



# Enantioselective formation of quaternary centers on $\beta$ -ketoesters with chiral palladium QUIPHOS catalyst

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## Abstract

Asymmetric formation of quaternary centers by allylic alkylation of  $\beta$ -ketoesters using the chiral palladium QUIPHOS catalyst has been achieved. The results obtained not only depend on the reaction conditions but also on the structural features of both  $\beta$ -ketoesters and allylating agents. Enantiomeric excesses of up to 95% have been observed. © 2000 Elsevier Science Ltd. All rights reserved.

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## 1. Introduction

The palladium-catalyzed asymmetric allylic alkylation (AAA) using soft carbon nucleophiles has been extensively studied in recent years and great attention has been devoted to the design of chiral ligands leading to high enantioselectivities.<sup>1</sup> AAA that involves a stabilized prochiral nucleophile is rather difficult to control since the incoming nucleophile that attacks the electrophilic  $\pi$ -allyl intermediate resides distal to the stereogenic centers in the transition state. Recently, a high level of enantioselectivity was observed in the formation of quaternary stereogenic centers by the use of  $C_2$ -symmetry diphosphines.<sup>2,3</sup> A conceptually different approach is based on unsymmetrical bidentate ligands with two different donor atoms (P, N).<sup>4</sup> These ligands are able to impart an electronic distortion upon the allyl moiety of the palladium complex and nucleophilic attack is predicted to occur *trans* to the better  $\pi$ -acceptor (P  $\gg$  N).<sup>5,6</sup> We have recently described the straightforward synthesis of a new class of P–pyridine and P–quinoline phosphine ligands and their successful use in AAA leading to up to 87 and 96% ee in alkylation and amination, respectively.<sup>7,8</sup> In continuation of our studies, we report here an extension of these investigations for the alkylation of  $\beta$ -ketoesters with the stereocontrolled formation of a quaternary carbon center using chiral QUIPHOS ligand **2**.

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## 2. Results

The reaction of 2-benzoyloxycarbonyl tetralone **1** with allyl acetate **4** using the chiral ligand **2** (QUIPHOS) in a palladium catalyzed reaction<sup>9</sup> was examined, as summarized in Table 1 (Scheme 1).

Table 1  
Palladium catalyzed AAA of  $\beta$ -ketoester **1**<sup>a</sup>

Entry	Allylating agent	Solvent	T (°C)	Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>
1	<b>4</b>	CH <sub>2</sub> Cl <sub>2</sub>	20	88	16
2	<b>4</b>	CH <sub>2</sub> Cl <sub>2</sub>	−10	80	30
3	<b>4</b>	THF	20	73	0
4	<b>4</b>	THF	−10	75	5
5	<b>4</b>	Toluene	20	68	35
6	<b>4</b>	Toluene	−10	89	54
7	<b>4</b>	Toluene	−60	83	52
8 <sup>d</sup>	<b>4</b>	Toluene	−10	62	16
9 <sup>e</sup>	<b>4</b>	Toluene	−10	74	12
10 <sup>f</sup>	<b>4</b>	Toluene	−10	62	39
11 <sup>g</sup>	<b>4</b>	Toluene	−10	73	28
12	<b>5</b>	Toluene	−10	84	46
13	<b>6</b>	Toluene	−10	34	21

<sup>a</sup> Experiment performed on a 6.25 mmol scale (see Section 4).

<sup>b</sup> Isolated yield.

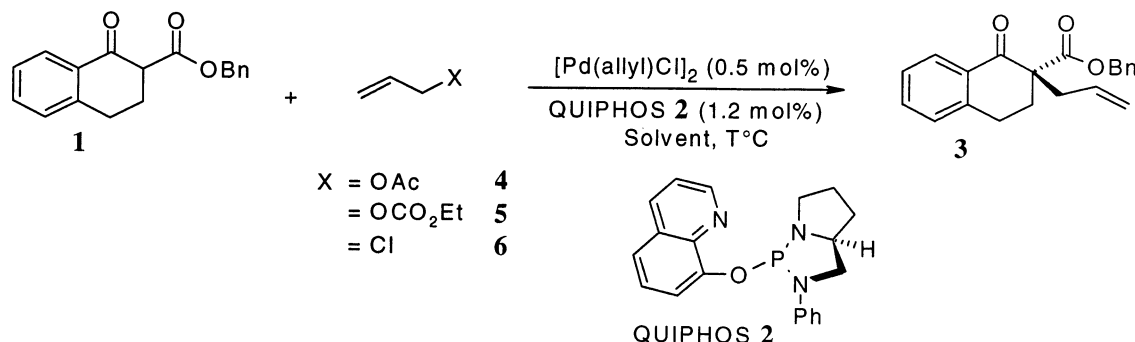
<sup>c</sup> Ee measured by HPLC analysis on a DAICEL CHIRALCEL OD-H column (eluent: hexane/2-propanol: 98/2, 0.5 mL/min, Tr(*R*) 18.1 min and Tr(*S*) 20.2 min).

<sup>d</sup> Reaction performed using NaH instead of TMG as base.

<sup>e</sup> Reaction performed using Na<sub>2</sub>CO<sub>3</sub> instead of TMG as base.

<sup>f</sup> Reaction performed with Pd(dba)<sub>2</sub> as palladium source.

<sup>g</sup> Reaction performed using Pd(PPh<sub>3</sub>)<sub>4</sub> as palladium source.



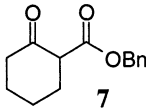
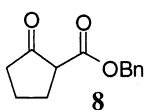
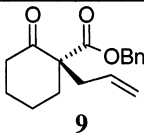
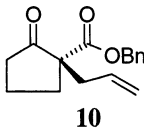
Scheme 1.

The results reveal the sensitivity of the reaction to the experimental conditions. Thus, THF and dichloromethane appeared unsatisfactory in terms of enantioselectivity (entries 1–4, Table 1), whereas the reactions performed in toluene at −10°C provide the expected product in 89% yield and 54% ee (entry 6, Table 1). A significant increase of the enantioselectivity from 35 to

54% was also observed lowering the reaction temperature from 20 to  $-10^{\circ}\text{C}$  (entries 5 and 6). It is noteworthy that no subsequent improvement in the enantiomeric excess was encountered performing the reaction at  $-60^{\circ}\text{C}$  (entry 7). Furthermore, the use of allyl ethylcarbonate **5** instead of allyl acetate **4** did not enhance the enantioselectivity whereas allyl chloride led to poor results (entries 12 and 13, 46 and 21% ee, respectively). Moreover, replacement of  $[\text{Pd}(\text{allyl})\text{Cl}]_2$  as palladium source by  $\text{Pd}(\text{dba})_2$  or  $\text{Pd}(\text{PPh}_3)_4$  does not improve the enantiomeric excesses (entries 10 and 11, respectively 39 and 28% ee). On the other hand, as mentioned by Trost et al.<sup>3a</sup> the choice of base and solvent have dramatic effects. Both parameters would be expected to influence the structure of the nucleophile in terms of the nature of the ion pair and the state of aggregation. Sodium hydride and sodium carbonate did not lead to notable ees (entries 8 and 9, Table 1) whereas a highly stabilized conjugated acid  $N,N,N',N'$ -tetramethylguanidinium (TMG-H)<sup>+</sup> in a nonpolar solvent (toluene) proved to be more expeditious.

On the basis of these results, the AAA was applied to  $\beta$ -ketoesters **7** and **8** using allyl acetate **4** and  $[\text{Pd}(\text{allyl})\text{Cl}]_2/\text{QUIPHOS}$  catalyst. The results are summarized in Table 2.

Table 2  
Palladium catalyzed AAA of  $\beta$ -ketoesters **7** and **8**<sup>a</sup>

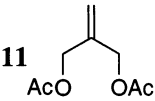
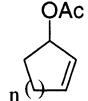
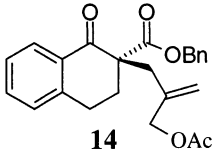
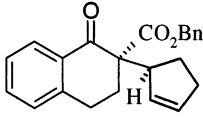
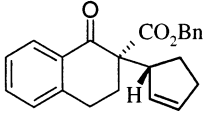
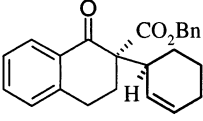
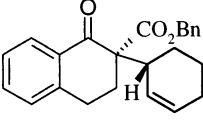
						
		<b>7</b>	<b>8</b>			
Entry	$\beta$ -Ketoester	Product	Solvent	T ( $^{\circ}\text{C}$ )	Yield (%) <sup>b</sup>	Ee (%)
1	<b>7</b>		Toluene	$-10$	81	17 <sup>c</sup>
2	<b>7</b>	<b>9</b>	THF	"	61	2 <sup>c</sup>
3	<b>7</b>	<b>9</b>	$\text{CH}_2\text{Cl}_2$	"	75	10 <sup>c</sup>
4	<b>8</b>		Toluene	20	82	25 <sup>d</sup>
5	<b>8</b>	<b>10</b>	$\text{CH}_2\text{Cl}_2$	"	86	68 <sup>d</sup>
6	<b>8</b>	<b>10</b>	Toluene	$-10$	81	50 <sup>d</sup>
7	<b>8</b>	<b>10</b>	$\text{CH}_2\text{Cl}_2$	$-10$	75	95 <sup>d</sup>

<sup>a</sup> Experiment performed on a 6.25 mmole scale (See Experimental Section). <sup>b</sup> Isolated yield. <sup>c</sup> Ee measured by HPLC analysis on a DAICEL CHIRALCEL OD-H column (eluent : heptane/2-propanol : 99.5/0.5, 0.5 mL/min, Tr(R) 13.4 min and Tr(S) = 14.4 min). <sup>d</sup> Ee measured by HPLC analysis on a DAICEL CHIRALCEL OD-H column (eluent : heptane/2-propanol : 99.5/0.5, 0.5 mL/min, Tr(R) 18.9 min and Tr(S) = 19.8 min).

Six-membered cyclic  $\beta$ -ketoester such as **7** led to disappointing results in terms of enantioselectivities since only enantiomeric excesses up to 17% have been encountered while the

corresponding alkylated product was isolated in quite good yields (61–81%) whatever the experimental conditions applied (entries 1–3, Table 2). Nevertheless, more satisfactory results were observed when performing the reaction on the cyclopentanone derivative **8**. The desired compound may be produced in 75% yield and an ee up to 95% ee (entry 7, Table 2). In contrast with AAA of **1** (see Table 1), dichloromethane proved to be superior to toluene. A possible explanation for this different behavior may be ascribed to substrate–solvent affinity such as  $\pi$ -stacking, possible only with substrate **1**. As an extension of this study, we have examined various allylating agents such as bis-acetate **11** and cyclic allylic esters **12** and **13** in the enantioselective alkylation of tetralone derivative **1** (Table 3).

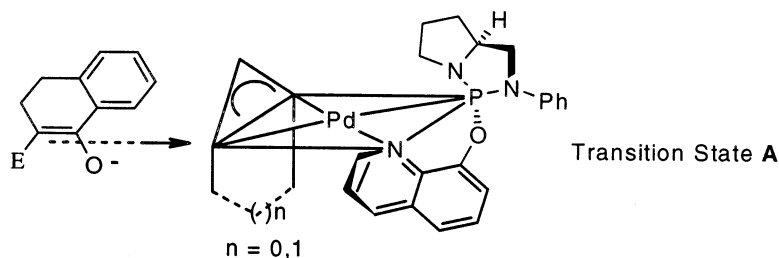
Table 3  
Palladium catalyzed AAA of  $\beta$ -ketoester **1** with allylating reagents **11**, **12** and **13**<sup>a</sup>

<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p><b>11</b></p> </div> <div style="text-align: center;">  <p><b>12</b> n = 1 <b>13</b> n = 2</p> </div> </div>					
Entry	Allylating reagent	Solvent	Product	Yield (%) <sup>b</sup>	Ee (%)
1	<b>11</b>	Toluene	 <b>14</b>	79	42 <sup>c</sup>
2	<b>11</b>	CH <sub>2</sub> Cl <sub>2</sub>	<b>14</b>	90	16 <sup>c</sup>
3	<b>12</b>	Toluene	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <b>15a</b> 60           </div> <div style="text-align: center;">  <b>15b</b> 40           </div> </div>	75	<b>15a</b> (65) <sup>d</sup> <b>15b</b> (72) <sup>d</sup>
4	<b>13</b>	Toluene	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <b>16a</b> 0           </div> <div style="text-align: center;">  <b>16b</b> 100           </div> </div>	78	85 <sup>e</sup>

<sup>a</sup> Experiment performed on a 6.25 mmole scale (See Experimental Section). <sup>b</sup> Isolated yield. <sup>c</sup> Ee measured by HPLC analysis on a DAICEL CHIRALCEL OD-H column (eluent : hexane/2-propanol : 90/10, 1 mL/min, Tr(R) 11.8 min and Tr(S)= 13.9 min). <sup>d</sup> Ee measured by HPLC analysis on a DAICEL CHIRALCEL OD-H column (eluent : heptane/2-propanol : 98/2, 0.5 mL/min, **15a** Tr(R) 9.4 min and Tr(S)= 8.5 min and **15b** Tr(R) 7.1 min and Tr(S)= 8.7 min). <sup>e</sup> Ee measured by HPLC analysis on a DAICEL CHIRALCEL OD-H column (eluent : heptane/2-propanol : 98/2, 0.5 mL/min, Tr(R) 12.1 min and Tr(S)= 12.7 min).

In all cases, the expected alkylation products were obtained and fully characterized but the stereochemical outcome of the reaction depends on the structure of the electrophile. Thus, diacetate **11** led to the formation of **14** in up to 79% yield and 42% ee (entry 1, Table 3). The cyclic allylic ester **12** led to the formation of **15a/15b** in a 60/40 diastereomeric ratio in quite good enantioselectivities (65 and 72% ee for **15a** and **15b**, respectively). In contrast, **13** provides

only formation of diastereomer **16b** (as depicted<sup>10</sup>) in 78% yield and 85% ee (entry 4, Table 3).<sup>11</sup> The enantioface selection for **1**, **7** and **8** can derive from an already established X-ray structure analysis of  $[\text{Pd}(\pi\text{-allyl})\text{QUIPHOS}]^+\text{ClO}_4^-$  complex.<sup>7d</sup> On the other hand, the electron density difference between the two allylic carbon termini favors the nucleophilic attack *trans* with respect to the Pd–P bond. On the basis of these considerations, and on the fact that the major alkylation product features *S* absolute configuration, we assume the predominant formation of diastereomeric transition state **A** (Scheme 2).



Scheme 2.

### 3. Conclusion

In summary, we have described the use of a new chiral palladium catalyst featuring QUIPHOS as ligand in the asymmetric alkylation of  $\beta$ -ketoesters with enantiomeric excesses up to 95% ee depending on the nature of the considered substrates.

### 4. Experimental

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AC100 and AC200 spectrometer in CDCl<sub>3</sub> as solvent. The chemical shifts (ppm) were determined relative to Me<sub>4</sub>Si. Toluene and THF were distilled from sodium/benzophenone ketyl prior to use.

#### 4.1. General procedure for catalytic asymmetric alkylation of $\beta$ -ketoesters (entry 6, Table 1)

To a solution of  $[\text{Pd}(\text{allyl})\text{Cl}]_2$  (11.3 mg, 0.031 mmol) and QUIPHOS **2** (52.3 mg, 0.150 mmol) in toluene (10 mL) at  $-10^\circ\text{C}$  was added allyl acetate **4** (1.0 mL, 9.4 mmol). The initial clear yellow solution faded and became cloudy. 1,1,3,3-Tetramethylguanidine (0.88 mL, 7.0 mmol) was added and the mixture returned to a clear yellow solution. 2-Benzyloxycarbonyl tetralone **1** (1.75 g, 6.25 mmol) was added slowly and the reaction mixture stirred for 24 h under argon atmosphere. Saturated NH<sub>4</sub>Cl solution (8 mL) was added to the reaction mixture and the aqueous phase extracted with diethylether (3×8 mL). The combined organic phases were dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (5% Et<sub>2</sub>O/petroleum ether) affording **3** as a colorless oil in 89% yield and 54% ee as determined by HPLC analysis. The spectra of the product were in agreement with those previously described in literature.<sup>3</sup>

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8. It is noteworthy that QUIPHOS **2** has been also successfully used as ligand in an enantioselective copper catalyzed Diels–Alder reaction and an asymmetric conjugate addition of diethylzinc to enones. (a) Brunel, J. M.; Del Campo, B.; Buono, G. *Tetrahedron Lett.* **1998**, 39, 9663–9666. (b) Delapierre, G.; Constantieux, T.; Brunel, J. M.; Buono, G. *Eur. J. Org. Chem.* **2000**, 2507–2511.
9. The absolute configuration of major enantiomer of **3** was determined by correlation with the known product (see Ref. 3).
10. **16b**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 2.23–2.49 (m, 8H), 2.67–2.72 (m, 1H), 2.76–2.92 (m, 2H), 5.08–5.21 (m, 4H), 7.07–7.30 (m, 7H), 7.70 (m, 1H), 7.94 (dd, *J*=2.1, 7.6 Hz, 1H). <sup>13</sup>C NMR (200 MHz, CDCl<sub>3</sub>) 26.4, 27.6, 27.8, 29.0, 29.7, 54.6, 66.1, 66.9, 124.4, 126.6, 126.9, 128.0, 128.6, 129.7, 133.9, 136.6, 139.4, 143.6, 172.4, 194.5.
11. Interestingly, the diastereomer **16b** observed in our conditions has been notified as the minor diastereomer formed under Trost conditions (see Ref. 3).