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Solid phase asymmetric alkylation reactions using 2-imidazolidinone chiral auxiliary

Quynh Pham Bao Nguyen [a], Jae Nyoung Kim [b], Taek Hyeon Kim [a,*]

[a] Department of Applied Chemistry and Center for Functional Nano Fine Chemicals, Chonnam National University, Gwangju 500-757, Republic of Korea
[b] Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju, 500-757, Republic of Korea

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ABSTRACT

A novel solid supported 2-imidazolidinone chiral auxiliary was prepared from *O*-benzyl-L-tyrosine and Wang resin. Asymmetric alkylation reactions in the solid phase proceeded with excellent stereoselectivities, which were even higher than those observed in the conventional solution phase method.

Polymer bound chiral auxiliaries, which enable the asymmetric synthesis of libraries of homochiral compounds, have received increasing interest within the last few years.[1] Such solid supported chiral auxiliaries offer some advantages as compared to their application in the solution phase, including a simple filtration procedure for the isolation of the desired compounds or the recovery of the expensive chiral auxiliaries, and their possible extension to a continuous flow system. In addition, the microenvironment of the polymeric backbone could lead to an improvement in the stereoselectivity for a given transformation.[2] Oxazolidinones remain the most extensively explored solid supported auxiliaries. Their utility in solid phase asymmetric alkylation,[3] aldol condensation,[4] Diels–Alder,[5] and 1,3-dipolar cycloadditions[6] has been reported. However, solid phase asymmetric alkylation using oxazolidinone chiral auxiliaries has not been accomplished in a highly stereoselective manner (max 90% ee) due to unfavorable steric effect from resin at 4-position of the oxazolidinone ring, and the key issue of polymer recyclability has not been addressed.[3a] Therefore, an improvement in stereoselectivity of solid supported oxazolidinone was then reported (max 97% ee) by using other anchoring system, in which the connection of the oxazolidinone chiral auxiliary to resin was performed from the 5-position of oxazolidinone ring instead of 4-position. The recycling of this solid supported oxazolidinone was also achieved by maintaining the stereoselectivity, but the yield was somewhat reduced due to the side reaction and it was only reused in the same reaction, viz. asymmetric allylation. In addition, the synthesis of this solid supported chiral auxiliary was started with uneasily available starting material.[3b]

2-Imidazolidinone has been reported to be a versatile auxiliary for asymmetric syntheses, exhibiting excellent levels of stereocontrol, greater stability, and recyclability.[7] In this Letter, we wish to report the preparation of a novel solid-supported chiral auxiliary based on 2-imidazolidinone and the preliminary results of our investigations concerning the asymmetric alkylation reactions on solid supports and the potential for recycling of the solid supported 2-imidazolidinone chiral auxiliaries.

Chiral 2-imidazolidinone **5** was prepared from commercially available *O*-benzyl-L-tyrosine in four steps (Scheme 1). The reduction of tyrosine to the corresponding alcohol **2** was easily accomplished with the previously reported procedure using $LiAlH_4$.[4a] Chiral 2-imidazolidinone **4** was prepared in moderate yield in two simple steps: the addition of phenyl isocyanate to **2** and cyclization using *t*-BuOK and TsCl.[8] Finally, the chiral auxiliary **5** was formed after removing the O-protecting benzyl group. One of the attractive features of the chiral auxiliary **5** is that it serves a dual purpose: it has a phenolic hydroxy group that allows for its attachment to resins and the chiral 2-imidazolidinone itself can serve as a chiral auxiliary to carry out asymmetric reactions.

The solid supported 2-imidazolidinone chiral auxiliary **6** was formed by immobilizing 2-imidazolidinone on Wang resin under Mitsunobu conditions using triphenyl phosphine and diisopropyl azodicarboxylate (DIAD) (Scheme 2). The loading capacity of the resin was difficult to determine accurately. It was determined by the evaluation of the mass increase of the resin after the attachment step,[2] and was confirmed by elemental analysis (%N).[4a] According to these methods, the loading yield of resin **6** was up to 80%. In the case of oxazolidinone chiral auxiliaries, the loading yields when N-propionylated oxazolidinone is directly coupled to various resins were only 30–60%.[3a] From our experiments, the loading yield of the N-propionylated imidazolidinone chiral auxiliary to Wang resin was lower (60–70%) than that of the imidazolidinone chiral auxiliary **5** to Wang resin (up to 80%). Acylation on the solid phase proceeded smoothly to yield resin **7** in quantitative yield. Obviously, the monitoring of the reaction progress on a solid support cannot be accomplished as easily as that in the case of solution chemistry, where thin layer chromatography (TLC) is used. However, chromatographic monitoring was possible after the

* Corresponding author. Tel.: +82 62 530 1891; fax: +82 62 530 1889.
E-mail address: thkim@chonnam.ac.kr (T.H. Kim).

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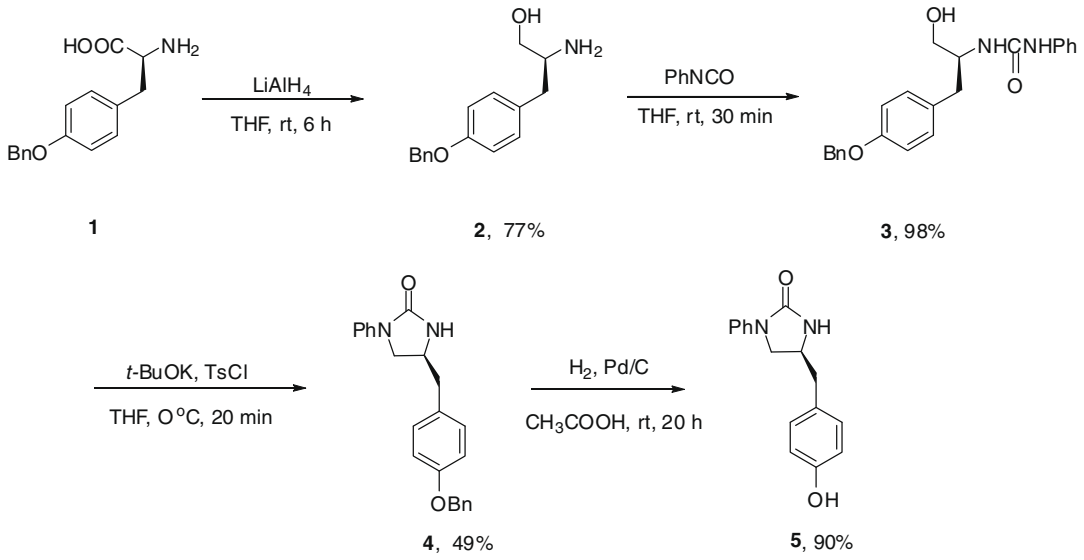
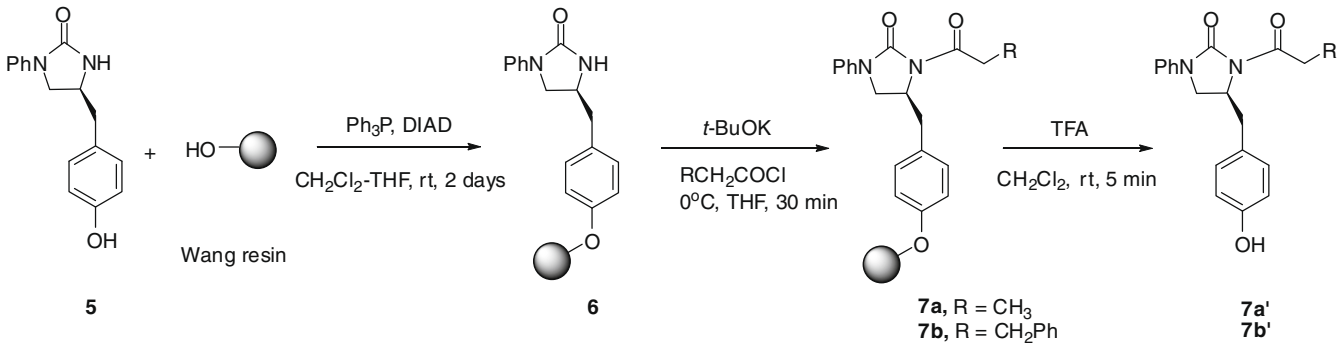


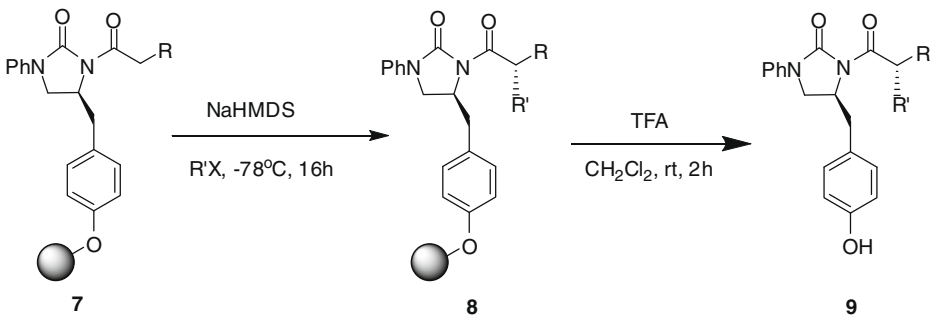
Scheme 1. Synthesis of 2-imidazolidinone chiral auxiliary in solution phase.



Scheme 2. Synthesis of solid supported N-acylated 2-imidazolidinone chiral auxiliary.

cleavage of the acylated resin **7** with trifluoroacetic acid (TFA) for 5 min at room temperature.

For the solid phase asymmetric alkylation reaction, resin **7** (loading capacity 1 mmol/g) was swollen in THF and cooled to −78 °C, followed by the dropwise addition of 1 M NaHMDS (3 equiv). After continuously stirring for 3 h at the same temperature, the alkyl halide (10 equiv) was added and reacted for 16 h. Then, the reaction mixture was quenched by adding saturated NH_4Cl. The resultant resin was separated from the reaction mixture by the filtration, followed by washing with THF/H_2O (1:1 v/v), THF, DMF, CH_2Cl_2, and MeOH sequentially and then dried in vacuo. Treatment of the alkylated resin **8** with TFA allowed the determination of yield as well as de value of the alkylation products by analysis of compound **9** (Scheme 3). The diastereomeric excess was easily obtained by ^1H NMR, which showed different chemical shifts for the two diastereoisomers (e.g., **9a** and **9c**).[9]



Scheme 3. Solid phase asymmetric alkylation reactions.

Table 1
Diastereoselective alkylations of solid supported chiral auxiliaries **7** and cleavage of **8**

Entry	Substrate	R	R′X	Product	Yield[a] (%)	de[b] (%)
1	**7a**	CH_3	$PhCH_2Br$	**8a**, **9a**	40	>99
2	**7b**	Bn	$CH_2{=}CHCH_2Br$	**8b**, **9b**	35	>99
3	**7b**	Bn	CH_3I	**8c**, **9c**	30	>99
4	**7b**	Bn	$CH{\equiv}CCH_2Br$	**8d**, **9d**	37	>99

[a] Yields of **9** after four steps based on original loading of Wang resin.
[b] Determined by ^1H NMR and HPLC (chiracel ODH column).

The validity of using this observation for determining the de value was also confirmed by HPLC analysis (see Supplementary data for details). As shown in Table 1, benzyl bromide, allyl bromide, methyl iodide, and propagyl bromide reacted very well to give the alkylated products with moderate to good yield and excellent de values (up to 99% de). The most striking feature of the solid supported chiral auxiliary **7** is that the sterically undemanding methylation, which is often difficult to control, proceeded with remarkable diastereoselectivity, which was even higher than that obtained from the same model in the solution phase reaction. Prasad reported that the methylation reaction of the 3-dihydrocinnamoyl-2-imidazolidinone in solution afforded a de of 89%,[10] but, in our case, viz. the alkylation reaction on the solid support, the methylated product was obtained with a de of up to 99%. This can be explained by considering that the microenvironment of the polymeric backbone of the solid supported chiral auxiliary could lead to an improvement in the diastereoselectivity for a given transformation.[2]

Resin **8** can be cleaved to the acid with LiOH without H_2O_2 to suppress the endocyclic cleavage of the chiral auxiliary or, more rapidly, by refluxing in 2 M NaOH/dioxane (1:1 v/v) for 4 h. The chiral acids **10a–d** were obtained in moderate yields, high purity, and excellent enantiomeric excess (ee >99%) (Table 2). The ee values of the chiral acids were determined by HPLC (chiralcel ODH column) after their conversion to the corresponding chiral esters with diazomethane (CH_2N_2).[11] As expected, no racemization occurred during the hydrolysis of the alkylated resin **8** in NaOH.

The recycling of the expensive auxiliary is the key issue in the development of solid supported chiral auxiliaries. However, there have been few extensive studies on the issue of efficient recycling. The recycling of the solid supported Evans' oxazolidinone was achieved by maintaining the stereoselectivity of the product, but the yield was somewhat reduced due to the side reaction and it was only reused in the same reaction, viz. asymmetric allylation.[3b] Procter reported the recycling of the same resin with different reactions.[12] However, in some cases, the final pure product could not be obtained, due to the incomplete cleavage in the previous cycle. After treatment the recovered resin **6** with TFA (Scheme 4), the clean generation of the chiral auxiliary **5** was obtained with purity >80% by HPLC analysis of crude product. That encouraged us to study the recycling of our chiral auxiliary. As expected, our solid supported chiral auxiliary **6**, which was very stable under NaOH cleavage conditions, could be reused three times with no significant drop in the enantiomeric excess or yield (Table 3).

In conclusion, we developed a new solid supported 2-imidazolidinone chiral auxiliary. Asymmetric alkylation reactions in the solid phase proceeded with good yield and excellent stereoselectivity, which were even higher than those obtained in the conventional solution phase methods. This solid supported chiral auxiliary was easily recovered by hydrolysis with sodium hydroxide to afford the chiral α-substituted carboxylic acid in excellent enantiomeric excess and high purity. In addition, our solid supported chiral auxiliary could be reused three times with no significant drop in the stereoselectivity or yield (Scheme 5).

Table 2
Transformation of alkylated resin **8** to acids

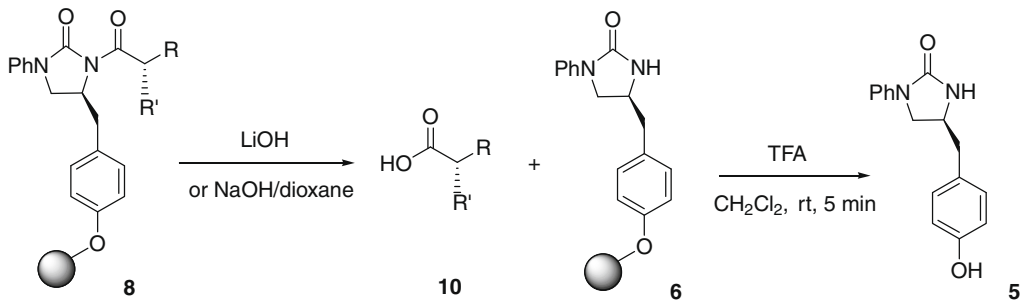
Entry	Substrate	Condition	Product	Yield[a] (%)	Purity[b] (%)	ee (%)
1	**8a**	LiOH	**10a**	24	—[d]	—
2	**8a**	NaOH/dioxane	**10a**	30	90	>99
3	**8b**	NaOH/dioxane	**10b**	21	90	>99
4	**8c**	NaOH/dioxane	**10c**	24	89	>99
5	**8d**	NaOH/dioxane	**10d**	20	95 (>99)[c]	>99

[a] Yield in four steps based on original loading of Wang resin.
[b] Determined by HPLC (chiracel ODH column) of crude product in *n*-hexane.
[c] Value in parentheses is purity after column chromatography.
[d] Not determined.

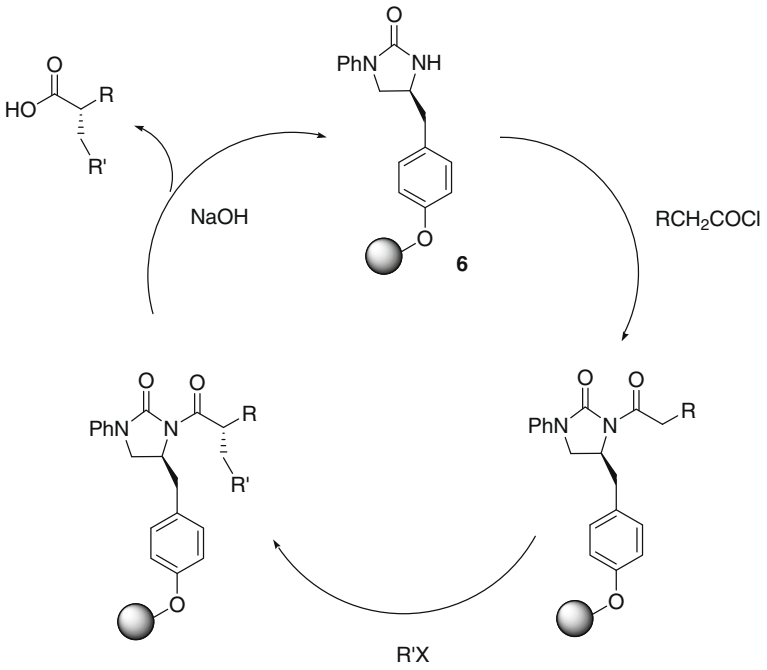
Table 3
Recyling of the solid supported chiral auxiliary **6**

Run	R	R′X	Product	Yield[a] (%)	Purity[b] (%)	ee (%)
1st	Me	BnBr	**10a**	30	90	>99
2nd	Bn	$CH_2{=}CHCH_2Br$	**10b**	22	75	>99
3rd	Bn	MeI	**10c**	23	80	>99
4th	Bn	$CH{\equiv}CCH_2Br$	**10d**	20	>99[c]	>99

[a] Yields in four steps from the resin **6** based on original loading of Wang resin.
[b] Determined by HPLC (chiracel ODH column) of crude product in *n*-hexane.
[c] After column chromatography.



Scheme 4. Hydrolysis and recovery of solid supported chiral auxiliary.



Scheme 5. Recycling of the solid supported chiral auxiliary **6**.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.127.

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9. *Compound* **9a**: ^{1}H NMR ($CDCl_3$) δ 6.68–7.36 (14H, m), 4.77 (1H, s), 4.63 (1H, m), 4.30 (1H, dd, J = 7.4, 14.3 Hz), 3.83 (1H, t, J = 9.2 Hz), 3.46 (1H, dd, J = 7.4, 9.5 Hz), 3.25 (1H, dd, J = 7.3, 13.2 Hz), 3.00 (1H, dd, J = 3, 13.5 Hz), 2.68 (1H, dd, J = 7.6, 13.2 Hz), 2.59 (1H, dd, J = 8.6, 13.5 Hz), 1.18 (1H, d, J = 8.7 Hz). *Compound* **9c**: ^{1}H NMR ($CDCl_3$) δ 6.71–7.61 (14H, m), 4.73 (1H, s), 4.50 (1H, m), 4.27 (1H, dd, J = 7.4, 13.4 Hz), 3.64 (1H, t, J = 9.2 Hz), 3.42 (1H, dd, J = 1.8, 9.4 Hz), 3.15 (1H, dd, J = 3.2, 13.4 Hz), 3.05 (1H, dd, J = 7.6, 13.3 Hz), 2.73 (2H, m), 1.28 (1H, dd, J = 7 Hz).
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