Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6663–6666

Palladium-catalyzed construction of amino acid derivatives possessing vicinal chiral quaternary and tertiary carbon centers at the α and β positions

Daiji Ikeda,[a] Motoi Kawatsura[a,b,*] and Junichi Uenishi[a]

[a]*Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8412, Japan*
[b]*Faculty of Engineering, Tottori University, Koyama, Tottori 680-8552, Japan*

Received 7 July 2005; revised 28 July 2005; accepted 28 July 2005
Available online 15 August 2005

Abstract—The palladium catalyzed regio- and diastereo-selective allylic alkylation of (*R*)-2-acetoxy-4-aryl-3-butene with *N*-(diphenylmethylidene)glycinate and *N*-(diphenylmethylidene)alaninate occurred. The stereochemistry was controlled by the use of *o*-(diphenylphosphino)carboxylic acid, and produced new amino acid derivatives possessing vicinal chiral quaternary and tertiary carbon centers at the α and β positions.

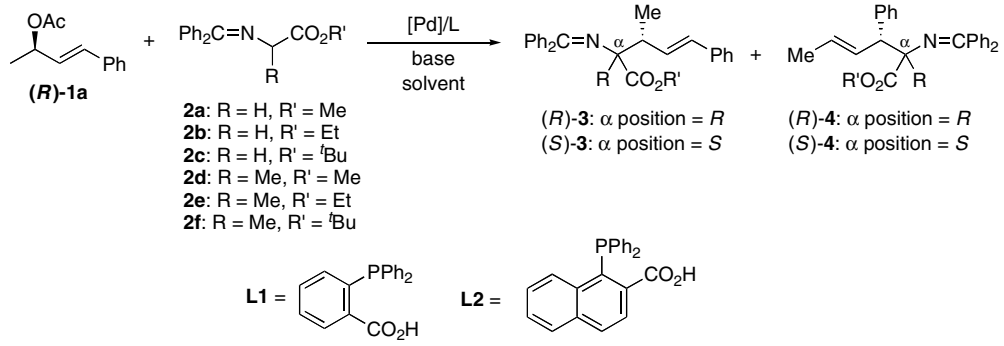
The construction of a chiral quaternary carbon center[1] catalyzed by a transition metal catalyst is one of the most challenging topics in organic synthesis. The palladium catalyzed asymmetric allylic alkylation[2] is also one of the most widely and frequently used carbon–carbon bond forming reactions catalyzed by transition metal complexes because of its high reactivity, high catalytic activity, and easy manipulation. The carbon nucleophiles successfully used for the asymmetric alkylation have been limited to stabilized carbanion generated from active methylene and methine compounds such as malonate esters, and there have been few investigations into the construction of chiral quaternary carbon centers by this reaction.[3] The use of α-substituted unsymmetrical β-diketones, α-substituted β-ketoesters, and α-substituted aminoester derivatives for the reaction with unsymmetric allylic esters generally gives a mixture of regio- and stereo-isomers with poor selectivity. However, if a chiral allylic acetate is employed,[4] the remaining problems for this reaction would be condensed to the control of the regio- and diastereo-selectivities, because the allylic alkylation reaction stereospecifically proceeds with a net retention of the stereochemistry. Recently, we reported the regio- and diastereo-selective construction of vicinal quaternary and tertiary carbon centers catalyzed by palladium catalyst with 2-(diphenylphosphino)benzoic acid as the ligand.[5] We now report the application of this catalyst system for the reaction with aminoester derivatives,[6] and we succeeded in controlling its regio- and diastereo-selectivities, and constructed the amino acid derivatives possessing vicinal chiral tertiary and quaternary, or tertiary and tertiary carbon centers at the α and β positions, respectively.

Several reaction conditions were examined for the palladium catalyzed regio- and diastereo-selective allylic alkylation of (*R*)-2-acetoxy-4-phenyl-3-butene (**1a**) with *N*-(diphenylmethylidene)glycinate (**2a**–**c**) and *N*-(diphenylmethylidene)alaninate (**2d**–**f**) using 2-(diphenylphosphino)benzoic acid (**L1**) as the ligand (Scheme 1).

These results are summarized in Table 1. The reaction of **1a** with the ethyl ester of *N*-(diphenylmethylidene)glycinate (**2b**) in the presence of 5 mol % $Pd(OAc)_2$/**L1** in dioxane gave **3ab** with 88% diastereoselectivity in 65% yield. The diastereoselectivity and yield were slightly low compared with the reaction of **1a** with 2-methylacetoacetate[5] (entry 2). The reaction conditions were optimized for the reaction of **1a** with **2b**. As the palladium precursor and base, the combination of $Pd_2(dba)_3$ and NaHMDS was the best for the yield

Keywords: Pd-catalyzed allylic alkylation; Regio- and diastereoselectivity; Vicinal chiral carbon centers; Amino acids derivatives.
* Corresponding author. Tel./fax: +81 857 31 5179; e-mail: kawatsur@chem.tottori-u.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.07.139



Scheme 1.

Table 1. Regio- and diastereo-selective allylic alkylation of (*R*)-**1a** with diphenylimino glycinate and diphenylimino alaninate **2a**–**f**[a]

Entry	2	[Pd]	L	Base	Solvent	Temperature (°C)	Yield[b] (%)	3:4[c]	(*R*)-3:(*S*)-3[c]
1	**2b**	$Pd(OAc)_2$	PPh_3	NaHMDS	Dioxane	0–rt	99 (**3ab**+**4ab**)	98:2	53:47
2	**2b**	$Pd(OAc)_2$	**L1**	NaHMDS	Dioxane	0–rt	65 (**3ab**+**4ab**)	98:2	88:12
3	**2b**	$Pd_2(dba)_3$	**L1**	NaHMDS	Dioxane	0–rt	86 (**3ab**+**4ab**)	98:2	91:9
4	**2b**	$Pd_2(dba)_3$	**L1**	NaH	Dioxane	0–rt	94 (**3ab**+**4ab**)	96:4	75:25
5	**2b**	$Pd_2(dba)_3$	**L1**	LiHMDS	Dioxane	0–rt	88 (**3ab**+**4ab**)	98:2	85:15
6	**2b**	$Pd_2(dba)_3$	**L1**	KHMDS	Dioxane	0–rt	99 (**3ab**+**4ab**)	95:5	55:45
7	**2b**	$Pd_2(dba)_3$	**L1**	NaHMDS	THF	−10	99 (**3ab**+**4ab**)	98:2	82:18
8	**2b**	$Pd_2(dba)_3$	**L1**	NaHMDS	Et_2O	−10	93 (**3ab**+**4ab**)	97:3	98:2
9	**2a**	$Pd_2(dba)_3$	**L1**	NaHMDS	Et_2O	−10	92 (**3aa**+**4aa**)	98:2	96:4
10	**2c**	$Pd_2(dba)_3$	**L1**	NaHMDS	Et_2O	−10	95 (**3ac**+**4ac**)	>99:1	>99:1
11	**2d**	$Pd_2(dba)_3$	**L1**	NaHMDS	Et_2O	−10	60 (**3ad**+**4ad**)	98:2	5:95
12	**2e**	$Pd_2(dba)_3$	**L1**	NaHMDS	Et_2O	−10	65 (**3ae**+**4ae**)	96:4	5:95
13	**2f**	$Pd_2(dba)_3$	**L1**	NaHMDS	Et_2O	−10	99 (**3af**+**4af**)	>99:1	47:53
14	**2f**	$Pd_2(dba)_3$	**L2**	NaHMDS	Et_2O	−10	60 (**3af**+**4af**)	>99:1	9:91

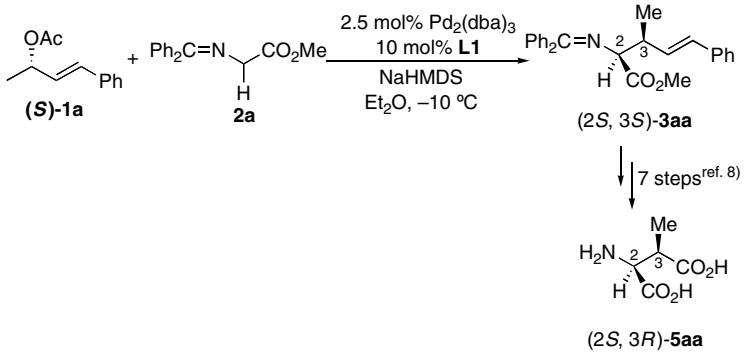
[a] Reaction conditions: (*R*)-**1** (1 mmol), **2a**–**e** (1.5 mmol), base (1.4 mmol), solvent (7.6 mL), $Pd(OAc)_2$ (0.05 mmol), or $Pd_2(dba)_3$ (0.025 mmol), ligand (0.1 mmol), 12 h.

[b] Isolated yield by silica gel column chromatography.

[c] The ratio was determined by 400 MHz ^1H NMR spectrum of the crude materials.

and stereoselectivities (entries 3–6). Ether was the best solvent for the diastereoselectivity of the reaction of **1a** with **2b**, and up to a 98% diastereoselectivity was obtained at −10 °C (entry 8). Methyl ester of *N*-(diphenylmethylidene)glycinate (**2a**) were also gave high stereoselectivities (entry 9). A highly stereo-controlled coupling was attained by the reaction with the *tert*-butyl ester of *N*-(diphenylmethylidene)glycinate (**2c**), while (*R*)-**3ac**[7] was obtained with >99% regioselectivity and >99% diastereoselectivity (entry 10). This coupling reaction gave optically active new amino acid derivatives, possessing a tertiary chiral carbon center at the α position which was adjacent to the tertiary carbon center.

The reaction with (*S*)-2-acetoxy-4-phenyl-3-butene ((*S*)-**1a**) and **2a** gave (2*S*,3*S*)-**3aa** with 96% diastereoselectivity and 98% regioselectivity in 92% yield (Scheme 2). The coupling products were easily converted to 3-methylaspartic acid ((2*S*,3*R*)-**5aa**)[8] with reported procedure,[9] and stereochemistry was confirmed the (2*S*,3*S*) for **3aa** by the comparison of the reported ^1H NMR data and specific rotation.[10]

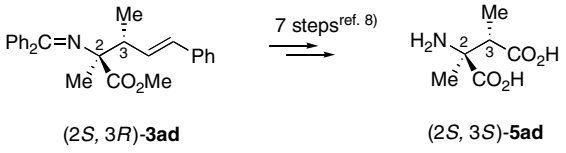


Scheme 2.

The reaction with the methyl or ethyl ester of *N*-(diphenylmethylidene)alaninate (**2d** and **2e**) indicated a slightly decreasing yield, regioselectivity and diastereoselectivity (Table 1, entries 11 and 12). The reaction with the *tert*-butyl ester of *N*-(diphenylmethylidene)alaninate (**2f**) gave a low diastereoselectivity (53%) while the isolated yield and regioselectivity were high (entry 13). This low diastereoselectivity was improved by using 1-(diphenylphosphino)-2-naphthoic acid (**L2**),[11] which gave a 91% diastereoselectivity with a 60% yield (entry 14). The coupling product **3ad**, possessing vicinal chiral quaternary and tertiary carbon centers at the α and β positions, was also converted to 3-methylaspartic acid ((2*S*,3*S*)-**5ad**)[12] (Scheme 3), and stereochemistry was confirmed by the (2*S*,3*R*) for **3ad** by the comparison of the reported ^{1}H NMR data and specific rotation.[9,13]

Table 2 summarizes the reactions of several allylic acetates (**1b–e**) with **2b** or **2e** (Scheme 4). Under the optimized conditions, all reactions proceeded in a highly regio- and diastereo-selective manner. In particular, the reactions of (*R*)-2-acetoxy-4-(1-naphthyl)-3-butene (**1d**) with **2b** proceeded in a highly stereo-controlled manner and gave almost a single stereoisomer (*R*)-**3db** in 82% isolated yield (Table 2, entry 3).

In conclusion, we have succeeded in the regio- and diastereo-selective palladium catalyzed allylic alkylation of (*R*)- or (*S*)-2-acetoxy-4-aryl-3-butene with *N*-(diphenylmethylidene)alaninate or *N*-(diphenylmethylidene)glycinate, and this reaction provides vicinal chiral quaternary and tertiary, or tertiary and tertiary carbon centers at the α and β positions, respectively. It is noteworthy that the face selectivity of the enolates was highly controlled by the use of *o*-(diphenylphosphino)carboxylic acid. A mechanistic study will be the subject of a future work.



Scheme 3.

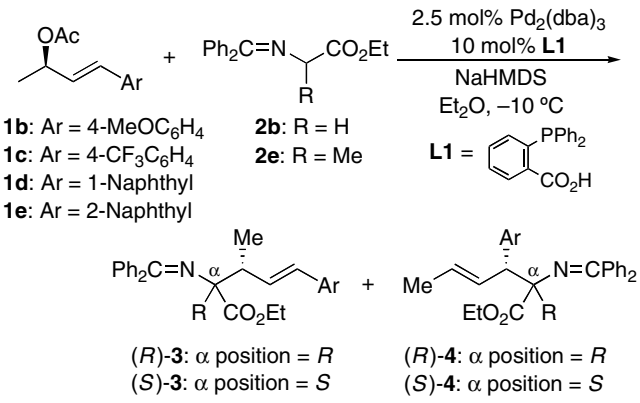
Table 2. Regio- and diastereo-selective allylic alkylation of (*R*)-**1b–e** with diphenylimino glycinate **2b** and diphenylimino alaninate **2e**[a]

Entry	1	2	Yield (%)[b]	3:4[c]	(*R*)-3:(*S*)-3[c]
1	**1b**	**2b**	85 (**3bb**+**4bb**)	98:2	97:3
2	**1c**	**2b**	81 (**3cb**+**4cb**)	98:2	97:3
3	**1d**	**2b**	82 (**3db**+**4db**)	>99:1	>99:1
4	**1e**	**2b**	80 (**3eb**+**4eb**)	>99:1	98:2
5	**1d**	**2e**	79 (**3de**+**4de**)	>99:1	14:86

[a] Reaction conditions: $Pd_2(dba)_3$ (0.025 mmol), **L1** (0.1 mmol), **1** (1 mmol), **2** (1.5 mmol), NaHMDS (1.4 mmol), ether (7.6 mL), −10 °C, 12 h.

[b] Isolated yield by silica gel column chromatography.

[c] The ratio was determined by 400 MHz ^{1}H NMR spectrum of the crude materials.



Scheme 4.

Acknowledgements

This work was partially supported financially by the Ministry of Education, Science, Sports, and Culture, Grant-in Aid for the Encouragement of Young Scientists (B), 15790021, and Mitsubishi Chemical Corporation Fund. We thank Professors Y. Ohfune and K. Sakaguchi (Osaka City University) for helpful information. M.K. also acknowledges the TORAY Award in Synthetic Organic Chemistry, Japan.

References and notes

1. (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591–4597; (b) Corey, E. J.; Perez, A. G. *Angew. Chem., Int. Ed.* **1998**, *37*, 389–401; (c) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066.
2. (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345; (b) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. M., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, pp 833–884; (c) Hayashi, T. *J. Organomet. Chem.* **1999**, *576*, 195–202; (d) Johnson, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, 1689–1708; (e) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422.
3. (a) Kuwano, R.; Uchida, K.; Ito, Y. *Org. Lett.* **2003**, *5*, 2177–2179; (b) Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6197–6201; (c) Trost, B. M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3492–3495; (d) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236–3237; (e) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759–6760; (f) Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed.* **1997**, *36*, 2635–2637; (g) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879–7880; (h) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309–3310.
4. (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4547–4554; (b) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 3236–3237.
5. Uenishi, J.; Kawatsura, M.; Ikeda, D.; Muraoka, N. *Eur. J. Org. Chem.* **2003**, 3909–3912.
6. (a) Baldwin, I. C.; Williams, J. M. J.; Beckett, R. P. *Tetrahedron: Asymmetry* **1995**, *6*, 679–682; (b) Kazmaier, U.; Zampe, F. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1468–1470; (c) Kazmaier, U.; Lindner, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3303–3306, and references cited therein.

7. General procedure (Table 1, entry 10): To a solution of $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol), 2-(diphenylphosphino)benzoic acid (30.6 mg, 0.10 mmol) and *tert*-butyl ester of diphenylimino glycinate **2c** (443 mg, 1.50 mmol) in anhydrous Et_2O (7.6 mL) was added (*R*)-2-acetoxy-4-phenyl-3-butene (**1a**) (190 mg, 1.0 mmol). The solution was cooled to −10 °C, then NaHMDS (1.4 mL of 1.0 M in THF, 1.40 mmol) was added slowly. The mixture was stirred at −10 °C for 12 h. The reaction mixture was quenched with water, and extracted with ether. The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The regio and diastereo ratios of **3** and **4** were determined by 400 MHz ^{1}H NMR for this crude material. The residue was chromatographed on silica gel (EtOAc/hexane = 1/9) to give 304 mg (95%) of **3ac**. major isomer (2*R*,3*R*)-**3ac**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.10 (m, 15H), 6.43 (d, $J = 15.9$ Hz), 6.33 (dd, $J = 15.9$, 8.2 Hz, 1H), 3.91 (d, $J = 5.4$ Hz, 1H), 3.08–2.99 (m, 1H), 1.42 (s, 9H), 1.07 (d, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 139.7, 137.7, 136.8, 132.5, 130.3, 128.8, 128.4, 128.3, 127.9, 126.2, 80.9, 71.1, 41.5, 28.1, 17.6; HR-EI-MS calcd for $C_{29}H_{31}NO_2$ (M^+) *m*/*z* 425.2355, found 425.2347. $[\alpha]_D^{26}$ 39.9 (*c* 1.00, $CHCl_3$).
8. Reagents and conditions: (i) 1 N HCl, THF, 0 °C, 1 h; (ii) Boc_2O, Na_2CO_3, H_2O/dioxane (1/2), rt, 1 h (97% in 2steps); (iii) O_3, AcOEt, −78 °C, 10 min, then Me_2S, rt, 1 h (65%); (iv) Jones oxidation, 0 °C, 2 h; (v) CH_2N_2, ether, rt, 30 min; (vi) 1 M NaOH, THF, 0 °C–rt, 19 h; (vii) TFA, CH_2Cl_2, 0 °C, 3.5 h (64% in four steps).
9. Sakaguchi, K.; Yamamoto, M.; Kawamoto, T.; Yamada, T.; Shinada, T.; Shimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **2004**, *45*, 5869–5872.
10. Compound (2*S*,3*R*)-**5aa**: ^{1}H NMR (300 MHz, D_2O): δ 3.68 (d, $J = 5.3$ Hz, 1H), 2.88 (dq, $J = 5.3$, 7.5 Hz, 1H), 1.29 (d, $J = 7.5$ Hz, 3H). $[\alpha]_D^{26}$ 32.5 (*c* 2.00, 5N HCl) {lit. $[\alpha]_D^{26}$ 34.3 (*c* 2.05, 5 N HCl)}.
11. Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968–5976.
12. Reagents and conditions: (i) 1 N HCl, THF, 0 °C, 1 h; (ii) Boc_2O, Na_2CO_3, H_2O/dioxane (1/2), rt, 72 h (71% in two steps); (iii) O_3, AcOEt, −78 °C, 10 min, then Me_2S, rt, 1 h (67%); (iv) Jones oxidation, 0 °C, 2 h; (v) CH_2N_2, ether, rt, 30 min; (vi) 1 M NaOH, THF, rt, 5 days; (vii) TFA, CH_2Cl_2, 0 °C, 4 h (49% in four steps).
13. Compounds (2*S*,3*S*)-**5ad**: ^{1}H NMR (300 MHz, D_2O): δ 2.75 (q, $J = 7.4$ Hz, 1H), 1.48 (s, 3H), 1.13 (d, $J = 7.4$ Hz, 3H). $[\alpha]_D^{26}$ 13.1 (*c* 1.00, 5 N HCl) {lit. $[\alpha]_D^{26}$ 11.9 (*c* 0.91, 5 N HCl)}.