Pergamon

Tetrahedron Vol. 51, No. 11, pp. 3235-3246, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00061-5

Palladium-Catalyzed Substitution of Esters of Naphthylmethanols, 1-Naphthylethanols, and Analogues by Sodium Dimethyl Malonate. Stereoselective Synthesis from Enantiomerically Pure Substrates.

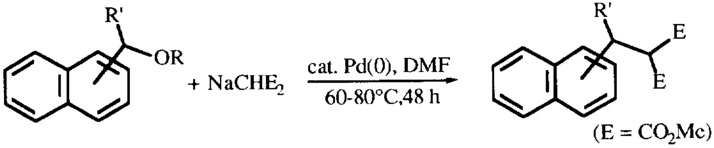
Jean-Yves Legros, Martial Toffano and Jean-Claude Fiaud

Laboratoire de Synthèse Asymétrique Associé au C.N.R.S. (URA n° 1497),
Institut de Chimie Moléculaire d'Orsay, Bâtiment 420, Université de Paris-Sud, 91405 Orsay, France.

Abstract: The palladium-catalyzed substitution of carbonates of the titled alcohols was performed at lower temperature than the previously reported reaction of the corresponding acetates. The use of enantiomerically pure carbonates gave substitution products with overall retention of the configuration (up to 97%).

Introduction

We recently described the palladium-catalyzed nucleophilic substitution of naphthylmethyl and 1-naphthylethyl acetates by sodium dimethyl malonate (Eq. 1, R = COMe). [1]



(1)

1:	1-naphthyl	R' = H
2:	2-naphthyl	R' = H
3:	1-naphthyl	R' = Me
4:	2-naphthyl	R' = Me

5:	1-naphthyl	R' = H
6:	2-naphthyl	R' = H
7:	1-naphthyl	R' = Me
8:	2-naphthyl	R' = Me

a: R = H; **b**: R = COMe; **c**: R = CO_2Me

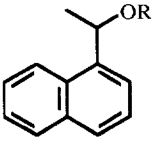
In the case of the secondary acetates (R' = Me), a temperature of 80°C was required for the reaction to reach completion and to record good yields in isolated products. [1]

We report now on the substitution at lower temperatures by the use of carbonates (Eq. 1, R = CO_2Me) instead of acetates. Investigations into the stereochemistry of the process were conducted aiming at performing stereoselective substitutions from optically active secondary alcohol derivatives and asymmetric syntheses from racemic substrates under optically active ligand control.

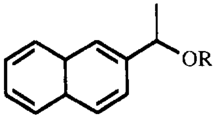
Results

1) Preparation of esters

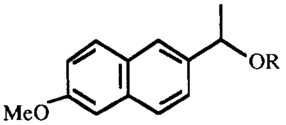
Acetates **1b-4b**, **9b-12b** were prepared by standard procedures [2] (Ac_2O, Et_3N, catalytic DMAP in ether). Carbonates **3c**, **4c**, **9c-12c** of aryl methyl carbinols were obtained efficiently through reaction of the lithium alcoholates with methyl chloroformate at low temperature (-78°C).



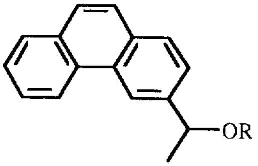
3



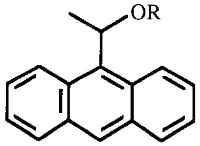
4



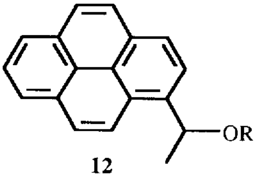
9



10



11



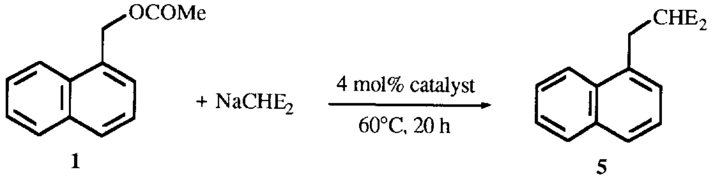
12

a: R = H; **b**: R = COMe; **c**: R = CO_2Me

2) Optimization of the reaction

The reaction of acetate **1b** with sodium dimethyl malonate was optimized with respect to the palladium complex, the ligand / palladium ratio, the phosphine ligand, and the solvent. Results are summarized in Table 1.

Table 1: Palladium-catalyzed substitution of acetate ***1b*** *by sodium dimethyl malonate*



Entry	Solvent	Pd complex	Added phosphine (eq. / Pd)	Yield (%) [a]
1	THF	$Pd(OAc)_2$	dppe [b] (1)	29
2	"	$Pd(dppe)_2$ [b]	none	25
3	"	$Pd(PPh_3)_4$	none	8
4	THF	$Pd(dba)_2$	none	23
5	"	"	dppe [b] (0.25)	59
6	"	"	" (0.5)	43
7	"	"	" (0.75)	75
8	"	"	" (1)	71
9	"	"	" (1.5)	76
10	"	"	" (2)	56
11	THF	$Pd(dba)_2$	dppm [c] (1.5)	4
12	"	"	dpppr [d] (1.5)	61
13	"	"	dppb [e] (1.5)	62
14	"	"	dpppe [f] (1.5)	32
15	"	"	dppf [g] (1.5)	48
16	"	"	PPh_3 (3)	6
17	Dioxane	$Pd(dba)_2$	dppe [b] (1.5)	55
18	DMPU [h]	"	"	58
19	CH_3CN	"	"	65
20	DMF	"	"	87

[a] GC yield using eicosane as internal standard. [b] dppe = 1,2-bis(diphenylphosphino)ethane. [c] dppm = bis(diphenylphosphino)methane. [d] dpppr = 1,3-bis(diphenylphosphino)propane. [e] dppb = 1,4-(bis(diphenylphosphino)butane. [f] dpppe = 1,5-bis(diphenylphosphino)pentane. [g] dppf = 1,1'-bis(diphenylphosphino)ferrocene. [h] DMPU = N,N'-dimethylpropyleneurea.

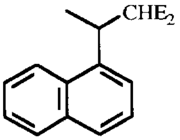
The best catalyst precursor was Pd(dba)$_2$ (dba = bis(dibenzylidene)acetone) (compare entries 1-3 to entries 7-9). Good yields of substitution product **5** were obtained with a diphosphine / palladium ratio ranging between 0.75 and 1.5. This last value was used in all subsequent reactions because of the better catalyst stability under these conditions: experiments from entries 4 to 8 led to decomposition to palladium black during the course of the reaction. With a higher ratio (entry 10), the yield decreased. It was however still higher than that shown in entry 2 with the same phosphine / palladium ratio, suggesting an influence of the ligand dba on the reactivity (see also entry 4).

The nature of the phosphine ligand was studied in entries 9 and 11 to 16. Of the ligands tested, dppe (1,2-bis(diphenylphosphino)-ethane) proved most effective. The formation of a five-membered palladacycle by coordination of the two phosphorus atoms of dppe is beneficial (entry 9). Other 1,n-bis(diphenylphosphino)-alkanes showed little (entry 11) or poorer (entries 12-14) reactivities. A modest activity was observed with dppf (1,1'-bis(diphenylphosphino)ferrocene) (entry 15). Monophosphines were almost completely inactive (entries 3 and 16).

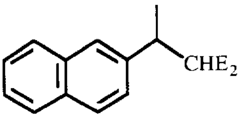
Finally, as the replacement of tetrahydrofuran by dimethylformamide as the solvent enhanced the yield from 76 to 87%, the conditions of entry 20 [4% (Pd(dba)$_2$ + dppe), DMF] were chosen for the following experiments.

3) Comparison of reactivities of acetates and carbonates

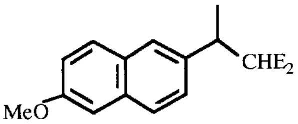
The palladium-catalyzed nucleophilic substitution of 1-naphthylethyl acetates by sodium dimethyl malonate took place readily at 80°C (Table 2, entries 1-4). In a competitive experiment, no notable difference in reactivity was observed between 1- and 2-naphthyl derivatives: reaction of an equimolecular mixture of **3b**, **4b** and sodium dimethyl malonate gave *ca* a 1:1 mixture of substitution products **7** and **8**, and *ca* a 1:1 mixture of **3b** and **4b** was recovered.



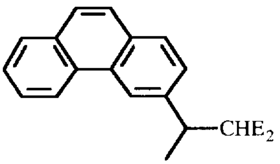
7



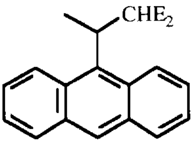
8



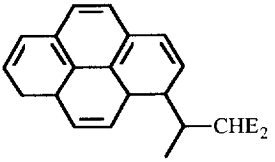
13



14



15

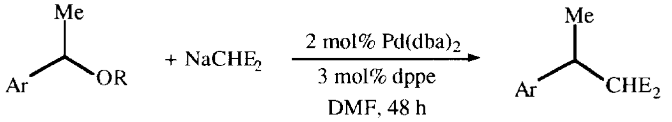


16

E = CO_2Me

We, [1] and others [3] postulated that the first step of the reaction was analogous to the first step of the palladium-catalyzed allylation of nucleophiles (Tsuji-Trost reaction), [4] i.e. the formation of a cationic η^3-allylic palladium intermediate complex (see discussion below). Allylic carbonates are known to be very reactive substrates (compared to acetates) in the palladium-catalyzed allylation reaction. [5] Indeed the same trend was observed in the substitution of 1-naphthylethyl derivatives **3c** and **4c**. Only partial conversion was recorded at room temperature (entries 9 and 10) whereas good yields of isolated products were obtained at 40°C (entries 7 and 8). Acetates were inert under the same reaction conditions, however. Palladium-catalyzed elimination [6] was shown to be a side reaction at higher temperatures in the case of the 1-(2-naphthyl)ethyl carbonate **4c** (entry 6).

Table 2: Palladium-catalyzed substitution of racemic acetates and carbonates



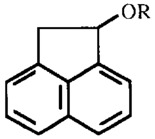
Entry	Substrate	Ar	R	t (°C)	Product	Isolated yield (%)
1	**3b**	1-naphthyl	COMe	60	**7**	37 [a]
2	**4b**	2-naphthyl	"	"	**8**	26 [a]
3	**3b**	1-naphthyl	"	80	**7**	79
4	**4b**	2-naphthyl	"	"	**8**	77
5	**3c**	1-naphthyl	CO_2Me	60	**7**	95
6	**4c**	2-naphthyl	"	"	**8**	69 [b]
7	**3c**	1-naphthyl	"	40	**7**	79
8	**4c**	2-naphthyl	"	"	**8**	85 [b]
9	**3c**	1-naphthyl	"	20	**7**	52 [a]
10	**4c**	2-naphthyl	"	"	**8**	33 [a]
11	**9c**	2-(6-MeO)naphthyl	CO_2Me	60	**13**	63 [c]
12	**9c**	“	"	40	**13**	47 [a,c]
13	**10c**	2-phenanthryl	CO_2Me	60	**14**	80
14	**11c**	9-anthracyl	“	100	**15**	< 30 [d]
15	**12c**	1-pyrenyl	CO_2Me	80	**16**	< 5 [e]

[a] Reaction does not reach completion. [b] Side product is 2-vinyl-naphthalene. [c] Side product is 2-methoxy-6-vinylnaphthalene. [d] Estimated yield (NMR), main product is 9-vinylanthracene.
[e] Estimated yield (NMR), main product is 1-vinylpyrene.

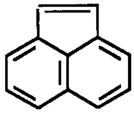
The electronic density on the aromatic ring seems to play an important role in this reaction: electron-rich acetate **9b** was totally recovered at 80°C, whereas carbonate **9c** gave only moderate (47-63%) yields of substitution product **13** contaminated by the elimination product.

Other substrates containing three (**10**, **11**) or four (**12**) fused-aromatic rings were prepared and subjected to the reaction conditions. Acetates **10b-12b** were totally unreactive at 80°C, whereas substitution onto naphthyl analogues **3b** and **4b** proceeded with high yield at the same temperature. 1-(3-Phenanthryl)ethyl carbonate **10c** gave product **14** at 60°C with comparable reactivity as **3c** and **4c** (entry 13). 1-(9-Anthracyl)ethyl and 1-(1-pyrenyl)ethyl carbonates **11c** and **12c** reacted only at high temperature (80-100°C) to give mainly the elimination products, 9-vinylanthracene (entry 14) and 1-vinylpyrene (entry 15) respectively.

Acetate **17b** and carbonate **17c** of 1-acenaphthenol **17a** were prepared and subjected to the above reaction conditions. These substrates gave only the elimination product, acenaphthylene **18** in good yield (95% from **17c** at 60°C).



17

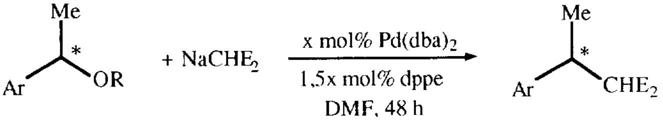


18

4) Stereochemistry of the reaction.

Results concerning the palladium-catalyzed substitution of enantiomerically pure esters (*S*)-**3** and (*R*)-**4** are summarized in Table 3. Influence of the leaving group RO^- was much more important for 1-(2-naphthyl)-ethyl derivatives than the corresponding 1-naphthyl regioisomer: in every case however, the use of carbonate as the leaving group allowed a better transfer of asymmetry than the acetate (compare entries 1 and 2, 3 and 4).

Table 3: Palladium-catalyzed substitution of enantiomerically pure acetates and carbonates



Entry	Substrate	Ar	R	t (°C)	x	Product	Isolated yield (%)	ee (%) [a]
1	(*S*)-**3b**	1-naphthyl	COMe	80	2	(*R*)-**7**	78	50
2	(*S*)-**3c**	1-naphthyl	CO_2Me	"	"	(*R*)-**7**	90	68
3	(*R*)-**4b**	2-naphthyl	COMe	"	"	(*S*)-**8**	78	31
4	(*R*)-**4c**	2-naphthyl	CO_2Me	"	"	(*S*)-**8**	67	74
5	(*S*)-**3c**	1-naphthyl	CO_2Me	60	0.5	[b]	-	-
6	(*S*)-**3c**	"	"	"	1	(*R*)-**7**	98	80
7	(*S*)-**3c**	"	"	"	2	(*R*)-**7**	92	72
8	(*S*)-**3c**	"	"	"	5	(*R*)-**7**	95	74
9	(*S*)-**3c**	"	"	"	20	(*R*)-**7**	98	73
10	(*R*)-**4c**	2-naphthyl	CO_2Me	60	0.5	(*S*)-**8**	80	97
11	(*R*)-**4c**	"	"	"	1	(*S*)-**8**	79	66
12	(*R*)-**4c**	"	"	"	2	(*S*)-**8**	92	72
13	(*R*)-**4c**	"	"	"	5	(*S*)-**8**	85	55
14	(*R*)-**4c**	"	"	"	20	(*S*)-**8**	80	62
15	(*R*)-**9c**	2-(6-MeO)naphthyl	CO_2Me	60	2	(*S*)-**13**	57 [c]	58

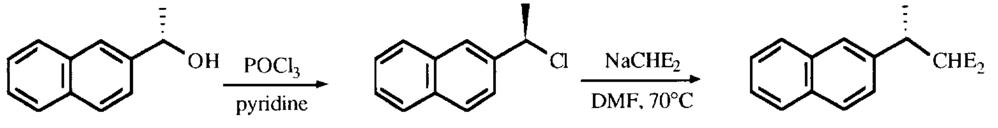
[a] Determined by HPLC (see experimental). [b] No reaction. [c] Side product is 2-methoxy-6-vinylnaphthalene.

Temperature is not of significant influence (entries 2 and 7, 4 and 12). The influence of the substrate to palladium ratio is dependent upon the regioisomer: carbonate (*S*)-**3c** gave a constant data for retention (*vide infra*) of stereochemistry of 73±1% on the use of 2 to 20mol% catalyst (entries 7-9). With 1mol%, it rose to 80%. A decrease of the catalyst amount to 0.5mol% did not allow the reaction to occur at a useful rate. A more complex feature was encountered for (*R*)-**4c**. The asymmetry transfer showed variations around a 64% value

(±8%) when the amount of catalyst varied in the range 1-20mol% (entries 11-14). With 0.5mol% palladium catalyst however, carbonate (*R*)-**4c** was substituted with retention of configuration (*vide infra*) with only a small loss of enantiomeric purity (97%ee, entry 10). No reaction took place on decreasing the amount of catalyst to 0.1mol%.

A 6-methoxy group on the naphthalene ring had a negative effect not only on the substrate reactivity (*vide supra*) but also on the stereochemistry. The substitution product **13** was obtained with 58%ee (entry 15, compared to 72%ee for product **8** under the same conditions, entry 12). Again some palladium-catalyzed elimination yielding 2-methoxy-6-vinylnaphthalene was observed.

In order to determine the stereochemistry of the substitution, optically active (+)-1-chloro-1-(2-naphthyl)ethane (*R*)-**19** was prepared [7] from alcohol (*S*)-**4a** and subjected to a classical S_N2 displacement with sodium dimethyl malonate to give (*R*)-**8** (66%ee) with double inversion (accounting for an overall retention of configuration from the alcohol, Eq. 2).



(2)

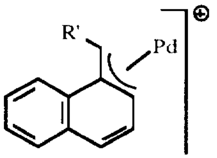
(*S*)- **4a** (*R*)- **19** (*R*)- **8**

Comparison by chiral HPLC analysis of this sample with the major enantiomer produced on reaction of (*R*)-**4c** with sodium dimethyl malonate allowed to assign the (*S*) configuration to compound **8** produced by this reaction. The palladium-catalyzed substitution of 1-(2-naphthyl)ethyl carbonate **4c** with sodium dimethyl malonate thus took place with overall retention of configuration, in analogy with the palladium-catalyzed substitution of allylic derivatives with stabilized carbanions [8] (Tsuji-Trost reaction).

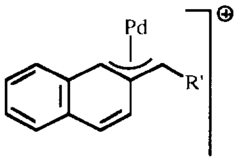
Discussion

We, [1] and others [3] postulated that the mechanism of this substitution was analogous to the mechanism of the palladium-catalyzed allylation of nucleophiles (oxidative addition to give a cationic η^3-allylpalladium complex, followed by nucleophilic attack). In our case, **20-22** would be intermediate complexes. These complexes have two allylic terminii, one belonging to the naphtalene ring and the other to the acyclic chain. The latter was regioselectively attacked by the nucleophile, the product resulting from the addition to the former never being observed.

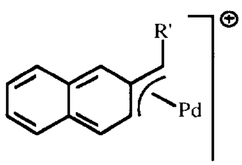
The inertness of benzyl alcohol derivatives in this reaction strongly supports the analogy with the Tsuji-Trost reaction: besides the naphthyl cationic complexes **20**, **21** and **22**, the benzyl analogue **23** is highly disfavored if we compare the loss of resonance energy from the corresponding substrates.



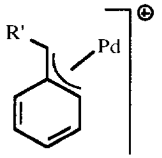
20



21



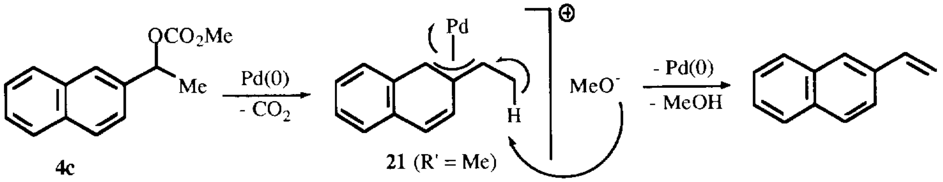
22



23

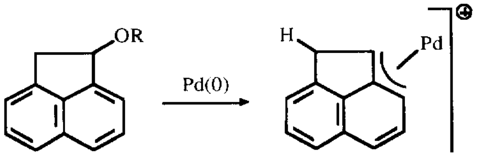
More electron-rich derivatives (by electron-releasing methoxy group or by added fused aromatic rings) are very poor substrates; acetates **9b-12b** were unreactive at 80°C and carbonates (except **10c**) gave very poor yields of substitution products. Derivatives **11** are more sterically congested than **3** and **4**, but steric hindrance may not be invoked for **9** and **12** (comparable to 1-(2-naphthyl)ethyl and 1-(1-naphthyl)ethyl derivatives **4** and **3** respectively). These results could be interpreted as a support for the oxidative addition being the rate-determining step: the presence of a methoxy group or of added electron-rich aromatic rings decrease the rate of coordination of the 1,2-double bond to an electron-rich palladium(0) complex.

Palladium-catalyzed elimination [6] leading to vinylarenes was observed in some reactions mainly when starting from carbonates. It results probably from an attack of the intermediate by the methylate anion formed in the oxidative addition step (Eq. 3). The acetate anion formed in the same way (on the use of an acetate as the substrate) is much less basic and hence cannot abstract a proton from the cationic intermediate.



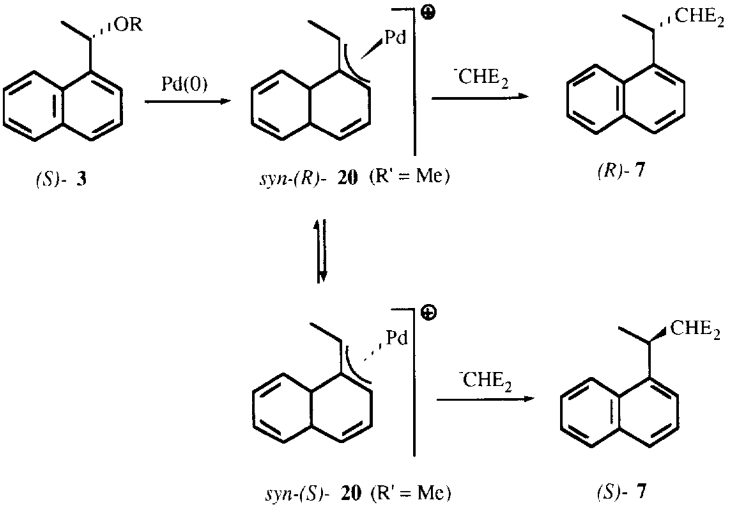
(3)

In the case of 1-acenaphthenyl derivatives **17**, the intermediate complex **24** have more acidic (benzylic) protons, one of these being abstracted even when starting from acetate **17b** to give exclusively the elimination product **18**.



17 **24**

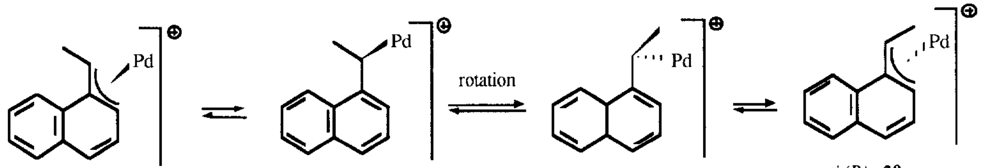
Since we have checked the configurational stability of reactants - acetate and carbonate - and malonate products, loss of enantiomeric purity during the substitution may be ascribed to an equilibration of the two enantiomeric intermediates *syn*-(*R*)-**20** and *syn*-(*S*)-**20** [9], from (*S*)-**3** (Eq. 4).



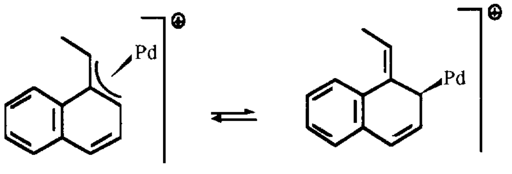
(4)

Two processes have been proposed for the isomerization of cationic η^3-allylpalladium complexes: a monomolecular η^3-η^1-η^3 process around one of the carbon termini of the allyl ligand [10] and a bimolecular S_N2

displacement by a palladium(0) complex.[11] The former process is in this case inoperant for the racemization of *syn*-**20**, neither by formation of the η^1-complex **25** which leads to *syn-anti* isomerization of **20** without change of its absolute configuration (Eq. 5), nor by formation of **26** (Eq. 6), assuming that the exo-methylidene group of the latter is not prone E-Z isomerization under the reaction conditions.

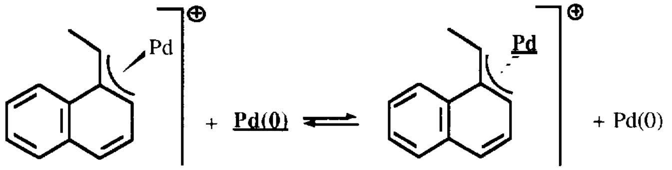


syn-(R)- **20** **25** *anti-(R)-* **20** (5)



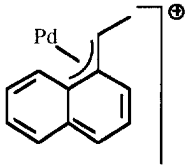
syn-(R)- **20** **26** (6)

Consequently, the only process able to equilibrate the two enantiomers of *syn*-**20** is the S_N2 process (Eq.7). As this process is bimolecular in palladium species (whereas the attack of the nucleophile is first order in Pd species), the rate of the enantiomerization process would be more affected by a change of palladium concentration than the rate of nucleophilic attack. Thus, the loss of stereochemistry should be palladium concentration dependent.[12] With a high substrate / palladium ratio, the racemization of *syn*-**20** is unlikely and the product is obtained with a good enantiomeric excess (80% for **7** and 97% for **8**). When the amount of palladium is increased, product **7** is obtained with a constant ee of 73±1%, whereas a linear decrease was expected: we have no simple explanation for this observation. More irregular results are obtained for the regioisomer **8**: ee = 64±8%. This tendency maybe results from the possibility of two regioisomeric intermediates **21** and **22** from 1-(2-naphthyl)ethyl carbonate **4c**. From 1-(1-naphthyl)ethyl carbonate **3c**, only one cationic palladium complex **20** may be invoked in this process, its regioisomer **27** being sterically hindered.



(7)

syn-(R)- **20** *syn-(S)-* **20**



27

A methoxy electron-releasing group decreased the oxidative addition (*vide supra*). As a result there would be a very large concentration of free palladium(0) that can participate in isomerization according to eq. 7: the product **13** is obtained with a lower enantiomeric excess than **8** (58% versus 72% in the same conditions).

Conclusion

We have set up experimental conditions for efficient palladium-catalysed substitution of esters (mainly carbonates) of naphthylmethanols and 1-naphthylethanols by sodium dimethyl malonate. The reaction proceeds with overall retention of configuration, suggesting a two step mechanism, in analogy with the Tsuji-Trost substitution of allylic substrates by nucleophiles.

Partial to complete retention of optical activity could be obtained from enantiopure substrates, depending upon the substrate to palladium ratio.

6-Methoxy-1-(2-naphthylethyl)carbonate **9c** showed both lower reaction rate and lower retention of stereochemistry than the unsubstituted analogue **4c**. This difference may be accounted for by considering that the oxidative addition is the rate-determining step. It can be understood as consequences of a less efficient coordination of an electron-rich aromatic ring to palladium(0), and of a large amount of Pd(0) available for enantiomerization of the cationic intermediate before attack by the nucleophile, respectively.

Work is in progress to extend the scope of the reaction (looking at the reactivity of other carbo and heteronucleophiles) and to find out the parameters which control the rate of enantiomerization process of the palladium intermediates. We hope then take advantadge of this knowledge to perform asymmetric syntheses of **7**, **8** and **13** from racemic substrates **3**, **4** and **9** using optically active ligands.

Experimental

General

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-250 MHz spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Infrared spectra were acquired using a Perkin-Elmer 883 spectrometer, and are reported in cm^{-1}. Optical rotations were measured at 20°C on a Perkin Elmer 241 polarimeter. Enantiomeric excesses were determined by HPLC analysis with chiral stationary-phase column, Chiracel OD-H (hexane: isopropanol 99:1).

All reactions involving palladium catalysis were carried out under argon using Schlenk techniques. Tetrahydrofuran (THF) was distilled under argon from sodium benzophenone ketyl immediatly before use. Dioxane, acetonitrile and dimethylformamide (DMF) were dried over CaH_2 and distilled prior to use. N,N'-Dimethylpropyleneurea (DMPU) was used as received.

The following materials were obtained from commercial sources: $Pd(dba)_2$ (where dba denotes dibenzylideneacetone) [13]; $Pd(OAc)_2$; $Pd(dppe)_2$ (where dppe denotes 1,2-bis(diphenylphosphino)ethane); $Pd(PPh_3)_4$; all the phosphines ligands tested. Alcohols **1a**, (±)-**3a**, (*S*)-**3a**, (±)-**4a**, (*R*)-**4a**, and **17a** are commercially available. (±)-**9a**, **10a**, and **11a** were obtained by hydride reduction of the corresponding aryl methyl ketone, [14] **12a** [15] by reaction of methylmagnesium bromide on commercially available 1-pyrene-carboxaldehyde. (*R*)-**9a** was prepared by RGL-catalyzed kinetic resolution [16] of the racemic material. [17]

Preparation of acetates

A typical procedure is as follows: [2] a mixture of 950 mg (6 mmol) of 1-naphthylmethanol **1a** and 75 mg (0.6 mmol) of 4-dimethylaminopyridine was stirred in 5 mL of triethylamine at 0°C, and 610 µl (6.5 mmol) of acetic anhydride was added dropwise. After the end of the addition, the reaction mixture was stirred at room temperature overnight, diluted with 20 ml of diethyl ether, washed successively with 1M aqueous HCl and saturated Na_2CO_3. The organic phase was dried ($MgSO_4$) and concentrated. The crude product was purified by Kügelrohr distillation to give 1.04 g (5.2 mmol, 87% yield) of acetate **1b**. [18]

The same procedure gave (±)-**3b** [19] (94% yield), (*S*)-**3b** [20] (98%), (±)-**4b** [21] (92%), (*R*)-**4b** [22] (99%), (±)-**9b** [23] (94%), **10b** [24] (96%), **11b** [25] (62%), **12b** [26] (43%), and **17b** [27] (95%).

Preparation of carbonates

The following procedure is representative [28]: a 25 mL solution of alcohol **3a** (1.72 g, 10 mmol) in THF was cooled to -78°C and 6.9 mL of a 1.6M commercial solution of n-butyllithium in hexane (11 mmol) was added dropwise. The reaction mixture was warmed to 0°C, then cooled to -78°C and methyl chloroformate (0.95 mL, 12 mmol) was added dropwise. After stirring overnight at room temperature, diethyl ether (20 mL) was added and the organic phase was washed with 2 x 20 mL of water. The aqueous phases were extracted with diethyl ether (2 x 20 mL) and the combined ethereal phases were dried ($MgSO_4$) and concentrated to give a quantitative yield of carbonate **3c**, suitable for analytical purpose.

3c: ^1H NMR 1.75 (3H, d, *J* = 6.5 Hz), 3.80 (3H, s), 6.50 (1H, q, *J* = 6.5 Hz), 7.40-7.65 (4H, m), 7.75-7.90 (2H, m), 8.10 (1H, dd, *J* = 8 and 1 Hz). ^{13}C NMR 22.0, 54.8, 73.7, 122.9, 123.1, 125.4, 125.7, 128.6, 128.9, 133.7, 162.4. IR 2987, 2959, 1746, 1441, 1269, 1239, 1061, 1040, 800, 939, 777. $C_{14}H_{14}O_3$ calculated: C 73.02, H 6.13; found C 72.83, H 6.13.

(*S*)-**3c**: $[\alpha]_D$ -42.6 (c = 2, EtOH).

4c: ^1H NMR 1.70 (3H, d, *J* = 6.5 Hz), 3.75 (3H, s), 5.90 (1H, q, *J* = 6.5 Hz), 7.40-7.55 (3H, m), 7.75-7.90 (4H, m). ^{13}C NMR 22.3, 54.6, 76.5, 123.4, 125.0, 126.1, 126.2, 127.6, 128.0, 128.4, 133.1, 138.3, 155.1. IR 3057, 2984, 1755, 1443, 1336, 1311, 1265, 1179, 1056, 939, 856, 817, 791, 749. $C_{14}H_{14}O_3$ calculated: C 73.02, H 6.13; found C 72.85, H 6.02.

(*R*)-**4c**: $[\alpha]_D$ +104.0 (c = 2, EtOH).

9c: ^1H NMR 1.70 (3H, d, *J* = 6.5 Hz), 3.75 (3H, s), 3.90 (3H, s), 5.85 (1H, q, *J* = 6.5 Hz), 7.10-7.20 (2H, m), 7.40-7.50 (1H, m), 7.70-7.80 (3H, m). ^{13}C NMR 22.3, 54.6, 55.3, 105.6, 119.1, 124.4, 125.1, 127.3, 128.5, 129.6, 134.4, 136.0, 155.2, 157.9. IR 1748, 1608, 1334, 1265, 1195, 1177, 1055,1029, 1014, 942, 879, 855, 790. $C_{15}H_{16}O_4$ calculated: C 69.21, H 6.20; found C 69.17, H 6.38.

(*R*)-**9c**: $[\alpha]_D$ +100.1 (c = 2, EtOH).

10c: ^1H NMR 1.75 (3H, d, *J* = 6.5 Hz), 3.75 (3H, s), 6.00 (1H, q, *J* = 6.5 Hz), 7.55-7.75 (5H, m), 7.85-7.95 (2H, m), 8.60-8.75 (2H, m). ^{13}C NMR 22.6, 54.7, 76.9, 120.2, 122.8, 124.4, 126.5, 126.6, 126.7, 127.2, 128.6, 129.0, 130.2, 131.8, 132.1, 139.2, 155.2. IR 2983, 2956, 2854, 1746, 1441, 1376, 1333, 1268, 1194, 1058, 999, 939, 887, 860, 841, 790, 747, 633. $C_{18}H_{16}O_3$ calculated: C 77.12, H 5.75; found C 77.21, H 5.61.

11c: ^1H NMR 2.00 (3H, d, *J* = 7 Hz), 3.70 (3H, s), 7.25 (1H, q, *J* = 7 Hz), 7.40-7.60 (4H, m), 8.00 (2H, dd, *J* = 7.5 and 2 Hz), 8.40 (1H, s), 8.50-8.65 (2H, m). ^{13}C NMR 21.5, 54.7, 73.0, 124.8, 126.1, 128.8, 129.0, 129.3, 131.2, 131.6, 155.4. IR 3053, 2952, 1753, 1441, 1264, 1186, 1157, 1104, 1074, 1033, 973, 935, 894, 881, 785, 733, 445. $C_{18}H_{16}O_3$ calculated: C 77.12, H 5.75; found C 76.87, H 5.81.

12c: ^1H NMR 1.85 (3H, d, *J* = 8 Hz), 3.80 (3H, s), 6.80 (1H, q, *J* = 8 Hz), 7.90-8.10 (3H, m), 8.10-8.30 (5H, m), 8.40 (1H, d, *J* = 12 Hz). ^{13}C NMR 22.6, 54.7, 73.8, 122.1, 123.2, 124.7, 124.8, 125.0, 125.1, 125.3, 125.9, 127.3, 127.4, 127.5, 128.0, 130.5, 131.0, 131.2, 134.5, 155.3. IR 2965, 1737, 1587, 1449, 1335, 1320, 1262, 1045, 1014, 940, 873, 842, 793, 769, 715. $C_{20}H_{16}O_3$ calculated: C 78.93, H 5.30; found C 78.70, H 5.49.

17c: ^1H NMR 3.40 (1H, dd, *J* = 18 and 2 Hz), 3.85 (3H, s + 1H, dd, *J* = 18 and 7 Hz), 6.55 (1H, dd, *J* = 7 and 2 Hz), 7.30 (1H, d, *J* = 7Hz), 7.45-7.70 (4H, m), 7.80 (1H, d, *J* = 8 Hz). ^{13}C NMR 38.6, 54.8, 79.3, 119.8, 122.0, 122.9, 125.7, 128.0, 128.1, 131.2, 137.9, 140.6, 141.0, 155.8. IR 1750, 1266, 1174, 1014, 986, 948, 792, 775. $C_{14}H_{12}O_3$ calculated: C 73.67, H 5.30; found C 73.88, H 5.39.

Palladium-catalyzed substitutions

As a representative experimental procedure (table 2, entry 5), carbonate **3c** (230 mg, 1 mmol) in 1 mL of DMF was added under argon to a mixture of $Pd(dba)_2$ (11.5 mg, 0.02 mmol) and dppe (12 mg, 0.03 mmol) in 1 mL of DMF. After 0.25 h stirring, this solution was added to a suspension of sodium dimethylmalonate [29] (308 mg, 2 mmol) in 1 mL of DMF. The reaction mixture was stirred at 60°C for 48 h, then diluted with ether (15 mL) and the organic phase washed with 2 x 10 mL of water. The aqueous phases were extracted with ether (2 x 10 mL) and the combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica, cyclohexane / ethyl acetate: 8/2) to give **7** (270 mg, 95%).

5: ${}^{1}H$ NMR 3.70 (6H, s), 3.70-3.90 (3H, m) [30], 7.30-7.40 (2H, m), 7.45-7.60 (2H, m), 7.70-7.80 (1H, m), 7.85-7.95 (1H, m), 8.00-8.10 (1H, m). ${}^{13}C$ NMR 31.7, 52.3, 66.8, 122.9, 125.2, 125.5, 126.1, 126.9, 127.6, 128.8, 131.3, 133.4, 133.7, 169.2. IR 2955, 1755, 1735, 1434, 1343, 1288, 1225, 1146, 799, 777. $C_{16}H_{16}O_4$ calculated: C 70.57, H 5.92; found C 70.86, H 5.81.

7: ${}^{1}H$ NMR 1.40 (3H, d, $J = 7$ Hz), 3.40 (3H, s), 3.80 (3H, s), 3.95 (1H, d, $J = 9$ Hz), 4.50 (1H, dq, $J = 9$ and 7 Hz), 7.3-7.40 (4H, m), 7.70 (1H, d, $J = 8$ Hz), 7.85 (1H, dd, $J = 8$ and 1 Hz), 8.20 (1H, d, $J = 8.5$ Hz). ${}^{13}C$ NMR 19.9, 34.0, 52.3, 52.5, 58.2, 123.0, 123.2, 125.3, 125.6, 126.1, 127.3, 128.9, 131.1, 134.0, 139.4, 168.4, 168.9. IR 3047, 2955, 1739, 1598, 1511, 1433, 1396, 1380, 1151, 1071, 1029, 911, 860, 797, 779, 733. $C_{17}H_{18}O_4$ calculated: C 71.31, H 6.34; found C 71.08, H 6.47.

(*R*)-**7**: $[\alpha]_D$ +28.5 (c = 1, MeOH) for a sample with 71.7% ee: $[\alpha]_D$ +39.8 (c = 1, MeOH) for enantiomerically pure (*R*)-**7**.

8: ${}^{1}H$ NMR 1.40 (3H, d, $J = 6.5$ Hz), 3.45 (3H, s), 3.65-3.90 (2H, m), 3.80 (3H, s), 7.30-7.50 (3H, m), 7.65 (1H, s), 7.75-7.85 (3H, m). ${}^{13}C$ NMR 20.1, 40.2, 52.2, 52.6, 59.0, 125.5, 125.6, 126.0, 127.6, 127.7, 128.2, 132.5, 133.8, 140.5, 168.3, 168.8. IR 2957, 1737, 1601, 1507, 1434, 1273, 1273, 1194, 1070, 1019, 895, 858, 818, 748. $C_{17}H_{18}O_4$ calculated: C 71.31, H 6.34; found C 71.03, H 6.36.

(*S*)-**8**: $[\alpha]_D$ +29.7 (c = 1, MeOH) for a sample with 66.0% ee: $[\alpha]_D$ +45.0 (c = 1, MeOH) for enantiomerically pure (*S*)-**8**.

13: ${}^{1}H$ NMR 1.40 (3H, d, $J = 6.5$ Hz), 3.40 (3H, s), 3.60-3.85 (2H, m), 3.80 (3H, s), 3.90 (3H, s), 7.05-7.20 (2H, m), 7.30 (1H, dd, $J = 8$ and 2 Hz), 7.60 (1H, s), 7.65-7.75 (2H, m). ${}^{13}C$ NMR 20.0, 40.0, 52.2, 52.5, 55.2, 59.1, 105.5, 118.8, 125.5, 126.0, 127.0, 128.8, 129.2, 133.5, 138.1, 157.5, 168.3, 168.8. IR 2954, 1760, 1736, 1633, 1607, 1434, 1266, 1030, 852, 476. $C_{18}H_{20}O_5$ calculated: C 68.34, H 6.37; found C 68.51, H 6.52.

(*S*)-**13**: $[\alpha]_D$ +22.5 (c = 2, EtOH) for a sample with 58.2% ee: $[\alpha]_D$ +38.7 (c = 2, EtOH) for enantiomerically pure (*S*)-**13**.

14: ${}^{1}H$ NMR 1.45 (3H, d, $J = 7$ Hz), 3.40 (3H, s), 3.75-3.90 (2H, m), 3.80 (3H, s), 7.40-7.75 (5H, m), 7.75-7.90 (2H, m), 8.50 (1H, s), 8.70 (1H, d, $J = 8$ Hz). ${}^{13}C$ NMR 20.2, 40.5, 52.5, 59.1, 121.3, 122.5, 125.7, 126.4, 126.5, 126.6, 128.5, 128.7, 130.0, 130.2, 131.0, 132.0, 141.2, 168.2, 168.7. IR 2955, 1733, 1603, 1433, 1265, 1201, 1147, 1071, 1022, 841, 802, 749, 636. $C_{21}H_{20}O_4$ calculated: C 74.98, H 5.99; found C 75.23, H 6.16.

S_N2 substitution of (R)-1-chloro-1-(2-naphthyl)ethane ***19***

(*R*)-**19** (140 mg, 0.74 mmol, prepared according to a reported procedure 7)) and sodium dimethyl malonate [28] (170 mg, 1.1 mmol) in 3 mL of DMF are heated at 100°C during 5 h. The same work-up as for palladium-catalyzed substitution gave (*R*)-**8** (180 mg, 85%) with 66% ee.

References and notes

1- Legros, J.Y.; Fiaud, J.C. *Tetrahedron Lett.* **1992**, *33*, 2509-2510.

2- Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569-583.

3- Baird, J.M.; Kern, J.R.; Lee, G.R.; Morgan, D.J.; Sparacino, M.L. *J. Org. Chem.* **1991**, *56*, 1928-1933.

4- Trost, B.M. *Pure & Appl. Chem.* **1981**, *53*, 2357-2370. Tsuji, J. in "The Chemistry of the Metal-Carbon Bond", Hartley, F.R.; Patai, S. Eds., J.Wiley & Sons, New York, **1985**, *3*, 163-199. Godleski, S.A. in "Comprehensive Organic Synthesis", Trost, B.M.; Fleming,I.; Semmelhack, M.F. Eds., Pergamon Press: Oxford, **1991**, *4*, 585-661.

5- Tsuji, J *Tetrahedron* **1986**, *42*, 4361-4401.

6- Such elimination reactions have been shown to occur on π-allylpalladium complexes generated from allylic esters: Hauser, F.M.; Tommasi, R.; Hewawasan, P.; Rho, Y.S. *J. Org. Chem.* **1988**, *53*, 3845-3849. Hayashi, T.; Kishi, K.; Uozumi, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 195-198, and references herein.

7- Givens, R.S.; Hrinczenko, B.; Liu, J.H.S.; Matuszewski, B.; Tholen-Collison, J. *J. Am. Chem. Soc.* **1984**, *106*, 1779-1789 and reference cited.

8- Fiaud, J.C.; Legros, J.Y. *J. Org. Chem.* **1987**, *52*, 1907-1911.

9- The configuration of intermediate **20** refers to the acyclic asymmetric carbon center (the only one recovered in the substrate and in the substitution product).

10- Faller, J.W.; Thomson, M.E.; Mattina, M.J. *J. Am. Chem. Soc.* **1971**, *93*, 2642-2653.

11- Granberg, K.L.; Bäckvall, J.E. *J. Am. Chem. Soc.* **1992**, *114*, 6858-6863 and references herein.

12- The effect of the concentration of Pd(0) on the loss of stereochemistry in palladium-catalyzed allylic alkylation has been observed previously: Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5921-5924, and reference 11.

13- $Pd(dba)_2$ was also prepared according to a reported procedure: Rettig, M.F.; Maitlis, P.M. *Inorg. Synth.* **1977**, *17*, 134-137.

14- 2-Acetyl-6-methoxynaphthalene was prepared according to: Arsenijevic, L.; Arsenijevic, V.; Horeau, A.; Jacques, J. *Org. Synth.* **1973**, *53*, 5-8. 3-Acetylphenanthrene and 9-acetylanthracene are commercially available products.

15- Hansen, P.E.; Berg, A. *Acta Chem. Scand., Ser. B* **1981**, *B35*, 131-137.

16- RGL = Rabbit Gastric Lipase. Kagan, H.B.; Tahar, M.; Fiaud, J.C. *Bioorg. Med. Chem.* **1994**, *2*, 15-21.

17- Legros, J.Y.; Toffano, M.; Fiaud, J.C., unpublished results.

18- Fischli, A. *Helv. Chim. Acta* **1979**, *62*, 882-893.

19- Pirkle, W.H.; Hauske J.R. *J. Org. Chem.* **1976**, *41*, 801-805.

20- Burk, M.J. *J. Am. Chem. Soc.* **1991**, *113*, 8518-8519. $[\alpha]_D$ -48.4 (c = 2, EtOH).

21- Taylor, R.; Smith, G.G.; Wetzel, W.H. *J. Am. Chem. Soc.* **1962**, *84*, 4817-4824.
^{1}H NMR 1.60 (3H, d, J = 7 Hz), 2.10 (3H, s), 6.05 (1H, q, J = 7 Hz), 7.45-7.55 (3H, m), 7.75-7.90 (4H, m). IR 3058, 2983, 2934, 1740, 1370, 1238, 1177, 1128, 1064, 1019, 941, 858, 817, 748.

22- see reference 3. $[\alpha]_D$ +120.0 (c = 2, EtOH).

23- Bosca, F.; Miranda, M.A.; Vano, L.; Vargas, F. *J. Photochem. Photobiol., A: Chem.* **1990**, *54*, 131-134.
^{1}H NMR 1.60 (3H, d, J = 6.5 Hz), 2.10 (3H, s), 3.90 (3H, s), 6.05 (1H, q, J = 6.5 Hz), 7,10-7.20 (2H, m), 7.45 (1H, d, J = 10 Hz), 7.65-7.80 (3H, m). IR 2986, 1741, 1609, 1374, 1260, 1241, 1221, 1196, 1061, 1025.

24- Price, C.C.; Halpern, B.D*J. Am. Chem. Soc.* **1951**, *73*, 818-820.
^{1}H NMR 1.65 (3H, d, J = 6.5 Hz), 2.10 (3H, s), 6.15 (1H, q, J = 6.5 Hz), 7.50-7.75 (5H, m), 7.80-7.95 (2H, m), 8.60-8.75 (2H, m). IR 2981, 1738, 1370, 1239, 1066, 1020, 940, 840, 747.

25- Simionescu, C.I.; Grigoras, M.; Barboiu, V *J. Polym. Sci., Polym. Chem. Ed.* **1985**, *23*, 2089-2098.

26- No correct elemental analysis could be obtained because of a slow degradation of the product.
^{1}H NMR 1.70 (3H, d, J = 7 Hz), 2.15 (3H, s), 6.95 (1H, q, J = 7 Hz), 7.90-8.30 (8H, m), 8.30-8.45. (1H, m). IR 1737, 1604, 1438, 1369, 1241, 1072, 1043, 1020, 844, 758, 736.

27- Fay, C.K.; Grutzner, J.B.; Johnson, L.F.; Sternhell, S.; Westerman, P.W. *J. Org. Chem.* **1973**, *38*, 3122-3136

28- Trost, B.M.; Li, L.; Guile, S.D*J. Am. Chem. Soc.* **1992**, *114*, 8745-8747.

29- Prepared from dimethyl malonate and sodium hydride on a 100 mmol-scale and stored under argon before use; see Fiaud, J.C.; Legros, J.Y. *J. Org. Chem.*, **1990**, *55*, 1840-1846.

30- These complex signals could be resolved by adding 5 mg of $Eu(fod)_3$ (where fod denotes 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) to 10 mg of a NMR sample of **5** to give: 4.15 (2H, d, J = 7.5 Hz), 4.45 (1H, t, J = 7.5 Hz).

(*Received in Belgium* 3 *October* 1994; *accepted* 11 *January* 1995)