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Asymmetric Palladium-Catalyzed Nucleophilic Substitution of Racemic 1-Naphthylethyl Esters

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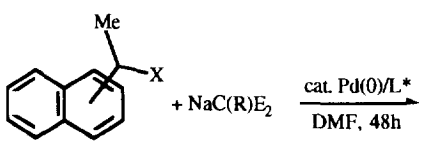
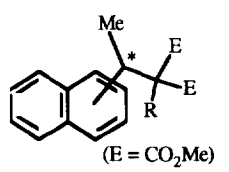
Abstract: The asymmetric palladium-catalyzed reaction of racemic 1-naphthylethyl acetates by nucleophiles gave substitution products with up to 61.5% enantioselectivity. The influences of the chiral ligand, temperature, nature of the leaving group of the substrate and of the nucleophile were studied.

We recently described the palladium-catalyzed nucleophilic substitution of naphthylmethyl and 1-naphthylethyl esters by sodium dimethyl malonate. [1] Starting from enantiomerically pure carbonates **1a** and **2a**, this reaction gave substitution products with up to 97% ee. [1b] We demonstrated also that the reaction proceeded with overall retention of configuration. [1b]

We report now on asymmetric synthesis of substitution products from racemic substrates **1** and **2** with different leaving groups under optically active ligand control.





(E = CO_2Me)

1: 1-naphthyl
2: 2-naphthyl

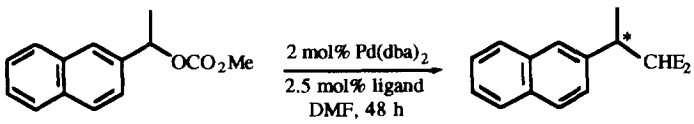
a: X = OCO_2Me
b: X = OCOMe
c: X = Cl
d: X = $OP(O)(OEt)_2$
e: X = OCOPh
f: X = $OCOC_6H_4$-4-NO_2
g: X = $OCOC_6H_4$-4OMe
h: X = OCOtBu

3: 1-naphthyl R = H
4 2-naphthyl R = H
5: 1-naphthyl R = Me
6: 2-naphthyl R = Me

We first examined the influences of the nature of the chiral diphosphine ligand and the reaction temperature on the enantioselectivity of the substitution reaction of carbonate **2a** with sodium dimethylmalonate. Results are summarized in Table 1. [2]

Product **4** was obtained in almost racemic form from the Pd/(*R*)-BINAP [3], Pd/(*R*)-PROPHOS [4] and Pd/(*S*,*S*)-DIOP [5]-catalyzed reactions (entries 1, 10 and 11). (*S*,*S*)-CHIRAPHOS [6] and (*S*,*S*)-BDPP [7] gave low (8 and 7.5% respectively) enantioselectivity (entries 4 and 7). Lowering the reaction temperature resulted in an increase of enantioselectivity up to 13% (at 20°C) in the case of BINAP ligand but was detrimental to the chemical yield (10%, entry 3). A very slight temperature effect was observed with CHIRAPHOS and BDPP ligands (entries 4 to 9) without loss of catalytic activity in the former case only. These results indicate that BDPP and CHIRAPHOS are the best optically active phosphine ligands, although carbonate **2a** is not a good substrate for asymmetric synthesis.

Table 1

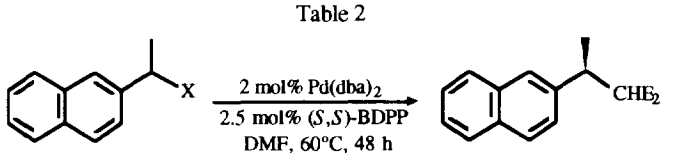


(±)- **2a** **4**

Entry	Ligand	T (°C)	Isolated yield (%)	ee (%)	Conf.
1	(*R*)-BINAP	60	98	0	-
2		40	63	8.5	*R*
3		20	10	13	*R*
4	(*S*,*S*)-CHIRAPHOS	60	91	10	*S*
5		40	98	8	*S*
6		20	90	9.5	*S*
7	(*S*,*S*)-BDPP	60	98	7.5	*S*
8		40	63	9	*S*
9		20	21	9.5	*S*
10	(*R*)-PROPHOS	60	87	2	*R*
11	(*S*,*S*)-DIOP	60	70	2.5	*R*

We studied the influence of the nature of the leaving group X^- of the substrate **2** on the enantioselectivity of the Pd/(*S*,*S*)-BDPP-catalyzed reaction (Table 2). Acetate **2b** gave a substantially higher ee that carbonate **2a** (30 versus 7.5% entries 1 and 2), but substitution product **4** was obtained with a lower isolated chemical yield. It should be mentioned however that conversion of the substrate was better with BDPP than with DPPE [8]. CHIRAPHOS was less effective than BDPP in the substitution reaction of **2b** (entry 3) and hence only the latter ligand was used in the following.

Table 2



(±)- **2a-h** (*S*)-**4**

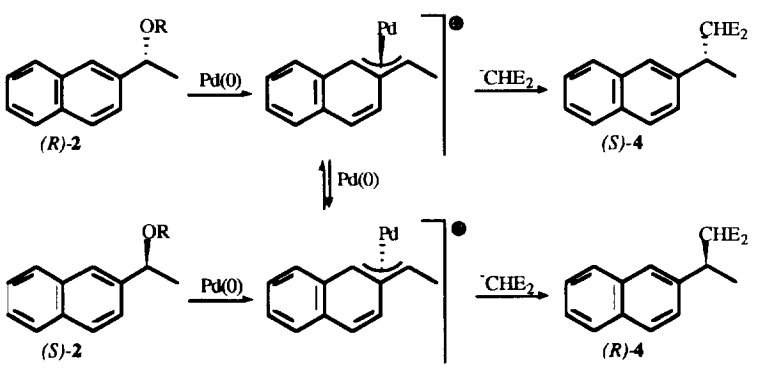
Entry	Substrate	X	Isolated yield (%)	ee (%)
1	**2a**	OCO_2Me	98	7.5
2	**2b**	OCOMe	63	30
3	"	"	76	12.5 [a]
4 [b]	**2c**	Cl	46	0
5	**2d**	$OP(O)(OEt)_2$	70	3.5
6	**2e**	OCOPh	87	6
7	**2f**	$OCOC_6H_4$-4NO_2	100	13.5
8	**2g**	$OCOC_6H_4$-4OMe	100	22
9	**2h**	OCOtBu	10	34

[a] Ligand is (*S*,*S*)-CHIRAPHOS. [b] at 25°C.

Chloride **2c** gave a moderate yield of racemic **4** at 20°C (entry 4): control experiments showed that non-catalyzed nucleophilic substitution on this substrate was very slow at this temperature and competitive at 60°C.

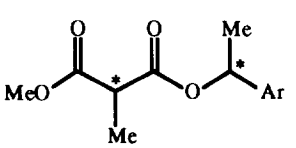
Other alcohol derivatives were tested: diethylphosphate **2d** and benzoate **2e** gave both low ee values for **4** (3.5 and 6% respectively, entries 5 and 6), while para-substitution on the aromatic nucleus of the latter by either an electron-withdrawing (NO_2 in **2f**) or -donating (OMe in **2g**) group enhanced the enantioselectivity (13.5 and 22% respectively, entries 7 and 8). Finally, pivalate **2h** gave the best result (34% ee, entry 9) with a low yield however. These results showed an interesting leaving group effect on the enantioselectivity. [9] The regioisomer **1h** gave **3** with 29% ee in the same conditions.

We postulated [1b] for this reaction an analogous mechanism to the one described for the palladium-catalyzed allylation of nucleophiles (Tsuji-Trost reaction). [10] According to this hypothesis, the enantioselectivity should be controlled by the relative kinetics of the equilibration process of the cationic intermediates and the nucleophilic attack by the malonate anion (Scheme). [11] Starting from an enantiomerically pure substrate with an achiral catalyst, [1b] the equilibration is responsible for the racemization of the two enantiomeric intermediates and should be avoided in order to obtain an enantiomerically active product. In contrast, starting from a racemic substrate, the interconversion of the two diastereomeric cationic complexes must occur rapidly to allow the reaction to be enantioselective. Since we found [1b] no clear tendency to influence the rate of equilibration, we chose to slow down the rate of nucleophilic attack. Sodium dimethyl methylmalonate, a bulkier nucleophile was employed and results concerning this study are collected in Table 3.



Scheme

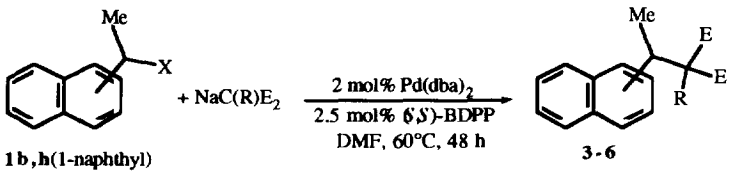
Acetates **1b** and **2b** reacted with $NaCHE_2$ to give products **3** with 27.5% (entry 1) and **4** with 30% ee (entry 4) respectively. Enantioselectivity raised up (61.5% from **1b**, entry 2, and 40.5% from **2b**, entry 5) on use of $NaC(Me)E_2$ as nucleophile, but products **5** and **6** were obtained with low yield and contaminated by **7a** and **7b** (each as a *ca* 1:1 diastereomer mixture) respectively. Products **7** resulted from nucleophilic attack of the methyl-substituted malonate on the carbonyle of **1b** and **2b**, followed by transesterification. This side-reaction resulted from a slower attack of the hindered nucleophile on the Pd^{II} intermediate and suggested the dimethyl methylmalonate anion being a less reactive nucleophile than dimethylmalonate anion in this substitution. [12]



7a: Ar = 1-naphthyl
7b: Ar = 2-naphthyl

In reactions starting from pivalates **1h** and **2h** (entries 3 and 6), the tBu group protected the carbonyl and suppressed this side reaction. However, the ee was reduced to 30% for **5** and 18% for **6**, confirming the great influence of the nature of the leaving group on the enantioselectivity of this reaction.

Table 3



1b,h(1-naphthyl)
2b,h(2-naphthyl)

3-6

Entry	Substrate	X	R	Product	Yield [a](%)	ee(%)
1	**1b**	OCOMe	H	**3**	82	27.5
2	"	"	Me	**5**	37 [b]	61.5
3	**1h**	OCOtBu	Me	**5**	23	30
4	**2b**	OCOMe	H	**4**	63	30
5	"	"	Me	**6**	46 [c]	40.5
6	**2h**	OCOtBu	Me	**6**	58	18

[a] Isolated yield. [b] Yield of intractable mixture of **5** and **7a** (*ca* 1:1). [c] Yield of inseparable mixture of **6** and **7b** (*ca* 1:1).

In order to improve enantioselectivity of the reaction, further investigations are underway to get more insight into the structure and behaviour (configurational stability, reactivity) of the palladium intermediates.

References and notes

1- a) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1992**, *33*, 2509-2510. b) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. *Tetrahedron* **1995**, *51*, 3235-3246.

2- Enantiomeric excesses were determined by HPLC analysis on a CHIRALCEL OD-H column.

3- (*R*)-BINAP = (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl. All the optically active diphosphine ligands used were purchased from Strem Chemicals.

4- (*R*)-PROPHOS = (*R*)-(+)-1,2-bis(diphenylphosphino)propane.

5- (*S,S*)-DIOP = (*S,S*)-(+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane.

6- (*S,S*)-CHIRAPHOS = (2*S*,3*S*)-(-)-2,3-bis(diphenylphosphino)pentane.

7- (*S,S*)-BDPP = (2*S*,3*S*)-(-)-2,4-bis(diphenylphosphino)pentane.

8- DPPE = 1,2-bis(diphenylphosphino)ethane. See reference 1a.

9- There are some precedents in the Tsuji-Trost reaction: a) Fiaud, J.-C.; Legros, J.-Y. *J. Org. Chem.* **1990**, *55*, 4840-4846. b) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron* **1994**, *50*, 465-474. c) Hiroi, K.; Abe, J. *Tetrahedron Lett.* **1990**, *31*, 3623-3626. d) Hiroi, K.; Abe, J. *Chem. Pharm. Bull.* **1991**, *39*, 616-621. e) Hiroi, K.; Haraguchi, M.; Masuda, Y.; Abe, J. *Chem. Lett.* **1992**, 2409-2412.

10- 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.

11- Partial kinetic resolution of the substrate when the reaction was not conducted to completion might also contribute to the obtention of optically active product. This is not the case here, because we have checked in some cases that the remaining ester substrate was racemic.

12- The inverse order of reactivity was reported in the Tsuji-Trost reaction: Sjögren, M.P.T.; Hansson, S.; Åkermark, B.; Vitagliano, A. *Organometallics* **1994**, *13*, 1963-1971. The enantioselectivities of the palladium-catalyzed allylic substitutions of 1,3-diphenyl-2-propenyl acetate by these two nucleophiles were compared and no substantial difference was reported: Trost, B.M.; Murphy, D.J. *Organometallics* **1985**, *4*, 1143-1145. Yamaguchi, M.; Shima, T.; Yamagishi T.; Hida, M. *Tetrahedron: Asymmetry* **1991**, *2*, 663-666.

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