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Regioselective palladium-catalysed prenylation of CH acids in the presence of diamidophosphite ligands and potassium carbonate

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The palladium-catalysed prenylation of CH acids with 3-methylbut-1-en-3-yl or prenyl acetates under phase-transfer conditions affords high yield of the linear regioisomer provided by the use of diamidophosphite ligands.

The palladium-catalysed reaction of stabilised anions of CH acids with allylic carboxylates is a good alternative to the use of poorly accessible complex allylic halides and is widely used in the fine synthesis.[1] However, a drawback of this approach is that it requires the preliminary conversion of CH acids into carbanions by the treatment with strong and expensive bases, *e.g.*, NaH or BSA, which is a serious restriction in the large-scale preparations. In the mid-1980s, Russian scientists found that the application of phase-transfer concept in Pd-catalysed allylation of CH acids allows one to use inexpensive safe bases, such as metal carbonates or hydroxides.[2] However, neryl acetate was found to be inactive under the proposed conditions.[2(a)] To the best of our knowledge, there is no other information about the application of this approach to the Pd-catalysed allylation with the involvement of (poly)prenyl acetates, although in a few more recent publications[3] describing mostly the asymmetric allylation of CH acids with 1-acetoxy-1,3-diphenylprop-2-ene in water or ionic liquids, the use of metal carbonates was documented. It should be noted that this approach implies the generation of both reacting species, *viz*., a CH-acid carbanion and a Pd π-allylic complex, in low quasi-stationary concentrations.

In the present study, we have extended the scope of Pd-catalysed allylation of certain CH acids, mostly of diethyl malonate **1**, under phase-transfer conditions (K_2CO_3 as the base) and succeeded in performing this reaction with prenyl-type acetates **2** and **2′** (both these reagents generally form the same intermediate π-allylic Pd complex, *cf*. refs. 4) with the use of modern ligands[†] (Scheme 1, Table 1).

The reaction with the use of tertiary 3-methylbut-1-en-3-yl acetate **2** and triphenylphosphine as the ligand afforded mostly branched product **3′** (Table 1, entries 1 and 2). More electron-donating tributylphosphine did not improve the regioselectivity (entries 3 and 4, *cf*. ref. 8). Surprisingly, the use of electron-rich sterically hindered phosphines (entries 5 and 6) led to a serious decrease in the reaction rate due, apparently, to the shielding of the Pd atom in the activated complex. The BINOL-derived phosphite and the amidophosphite ligands[5–7] (**L1** and **L2**) proved to be essentially inactive (entries 7 and 8). Meanwhile, to our great satisfaction, the next phosphite-type monodentate ligand, *viz*., diamidophosphite[7] **L3**, having a stronger coordination ability, allowed us to achieve the 68–77% fraction of linear product **3** and the conversion of 100% (entries 9 and 10). Other related diamidophosphites **L4**–**L6** provided high yields, as well as good **3**/**3′** ratios (entries 11–14), whereas the regioselectivity in the reaction with the use of the more sterically hindered ligand **L7** was much lower (entry 15). Variations of the nature of the solvents and the use of Bu_4NBr as the phase-transfer catalyst (PTC) showed that DMF was the solvent of choice (entries 9 and 10). Note that diprenylation of malonate **1** was not observed in spite of the fact that a substantial excess of reagent **2** was used.[‡]

[†] Phosphine ligands were commercially available. Ligands **L1**–**L3** were prepared according to the literature procedures [see refs. 5, 6 and 7(*a*), respectively]. Diamidophosphite ligands **L4**–**L7** were prepared analogously to the relative ligand **L3** [see refs. 7(*a*),(*b*)] from the cheap L-glutamic acid. Obviously, the chirality of these ligands thus prepared is not important in this study dealing with non-chiral compounds.

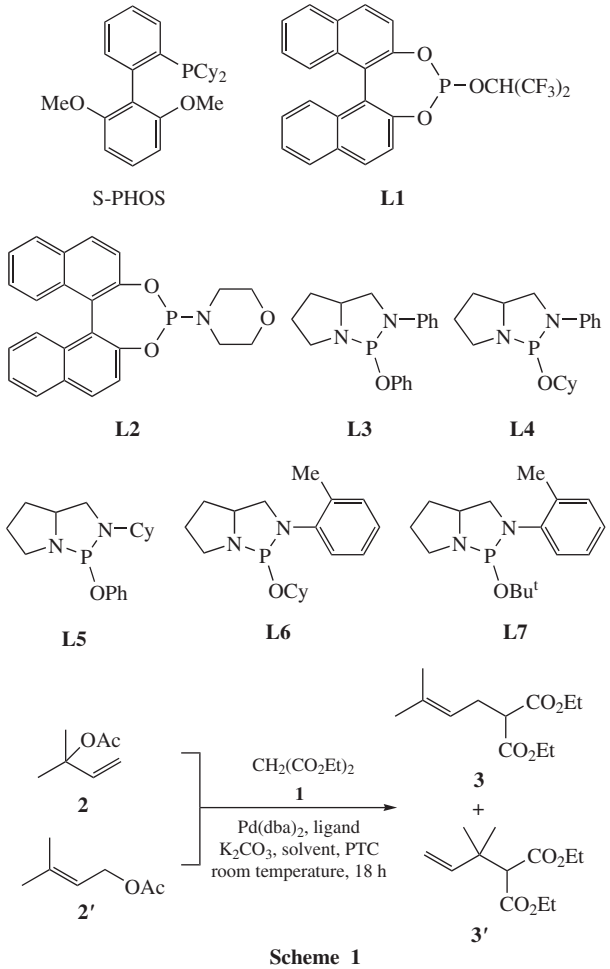
*(2*R*,5*S*)-2-Cyclohexyloxy-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]-octane* **L4**: colourless oil. ^{31}P NMR ($CDCl_3$) δ: 112.71 (50%, *S*p), 128.92 (50%, *R*p). ^{13}C NMR ($CDCl_3$) δ: 145.6 (d, $^2J_{C,P}$ 16.1 Hz), 128.7, 118.3, 114.6 (d, $^3J_{C,P}$ 11.9 Hz), 72.1, 62.6, (d, $^2J_{C,P}$ 8.4 Hz), 54.1 (d, $^2J_{C,P}$ 7.0 Hz), 48.1 (d, $^2J_{C,P}$ 37.8 Hz), 34.4 (d, $^3J_{C,P}$ 44.4 Hz), 31.6, 25.9, 25.3, 24.2 (d, $^2J_{C,P}$ 11.5 Hz). Found (%): C, 67.20; H, 8.37; N, 9.01. Calc. for $C_{17}H_{25}N_2OP$ (%): C, 67.08; H, 8.28; N, 9.20.

*(2*R*,5*S*)-2-Phenoxy-3-cyclohexyl-1,3-diaza-2-phosphabicyclo[3.3.0]-octane* **L5**: colourless oil. ^{31}P NMR ($CDCl_3$) δ: 127.01 (13%, *S*p), 139.17 (87%, *R*p). ^{13}C NMR (major form, $CDCl_3$) δ: 153.2 (d, $^2J_{C,P}$ 12.1 Hz), 129.1, 119.3, 114.1, 57.2 (d, $^2J_{C,P}$ 9.1 Hz), 56.8, 52.2 (d, $^2J_{C,P}$ 6.1 Hz), 47.9 (d, $^2J_{C,P}$ 34.5 Hz), 32.7, 30.5, 27.8, 24.7, 23.2. Found (%): C, 67.28; H, 8.41; N, 9.03. Calc. for $C_{17}H_{25}N_2OP$ (%): C, 67.08; H, 8.28; N, 9.20.

*(2*R*,5*S*)-2-Cyclohexyloxy-3-(2-methylphenyl)-1,3-diaza-2-phosphabicyclo-[3.3.0]octane* **L6**: colourless oil. ^{31}P NMR ($CDCl_3$) δ: 123.12 (17%, *S*p), 134.2 (83%, *R*p). ^{13}C NMR (major form, $CDCl_3$) δ: 143.1 (d, $^2J_{C,P}$ 7.4 Hz), 132.5, 130.6, 128.0, 126.0, 123.0, 72.75 (d, $^2J_{C,P}$ 16.7 Hz), 63.18 (d, $^2J_{C,P}$ 7.7 Hz), 54.7, 49.0 (d, $^2J_{C,P}$ 35.6 Hz), 34.5 (d, $^2J_{C,P}$ 4.0 Hz), 34.3 (d, $^2J_{C,P}$ 4.0 Hz), 31.4, 26.4 (d, $^3J_{C,P}$ 4.0 Hz), 25.2, 24.0 (d, $^3J_{C,P}$ 3.9 Hz), 19.6 (d, $^3J_{C,P}$ 13.9 Hz). Found (%): C, 68.05; H, 8.69; N, 8.71. Calc. for $C_{18}H_{27}N_2OP$ (%): C, 67.90; H, 8.55; N, 8.80.

*(2*R*,5*S*)-2-*tert*-Butoxy-3-(2-methylphenyl)-1,3-diaza-2-phosphabicyclo-[3.3.0]octane* **L7**: colourless oil. ^{31}P NMR ($CDCl_3$): 112.71 (40%, *S*p), 128.92 (60%, *R*p). ^{13}C NMR (*R*-form, $CDCl_3$) δ: 143.2 (d, $^2J_{C,P}$ 5.5 Hz), 132.2, 130.4, 125.9, 122.6, 122.3, 73.5 (d, $^2J_{C,P}$ 10.6 Hz), 63.6 ($^2J_{C,P}$ 10.2 Hz), 54.0 ($^2J_{C,P}$ 4 Hz), 49.37 ($^2J_{C,P}$ 36.6 Hz), 31.3, 30.5 ($^2J_{C,P}$ 9.1 Hz), 26.5 (d, $^2J_{C,P}$ 4.4 Hz), 19.5 (d, $^3J_{C,P}$ 15.0 Hz). ^{13}C NMR (*S*-form, $CDCl_3$): 143.7 (d, $^2J_{C,P}$ 9.1 Hz), 131.6, 130.5, 125.7, 122.2, 121.2, 72.7 (d, $^2J_{C,P}$ 7.0 Hz), 62.8 ($^2J_{C,P}$ 7.3 Hz), 53.5 ($^2J_{C,P}$ 5 Hz), 44.0 ($^2J_{C,P}$ 2.2 Hz), 30.7, 30.7 ($^2J_{C,P}$ 9.2 Hz), 28.2, 19.4 (d, $^3J_{C,P}$ 17.6 Hz). Found (%): C, 65.89; H, 8.79; N, 9.43. Calc. for $C_{16}H_{25}N_2OP$ (%): C, 65.73; H, 8.62; N, 9.58.

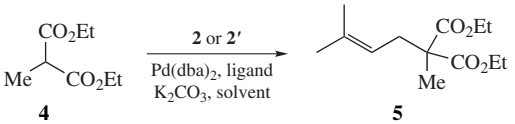
[‡] Application of the conditions from Table 1 (except for PCy_3 and S-PHOS ligands) on the reaction between diethyl malonate and unsubstituted allyl acetate (2.4 equiv.) afforded 100% of diallylation product.



Scheme 1

The use of linear prenyl acetate **2′** gave lower yields (Table 1, entries 16–20). This fact may be attributed to the fact that the reaction of palladium species with the trisubstituted double bond of this olefinic acetate is slower.

The results obtained with C-substituted diethyl methylmalonate **4** are presented in Scheme 2. The reaction of the latter with 3-methylbut-1-en-3-yl acetate **2** afforded product **5** in high yield only with the use of diamidophosphite ligand **L4** (entry 4), the branched isomer being never formed. Sterically hindered diethyl cyclohexylmalonate did not undergo prenylation under the conditions used. It should be noted that the reaction of the latter compound even with active unsubstituted allyl acetate was always incomplete.



Entry	Allylic acetate	Ligand	Solvent	Yield (%)
1	**2**	PPh_3	DMF	0
2	**2**	PBu_3	DMF	0
3	**2**	PBu_3	DMSO	36
4	**2**	**L4**	DMF	94
5	**2′**	**L4**	DMF	0

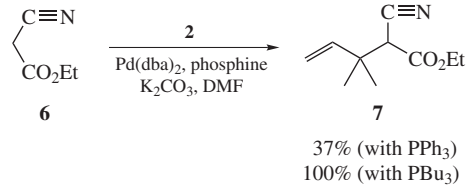
Scheme 2

An important role of the nature of CH acids was confirmed by the fact that the reaction of ethyl cyanoacetate **6** having a higher CH acidity and a lower nucleophilicity of the corresponding carbanion with acetate **2** gave only branched product **7** (Scheme 3).

Table 1 Reaction of diethyl malonate **1** with 3-methylbut-1-en-3-yl (**2**) or prenyl (**2′**) acetates in the presence of various ligands.[a]

Entry	Allylic acetate	Solvent	PTC	Ligand	Product, GC data	
					Total yield (%)	**3**:**3′**
1	**2**	DMF	none	PPh_3	100	16:84
2	**2**	CH_2Cl_2	Bu_4NBr	PPh_3	53	6:94
3	**2**	DMF	none	PBu_3	76	44:56
4	**2**	CH_2Cl_2	Bu_4NBr	PBu_3	81	17:83
5	**2**	DMF	none	PCy_3	—	—
6	**2**	DMF	none	S-PHOS	44	48:52
7	**2**	DMF	none	**L1**	—	—
8	**2**	DMF	none	**L2**	—	—
9	**2**	DMF	none	**L3**	100[b]	77:23
10	**2**	DMSO[c]	none	**L3**	100	68:32
11	**2**	DMF	none	**L4**	100	77:23
12	**2**	DMF	none	**L5**	98	77:23
13	**2**	CH_2Cl_2	Bu_4NBr	**L5**	98	69:31
14	**2**	DMF	none	**L6**	97	67:33
15	**2**	DMF	none	**L7**	84	26:74
16	**2′**	DMF	none	PPh_3	—	—
17	**2′**	DMF	none	PBu_3	57	40:60
18	**2′**	DMSO	none	PBu_3	98	43:57
19	**2′**	DMF	none	**L3**	18	77:23
20	**2′**	DMF	none	**L4**	94	71:29

[a]Reaction conditions: 1.2 equiv. allylic acetate, 1.5 equiv. K_2CO_3, solvent 2 cm^3 $mmol^{-1}$, 2 mol% $Pd(dba)_2$, 8 mol% phosphine or 4 mol% diamidophosphite, 10 mol% PTC, 20 °C, 18 h. [b]Isolated yield was 79%. [c]The yields in DMA and NMP were ~90%; in DMPU, 64% (**3**:**3′** ~ 70:30); by contrast, the reaction in HMPA did not proceed.



Scheme 3

In conclusion, we showed that the palladium-catalysed prenylation of CH acids can be efficiently performed in simple systems containing potassium carbonate and diamidophosphite ligands.[§] The ratios between linear and branched products were similar to those reported earlier for technically difficult procedures involving strong bases.[4,9] The approach under study may promote the development of advanced preparations of useful acyclic terpenoids.[1(a),10]

[§] *Diethyl (3-methylbut-2-en-1-yl)malonate* **3b** *(typical procedure).* A Schlenk tube equipped with a stirring magnet and charged with diethyl malonate **1** (80 mg, 0.5 mmol) and DMF (1 ml) was three times deaerated by evacuation and filling with argon. Diamidophosphite **L3** (12 mg, 0.04 mmol) and $Pd(dba)_2$ (6 mg, 0.01 mmol) were added and the mixture was stirred for *ca.* 5 min until change in the colour occurred. 3-Methylbut-1-en-3-yl acetate **2** (96 mg, *ca.* 108 μl, 1.5 mmol) was added, and the mixture was stirred for 10 min, followed by finely powdered potassium carbonate (138 mg, 1 mmol). Each opening of the Schenk tube was followed by evacuation and filling with argon. The mixture was stirred at ambient temperature for 18 h. A probe was treated with water, extracted with hexane and analysed by gas chromatography, which showed the absence of the starting malonate **1** and the presence of two products **3** and **3′** (77:23). To isolate the products, the reaction mixture was treated with water, extracted with diethyl ether, the extracts were dried (Na_2SO_4) and concentrated. The residue was subjected to column chromatography (gradient 0→5% EtOAc in light petroleum) to afford 180 mg (79%) of the mixture **3** and **3′** (77:23 according to ^{1}H NMR data). Chemical shifts in the ^{1}H and ^{13}C NMR spectra were in good agreement with the literature.[4(b),9(a)]

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