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A CONVENIENT PROCEDURE FOR SMOOTH PALLADIUM-CATALYZED ALLYLIC ALKYLATION BY SODIUM DIMETHYL MALONATE AND CYCLOPENTADIENIDE. A NEW SYNTHESIS OF ALLYLIC SUBSTITUTED CYCLOPENTADIENES.

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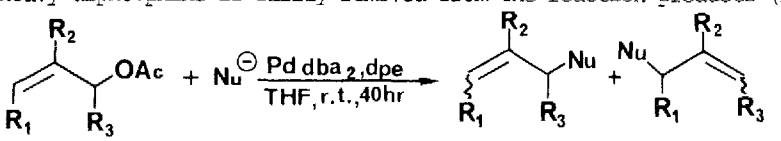
Summary: The use of the $Pd(dba)_2^{\dagger}$/dpe catalytic system in allylic alkylation allows sodium dimethyl malonate to react with allylic acetates at room temperature. According to this procedure, a novel synthesis of allylic substituted cyclopentadienes is described through the use of cyclopentadienide anion as a nucleophile.

The palladium-catalyzed reaction of allylic acetates with carbanions, carried out in the presence of a phosphine ligand, is a good method for carbon-carbon bond formation[1]. Applications to the synthesis of natural products[2] and to asymmetric synthesis[3] have been reported. The intramolecular version of this reaction allows a cyclization into macrolide skeletons[4]. The reactions are usually performed at THF reflux temperature with $Pd(PPh_3)_4$ as a catalyst (1 to 10%), and a relatively high amount of phosphine as additional ligand (phosphine to palladium ratio up to 20).

We would like to report a modification of the reaction allowing a decrease in the reaction temperature and the quantity of phosphine ligands required by replacement of the fairly unstable $Pd(PPh_3)_4$ complex for the stable, easy to handle Pd(0) complex $Pd(dba)_2^{\dagger}$[5]. With this complex, only small quantities (1 mole per mole of complex) of the chelating phosphine ligand dpe {bis(diphenylphosphino)-ethane} are required to run the reaction at room temperature; the heavy diphosphine is easily removed from the reaction products (Kugelrohr distillation).



$Nu^{\ominus} = {}^{\ominus}CH(CO_2Me)_2$

$Cp^{\ominus}$ = cyclopentadienyl anion

R_1, R_2, R_3 = see Tables

In a typical procedure, 500 mg (2.6 mmol) carveyl acetate, 10.3 mg (26 µmol) bis(diphenylphosphino)-ethane, and 14.8 mg bis(dibenzylideneacetone)-palladium[6] in 5 ml of dry THF were stirred for 10 min. A solution of the sodium salt of dimethyl malonate in 10 ml of dry THF, generated from 660 mg (5.0 mmol) dimethyl malonate and 140 mg (3.0 mmol) sodium hydride (50% mineral oil dispersion) was then added at once and the resultant mixture stirred for 48 hr at room temperature. The reaction mixture was partitioned between ether and water, and the aqueous layer extracted with additional ether. Combined ethereal extracts were dried over $MgSO_4$, and evaporation of the solvent in vacuo left an oil which was submitted to Kugelrohr

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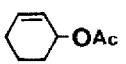
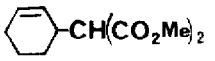
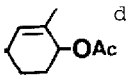
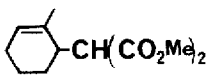
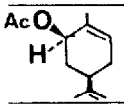
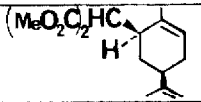
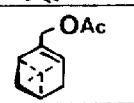
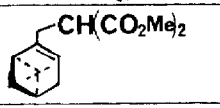
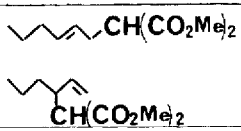
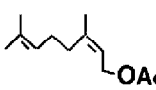
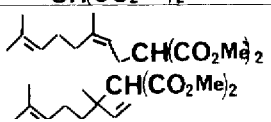
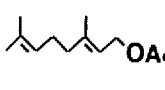
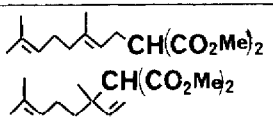
† dba stands for dibenzylideneacetone

Table 1
Palladium-catalyzed alkylation[a] of allylic acetates with the sodium salt of dimethyl malonate in THF

	Substrate	Product[b]	Yield[c] (%) (isomeric composition[e])	b.p./Torr (°C)	^{1}H NMR (CCl_4, 90 MHz) δ (ppm)
1			75.4 (<5%)[f]	100-105/1	5.65 (m,2H); 3.60 (s,6H) 3.30 (d,1H); 2.90 (m,1H) 2.00-1.50 (m,6H)
2	 [d]		71.4	100-105/1	5.42 (m,1H); 3.60 (2s,6H) 3.47 (d,1H); 2.70 (m,1H) 1.90-1.50 (m,9H)
3			83.3 (<5%)[f]	125-130/0.5	5.60 (m,1H); 4.78 (s,2H) 3.75 (2s,6H); 2.92 (m,1H) 2.30-1.12 (m,12H)
4			64.6	120-130/0.3	5.25 (m,1H); 3.65 (s,6H)
5			54.9 (91) (9)	90-95/0.3	3.65 (s,6H)
6			61.9 (76) (23)	125-130/0.1	3.65 (s,6H)
7			46.8 (95) (5)	125-130/0.1	3.65 (s,6H)

a- 48 hr, room temp.; catalyst $Pd(dba)_2$ (2.6×10^{-5} mole), dpe (2.6×10^{-5} mole) (PPh_3 did not induce any reaction), allylic substrate (2.6×10^{-3} mole), sodium dimethyl malonate (3.0×10^{-3} mole).

b- New compounds have been fully characterized by spectra and elemental composition: C ± 0.2%, H ± 0.2%.

c- Yield in isolated product.

d- Cis-carveol was obtained by reduction of carvone with LAH in ether at 0°C.[7]

e- Determined by GLC : Carlo Erba Fractovap GI 430, 4% OV 17 on a Chromosorb Q 2m column.

f- Yields obtained in our hands by the procedure described in ref. 8.

distillation to give 570 mg (83%) of the pure (glc) substitution product (bp 0.5 mmHg 125-130°C).

In the Table 1 are collected the results obtained in the alkylation of some allylic acetates with sodium dimethyl malonate in THF.

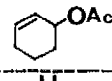
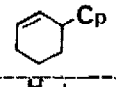
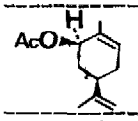
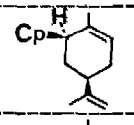
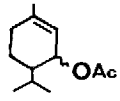
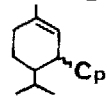
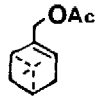
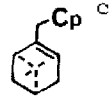
As the previous procedure[8], our experimental conditions promote an overall retention of stereochemistry of the substitution of the acetate group by sodium dimethyl malonate, as exemplified by example 3 where cis carveyl acetate leads to the cis addition compound. Alkylation of the geranyl and neryl acetates in our conditions preserves too the integrity of the stereochemistry of the allylic double bond. While Trost's procedure predominantly afforded from neryl acetate the branched alkylated compound (67%), our catalytic system promotes mainly terminal compound (76%). Moreover, alkylation of geranyl acetate shows a higher regiospecificity, leading to almost exclusively (95%) terminal attack of the allylic moiety (compared to a previous 85:15 ratio of terminal to branched product[8]).

The palladium-catalyzed reaction of sodium dimethyl malonate anion onto allyl acetates, using $Pd(dba)_2$/dpe as a catalytic system offers advantages over the currently used up to now $Pd(PPh_3)_4/PPh_3$ system: it allows reaction to proceed at room temperature, significant improvements in the regioselectivity and convenient work-up due to the easy removal of the small amount of required phosphine ligands. Up to now, suitable nucleophiles used in allylic alkylation were restricted to malonates, sulfonyl , sulfinylacetates, and diphenylsulfone anions[1].

We now report that the mild reaction conditions described above allow the use of the cyclopentadienyl anion as a nucleophile, leading to allylic cyclopentadienes from allylic acetates (Table 2).

Table 2

Synthesis of allylic substituted cyclopentadienes[a]

Substrate	Product[b]	Isolated yield(%)	b.p./Torr (°C)	^1H NMR (CCl_4, 90 MHz) δ(ppm)
		40.0	55/0.3	6.45-5.85(m,3H),5.60(s,2H), 3.10(m,14),2.80(s,24),2.10-1.35(m,6H)
		68.5	100/0.1	6.35-6.05(m,3H),5.50(m,1H),4.70(s,2H) 2.90(s,14),2.75(m,2H),2.15-1.95 (m,11H)
		55.8	140/1.5	6.45-5.80(m,3H), 5.55(s,1H) 3.15-2.70(m,3H), 2.05-0.70(m,15H)
		39.9	80/0.1	6.40-5.85(m,3H), 5.20(m,1H) 3.10-2.70(m,4H), 2.40-1.95(m,6H) 1.20(s,3H), 0.75(s,3H)

a) Similar procedure as Table 1. -b) New compounds have been fully characterized by spectra and elemental composition, C ± 0.4%, H ± 0.2%. Cp = 1,3-cyclopentadiene substituted on 1 or(and) 2 positions by the allylic group. - c) $[\alpha]_D^{20}$ - 31.5° (hexane; c = 6.7).

The experiments were carried out as described above, merely replacing the sodium dimethyl malonate anion by a cyclopentadienide solution generated from 396 mg(6.0 mmol) freshly distilled cyclopentadiene and 214 mg (4.0 mmol) sodium hydride (as 50% mineral oil dispersion). From carveyl acetate (2.6 mmol), Kugelrohr distillation (100°C/0.1 mm Hg) of the crude product gave 353 mg (69%) of the pure (glc) carveyl cyclopentadiene.

Reaction from piperitenyl acetate,conducted from a cis/trans mixture afforded a cis/trans mixture of cyclopentadienes, that could not be separated. Myrtenyl acetate led to a chemically and optically pure myrtenyl cyclopentadiene.

The use of cyclopentadienide anion as a nucleophile constitutes a new route to substituted allylic cyclopentadienes and especially chiral ones.Chiral cyclopentadienes[9] are now required for the preparation of chiral complexes[10] to be used in asymmetric catalyzed reactions[11].

Further investigations are now in progress to prepare new chiral cyclopentadienes and to broaden the scope of the palladium-catalyzed allylic alkylation through the search for new classes of reacting nucleophiles.

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