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Diastereoselective [2+2] photocycloaddition of polymer-supported cyclic chiral enone with ethylene

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Abstract—The phenylmenthyl derivative, previously shown to be very effective chiral auxiliaries in the diastereoselective [2+2] photocycloaddition of cyclic enones with the simplest olefin, ethylene, was attached to poly(ethylene glycol)-grafted Wang resin. We then investigated the diastereoselective [2+2] photocycloaddition on solid support in several solvents. As the result, we accomplished good selectivity in toluene as well as the recycle of the polymer-supported chiral auxiliary. This is the first example that bicyclo[4.2.0]octane derivative has been obtained photochemically on the solid support.

Efficient constructions of stereogenic centers are of increasing interest in synthetic organic chemistry. The utilization of a chiral auxiliary is one of the most promising methods for this purpose, and the wide variety of chiral auxiliaries has been reported for asymmetric synthesis.[1] From the pioneering work of Corey's group,[2] 8-phenylmenthyl derivatives as chiral auxiliaries have received great attention, and many applications are found in the literature.[3] Recently we reported that the diastereoselective [2+2] photocycloaddition of cyclohexenonecarboxylates having 8-phenylmenthol derivatives as a chiral auxiliary to the simplest olefin, ethylene, proceeded in good yields and diastereoselectivities.[4]

Immobilization of chiral auxiliaries to polymer support[5] results in the easier isolation of the product. In addition, solid-phase reaction sometimes provides a unique product as well as selectivity that may be difficult to achieve by conventional methods.[6] This is most likely due to the unique interaction at the interface between solid and liquid, and the highly hydrophobic environment within the polymer support. Numerous reports of solid-phase organic synthesis are often published,[7] but photochemical reaction on solid support is rarely reported[8] in spite of its powerful potential for the construction of strained rings. Especially, to our best knowledge, none of the diastereoselective photochemical reactions on beads has yet been disclosed. We here report on the first diastereoselective [2+2] photocycloaddition by the use of polymer-supported 8-phenylmenthyl derivative as a chiral auxiliary.

For the assembly of the polymer-supported chiral auxiliary, (−)-8-[(*p*-methoxy)phenyl]menthol **1** was prepared from (*R*)-(+)-pulegone according to the modified Corey's procedure.[9] After the protection of the secondary alcohol, demethylation was carried out with borane tribromide to give (−)-8-[(*p*-hydroxy)phenyl]menthyl acetate **2**. The alkyl linker part was introduced into **2**, then the terminal silyl protection was removed to prepare the linker-attached chiral auxiliary **3**. We chose Wang resin because of its easiness of handling. In addition, selectivity of the photochemical reaction can be easily determined by ^{1}H NMR as d.e. when the cycloadduct having the chiral auxiliary is cleaved from the resin. The 8-phenylmenthyl derivative **3** was first loaded onto Wang polystyrene resin. However, acetyl protection was hardly removed, probably due to the lack of affinity of polystyrene resin to the hydrolysis conditions. In order to circumvent the problem, poly(ethylene glycol)-grafted polystyrene Wang (PS-PEG-Wang) resin (purchased from Watanabe Chemical Industries, LTD., 1% divinylbenzene cross-linked, 100–200 mesh) was employed. The chiral auxiliary **3** was coupled with trichloroacetimidate type PS-PEG-Wang

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Keywords: Diastereoselectivity; [2+2] Photocycloaddition; (−)-8-Phenylmenthyl; Chiral auxiliary; Polymer support.

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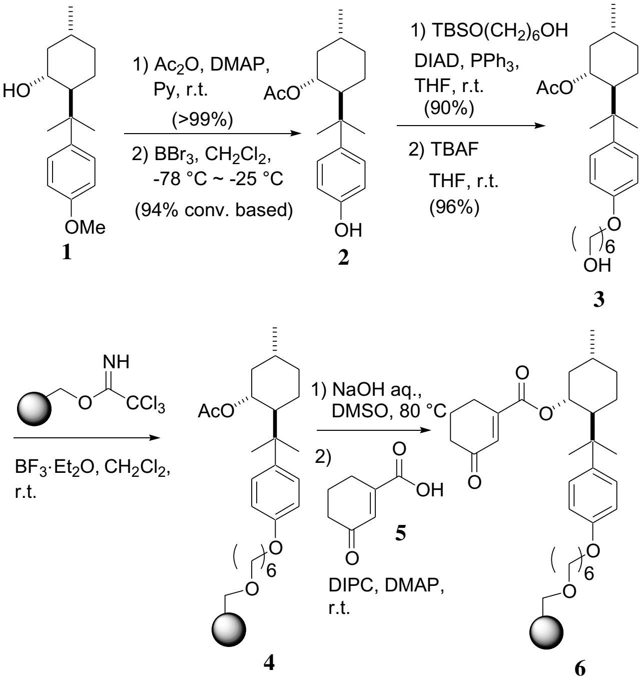

Figure 1. Synthesis of polymer-supported chiral auxiliary.

resin[10] to provide **4**. Removal of the acetyl protection was achieved under aqueous basic conditions followed by condensation of cyclohexen-3-one-1-carboxylicacid **5** to give the polymer-supported chiral enone **6** (Fig. 1). The loading level was estimated to be 0.19 mmol/g by the cleavage of a small amount of the resin **6** (81% against the original loading of PS-PEG-Wang).[11]

The effects of a solvent on the selectivity were investigated. Photochemical reaction was carried out at −78 °C in an appropriate solvent for 5 h by irradiating a suspension of polymer-supported cyclohexenone carboxylate **6**, saturated with ethylene with Pyrex-filtered light ($\lambda > 280$ nm) from a high-pressure mercury lamp (500 W) (Fig. 2). The resin was filtered and washed with MeOH and CH_2Cl_2, then treated with 30% TFA in CH_2Cl_2 at room temperature for 30 min. The resin was filtered off, and evaporation of the filtrate gave a mixture of two diastereomers **10**. The d.e. was determined by comparing the areas of distinct signals of the diastereomers in the ^{1}H NMR spectrum as described previously.[4] The results are summarized in Table 1. For comparison, the results of photochemical reactions in the solution-phase with (−)-8-[(*p*-methoxy)phenyl]menthyl derivative **7** are also presented. In all cases, the reaction proceeded and toluene was found to be the best to provide the product in 68% yield with 72% d.e. (entry 2). This selectivity is slightly better than that in the solution-phase synthesis in toluene. Methylcyclohexane provided the product in 81% d.e. in the solution-phase, while the corresponding solid-phase synthesis afforded the product in 65% d.e. with the low chemical yield (entry 1). This result was influenced by the low swelling of the resin in methylcyclohexane. Interestingly, in MeOH the cycloadduct was obtained in moderate yield and selectivity whereas the corresponding reaction in the solution-phase gave the product in low yield and selectivity due to the low solubility of **7** against MeOH (entry 4). The partial degradation of the polymer backbone was observed during the photochemical reaction. The degrees of the chop were varied among the solvents and affected to the yields. Our laboratory is now addressing this event. Our attempt of this photochemical reaction in water at room temperature resulted in the complex mixture.

Table 1. Investigation of the effect of solvents

Entry	Solvent	Yield (%)		D.e. (%)	
		8[a,b]	**9**[c,d]	**8**	**9**
1	Methylcyclohexane	20[e]	79	65	81
2	Toluene	68	59	72	66
3	CH_2Cl_2	30[f]	95	58	50
4	MeOH	57	14	48	3

[a] The yields were determined by ^{1}H NMR.

[b] The reaction were carried out for 5 h.

[c] Isolated yields.

[d] The reactions were carried out for 0.5–2 h.

[e] The starting material was remained in 30%.

[f] The starting material was remained in 14%.

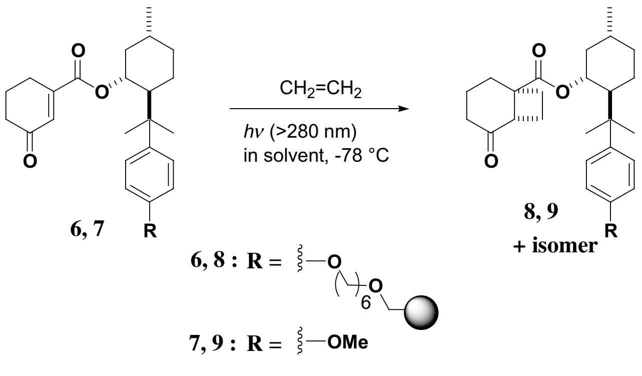

Figure 2. Diastereoselective [2+2] photocycloaddition.

Next, we attempted to recycle the polymer-supported chiral auxiliary. The synthesis of the chiral auxiliary **1** was quite tough and the resin is still somewhat expensive. Thus the reuse of this precious polymer-supported chiral auxiliary is desirable. After the photochemical reaction in toluene as described above, bicyclo[4.2.0]octan-2-one-6-carboxylic acid **11** was released from the resin by hydrolysis (NaOH aq, DMSO, 80 °C). The recovered polymer-supported chiral auxiliary **12** was then coupled with cyclohexen-3-one-1-carboxylic acid **5** to reproduce **6**. The photochemical reaction was carried out again to provide **8**. To determine the yield and diastereoselectivity, a small amount of **8** was treated with TFA to give **10**. The results are summarized in Table 2. Although the loading level was decreased by the recycle due to the partial degradation, both yields and selectivities were stable at each photochemical reaction (Fig. 3).

In conclusion, the polymer-supported chiral auxiliary was efficiently prepared and utilized for the diastereo-

Table 2. Recycle of polymer-supported chiral auxiliary

Cycle	Loading of **6** (%)[a]	Yield of **10** (%)[b]	D.e. of **10** (%)[c]
1	75	82	71
2	67	78	65
3	50	86	69

[a] Based on the original loading of Wang resin (0.24 mmol/g).
[b] Based on the loading of **6** in each step.
[c] The d.e.s were determined by ^{1}H NMR.

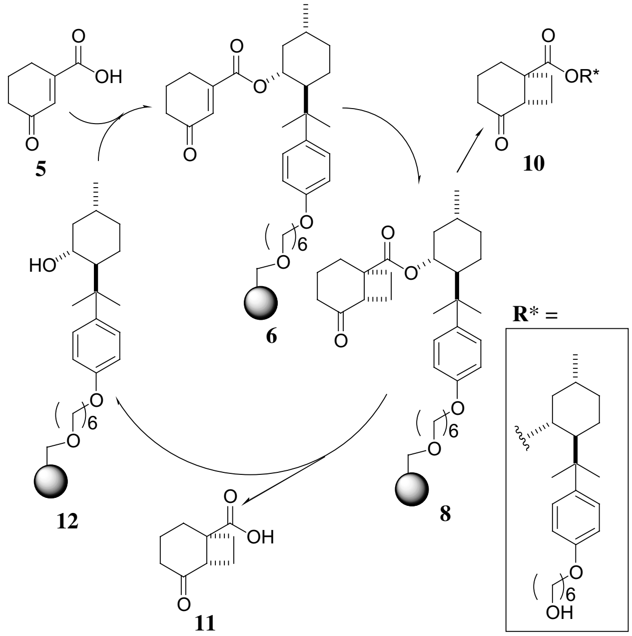

Figure 3. Recycle of polymer-supported chiral auxiliary.

selective [2+2] photocycloaddition reaction. The cycloadduct was obtained in good yields and diastereoselectivities. Besides that, the polymer-supported chiral auxiliary was reusable up to three cycles. The present polymer-supported chiral auxiliary is applicable to a series of diastereoselective reactions.[3] Our further investigation to address the degradation and to seek more effective supports as well as to apply the polymer-supported chiral auxiliary to stereoselective thermodynamic reactions will be reported in due course.

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