

Palladium-catalyzed asymmetric alkylation of 2-azaallyl acetates for the synthesis of β -carboxyaspatic acid derivatives¹

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Received 12 May 1998; accepted 17 July 1998

Abstract

Palladium-catalyzed asymmetric alkylation of 2-azaallyl acetate, *N*-(diphenylmethylene)acetoxyglycine ester with a sodium salt of malonate ester was successfully carried out. High enantioselectivities were achieved using sodium dimethyl methylmalonate (98%ee) or sodium dimethyl malonate (93%ee) as a nucleophile with *t*-butyl ester of 2-azaallyl acetate in the presence of (*S*)-BINAP in acetonitrile. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Asymmetric alkylation; Palladium catalyst; 2-Azaallyl acetate; β -Carboxyaspatic acid derivatives

1. Introduction

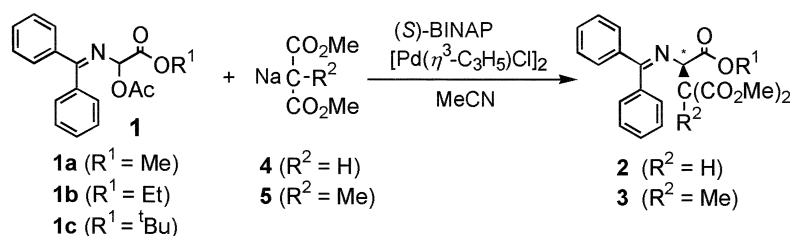
Palladium-catalyzed asymmetric allylic alkylation is a powerful tool for the syntheses of optically active compounds [1,2]. Allyl acetate derivatives are alkylated by the anion of active methylene compounds, such as malonate ester,

in the presence of palladium catalyst, and successful asymmetric reactions with chiral ligands have been reported [1–4]. O'Donnell et al. [5] have reported the palladium-catalyzed alkylation of 2-azaallyl acetate derivatives **1** with sodium dimethyl malonate or its derivative giving the product **2** or **3**, β -carboxyaspatic acid (ASA) or its derivatives and the asymmetric synthesis of **2** or **3** in the presence of chiral diphosphines [6,7]. Since 2-azaallyl acetate derivatives **1** are readily prepared, palladium-catalyzed alkylation of **1** is of great practical use for the asymmetric syntheses of ASA and its derivatives. Recently, selectivity was raised up to 86%ee by extensive studies [8], however, the enantioselectivity was not satisfactory yet. It

Abbreviations: (*S*)-BINAP = (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; (*S,S*)-NorpPhos = (*S,S*)-2,3-bis(diphenylphosphino)bicyclo[2.2.1]heptane; (*S*)-(*R*)-BPPFA = (*S*)-*N,N*-dimethyl-1-[(*R*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine; (*S,S*)-chiraphos = (*S,S*)-2,3-bis(diphenylphosphino)butane

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¹ A part of this study has been presented at the 69th Annual Meeting of the Chemical Society of Japan, Kyoto, 1995, Abstr., 2H414.



Scheme 1. Asymmetric allylation of 2-azaallyl acetate.

seems to us worthwhile publishing our recent results since we found the better conditions to realize high enantioselectivity in more than 90% ee.

2. Results and discussion

We now report the successful palladium-catalyzed asymmetric allylic alkylation of *t*-butyl ester of 2-azaallyl acetate **1c** with sodium

dimethyl malonate **4** or sodium dimethyl methylmalonate **5** in the presence of (*S*)-BINAP which gave optically active ASA derivatives, protected β -carboxyaspatic acid **2c** or protected β -methyl- β -carboxyaspatic acid **3c**, in high enantioselectivity (Scheme 1).

Table 1 shows that the results of the Pd-catalyzed asymmetric allylic alkylation of the Schiff-base acetate **1** by sodium malonate ester or sodium methylmalonate ester in the presence of chiral diphosphine, (*S*)-BINAP. According to

Table 1

Pd-catalyzed asymmetric allylic alkylation of *N*-(diphenylmethylene)acetoxycarbonyl glycine ester by sodium dimethyl malonate or sodium dimethyl methylmalonate^a

Run	R ¹ (subs)	R ² (Nu)	Product	Time (h)	Temperature (°C)	Yield (%)	%ee ^a (configuration) ^b
1	Me (1a)	H (4)	2a	2	25	90	16(<i>R</i>)
2	Me (1a)	Me (5)	3a	6	25	0	– ^f
3	Et (1b)	H (4)	2b	4	25	69	33(<i>R</i>)
4 ^c	Et (1b)	H (4)	2b	4	25	76	4(<i>R</i>)
5	Et (1b)	Me (5)	3b	18	25	64	70(<i>R</i>)
6	Et (1b)	Me (5)	3b	24	0	36	76(<i>R</i>)
7	<i>t</i> -Bu (1c)	H (4)	2c	4.5	25	91	86(<i>R</i>)
8	<i>t</i> -Bu (1c)	H (4)	2c	24	0	83	93(<i>R</i>)
9	<i>t</i> -Bu (1c)	Me (5)	3c	24	25	43	98(<i>R</i>)
10 ^d	<i>t</i> -Bu (1c)	Me (5)	3c	24	25	81	69(<i>R</i>)
11 ^e	<i>t</i> -Bu (1c)	Me (5)	3c	24	25	0	–

^a Determined by 400 MHz ¹H NMR using Eu(hfc)₃.

^b Absolute configuration was determined from the optical rotation of the aspartic acid derived from the product **2** or from the circular dichroism spectra of **3**.

^c Using (*S*)-DIOP instead of (*S*)-BINAP.

^d Using (*S*)-(*R*)-BPPFA instead of (*S*)-BINAP.

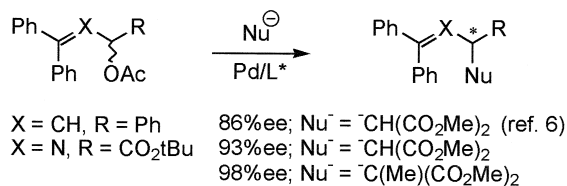
^e Using (*S,S*)-Norphos or (*S,S*)-chiraphos instead of (*S*)-BINAP.

^f *N*-(diphenylmethylene)glycine methyl ester was obtained.

^g The chiral ligand (0.039 mmol), the substrate (0.35 mmol), and [(π -C₃H₅)PdCl₂] (0.035 mmol) were dissolved in dry MeCN (4 ml) at 0°C. To a stirred suspension of sodium dimethyl malonate prepared from sodium hydride (0.63 mmol) and the ester (1.05 mmol) in MeCN (5 ml) was added the above mixture, then the mixture was stirred at 25°C (or 0°C in run 6 or 8) under nitrogen. After the reaction, saturated ammonium chloride aqueous solution (1 ml) was added and evaporated. The residue was dissolved in diethyl ether (15 ml), filtered, and evaporated. The product was isolated by flash chromatography (silica gel, AcOEt/hexane = 1/4).

O'Donnell and co-workers, the use of $\text{Pd}(\text{OAc})_2$ as the catalyst precursor was more effective than those of $[\text{PdCl}(\pi\text{-C}_3\text{H}_5)]_2$, $\text{Pd}_2(\text{dba})\cdot\text{CHCl}$, or $\text{Pd}(\text{dba})$ [4a], however, in our hands, the use of π -allyl dimer $[\text{PdCl}(\pi\text{-C}_3\text{H}_5)]_2$ was more effective than that of $\text{Pd}(\text{OAc})_2$. The product was obtained in moderate to high yields after column chromatographic separation. Enantiomeric excess of the product was determined by ^1H NMR spectra in the presence of chiral shift reagent $\text{Eu}(\text{hfc})_3$.

The enantioselectivity was dependent on the ester group of the substrates **1**. A bulkier ester group gave better selectivity: 86%ee for the *t*-butyl ester **1c** (run 7) > 33%ee for the ethyl ester **1b** (run 3) > 16%ee for the methyl ester **1a** (run 1). The selectivity was also affected by the structure of the nucleophile. The reaction of $\text{NaC}(\text{Me})(\text{CO}_2\text{Me})_2$ **5** with the ethyl ester **1b** gave the ASA derivative **3b** in 70%ee (run 5), which is better than that in run 3 (33%ee) with $\text{NaCH}(\text{CO}_2\text{Me})_2$ **4**, and with the *t*-butyl ester **1c** gave **3c** in 98%ee (run 9), better than run 7 (86%ee), although the reaction with the methyl ester **1a** gave no aimed product but *N*-(diphenylmethylene)glycine methyl ester (run 2). The reaction of $\text{NaCH}(\text{CO}_2\text{Me})_2$ **4** was less selective (run 7), however, the selectivity increased at low temperature (run 6, 8). The reaction of sodium dimethyl isopropylmalonate or sodium dimethyl phenylmalonate gave unknown by-products, and no reaction occurred with $\text{NaC}(\text{NHCOMe})(\text{CO}_2\text{Me})_2$. The reaction of sodium diisopropyl malonate with the ethyl ester **1b** gave the ASA derivative in 26%ee. Acetonitrile is the best solvent among those examined. No reaction occurred in CH_2Cl_2 , and the reaction took much time and the selectivity was

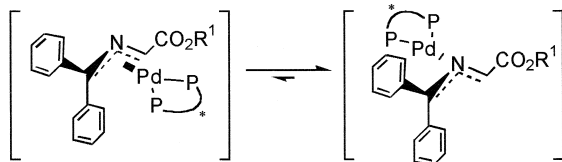


Scheme 3. Comparison with the reaction of trisubstituted allyl acetate.

lower in THF. As for the chiral ligands, the best selectivity was obtained with (*S*)-BINAP. The selectivity was modest or low with (*S*)-(*R*)-BP-PFA (run 10) or (*S,S*)-DIOP, and no reaction with (*S,S*)-Norphos or (*S,S*)-chiraphos (run 11).

O'Donnell et al. [8] have reported that the reaction of **1c** and sodium dimethyl methylmalonate **5** in the presence of $\text{Pd}(\text{OAc})_2$ gave **3c** in 80%ee at 25°C (86%ee at 0°C), and that of **1c** and sodium dimethyl malonate **4**, less bulky nucleophile, gave **2c** in 85%ee. It is in contrast with our experiments that bulkier nucleophile, sodium dimethyl methylmalonate **5**, gave better selectivity with slower reaction rate (run 3 and 5 with **1b**; run 7 and 9 with **1c**). The reaction of **1c** and sodium dimethyl methylmalonate **5** with $\text{Pd}(\text{OAc})_2$ precursor gave **3c** in 80%ee [8], but with $[(\pi\text{-C}_3\text{H}_5)\text{PdCl}]_2$ precursor gave **3c** in 98%ee (run 9).²

The selectivity is mainly affected by the ratio of the diastereomeric 2-aza- π -allyl palladium intermediates as shown in Scheme 2: the major intermediate produces the major products [8,10,11].³ Further, the bulkiness of the nucleophile may influence the selectivity. These interpretation is similar to those proposed by Bosnich and coworkers for asymmetric allylic



Scheme 2. Diastereomeric 2-aza- π -allyl palladium intermediate.

² The reason why the catalyst precursors affects the selectivity is not certain at this moment, however, it is possible that BINAP is oxidized to phosphine oxide, BINAP(O), by $\text{Pd}(\text{OAc})_2$, which gives rise to lower the selectivity [9].

³ MM2 calculation have been performed for the diastereomeric intermediates and shown that the intermediate giving the major product is 2.3 kcal/mol more stable than the other one. The MM2 calculations have been done by the CAChe system using the force field developed by Peña-Cabera et al. [12,13] with slight modifications.

alkylation of 1,1,3-triphenylallyl acetate with $\text{NaCH}(\text{CO}_2\text{Me})_2$ **4** using (*S,S*)-chiraphos (up to 86% ee) [10,11]. The similar degree of selectivity or more has been obtained for 2-azaallyl acetate ester derivative **1** compared to the reaction of 1,1,3-triphenylallyl acetate (Scheme 3).

Thus, satisfactory selectivity was obtained in the reaction of *t*-butyl ester of 2-azaallyl acetate **1c** and sodium dimethyl malonate (93% ee) or sodium dimethyl methylmalonate (98% ee) with (*S*)-BINAP to give optically active ASA derivatives.

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