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A convenient method for asymmetric alkylation of glycine imine esters using solid supports

Haitao Yu and Hideko Koshima*

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790-8577, Japan

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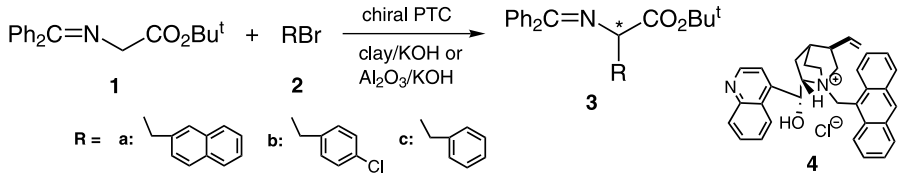
Abstract—Asymmetric alkylation of butyl glycinate-benzophenone Schiff base proceeded smoothly on clays and alumina at room temperature to afford alkylated products in high yields and good enantioselectivities.

Asymmetric synthesis of naturally occurring and synthetic α-amino acids using a simple and easily scalable procedure remains as an important synthetic challenge.[1] An attractive method, which is asymmetric phase-transfer catalytic (PTC) alkylation of *N*-diphenylmethylene glycine *t*-butyl ester (**1**) has been known.[2] The search for novel chiral PTC catalysts for this reaction has intrigued many scientists.[3] The liquid–liquid PTC reactions usually require mechanical and vigorous stirring for many hours and sometimes result in unfortunate irreproducibility and inefficiency. In order to overcome the problems, it is desirable to develop new procedure for the asymmetric alkylation reaction. Recently, rate enhancement has been reported in the liquid–liquid PTC alkylations under ultrasonic irradiation.[4] Asymmetric alkylation under micellar conditions has been also achieved.[5]

Recent years have witnessed a phenomenal growth in the use of high surface area inorganic solids as reaction media for organic transformations.[6] The advantages of the reactions are that they provide enhanced reaction rate, greater selectivity and manipulative simplicity. To the best of our knowledge there is no report which deals with the PTC alkylation of glycine imine esters with solid supports such as clay and alumina. Herein, we first report a convenient method for the preparation of alkylation compounds from *N*-diphenylmethylene glycine *t*-butyl ester (**1**) with aralkyl bromide (**2**) in the presence of commercially available *N*-anthracenylmethylcinchonidinium chloride (**4**) as a chiral PTC catalyst using solid supports (Scheme 1).

As the results of our preliminary optimization of the conditions using 2-(bromomethyl)naphthalene (**2a**), when the CH_2Cl_2 solution of **1**, **2a** and catalyst **4** was added dropwise into kaolin preloaded with KOH,[7] and the mixture was stood on for 1 h under 'silent' conditions without any heating and stirring (Method A[8a]), a clean product **3a** was effectively obtained in high yield and good enantioselectivity (entry 1 in Table 1). Little advantage in terms of enantioselectivity was gained by stirring or ultrasonic irradiation. Here the presence of CH_2Cl_2 on the solid supports was crucial, because complete removal of CH_2Cl_2 led to prolong the reaction time, not complete even after six days. The amount of CH_2Cl_2 that can just dissolve the starting mixture and cannot make the support to form slurry was found to be best and yield the clean product.



Scheme 1.

* Corresponding author. Tel.: +81-89-927-8523; fax: +81-89-927-9923; e-mail: koshima@eng.ehime-u.ac.jp

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Table 1. Asymmetric alkylation of *N*-diphenylmethylene glycine *t*-butyl ester (**1**) on solid supports[a]

Entry	RBr	Product	Condition			Yield[b] (%)	Ee[c] (%)	Config.[d]
			Support	Method	Time (min)			
1	**2a**	**3a**	Kaolin	A	60	95	79	*S*
2	**2a**	**3a**	Mont-K10	A	60	93	75	*S*
3	**2a**	**3a**	Al_2O_3	A	60	92	75	*S*
4	**2a**	**3a**	Kaolin	A[e]	300	93	83	*S*
5	**2b**	**3b**	Kaolin	A	46	92	78	*S*
6	**2c**	**3c**	Kaolin	A	30	91	72	*S*
7	**2a**	**3a**	Kaolin	B	7	68	34	*S*
8	**2a**	**3a**	Mont-K10	B	8	58	32	*S*
9	**2a**	**3a**	Al_2O_3	B	5	82	44	*S*
10	**2b**	**3b**	Al_2O_3	B	4	79	34	*S*
11	**2c**	**3c**	Al_2O_3	B	4	67	58	*S*

[a] Support loaded with KOH.[7]
[b] Isolated yield.
[c] The ee was determined by HPLC analysis using a chiral column (Chiralcel OD) with hexane/2-propanol as solvent.
[d] The absolute configuration was assigned by the HPLC retention times of both enantiomers determined previously.[2,3b]
[e] Reaction at −20°C. Others at room temperature.

In comparison, we made reexamination of usual liquid–liquid PTC reaction according to the literature procedure.[3b] The reaction of **1** (0.34 mmol) with **2a** (0.38 mmol) in the presence of catalyst **4** (0.034 mmol) in toluene (3 mL) and 50% KOH (0.7 mL) at room temperature gave almost comparable results of 90% yield and 86% ee, but required quite a long reaction time of 18 h for completion.

Yields and enantioselectivities of products among kaolin, montmorillonite K-10 and alumina were compared in the reaction of **1** with **2a**, a slightly better result was obtained using kaolin (entries 1–3). Lowering the reaction temperature to −20°C slightly increased the enantioselectivity but prolonged the reaction time for 5 h (entry 4). With our optimized reaction conditions in hand, other aralkyl bromides **2b** and **2c** afforded similar good results (entries 5 and 6). These results showed that structural differences among the three solid supports scarcely affected the activity and enantioselectivity. Namely, the role of solid supports for the rate enhancement is thought to be the smooth and homogeneous dispersion of reactants and products on the large surfaces by the help of CH_2Cl_2 as a carrier. The supports could be recycled three times without losing their activity by washing with CH_2Cl_2 and evaporating all CH_2Cl_2 after the reaction.

Finally, in order to attain further acceleration of the reaction, microwave irradiation was applied for the alkylation using the solid supports (Method B[8b]). The reactions were dramatically accelerated and completed within several minutes but unfortunately resulted in the considerable decrease of enantioselectivities (entries 7–11).

In summary, we have discovered and explored that the rapid asymmetric alkylation of glycine imine esters using commercial available and low cost solid supports. The reaction involves simple operations without any aqueous work-up, mild conditions and provides high yields and good enantioselectivities.

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7. Support/KOH was prepared as follow: Support (alumina, montmorillonite K-10 or kaolin clay) (3 g) was added to 4 mL of 25% KOH solution, and the mixture was sonicated for a period of 4 h. The water was removed under reduced pressure. The resultant solids were irradiated with microwave for 15 min and ground to a powder.
8. ***Typical procedure***: (a) Method A: A solution of catalyst **4** (0.005 mmol), *N*-diphenylmethylene glycine *t*-butyl ester (**1**) (0.05 mmol) and **2a** (0.06 mmol) in CH_2Cl_2 (0.2 mL) was dispersed on kaolin/KOH (0.5 g, 51 equiv. KOH to **1**) and the mixtures was stood on at room temperature for appropriate time. After completion of the reaction (moni-

tored by TLC), the reaction mixture was extracted with CH_2Cl_2 (2×5 mL) from the support. The product was separated by preparative HPLC using C18 column with methanol/water 60/40 (v/v) with a gradient of 60–100% methanol. (b) Method B: A solution of catalyst **4** (0.005 mmol), *N*-diphenylmethylene glycine *t*-butyl ester (**1**) (0.05 mmol) and **2a** (0.06 mmol) in CH_2Cl_2 (0.2 mL) was dispersed on alumina/KOH (0.5 g, 51 equiv. KOH to **1**). After evaporation of the solvent, the so-obtained mixture was irradiated by microwave with a Sanyo EM-LA1 (500 W) for appropriate minutes. The separation is the same as above.