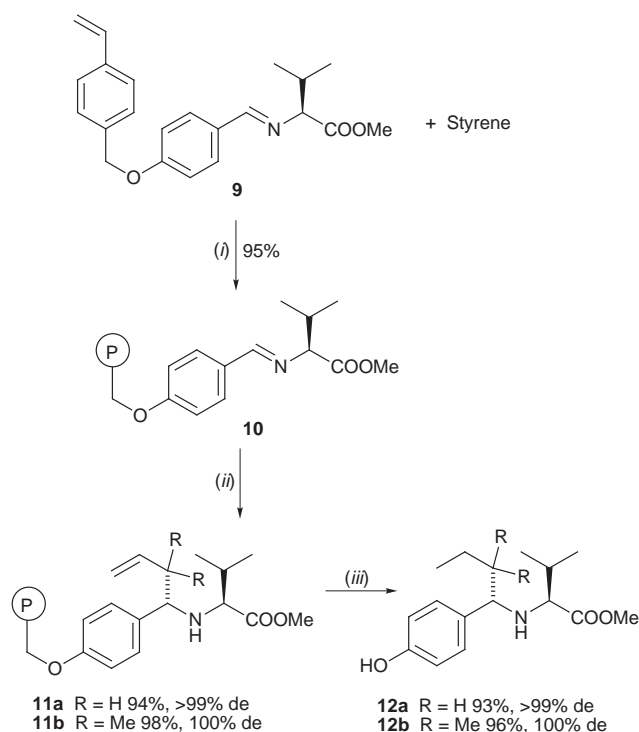
<sup>d</sup> Conversion determined by GC. <sup>e</sup> Isolated yield.

polymer. Enantiopure imine monomers **3** and **9** were thus prepared and polymerized with styrene under radical polymerization conditions to give **4** and **10**, respectively. These polymers were then allylated with the allylzinc reagent. As shown in Scheme 2 and 3, polymers **5** and **11** were obtained in excellent yield with almost perfect diastereoselectivity (>99% de). In these polymer reactions, no lowering of the diastereoselectivity was observed compared to the model reactions described above. It should be also emphasized that the polymers possessing an allylic hydrogen such as **5** and **11a** were not successfully synthesized by polymerization of the corresponding chiral monomers, since such monomers caused degradative chain transfer during the radical polymerization. The prenylzinc reagent also reacted with **10** to afford **11b** in excellent yield and selectivity (Scheme 3).<sup>6</sup> The diastereoselectivities in these polymeric reactions could easily be confirmed by the <sup>1</sup>H NMR spectra of the polymeric products (**5**, **11**).<sup>7</sup>

In order to obtain more precise information about the chiral pendant group on the polymers **5** and **11**, we examined some cleavage reactions. Since various attempts to cleave the



**Scheme 2** Reagents and conditions: (i) AIBN, 2,2'-azobisisobutyronitrile, C<sub>6</sub>H<sub>5</sub>Me, 80 °C, 48 h; (ii) CH<sub>2</sub>=CHCH<sub>2</sub>Br–Zn–CeCl<sub>3</sub>·7H<sub>2</sub>O, THF, r.t., 4 h; (iii) LiAlH<sub>4</sub>, THF, <0 °C, 3 h; (iv) H<sub>5</sub>IO–MeNH<sub>2</sub>, MeOH–THF, r.t., 1 h; (v) KOH–DMF



**Scheme 3** Reagents and conditions: (i) AIBN, C<sub>6</sub>H<sub>5</sub>Me, 80 °C, 48 h; (ii) CH<sub>2</sub>=CHCH<sub>2</sub>Br or Me<sub>2</sub>C=CHCH<sub>2</sub>Br–Zn–CeCl<sub>3</sub>·7H<sub>2</sub>O, THF, r.t., 4 h; (iii) H<sub>2</sub>/Pd–C, THF

sulfonate linkage in **5** gave a mixture of undesired side products, we took the somewhat devious route shown in Scheme 2. This stepwise cleavage, however, proceeded smoothly on the polymer to give homoallylamine **8** which is structurally identical to that derived from the model compound **2b**. The enantioselectivity of **8** was determined to be >99% ee by HPLC analysis.<sup>8</sup> On the other hand, the cleavage of the benzyl ether linkage in **11** could be achieved in a single hydrogenolysis step to afford **12** in high chemical yield (Scheme 3). <sup>1</sup>H NMR and HPLC analysis of **12** revealed >99% de and 100% de for **12a** and **12b**, respectively. These diastereoselectivities of the cleavage products are exactly equal to those obtained in the polymers **5** and **11**.

In conclusion, we have developed a new method of asymmetric transformation on the polymeric prochiral functionality, which allowed us to synthesize novel polymers having a chiral pendant group. Particularly striking are the excellent results with the allylzinc reagent where the chiral polymers were obtained in quantitative yield with perfect stereoselectivity. The obtained polymer-supported chiral amino acids and amino alcohols are almost free of side products including stereoisomeric structures, and are finding extensive applications in catalytic asymmetric synthesis.

## Experimental

### Asymmetric allylation of the polymeric imine **4**

To a stirred suspension of Zn powder (0.13 g, 2 mmol) in THF (5 ml), was added CeCl<sub>3</sub>·7H<sub>2</sub>O (56 mg, 0.5 mmol) at 0 °C. A THF (10 ml) solution of **4** (1 mmol) and allyl bromide (0.15 g, 1.2 mmol) were then added. After 4 h at room temperature, the mixture was diluted with CHCl<sub>3</sub> (50 ml), quenched with NaOH aqueous solution (2M, 10 ml) and stirred for 5 min. The organic layer was separated, washed with brine and concentrated at ca. 20 ml under reduced pressure. The resulting polymer solution was then precipitated into methanol to give a fine powder of **5**. 97% yield, *M<sub>n</sub>* = 42 000, *M<sub>w</sub>* : *M<sub>n</sub>* = 2.0. <sup>1</sup>H NMR (270 MHz): peaks attributed to polystyrene backbone, δ 7.2–6.2 (Ar), 2.2–1.2 (CH, CH<sub>2</sub>); peaks attributed to the chiral pendant moiety having (*S*, *S*) configuration, δ 5.75

(1H, CH<sub>2</sub>=CH), 5.1 (2H, CH<sub>2</sub> = CH), 3.7, (3H, CO<sub>2</sub>CH<sub>3</sub>), 3.5 (1H, Ar—CH—N), 2.7 (1H, CH—CO), 0.95 [6H, (CH<sub>3</sub>)<sub>2</sub>CH]. No peak at 3.0 ppm assignable to the (R, S) isomer was detected from the NMR spectrum.

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- 5 Diastereoselectivity was determined by <sup>1</sup>H NMR and HPLC analysis according to the Umani-Ronchi method for the allylation of benzaldimine.<sup>4a</sup> The configuration of the obtained homoallylamines **2b** and **2c** is estimated to be (S, S) from the results obtained from the allylation of benzaldimine.
- 6 The polymer **11b** was alternatively prepared by copolymerization of styrene with the corresponding chiral monomer and showed an identical <sup>1</sup>H NMR spectrum to that obtained in Scheme 3.
- 7 Methine protons α to the tester group in **5**, **11a** and **11b** appear at 2.70, 2.75 and 2.80 ppm, respectively, for the (S, S) isomer. Peaks for the (R, S) isomers appear at around 3.0 ppm.
- 8 Enantiomeric excesses were determined by HPLC using a chiral stationary phase [Daicel Chiralcel OD-H, hexane-isopropyl alcohol–diethylamine (90 : 10 : 0.1)].

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