Regiocontrol in palladium-catalysed allylic alkylation by addition of lithium iodide

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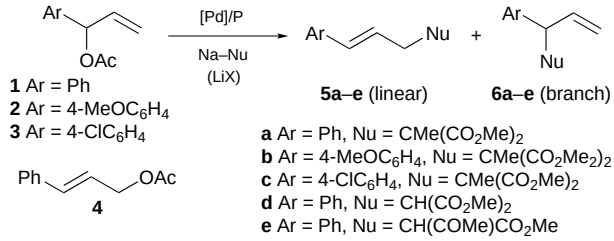
Regioselectivity in the palladium-catalysed allylic alkylation of 1-arylprop-2-enyl acetates [ArCH(OAc)CH=CH_2] or (*E*)-3-phenylprop-2-enyl acetate (PhCH=$CHCH_2OAc$) with sodium enolates of soft carbon nucleophiles is controlled by addition of a catalytic amount of lithium iodide to give lienar products [(*E*)-ArCH=$CHCH_2$Nu] exclusively; their branch isomers [ArCH(Nu)CH=CH_2] were not detected.

In synthetic organic chemistry, palladium-catalysed allylic alkylation of allyl esters is a useful reaction for the formation of carbon–carbon bonds.[1] One of the challenging problems in catalytic allylic alkylation is control of the regiochemistry in the reaction that proceeds through unsymmetrically substituted π-allylpalladium intermediates. For example, the π-allylpalladium complex containing one substituent at the C-1 position usually produces both linear and branch isomers, the ratio being dependent on the substituents, nucleophiles and reaction conditions.[1–3] Here we report exclusive formation of the linear isomer in a palladium-catalysed allylic alkylation, which is realized by addition of a catalytic amount of lithium iodide.[4]

In the presence of 2 mol% of the palladium catalyst generated by mixing $[PdCl(\pi\text{-}C_3H_5)]_2$ with PPh_3 (2 equiv. to Pd), allyl acetates **1**–**4** were allowed to react with soft carbon nucleophiles in THF at 0 °C (Scheme 1). The regioselectivity of the reaction was found to be dramatically changed by the addition of lithium iodide. Thus, the reaction of 1-phenylprop-2-enyl acetate **1** with the sodium salt of dimethyl methylmalonate in the absence of lithium iodide gave a 96% yield of alkylation product; consisting of linear isomer (*E*)-**5a** and branch isomer **6a** in a ratio of 77 : 23 (entry 1, Table 1). On the other hand, the reaction carried out in the presence of 10 mol% of lithium iodide gave a quantitative yield of linear isomer **5a** with 100% regioselectivity (entry 2). The regioselectivity was not strongly affected by the addition of lithium fluoride, chloride or bromide, branch isomer **6a** being formed with about 20% regioselectivity (entries 3–5). High linear selectivity was also observed in the reaction in the presence of sodium iodide (entry 6), indicating that the iodide anion is important for control of the regioselectivity. The amount of lithium iodide additive can be decreased to 2 mol%, which is the same amount as that of the palladium catalyst (entry 7). Use of the palladium catalyst generated from $[PdI(\pi\text{-}C_3H_5)]_2$ instead of $[PdCl(\pi\text{-}C_3H_5)]_2$ showed the same linear selectivity in the absence of additional iodide anion (entry 8).

The selectivity in forming the linear isomer in the presence of lithium iodide was also observed in the reaction of 1-arylprop-2-enyl acetates **2** and **3** and 3-phenylprop-2-enyl acetate **4** with the sodium salt of dimethyl methylmalonate (entries 9–13) and

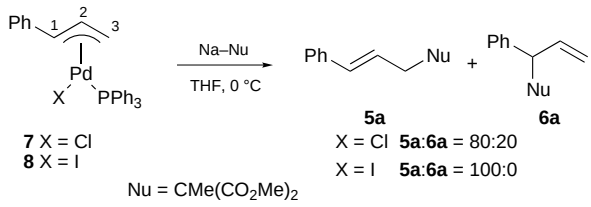


Scheme 1

Table 1 Effects of lithium salts on allylic alkylation of allyl acetates **1**–**4** catalysed by palladium–phosphine complexes[a]

Entry	Allyl ester	MX/equiv.	Phosphine ligand[b]	Nu	*t*/h	Yield (%)[c] **5** + **6**	Ratio[d] **5**:**6**
1	**1**	none	PPh_3	$CMe(CO_2Me)_2$	12	96	77 : 23
2	**1**	LiI (0.1)	PPh_3	$CMe(CO_2Me)_2$	24	99	100 : 0
3	**1**	LiF (0.1)	PPh_3	$CMe(CO_2Me)_2$	24	89	78 : 22
4	**1**	LiCl (0.1)	PPh_3	$CMe(CO_2Me)_2$	24	96	82 : 18
5	**1**	LiBr (0.1)	PPh_3	$CMe(CO_2Me)_2$	24	90	80 : 20
6	**1**	NaI (0.1)	PPh_3	$CMe(CO_2Me)_2$	24	93	98 : 2
7	**1**	LiI (0.02)	PPh_3	$CMe(CO_2Me)_2$	24	97	100 : 0
8[e]	**1**	none	PPh_3	$CMe(CO_2Me)_2$	24	96	100 : 0
9	**2**	none	PPh_3	$CMe(CO_2Me)_2$	12	98	72 : 28
10	**2**	LiI (0.1)	PPh_3	$CMe(CO_2Me)_2$	24	92	100 : 0
11	**3**	none	PPh_3	$CMe(CO_2Me)_2$	12	96	86 : 14
12	**3**	LiI (0.1)	PPh_3	$CMe(CO_2Me)_2$	24	89	100 : 0
13[f]	**4**	LiI (0.1)	PPh_3	$CMe(CO_2Me)_2$	24	99	100 : 0
14	**1**	none	PPh_3	$CH(CO_2Me)_2$	12	94	83 : 17
15	**1**	LiI (0.1)	PPh_3	$CH(CO_2Me)_2$	12	91	100 : 0
16	**1**	none	PPh_3	$CH(COMe)CO_2Me$	12	95	92 : 8
17	**1**	LiI (0.1)	PPh_3	$CH(COMe)CO_2Me$	12	89	100 : 0
18[f]	**1**	none	dppe	$CMe(CO_2Me)_2$	12	92	89 : 11
19[f]	**1**	LiI (0.1)	dppe	$CMe(CO_2Me)_2$	12	61	89 : 11

[a] All reactions were carried out in THF under nitrogen: THF (1.0 ml), allylic acetate (0.20 mmol), NaNu (0.40 mmol), $[PdCl(\pi\text{-}C_3H_5)]_2$ (0.002 mmol) and phosphine ligand at 0 °C. [b] The ratio of Pd : Phosphine = 1 : 2. [c] Isolated yield by silica gel column chromatography. [d] The ratio was determined by ^1H NMR analysis of the products. [e] $[PdI(\pi\text{-}C_3H_5)]_2$ was used. [f] Carried out at 20 °C.



Scheme 2

in the reactions with dimethyl malonate and methyl acetoacetate (entries 14–17).

It is noteworthy that the addition of lithium iodide is not effective for the reaction catalysed by a palladium–bisphosphine complex. Thus, the reaction of **1** with dimethyl methylmalonate in the presence of a palladium catalyst prepared from $[PdCl(\pi\text{-}C_3H_5)]_2$ and 1,2-bis(diphenylphosphino)ethane (dppe) gave a mixture of **5a** and **5b** in a ratio of 89 : 11, irrespective of the addition of lithium iodide (entries 18 and 19). These results suggest that, in the reaction catalysed by triphenylphosphine–palladium, the iodide coordinates to the π-allylpalladium intermediate to form the intermediate $PdI(\pi\text{-allyl})(PPh_3)$, and that the iodide on the palladium controls the regioselectivity of the nucleophilic attack. Using the dppe ligand, the intermediate will be the cationic complex $[Pd(\pi\text{-allyl})(dppe)]^+X^-$, where iodide is not directly bonded to palladium.

Palladium complex $PdCl[\pi\text{-}(1\text{-phenyl})allyl](PPh_3)$ **7** and its iodide analogue **8** were prepared by mixing $[PdX[\pi\text{-}(1\text{-phenyl})allyl]]_2$ (X = Cl and I)[5] with PPh_3 (1 equiv. to Pd) and were characterized by ^{31}P, ^1H and ^{13}C NMR spectroscopy.† Both have the substituted carbon (C-1) of the π-allyl *trans* to the phosphorus atom of PPh_3 and the unsubstituted carbon (C-3) *cis* to phosphorus, as determined by the large coupling constants (J = 10.1 Hz in **7** and 10.5 Hz in **8**) between the C-1 proton and phosphorus, and no coupling between the C-3 protons and phosphorus. Stoichiometric reaction of chloride complex **7** with the sodium enolate of dimethyl methylmalonate in THF at 0 °C gave **5a** and **6a** in a ratio of 80 : 20, while the reaction of iodide complex **8** gave **5a** with 100% regioselectivity (Scheme 2). These selectivities are in good agreement with those observed in the catalytic reactions, demonstrating that the iodide ligand bonded to the π-allylpalladium intermediate controls the regioselectivity. Comparing the ^{13}C NMR spectra of **7** and **8**, the chemical shift for C-3 of the π-allyl group of **8** appears at lower field than that for **7** by 6.5 ppm and the chemical shift for C-1 of **8** appears at higher field than that for **7** by 3.1 ppm. The difference in the chemical shifts may support the idea that the C-3 carbon of the iodide complex **8** undergoes the nucleophilic attack giving linear isomer **5a** more selectively than that of **7**.[6]

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Footnotes and References

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† *Selected data* for **7**: $\delta_H(CDCl_3, -40\ °C)$ 2.88 (d, J 6.8, 1 H, *syn*-H on C-3), 2.97 (d, J 11.7, 1 H, *anti*-H on C-3), 5.37 (dd, J_{H-H} 13.2, J_{H-P} 10.1, 1 H, H on C-1), 6.08 (ddd, J 6.8, 11.7, 13.2, 1 H, H on C-2), 7.36–7.88 (m, 20 H); $\delta_P(CDCl_3, -40\ °C)$ 24.2 (s); $\delta_C(CDCl_3, -40\ °C)$ 58.2 (C-3), 99.6 (J_{C-P} 26.9, C-1), 111.4 (J_{C-P} 5.2, C-2). For **8**: $\delta_H(CDCl_3, -40\ °C)$ 3.47 (d, J 6.8, 1 H, *syn*-H on C-3), 3.14 (d, J 12.2, 1 H, *anti*-H on C-3), 5.21 (dd, J_{H-H} 13.0, J_{H-P} 10.5, 1 H, H on C-1), 6.08 (ddd, J 6.8, 12.2, 13.0, 1 H, H on C-2), 7.26–7.63 (m, 20 H); $\delta_P(CDCl_3, -40\ °C)$ 27.9 (s); $\delta_C(CDCl_3, -40\ °C)$ 64.7 (C-3), 96.5 (J_{C-P} 29.0, C-1), 111.0 (J_{C-P} 5.2, C-2).

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