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Highly Stereoselective Palladium(0)-Catalyzed Allylation of Active Methylene Compounds with Allyl Imidates under Neutral Conditions

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In the presence of a catalytic amount of Pd(0), active methylene compounds were allylated by allyl imidates under neutral conditions. In allylation with 3,3-disubstituted allyl imidates, e.g., geranyl and neryl imidate the effect of solvent and ligand to the *E/Z* ratio are investigated. The reaction in dimethyl sulfoxide by addition of diphosphine, e.g., 1,2-bis(diphenylphosphino)ethane, or large excess of triphenylphosphine as additive ligand gave best results. In these conditions, various active methylene compounds were allylated stereoselectively, especially complete retention of starting olefin geometry was achieved with neryl imidate.

Palladium-catalyzed allylation of carbanions is one of the useful methods for carbon–carbon bond formation; allyl acetates are commonly used as precursors of π-allylpalladium intermediates in the presence of a stoichiometric amount of bases such as NaH for the generation of a carbanion to be allylated.[1] It would be more valuable if the reaction could be carried out without addition of a base. Allylation using allyl carbonates under neutral conditions has also been reported.[1c]

Many bioactive compounds which have *trans*-isoprene units are known, and in recent years several kinds of polyprenols containing *cis*-isoprene units such as betulaprenols,[2,3] undecaprenol,[4] dolichols,[5] and others[6] have been isolated. An efficient method for stereoselective introduction of isoprene units is strongly desired, but stereoselective allylation via π-allylpalladium species had not been achieved until we recently reported that active methylene compounds were allylated by *O*-(allyloxycarbonyl)oximes with high stereoselectivity in the presence of catalytic amounts of bases.[7]

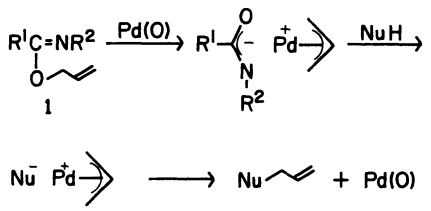
The present paper describes the highly stereoselective allylation of various active methylene compounds with allyl imidates under neutral conditions.

Results and Discussion

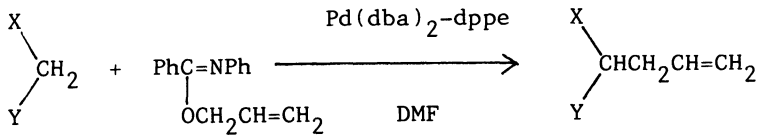
Although stoichiometric amounts of the bases were needed, palladium catalyzed allylic alkylation to active methylene compounds took place with allyl acetates smoothly. We anticipated that allylimidates **1**, imine analogues of esters, would be reactive toward palladium to generate π-allylpalladium species[8] and would also be capable of liberating imidate anions which are basic enough to generate carbon nucleophiles from active methylene compounds (Scheme 1).

A series of imidates was prepared by either the reaction of imidoyl chloride with alkoxide[9] or the reaction of ethyl imidate with allylic alcohols.[10]

The reaction of allyl *N*-phenylbenzimidate (**1a**)



Scheme 1.



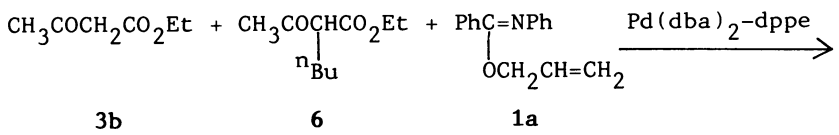
3 1a 4 + 5

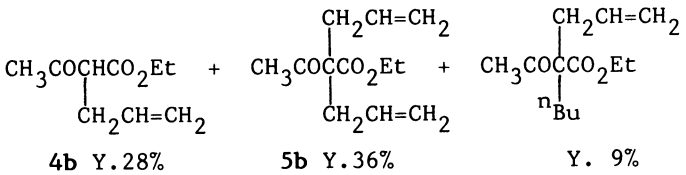
Scheme 2.

Table 1. Palladium-Catalyzed Allylation of Active Methylene Compounds **3** with Allyl *N*-Phenylbenzimidate (**1a**)[a]

Compd	**3**		(pK_a)	Time/h	Product (yield/%)[b]	
					4	**5**
3a:	X=Y=MeCO		(9)	1	**4a**: (25)	**5a**: (55)
3b:	X=MeCO	Y=CO_2Et	(11)	1.5	**4b**: (31)	**5b**: (35)
				3[c]	**4b**: (24)	**5b**: (29)
3c:	X=Y=CO_2Et		(13)	4	**4c**: (55)	**5c**: (28)
3d:	X=Ph	Y=PhCO	(16)	5	**4d**: (69)	
3e:	X=Ts	Y=MeCO		7[d]	**4e**: (58)	**5e**: (18)

a) The reaction was carried out by using 2 mol% of Pd(dba)$_2$-dppe in DMF at r.t. Ts=*p*-$CH_3C_6H_4SO_2$. b) Isolated yield. c) PPh_3 (4 equiv to Pd(0)) was used instead of dppe. d) The reaction was carried out at 85 °C.





Scheme 3.

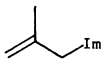
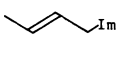
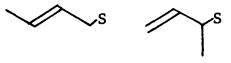
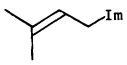
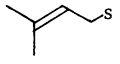
(R^1=Ph, R^2=Ph) with various active methylene compounds **3** was found to proceed smoothly in the presence of bis(dibenzylideneacetone)palladium (Pd(dba)$_2$) (2 mol%) and 1,2-bis(diphenylphosphino)ethane (dppe) (2 mol%) in *N*,*N*-dimethylformamide (DMF) to yield a mixture of monoallylated **4** and diallylated compounds **5** in good combined yields (Scheme 2). The results are summarized in Table 1. The ratio of diallylation to monoallylation products decreased in almost the reverse order of the acidity of active methylene compounds. Various kinds of imidates **1** (R^1=Ph, H, Me, R^2=Ph, H) were similarly effective for this allylation reaction. Tetrahydrofuran (THF), chloroform, benzene, acetonitrile, dimethyl sulfoxide (DMSO), and hexamethylphosphoric triamide (HMPA) were also effective as solvents; the addition of triphenylphosphine (PPh_3) or dppe is absolutely necessary, but the allylation did not take place with tributylphosphine, trimethyl phosphite, or tri-*o*-tolylphosphine.

To examine the concurrent formation of the diallylation products a competition experiment was conducted. When an equimolar mixture of ethyl acetoacetate (**3b**) and ethyl 2-butyl-3-oxobutanoate (**6**) was treated with imidate **1a**, the allylation of **6** took place only to a small extent (9% yield) in comparison with the formation of the diallylation product **5b** from **3b** in 36% yield (Scheme 3). These results imply that the allylation does not proceed by a simple mechanism. Hence, use of a large excess of active methylene compound was effective at suppressing the diallylation; when 10 equiv of **3b** was used, monoallylation product was obtained in 77% yield and the diallylated product was no longer formed.

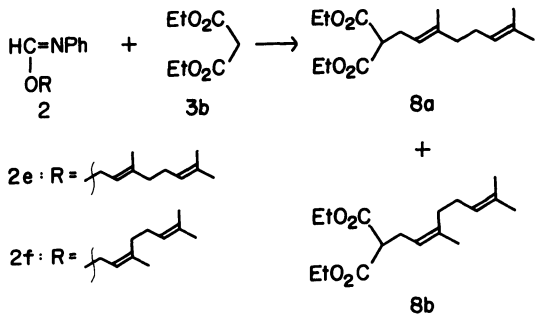
The regiochemistry of allylation with unsymmetrically substituted allylic systems is an important problem from both synthetic and mechanistic viewpoints. The results of allylation of *p*-tolylsulfonylacetone (**3e**) with several substituted allyl imidates are summarized in Table 2. It is noteworthy that diallylated products were no longer detected. The less substituted site of the allylic system in the imidate reacted preferentially, and prenyl imidate **2d** gave only one regioisomer **7d**. Moreover, the 2-butenylated product **7b** was a pure trans isomer irrespective of the structure of the starting imidate **2b** or **2c**.

The stereochemistry of allylation with 3,3-disubstituted allyl imidates was next examined using geranyl imidate **2e** and neryl imidate **2f** (Scheme 4). In these types of allylation good yields were obtained only in polar solvents; in chloroform, benzene, or THF, the yields were poor or the reaction did not take place. In general, the reaction of the π-allylpalladium complex is strongly influenced by the solvent and the

Table 2. Allylation of *p*-Tolylsulfonylacetone (**3e**) with Substituted Allyl Imidate[a]

Imidate	Time/h	Yield[b]/%	Product (ratio[c])/%)
 **2a**	7	98	 **7a**: (100)
 **2b**	22	85	 **7b**: (75) **7c**: (25)
 **2c**	19	57	**7b**: (71) **7c**: (29)
 **2d**	19	61	 **7d**: (100)

a) The reaction was carried out by using 2 mol% of $Pd(dba)_2$-dppe in DMF at 85 °C. Im=–OCH(=NPh); S=$TsCHCOCH_3$. b) Isolated yield. c) Determined by GLC.



Scheme 4.

ligand.[1] However, few reports have been given with respect to the stereochemistry.[11] Therefore, initially, the effect of the solvent to the *E/Z* ratio of products was examined in detail (Table 3). When geranyl imidate **2e** was used in combination with dppe, the greater the donor number[12] of the solvent, the higher was the stereoselectivity. On the other hand complete retention of the stereochemistry of the starting neryl imidate **2f** was attained by the use of DMSO as solvent. It is well-known that the pathway for isomerization of the allyl moiety involves π-allyl to σ-allyl interconversion and bond rotation,[13] and this higher selectivity indicates that nucleophilic attack is faster than syn-anti isomerization. Indeed, the allylation proceeded most rapidly in DMSO among the solvent tested. When PPh_3 was used as ligand, the amount of PPh_3 was crucial for the stereoselectivity. No stereoselectivity (*Z*:*E*=50:50) was observed with 2 equiv. of PPh_3 to Pd(0) in allylation of diethyl malonate (**3c**) with **2f** in DMSO, satisfactory results were obtained with 8 equiv. of PPh_3 (*Z*:*E*=90:10). Notably complete retention of stereochemistry was attained by using a large excess (15 equiv to Pd(0)) of PPh_3. Similarly, no stereoisomer was formed with a large excess of methyldiphenylphosphine.

Table 3. Allylation of Diethyl Malonate (**3c**) with **2e** and **2f** in Several Polar Solvents[a]

Imidate	Solvent (donor No.)	Time h	Yield[b] %	*E/Z* ratio[c] **8a** : **8b**
2e	DMF (26.6)	7	79	76: 24
2e	NMP[d] (27.3)	18	59	82: 18
2e	DMSO (29.8)	4	79	97: 3
2f	DMF	28	73	51: 49
2f	DMAc[e]	19	48	52: 48
2f	DMSO	5	76	0:100
2f	HMPA	19	65	52: 48

a) The reaction was carried out by using 2 mol% of $Pd(dba)_2$-dppe at 85 °C. b) Isolated yield. c) Determined by GLC. d) *N*-Methyl-2-pyrrolidone. e) *N,N*-Dimethylacetamide.

Table 4. Stereoselective Allylation toward Various Active Methylene Compounds with **2e** and **2f**[a]

Compd	Imidate	Time/h	Yield[b]/%	*E/Z* ratio[c]
3b	**2e**	2	71[d]	100: 0
4b	**2e**	1	91	99: 1
3b	**2f**	3	73[d,e]	0:100
4b	**2f**	1	88	0:100
6	**2f**	1	82	0:100
3c	**2e**	4	79[f]	97: 3
4c	**2e**	2	76	99: 1
3c	**2f**	5	76[g]	0:100
4c	**2f**[h]	1	82	0:100
3e	**2e**[h]	15	81	98: 2
3e	**2f**[h]	19	93	11: 89
$TsCH_2CO_2Et$ **3f**	**2e**[h]	18	73	96: 4
3f	**2f**[h]	18	69[i]	1: 99

a) The reaction was carried out by using 2 mol% of $Pd(dba)_2$-dppe in DMSO at 85 °C. b) Isolated yield. c) Determined by GLC. d) After hydrolysis and decarboxylation. e) Containing 15% of regioisomer. f) Containing 7% of regioisomer. g) Containing 14% of regioisomer. h) Excess of PPh_3 (15 equiv) to Pd(0)) was used instead of dppe. i) Containing 17% of regioisomer.

Table 4 shows the results of allylation of various active methylene compounds with geranyl imidate (**2e**) and neryl imidate (**2f**) in DMSO. Ethyl acetoacetate (**3b**) was allylated with **2e** and **2f** with complete retention of the olefin geometry to yield, after hydrolysis and decarboxylation, stereochemicaly pure geranylacetone

and nerylacetone in 71% and 73% yield, respectively. Substituted ethyl acetoacetates **4b**, **6** and diethyl malonate (**3c**), and diethyl allylmalonate (**4c**) were also allylated stereoselectively, especially with **2f**, no stereoisomer was observed. Sulfonylacetone **3e** and ethyl *p*-tolylsulfonylacetate (**3f**) were also allylated stereoselectively by using a large excess of PPh_3 as ligand.

In other neutral allylations, e.g., allylation with allyl carbonates, complete retention of stereochemistry was not achieved, especially the reaction of neryl carbonate with methyl acetoacetate which gave almost equal amounts of geranylacetone and nerylacetone.[1c] Therefore the present allylation with allyl imidates is thought to be valuable as a method for the stereoselective introduction of trisubstituted allylic moieties under neutral conditions.

Experimental

General. Boiling points are uncorrected. IR spectra were measured on a Hitachi 260-10 spectrometer. ^1H NMR spectra were obtained with a JEOL JNM-C-60M or a JEOL FT-90-Q using $CDCl_3$ as solvent and with tetramethylsilane as internal standard. Column chromatography was normally effected with Wakogel C-200 (Wako Pure Chemical Industries). GLC analyses were performed on a Shimadzu GC-9A chromatograph using a column packed with Silicone OV-17 (3 mm×2 m), and the peak areas were calculated on a Shimadzu chromatopack C-R3A.

Materials. $Pd(dba)_2$ was prepared according to a literature method.[14] The structure of the known compounds were established on the basis of their spectroscopic properties and from descriptions in the literature. Allylic imidates were prepared by methods described in the literature.[9] The following new compounds were prepared by the method of Roberts.[10]

3-Methyl-2-butenyl *N*-Phenylformimidate (2d): Bp 91—92 °C/0.45 mmHg (1 mmHg≈133.322 Pa); IR(neat) 1650, 1190, 770, and 700 cm^{-1}; ^1H NMR δ=1.71 (6H, s), 4.63 (2H, d, J=7 Hz), 5.35 (1H, t, J=7 Hz), 6.7—7.2 (5H, m), 7.47 (1H, s).

Found: C, 76.38; H, 7.68; N, 7.56%. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40%.

(*E*)-3,7-Dimethyl-2,6-octadienyl *N*-Phenylformimidate (2e): Bp 139—141 °C/0.38 mmHg; IR (neat) 1640, 1185, 760, and 700 cm^{-1}; ^1H NMR δ=1.59, 1.65, and 1.71 (9H, each s), 2.01 (4H, bs), 4.64 (2H, d, J=7 Hz), 4.98 (1H, bs), 5.33 (1H, t, J=7 Hz), 6.6—7.1 (5H, m), and 7.44 (1H, s).

Found: C, 79.15; H, 9.32; N, 5.29%. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44%.

(*Z*)-3,7-Dimethyl-2,6-octadienyl *N*-Phenylformimidate (2f): Bp 141—143 °C/0.35 mmHg; IR (neat) 1640, 1185, 760, and 700 cm^{-1}; ^1H NMR δ=1.59, 1.65, and 1.75 (9H, each s), 2.10 (4H, bs), 4.64 (2H, d, J=7 Hz), 5.01 (1H, bs), 5.37 (1H, t, J=7 Hz), 6.7—7.2 (5H, m), and 7.50 (1H, bs).

Found: C, 79.58; H, 9.20; N, 5.58%. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44%.

General Procedure for Allylation of Active Methylene Compounds. To a stirred mixture of active methylene compound (0.4 mmol), $Pd(dba)_2$ (5 mg, 2 mol%), and dppe (3 mg, 2 mol%) in DMF (10 ml), was added a solution of imidate (0.4 mmol) in DMF (2 ml). The resulting mixture was stirred at 85 °C under nitrogen, poured into water, and extracted with diethyl ether. The organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed and the residue was purified by column chromatography (silica gel; hexane/ethyl acetate).

Reaction of 2-Propenyl *N*-Phenylbenzimidate (1a) with Ethyl Acetoacetate (3b) and Ethyl 2-Butyl-3-oxobutanoate (6). To a stirred mixture of **3b** (406 mg, 3.1 mmol), **6** (581 mg, 3.1 mmol), $Pd(dba)_2$ (36 mg), and dppe (25 mg) in DMF (10 ml), was added a solution of **1a** (740 mg, 3.1 mmol) in DMF (2 ml). The resulting mixture was stirred at room temperature for 2 h and treated according to the general procedure, affording **4b** (149 mg, 28%), **5b** (118 mg, 36%) and ethyl 2-butyl-2-(2-propenyl)-3-oxobutanoate (64 mg, 9%).

Allylation of *p*-Tolylsulfonylacetone (3e) with Substituted Allyl Imidate (Table 2). Substituted allyl imidate (0.4 mmol) and **3e** (85 mg, 0.4 mmol) were stirred in DMF (10 ml) at 85 °C under nitrogen in the presence of $Pd(dba)_2$ (5 mg, 2 mol%) and dppe (3 mg, 2 mol%). Allylated sulfones were obtained according to the general procedure. The ratio of **7b** and **7c** was determined by GLC (column 230 °C, **7b**; retention time=7.6 min, **7c**; retention time=6.5 min).

Allylation of Diethyl Malonate (3c) with 2e and 2f in Several Polar Solvents (Table 3). To a stirred mixture of **3c** (311 mg, 1.9 mmol), $Pd(dba)_2$ (22 mg, 2 mol%), and dppe (15 mg, 2 mol%) in solvent (20 ml), was added a solution of imidate **2e** or **2f**. The resulting mixture was stirred at 85 °C under nitrogen, and treated according to the general procedure. The E/Z ratio was determined by GLC (column 180 °C, **8a**; retention time=9.9 min, **8b**; retention time=8.7 min).

Allylation toward Various Active Methylene Compounds with 2e and 2f (Table 4). To a stirred mixture of the active methylene compound (1.9 mmol), $Pd(dba)_2$ (22 mg, 2 mol%), and dppe (15 mg, 2 mol%) in DMSO (20 ml) was added a solution of imidate **2e** or **2f**. The resulting mixture was stirred at 85 °C under nitrogen, and treated according to the general procedure. The following new compound were obtained using the above procedure.

Ethyl (*E*)-2-(3,7-Dimethyl-2,6-octadienyl)-2-(2-propenyl)-3-oxobutanoate: IR (neat) 1735, 1710, 1215, and 920 cm^{-1}; ^1H NMR δ=1.26 (3H, t, J=7 Hz), 1.60 (6H, s), 1.68 (3H, S), 2.00 (4H, bs), 2.12 (3H, s), 2.58 (4H, d, J=7 Hz), 4.19 (2H, q, J=7 Hz), 4.8—5.1 (4H, m), 5.62 (1H, ddt, J=18, 9, 7 Hz).

Found: C, 74.57; H, 9.78%. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87%.

Ethyl (*Z*)-2-(3,7-Dimethyl-2,6-octadienyl)-2-(2-propenyl)-3-oxobutanoate: IR (neat) 1735, 1710, 1215, and 920 cm^{-1}; ^1H NMR δ=1.25 (3H, t, J=7 Hz), 1.60, 1.68 (6H, each s), 2.03 (4H, bs), 2.11 (3H, s), 2.57 (2H, d, J=7 Hz), 4.18 (2H, q, J=7 Hz), 4.88 (1H, t, J=7 Hz), 5.10 (1H, bs).

Found: C, 74.39; H, 10.64%. Calcd for $C_{20}H_{30}O_3$: C, 74.49; H, 10.63%.

Diethyl (*Z*)-2-(3,7-Dimethyl-2,6-octadienyl)-2-(2-propenyl)-malonate: IR (neat) 1730, 1220, and 920 cm^{-1}; ^1H NMR δ=1.24 (3H, t, J=7 Hz), 1.60 (3H, s), 1.68 (6H, s), 2.03 (4H, bs), 2.62 (H, d, J=7 Hz), 4.17 (4H, q, J=7 Hz), 4.9—5.2 (4H, m), 5.68 (1H, ddt, J=18, 9, 7 Hz).

Found: C, 71.68; H, 9.39%. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59%.

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