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TETRAHEDRON: *ASYMMETRY*

# Palladium-catalyzed allylic alkylation of *tert*-butyl(diphylmethylene)-glycinate with simple allyl esters under chiral phase transfer conditions

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**Abstract**—The first example of palladium-catalyzed allylic alkylation of an imino ester with simple allyl esters in the presence of a chiral quaternary ammonium salt is reported. The presence of molecular sieves was found to have a beneficial effect on the enantioselectivity of the reaction by scavenging water from the system. Alkylated products with e.e.s of up to 61% were obtained.
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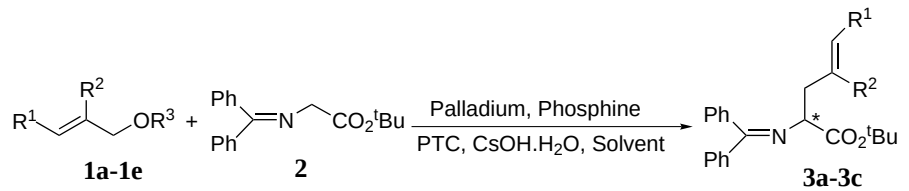
## 1. Introduction

The synthesis of non-proteinogenic amino acids has been an area of great interest, since they have been employed as building blocks for the preparation of products with biological activities.[1] Among them, compounds containing an allyl moiety are of particular interest, because they can be easily transformed into a wide range of novel non-proteinogenic amino acids by simple reactions.[2] Recently, imino esters were used as nucleophiles in palladium-catalyzed asymmetric allylic alkylation reactions to afford alkylated amino acids, however the enantioselectivity was not high with simple allyl acetates as substrates.[3] Although the highly enantioselective alkylation of imino esters under chiral PTC conditions has been reported,[4] this transformation suffers from the limitation of the allyl halide sources and thus it is difficult to extend this procedure to synthesize enantiomerically pure amino acids containing allyl groups. A potentially promising procedure for the preparation of allyl amino acids involves combining a palladium catalyst with a chiral PTC as co-catalyst to promote the allylic alkylation of an imino ester, which would avoid the disadvantages of both Pd-catalyzed




**1a-1e** + **2** → **3a-3c**

**1a**. $R^1$= H, $R^2$= H, $R^3$= Ac; **1b**. $R^1$= Ph, $R^2$= H, $R^3$= Ac;
**1c**. $R^1$=H, $R^2$=H,$R^3$=Boc; **1d**. $R^1$=H, $R^2$=H, $R^3$=COOEt;
**1e**. $R^1$= Ph, $R^2$= H, $R^3$= Boc; **1f**. $R^1$=Ph, $R^2$=H,$R^3$=COOEt;
**1g**. $R^1$=H, $R^2$=Me, $R^3$=Ac

**3a**. $R^1$=H, $R^2$=H;
**3b**. $R^1$=Ph, $R^2$=H;
**3c**. $R^1$=H, $R^2$=Me;

**Scheme 1.**

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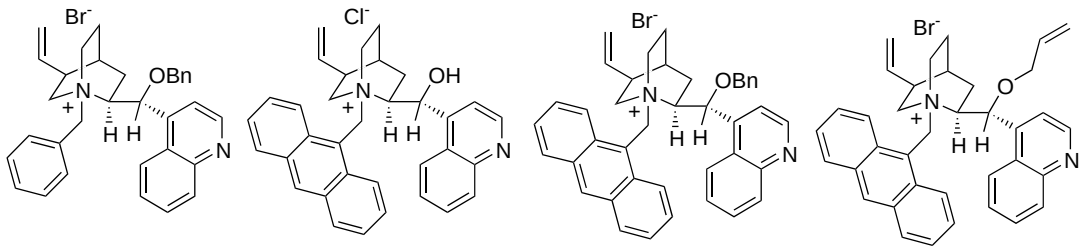
asymmetric allylic alkylation and phase transfer catalyzed alkylation methodologies. Herein, we report our preliminary efforts directed towards this transformation (Scheme 1).



**4** **5** **6** **7**

## 2. Results and discussion

### 2.1. The Pd complexes catalyzed allylic alkylation of iminoester 2 with allyl estate 1a in the presence of chiral ammonium salts 4–7

In the presence of 1 mol% palladium complex, 2.5 mol% $PPh_3$, the allylic alkylation of imino ester **2** with allyl acetate **1a** in toluene was investigated using 10 mol% of each of the chiral PTCs **4**–**7**. The results are summarized in Table 1.

The allyl ester reacted smoothly with the imino ester **2**, leading to the product **3a** in high yield, but the enantioselectivity was poor. Of the chiral PTCs **4**–**7**, **7** developed by Corey induced the best enantioselectivity for this transformation. By comparing entries 2 and 4, it was found that the allylic group bonded to oxygen on the chiral PTC played an important role for the improvement of the enantioselectivity. $[Pd(allyl)Cl]_2$ behaved a little more efficiently in both reactivity and enantioselectivity than $Pd(dba)_2$ (entries 6 and 7). Using $CH_2Cl_2$ in place of toluene as solvent resulted in lower reactivity and enantioselectivity (entries 5 and 6). Lowering the temperature to 0°C led to higher e.e. of 40% (entry 4). However, further lowering the reaction temperature to −78°C resulted in a dramatic decrease in both yield and enantioselectivity (entry 8).

### 2.2. The effect of molecular sieves

During investigation of the effect of additives on the enantioselectivity, we observed that molecular sieves (MS) could improve the e.e. of the products. This result prompted us to study the function of the MS additive in this reaction. The results are summarized in Table 2.

Without molecular sieves in the reaction system, only 40% e.e. was induced by PTC **7** (entry 1). The e.e.s were improved to 59 and 61%, respectively, by addition of the 3 Å and 4 Å MS in the reaction mixture (entries 2 and 3). In other reactions, such as the Heck reaction, Sharpless epoxidation, aziridation etc., the similar beneficial effects of MS on the enantioselectivity were also found. However, the function of MS was quite different in these reactions.[5] Comparison of entries 2 and 4 in Table 2 indicates that the beneficial effect on the enantioselectivity results from the water-scavenging property of MS. With dry 3 Å and 4 Å MS as the additives, e.e.s of up to 61% were obtained. However, when water-saturated 3 Å MS was added to the reaction mixture, the product e.e. dropped to 35% (entry 4). In a biphasic water/toluene system e.e. of only 10% was obtained (entry 5). The detrimental effect of water on

**Table 2.** The effect of molecular sieves on the enantioselectivity[a]

| Entry | Additive | Time (h) | Yield (%)[b] | E.e. (%)[c] |
|---|---|---|---|---|
| 1 | – | 12 | 94 | 40 |
| 2 | 3 Å MS | 8 | 99 | 59 |
| 3 | 4 Å MS | 8 | 89 | 61 |
| 4 | 3 Å MS ($H_2O$) | 12 | 82 | 35 |
| 5 | $H_2O$ | 12 | 55 | 10 |

[a] The reaction of **1a** with **2** was carried out in the presence of 1 mol% $[Pd(allyl)Cl]_2$ and 2.5 mol% $PPh_3$ with toluene as solvent.
[b] Isolated yield based on imino ester.
[c] Determined by HPLC.

**Table 1.** The Pd complexes catalyzed allylic alkylation of imino ester **2** with allyl acetate **1a** under PTC conditions

| Entry | Pd | PTC | Solvent | Temp. (°C) | Time (h) | Yield (%)[a] | E.e. (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | $[Pd(allyl)Cl]_2$ | **4** | Toluene | 0 | 14 | 92 | 3 |
| 2 | $[Pd(allyl)Cl]_2$ | **5** | Toluene | 0 | 12 | 87 | 0 |
| 3 | $[Pd(allyl)Cl]_2$ | **6** | Toluene | 0 | 12 | 91 | 12 |
| 4 | $[Pd(allyl)Cl]_2$ | **7** | Toluene | 0 | 12 | 94 | 40 |
| 5 | $[Pd(allyl)Cl]_2$ | **7** | $CH_2Cl_2$ | 25 | 27 | 80 | 27 |
| 6 | $[Pd(allyl)Cl]_2$ | **7** | Toluene | 25 | 3 | 92 | 30 |
| 7 | $Pd(dba)_2$ | **7** | Toluene | 25 | 24 | 80 | 27 |
| 8 | $[Pd(allyl)Cl]_2$ | **7** | Toluene | −78 | 30 | 15 | 14 |

[a] Isolated yield based on imino ester.
[b] Determined by the HPLC.

the selectivity of the reaction probably results from the destruction of the tight ion pair formed between the chiral quaternary ammonium salt and the enolate by water.

### 2.3. The effect of chiral phosphines

In order to make further improvements in the selectivity, we replaced $PPh_3$ with homochiral phosphine ligands. We expected that double chiral induction would occur in the palladium-catalyzed allylic alkylation in the presence of two-component catalyst of chiral phosphine and chiral ammonium salt. As shown in Table 3, using (*S*)-BINAP as the ligand with *n*-$Bu_4N^+Br^-$ as phase transfer catalyst gave product with only 39% e.e. with the (*R*)-enantiomer predominating (entry 1). Employing the chiral ammonium bromide **7** in place of *n*-$Bu_4N^+Br^-$, led to poor e.e. of 20% (entry 2). Thus, it was concluded that (*S*)-BINAP and PTC-**7** were mismatched and resulted in decreased enantioselectivity. Using (*R*)-BINAP as a chiral phosphine ligand in the presence of PTC **7**, the e.e. increased markedly to 60% and the (*S*)- enantiomer predominated, a similar product yield and e.e. was also obtained from the reaction with PTC **7** in the presence of $PPh_3$ (entries 3 and 4).

### 2.4. Asymmetric allylic alkylation of imino ester with different allyl esters

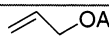
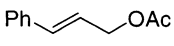
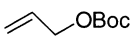
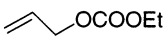
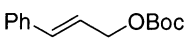
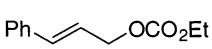
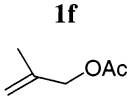
Under the optimal conditions, we extended the reaction to other simple allyl substrates. These results are summarized in Table 4. It seemed that the substituents on the allylic compounds might affect the reaction, compounds containing more steric hindrance groups led to lower reactivity and enantioselectivity. For instance,

**Table 3.** The palladium-catalyzed allylic alkylation of imino ester with **1a** in the presence of chiral BINAP and phase transfer catalyst[a]

| Entry | Ligands | PTC | Time (h) | Yield (%)[b] | E.e. (%)[c] (config.)[d] |
|---|---|---|---|---|---|
| 1 | (*S*)-BINAP | *n*-$Bu_4N^+Br^-$ | 24 | 69 | 39 (*R*) |
| 2 | (*S*)-BINAP | **7** | 24 | 75 | 20 (*R*) |
| 3 | (*R*)-BINAP | **7** | 24 | 98 | 60 (*S*) |
| 4 | $PPh_3$ | **7** | 8 | 95 | 59 (*S*) |

[a] The reaction was carried out at 0°C in the presence of 1 mol% of $[Pd(allyl)Cl]_2$ and 2.5 mol% of phosphine with 3 Å MS.
[b] Isolated yield based on imino ester.
[c] Determined by HPLC.
[d] Determined by comparison of the optical rotation with the literature value.[4a]

**Table 4.** Palladium-catalyzed asymmetric allylic alkylation of imino ester with different allyl esters in the presence of chiral ammonium bromide **7**

| Entry | Allylic substrate | Product | Time (h.) | Yield (%) [a] | E.e.% [b](config.)[c] |
|---|---|---|---|---|---|
| **1** |  **1a** | **3a** | 8 | 95 | 59(*S*) |
| **2** |  **1b** | **3b** | 27 | 64 | 55(-) |
| **3** |  **1c** | **3a** | 14 | 87 | 10(*S*) |
| **4** |  **1d** | **3a** | 14 | 93 | 37(*S*) |
| **5** |  **1e** | **3b** | 10 | 34 | 24(-) |
| **6** |  **1f** | **3b** | 10 | 75 | 38(-) |
| **7** |  **1g** | **3c** | 10 | 92 | 47(*S*) |

[a] Isolated yield based on imino ester. b. Determined by HPLC. c. The absolute configuration was determined by comparing the optical with the literature value.[4a]

59% e.e. was obtained for substrate **1a** (entry 1), but there were small decreases in the enantioselectivities for the products from substrates **1b** and **1g** of 55 and 47% e.e., respectively (entries 2 and 7). The branched products for allyl esters **1b**, **1e** and **1f** were not observed from this transformation. Better leaving groups, on the substrates (**1c**–**1f**), such as carbonate, resulted in dramatic decreases in selectivity for the transformation (entries 3–6).

## 3. Conclusion

The first example of palladium-catalyzed allylic alkylation of imino ester with simple allylic substrates in the presence of chiral quaternary ammonium salts was presented. Molecular sieve additives improved the enantioselectivity by scavenging water from the reaction system. This catalyst system exhibited high reactivity and gave products with moderate e.e.s of up to 61%.

## 4. Experimental

### 4.1. General data

All allylic substrates were prepared from the corresponding allyl alcohols.[6] The chiral phase transfer catalysts **4**–**6** were prepared according to the literature procedures[4a] and compound **7** was purchased from Aldrich. Toluene was distilled from sodium benzophenone ketyl under nitrogen. Dichloromethane was distilled from $CaH_2$. The palladium complexes were gifts from Professor Yoshinori Yamamoto at Tohoku University in Japan.

Melting points were measured on a digital melting point apparatus and were uncorrected. Mass spectra were recorded on Finnigan LCQ DECA instrument. IR spectra were obtained on a Nicolet 200SXV spectrometer. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AC-E 300 instrument. Product e.e.s were determined by HPLC on a Beckman-110A chromatography with a Backman 165 variable wavelength detector. The Chiralcel OD column was purchased from Daicel Chemical Industries, Ltd.

### 4.2. General procedure of allylic alkylation of *tert*-butylglycinate benzophenone imine 2

To a mixture of *tert*-butylglycinate benzophenone imine **2** (147 mg, 0.5 mmol), *O*-allyl-*N*-9-anthracenylmethylcinchonidium bromide **7** (30.3 mg, 0.05 mmol), 3 Å MS (1.0 g) and $CsOH{\cdot}H_2O$ (168 mg, 1 mmol) in toluene (1 mL) at 0°C was added a pre-formed solution (2 mL) of $[Pd(allyl)Cl]_2$ (3.8 mg, 10 μmol), $PPh_3$ (13.1 mg, 50 μmol) and allylic substrates (**1a**, 1 mol or **1b**–**1e**, 0.5 mol) via cannula. The reaction mixture was degassed with three freeze–thaw cycles and stirred vigorously at 0°C. The reaction mixture was filtered to remove solid, washed with ether (2×2 mL) and evaporated to dryness on a rotary evaporator. The residue was purified by flash chromatography on silica gel eluting with petroleum ether–ether (7:1) to give the products.

**3a**: 95% yield, 59% e.e. with (*S*)-isomer major was determined by HPLC (Chiralcel OD column, heptane-2-propanol, 99.5:0.5, $\lambda = 254$ nm); flow rate: 0.5 mL/min; *S*-isomer, $t_R$ 10.64 min and *R*-isomer $t_R$ 11.72 min. The NMR data are consistent with those reported in the literature.[4a]

**3b**: 64% yield, 55% e.e. was determined by HPLC (Chiralcel OD column, heptane-2-propanol, 99.5:0.5, $\lambda = 254$nm); flow rate: 1.0 mL/min; $t_R$-*major* 9.45 min and $t_R$-*minor* 12.83 min. $^1$H NMR (300 MHz,$CDCl_3$) $\delta$ (ppm) 1.48 (s, 9H, $C(CH_3)_3$), 2.80–2.87 (m, 2H), 4.11–4.15 (t, $J = 7.2$ Hz, 1H, NCH), 6.13–6.22 (m, 1H, PhC=CH), 6.45 ( d, $J = 15.0$ Hz, 1H, PhCH=C), 7.18–7.68 (m, 15H, ArH); IR: $\nu_{max}/cm^{-1}$ 1729 (C=O); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 28.0, 37.3, 66.1, 81.0, 126.0, 126.4, 127.0, 127.9, 128.3, 128.4, 128.5, 128.8, 130.2, 132.4, 136.6, 137.4, 139.6, 170.2, 170.8; MS (ESI) *m*/*e* 412.4 ($M+H^+$), 434.3 ($M+Na^+$, 100).

**3c**: 92% yield, 47% e.e. was determined by HPLC (Chiralcel OD column, heptane/propan-2-ol, 99.5:0.5, $\lambda = 254$ nm); flow rate: 1.0 mL/min; (*S*)-isomer, $t_R$ 5.45 min and (*R*)-isomer $t_R$ 7.59 min. The NMR data are consistent with those reported in the literature.[4a]

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