Regio- and enantio-selective allylic alkylation catalysed by a chiral monophosphine–palladium complex

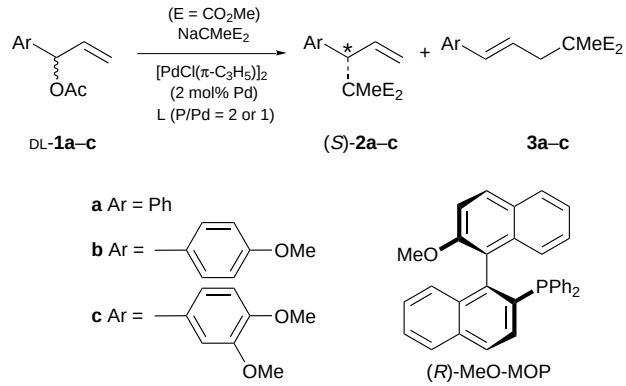
Tamio Hayashi,* Motoi Kawatsura and Yasuhiro Uozumi

Department of Chemistry, Faculty of Science, Kyoto University, Sakyo, Kyoto 606-01, Japan

Allylic alkylation of racemic 1-arylprop-2-enyl acetates [ArCH(OAc)CH=CH_2] with the sodium enolate of dimethyl methylmalonate in the presence of a palladium catalyst coordinated with (*R*)-2-diphenylphosphino-2′-methoxy-1,1′-binaphthyl [(*R*)-MeO-MOP] proceeds with high branch selectivity (90%) to give chiral products [ArC*H(Nu)CH=CH_2] of up to 87% ee.

Palladium-catalysed allylic substitution reactions including catalytic asymmetric reactions have attracted considerable attention owing to their synthetic utility and mechanistic interest.[1] One of the major problems in developing catalytic asymmetric allylic substitutions is undesirable regiochemistry which limits the substitution patterns of allylic substrates. As a typical example, the substitution with soft carbon nucleophiles that proceeds through π-allylpalladium intermediates containing one substituent at the C-1 position produces the linear isomer rather than the branch isomer.[1] It follows that the reaction cannot be extended to asymmetric synthesis because the linear isomer lacks the chiral carbon centre. The regioselectivity in forming the branch isomer is usually very low except when methyl is the substituent.[2] Here we report that the use of 2-diphenylphosphino-2′-methoxy-1,1′-binaphthyl (MeO-MOP),[3] which is a sterically bulky chiral monophosphine ligand, for the allylic alkylation of 1-arylprop-2-enyl acetates **1** reversed the regiochemistry to give branch isomers **2** with high selectivity and up to 87% ee in this new allylic alkylation system.

The results obtained for the allylic substitution of racemic 1-arylprop-2-enyl acetates dl-**1** in the presence of palladium–phosphine complexes (Scheme 1) are summarized in Table 1. The reaction of dl-1-phenylprop-2-enyl acetate **1a** with the sodium salt of dimethyl methylmalonate in THF at −20 °C in the presence of 2 mol% of palladium catalyst generated from $[PdCl(\pi\text{-}C_3H_5)]_2$ and 1,2-bis(diphenylphosphino)ethane (dppe) gave linear isomer (*E*)-**3a** with 93% regioselectivity (entry 1). The linear selectivity (79–85% regioselectivity) was also observed in the reaction with a palladium catalyst coordinated with triphenylphosphine (entries 2 and 3). It is noteworthy that the reaction catalysed by palladium–PPh_3 requires 2 equiv. of triphenylphosphine (to Pd) for the allylic substitution to proceed smoothly. With 1 equiv. of triphenylphosphine, the reaction stops at about 60% conversion. The opposite regioselectivity was observed in the same substitution reaction of **1a** by use of MeO-MOP as a ligand, which gave branch isomer **2a** with 79% regioselectivity at −20 °C (entries 4 and 5). With the palladium–MeO–MOP catalyst, the ratio of phosphine to palladium did not affect either the catalytic activity or the regioselectivity. Higher regioselectivity in forming the branch isomer was observed in the reaction of 1-arylprop-2-enyl



Scheme 1

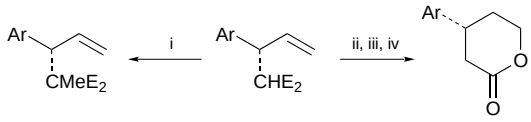
Table 1 Regio- and enantio-selective allylic alkylation of acetate **1** catalysed by palladium–phosphine complexes[a]

Entry	Allyl ester	Ligand (ratio P : Pd)	Conditions		Yield (%)[b]	Ratio[c]	Ee (%) of **2** (config.)
			T/°C	*t*/h	**2** and **3**	**2** : **3**	
1	**1a**	dppe (2 : 1)	−20	4	92	7 : 93	—
2	**1a**	PPh_3 (2 : 1)	−20	4	99	15 : 85	—
3	**1a**	PPh_3 (1 : 1)	−20	24	63	21 : 79	—
4	**1a**	(*R*)-MeO-MOP (2 : 1)	−20	6	99	79 : 21	68[d]
5	**1a**	(*R*)-MeO-MOP (1 : 1)	−20	6	99	79 : 21	68[d]
6	**1a**	(*R*)-MeO-MOP (1 : 1)	−30	6	97	82 : 18	86[d,e]
7	**1b**	dppe (2 : 1)	−20	2	96	27 : 73	—
8	**1b**	PPh_3 (2 : 1)	−20	6	97	30 : 70	—
9	**1b**	PPh_3 (1 : 1)	−20	24	58	28 : 72	—
10	**1b**	(*R*)-MeO-MOP (2 : 1)	−20	2	97	86 : 14	76[f] (*S*)
11	**1b**	(*R*)-MeO-MOP (1 : 1)	−20	2	99	85 : 15	76[f] (*S*)
12	**1b**	(*R*)-MeO-MOP (1 : 1)	−30	2	96	90 : 10	87[f] (*S*)[e]
13	**1c**	(*R*)-MeO-MOP (1 : 1)	−30	2	99	89 : 11	85[g,e]

[a] All reactions were carried out in THF under nitrogen: THF (1.0 ml), allylic acetate (0.20 mmol), $NaCMe(CO_2Me)_2$ (0.40 mmol), $[PdCl(\pi\text{-}C_3H_5)]_2$ (0.002 mmol) and phosphine ligand. [b] Isolated yield by silica gel column chromatography. [c] The ratio was determined by ^1H NMR analysis of the products. [d] Determined by GLC analysis with CP Cyclodex β236M after demethoxycarbonylation of one of the two methoxycarbonyl groups. [e] Specific rotations of **2a** (entry 6), **2b** (entry 12) and **2c** (entry 13) were $[\alpha]_D^{20}$ +46.4, +50.3 and +45.0 (*c* 1.1–1.8, $CHCl_3$), respectively. [f] Determined by HPLC analysis with Chiralpak AD (hexane–propan-2-ol = 9 : 1). [g] Determined by HPLC analysis with Chiralcel OD-H (hexane–propan-2-ol = 9 : 1).

acetates **1b** and **1c** which contain methoxy group(s) on the aromatic ring (entries 10–13). At the reaction temperature of −30 °C, 1-(4-methoxyphenyl)prop-2-enyl acetate **1b** gave branch isomer **2b** with 90% regioselectivity (entry 12). The enantiomeric purity of **2b** determined by a chiral stationary phase column (Chiralpak AD) was 87% ee and its absolute configuration was assigned to be (+)-(*S*) by correlation with known (*R*)-(−)-4-(4-methoxylphenyl)tetrahydro-2*H*-pyran-2-one[4] **4** by way of (*R*)-(+)-dimethyl (1-arylprop-2-enyl)malonate **5** (Scheme 2). Here again the palladium catalyst containing dppe or triphenylphosphine gave linear isomer **3b** preferentially (entries 7–9). The reaction of allylic acetate **1c** in the presence of MeO-MOP at −30 °C also gave the corresponding alkylation product **2c** of 85% ee with high branch selectivity (entry 13). Thus, chiral monodentate phosphine ligand, MeO-MOP, is playing a key role on the high branch selectivity in the catalytic allylic alkylation of 1-arylprop-2-enyl acetates. This type of asymmetric alkylation is considered to be difficult with chelating bisphosphine ligands so far used mostly for the asymmetric allylic alkylation which proceeds by way of palladium intermediates containing 1,3-disubstituted π-allyl moieties such as 1,3-diphenyl.[1,5]

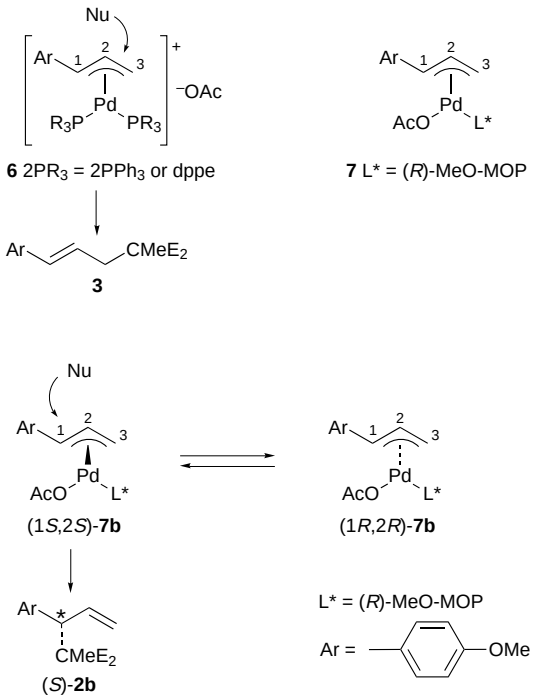
The preferential formation of linear isomers in the allylic alkylation of **1** catalysed by palladium–dppe or palladium–PPh_3 is as expected because cationic [π-(1-aryl)allyl]bis-(phosphine)palladium(ii) intermediate **6** formed by oxidative addition of **1** to bis(phosphine)palladium(0) will undergo nucleophilic attack on the less hindered end of the π-allyl, namely, C-3 position of π-(1-aryl)allyl group (Scheme 3). It gives the thermodynamically more stable product **3** where the double bond is conjugated with aromatic ring. On the other hand, the reaction with MeO-MOP ligand should proceed *via* neutral [π-(1-aryl)allyl](acetato)(phosphine)palladium(ii) intermediate **7** because the steric bulkiness of the MOP ligand does not allow the palladium to form a cationic bis(phosphine) complex which is analogous to **6**.



Ar = 4-$MeOC_6H_4$, E = CO_2Me

(*S*)-(+)-**2b** (*R*)-(+)-**5** (*R*)-(−)-**4**

Scheme 2 *Reagents and conditions*: i, (*R*)-(+)-**5** {$[\alpha]_D^{20}$ + 15.9 (*c* 1.0, $CHCl_3$)}, MeI, NaOMe, MeOH, reflux, 86% {$[\alpha]_D^{20}$ + 40.7 (*c* 1.7, $CHCl_3$)}; ii, LiCl, Me_2SO, H_2O 120 °C, 79%, iii, BH_3·THF, 77%; iv, *p*-TsOH, benzene, 96% {$[\alpha]_D^{20}$ −6.2 (*c* 1.0, $CHCl_3$)}



Scheme 3

The π-allylpalladium complex **7b** (Ar = 4-$MeOC_6H_4$) was prepared by mixing the [π-(1-aryl)allyl](acetato)palladium(ii) dimer with 1 equiv. (to Pd) of (*R*)-MeO-MOP and it was characterized by ^{31}P and ^{1}H NMR spectra. In $CDCl_3$ at −50 °C the complex exists as a mixture of isomers in a ratio of 9 : 1.† The main isomer has substituted carbon (C-1) of the π-allyl *trans* to the phosphorus atom of MeO-MOP and the unsubstituted carbon (C-3) *cis* to phosphorus, which is determined by a large coupling constant (J = 8.2 Hz) between C-1 proton and phosphorus and no couplings between C-3 protons and phosphorus. Our structural studies of related PdCl(π-allyl)-(MeO-MOP) complexes[6] also showed that the unsubstituted π-allyl carbon adopts the *cis* position to phosphorus. The nucleophile attacks the C-1 carbon which is more weakly bonded to palladium due to a stronger *trans* influence of phosphine ligand to give branch product preferentially. The stoichiometric reaction of π-allylpalladium complex **7b** with the sodium enolate of dimethyl methylmalonate in THF at −20 °C gave (*S*)-**2b** of 90% ee with 88% regioselectivity, which is in good agreement with the catalytic reactions in terms of both regio- and enantio-selectivity.

We thank the Ministry of Education, Japan, for a Grant-in-Aid for Scientific Research for partial financial support of this work.

Footnote

† *Selected NMR data* for the major isomer of **7b**: ^{1}H NMR ($CDCl_3$ at −50 °C) δ 1.51 (s, 3 H), 1.56 (d, J = 11.6 Hz, 1 H, *anti*-H on C-3), 2.66 (d, J = 6.3 Hz, 1 H, *syn*-H on C-3), 3.03 (s, 3 H), 3.28 (m, 1 H, H on C-2), 3.89 (s, 3 H), 5.41 (dd, J_{H-H} = 13.5 Hz, J_{H-P} = 8.2 Hz, 1 H, H on C-1), 6.87–8.10 (m, 26 H). ^{31}P NMR ($CDCl_3$ at −50 °C) δ 23.2 (s). ^{31}P NMR for minor isomer of **7b**: δ 24.8 (s).

References

1 For reviews on catalytic asymmetric allylic substitutions: B. M. Trost and D. L. Van Vranken, *Chem. Rev*., 1996, **96**, 395; T. Hayashi, in *Catalytic Asymmetric Synthesis*, ed. I. Ojdima, VCH, New York, 1993; p. 325; C. G. Frost, J. Howarth and J. M. J. Williams, *Tetrahedron: Asymmetry*, 1992, **3**, 1089; G. Consiglio and M. Waymouth, *Chem. Rev*., 1989, **89**, 257.

2 For examples: T. Hayashi, K. Kishi, A. Yamamoto and Y. Ito, *Tetrahedron Lett*., 1990, **31**, 1743; B. M. Trost, M. J. Krische, R. Radinov and G. Zanoni, *J. Am. Chem. Soc*., 1996, **118**, 6297.

3 Y. Uozumi and T. Hayashi, *J. Am. Chem. Soc*., 1991, **113**, 9887; Y. Uozumi, A. Tanahashi, S.-Y. Lee and T. Hayashi, *J. Org. Chem*., 1993, **58**, 1945; Y. Uozumi, N. Suzuki, A. Ogiwara and T. Hayashi, *Tetrahedron*, 1994, **50**, 4293.

4 D. Enders and B. E. M. Rendenbach, *Chem. Ber*., 1987, **120**, 1223.

5 For recent examples: B. M. Trost and R. C. Bunt, *Angew. Chem., Int. Ed. Engl*., 1996, **35**, 99; G. Zhu, M. Terry and X. Zhang, *Tetrahedron Lett*., 1996, **37**, 4475; W. Zhang, T. Kida, Y. Nakatsuji and I. Ikeda, *Tetrahedron Lett*., 1996, **37**, 7995; N. Nomura, Y. C. Mermet-Bouvier and T. V. RajanBabu, *Synlett*, 1996, 745; H. C. L. Abbenhuis, U. Burckhardt, V. Gramlich, C. Kollner, P. S. Pregosin, R. Salzmann and A. Togni, *Organometallics*, 1995, **14**, 759.

6 T. Hayashi, H. Iwamura, M. Naito, Y. Mausumoto, Y. Uozumi, M. Miki and K. Yanagi, *J. Am. Chem. Soc*., 1994, **116**, 775; T. Hayashi, H. Iwamura, Y. Uozumi, Y. Matsumoto and F. Ozawa, *Synthesis*, 1994, 526.

Received, 2nd January 1996; Com. 7/00045F