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Asymmetric palladium-catalyzed benzylic nucleophilic substitution: high enantioselectivity with the DUPHOS family ligands

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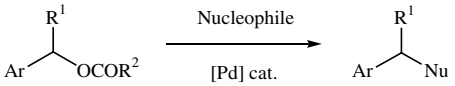
Abstract—The asymmetric palladium-catalyzed benzylic reaction of 1-(2-naphthyl)ethyl acetate and its 6-methoxy substituted analogue with dimethyl malonate anion led to substitution products with up to 90% ee when the *i*Pr-DUPHOS chiral ligand was used.

1. Introduction

Palladium-catalyzed nucleophilic substitution on benzylic esters has been developed in our laboratory over the past decade (Eq. 1).[1–9] A condensed aromatic system (Ar = naphthyl, phenanthryl, quinolyl, isoquinolyl, benzofuryl, benzothienyl) is needed to obtain a satisfactory yield of substitution product with a catalytic system including $Pd(dba)_2$ [dba = bis(dibenzylidene)acetone] and a diphosphine ligand. Recently, the reactivity of benzyl methyl carbonate (Ar = Ph, R^1 = H, R^2 = OMe) was disclosed using a quite different catalyst [Pd-(η^3-C_3H_5)(COD)·BF_4 in combination with dppf as the diphosphine ligand].[10] However, no reaction on racemic chiral esters (R^1 = Me) has been reported.



R^1 = H, Me; R^2 = Me,OMe

Nucleophile = $MCH(CO_2Me)_2$, HCO_2M (Nu = H), amine (1)

The asymmetric version of this reaction was realized on racemic substrates (Ar = 1- or 2-naphthyl, R^1 = Me) with the dimethylmalonate anion as nucleophile.[3,8] Poor enantioselectivities (<35%) were recorded with bidentate chiral BINAP, PROPHOS, DIOP, CHIRAPHOS or BDPP[11] ligands.[3] Me-DUPHOS[11] gave a much better result (up to 74% ee) but to the detriment of the chemoselectivity of the reaction and hence the chemical yield of the substitution product. The major pathway in this case was a base-promoted elimination leading to vinylnaphthalene.[8]

Herein we report that the substituents of the DUPHOS phospholane rings have a notable influence on the enantioselectivity of the reaction. An enantiomeric excess of 90% was reached with *i*Pr-DUPHOS using slightly modified reaction conditions.

2. Results and discussion

The following chiral diphosphine ligands were tested in the optimized experimental conditions precedently determined (Fig. 1).[8] The (*R*,*R*)-Et ferroTANE® was chosen because of its similarity in terms of bite angle with the dppf ligands used by Kuwano et al.[10] Since the Trost ligands have proven to be very efficient in a great number and variety of asymmetric allylic alkylation (AAA) reactions,[12] we decided to study their efficiency in our asymmetric benzylic alkylation reaction. The substitution was conducted on two substrates: 1-(2-naphthyl)ethyl acetate **1a** and its 6-methoxy analogue **1b** (Eq. 2). The results are shown in Table 1.

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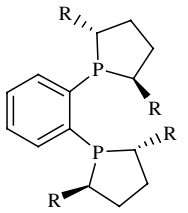
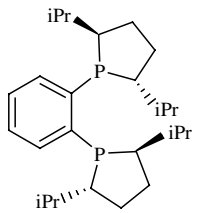
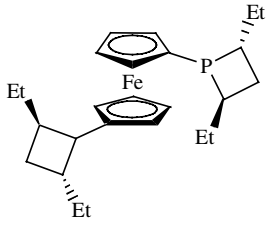


R = Me: (*R,R*)-Me-DUPHOS

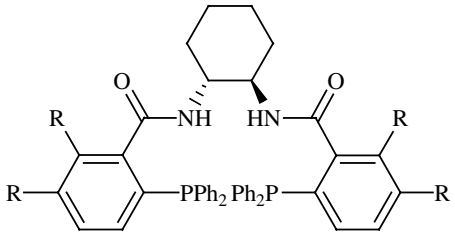


(*R,R*)-iPr-DUPHOS

R = Et: (*R,R*)-Et-DUPHOS



(*R,R*)-Et-FerroTANE®



R = H: (*R,R*)-Trost phenyl ligand

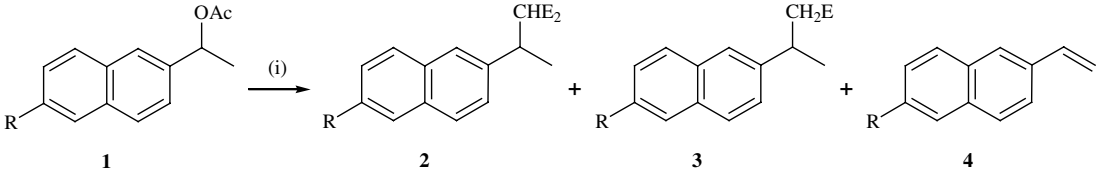
R = $(CH)_4$: (*R,R*)-Trost naphthyl ligand

Figure 1. Chiral ligands.

Trost (phenyl or naphthyl) ligands lead to palladium complexes, which are totally unreactive in the benzylic substitution. Substrates **1a** and **1b** were recovered from the reaction mixture after 48 h stirring at 70 °C. The inertness of these diphosphines may result from a strong steric hindrance between the chiral palladium(0) complex and the aromatic substrate, preventing the oxidative addition step, the first step of the catalytic transformation.

With all reactive phosphines, with the exception of (*R,R*)-Me-DUPHOS, a mixture of three reaction products was obtained: the expected substituted chiral malonate **2**, the vinylnaphthalene **4** and a third compound **3** resulting from demethoxycarbonylation of **2** (Krapcho reaction).[13] We checked that **3a** was obtained from **2a** in the presence of KOAc (produced during the catalytic process) in DMSO at 70 °C. This transformation has precedent under these conditions although at higher (115–140 °C) temperatures.[14] Demethoxycarbonylation was previously observed by us in palladium-catalyzed benzylic substitutions on benzofuran- and benzothiophene-based substrates[9] and also by others during the course of Pd-catalyzed reactions.[15] Unfortunately, we did not succeed in the analytical resolution of **3** and hence unable to check that malonate **2** and decarboxylation product **3** had the same enantiomeric composition (it should be the case if the former was the precursor of the latter). Due to the formation of side product **3**, the selectivity of the reaction (substitution vs elimination) was determined as the **(2 + 3)/4** ratio.

(*R,R*)-Et-ferroTANE® gave a good selectivity in favour of the substitution product (92/8 from **1a** and 80/20 from **1b**), but with poor to moderate enantioselectivity (35% and 16%, respectively, entries 1 and 5). In contrast,



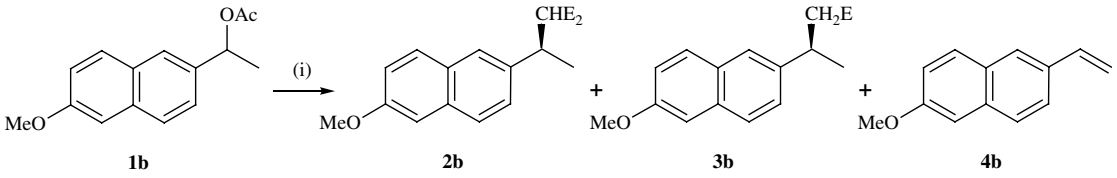
1 **2** **3** **4** (2)

a R = H; **b** R = OMe; E = CO_2Me

(i) 2 eq. $KCHE_2$, 2 mol% $Pd(dba)_2$, 3 mol% chiral ligand, DMSO, 70 °C, 48h.

Table 1. Effect of the chiral ligand structure (Eq. 2)

Entry	Chiral ligand	Substrate	**2**		**3** (%)	**4** (%)	Substitution/elimination ratio
			Yield (%)	Ee (%)			
1	(*R,R*)-Et-FerroTANE®	**1a**	51	35 (*S*)	14	6	92/8
2	(*R,R*)-Me-DUPHOS	**1a**	37	66 (*S*)	0	61	38/62
3	(*R,R*)-Et-DUPHOS	**1a**	25	74 (*S*)	7	48	40/60
4	(*R,R*)-*i*Pr-DUPHOS	**1a**	30	80 (*R*)	10	44	48/52
5	(*R,R*)-Et-FerroTANE®	**1b**	53	16 (*S*)	19	18	80/20
6	(*R,R*)-Me-DUPHOS	**1b**	16	78 (*S*)	0	75	18/82
7	(*R,R*)-Et-DUPHOS	**1b**	17	80 (*S*)	5	59	27/73
8	(*R,R*)-*i*Pr-DUPHOS	**1b**	24	87 (*R*)	7	42	43/57



1b 2b 3b 4b (3)

(i) 2 eq. $KCHE_2$, 2 mol% $Pd(dba)_2$, 3 mol% (*R,R*)-iPr-DUPHOS, DMSO, 48h.

DUPHOS ligands led to vinylnaphthalene **4** as the major product and to a better asymmetric induction from methoxy-substituted acetate **1b** than from the parent substrate **1a**. Enantiomeric excess as well as the substitution/elimination ratio increased with steric hindrance on phospholane rings of the chiral ligand. 1-(2-Naphthyl)-ethyl acetate **1a** gave substitution product **2a** in 80% ee using a Pd/(*R,R*)-*i*Pr-DUPHOS catalyst (entry 4). Methoxy analogue **1b** was more prone to elimination, but **2b** was obtained with 87% ee in 24% isolated yield with the same catalyst (entry 8). These results show an interesting electronic effect in this substitution. Obtention of opposite enantiomers of product **2** using DUPHOS ligands with the same (*R,R*) descriptors (entries 2, 3 vs 4 and 6, 7 vs 8) resulted only from the application of the CIP sequential rules: (*R,R*)-*i*Pr-DUPHOS has an inverted stereochemistry compare to Me or Et analogues (see Fig. 1).

The effect of temperature on the reaction selectivities was then briefly examined on substrate **1b** (Eq. 3, Table 2). Decreasing or increasing the oil bath temperature from 20 °C resulted in both cases to a slight decrease in the enantiomeric excess of the product **2b**. As expected, demethoxycarbonylation was favoured at higher temperatures, leading to a very poor isolated yield (4%) of **2b** at 90 °C. The substitution/elimination ratio was also affected by the temperature, the former process becoming the major pathway at 90 °C.

A reaction temperature of 70 °C seemed to be a good compromise between enantioselectivity and isolated yield of the substitution product **2**. Although the elimination was slightly preferred at this temperature, vinylnaphthalene **4** could be easily recycled to benzylic substrate **1**.

Finally, an asymmetric induction of 90% was obtained conducting the palladium-catalyzed substitution with a slow addition (over 6.5 h) of the nucleophile to the substrate **1b**/catalyst solution. The modification of the malonate concentration indirectly affected the efficiency of the interconversion of the two cationic η^3-benzylic intermediates, which are involved in the expression of the asymmetric induction (Fig. 2).[8] The major elimination pathway observed with DUPHOS ligands may also contribute to the high enantioselectivity of the substitution reaction. The two cationic diastereomeric η^3-benzylic intermediates may eliminate at different rates; one predominantly giving substitution product **2** and the other being more prone to elimination. This kinetic resolution phenomenon enhanced the asymmetric induction of the substitution at the expense of the yield.[8]

3. Conclusion

In conclusion, optimization of the DUPHOS ligand structure and of experimental conditions allowed us to reach an enantiomeric excess of 90% for dimethyl 2-[1-(2-6-methoxynaphthyl)ethyl]propanedioate **2b** in the palladium-catalyzed benzylic nucleophilic substitution. Work is currently in progress in order to understand the factors governing the substitution/elimination selectivity and the electronic effect of the substrate on the asymmetric induction.

4. Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-250 MHz spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Coupling constants are reported in hertz. All reactions involving palladium catalysis were carried out using Schlenk techniques under an argon atmosphere. Dimethylsulfoxide (DMSO) was dried over CaH_2 and distilled prior to use. $Pd(dba)_2$ (dba denotes dibenzylideneacetone)[16] and acetates **1a** and **1b**[2] were prepared according to reported procedures.

Table 2. Effect of the temperature and addition conditions (Eq. 3)

Entry	*T* (°C)	**2b**		**3b** (%)	**4b** (%)	Substitution/elimination ratio
		Yield (%)	Ee (%)			
1[a]	50	26	82	0	45	37/63
2[a]	70	24	87	7	42	43/57
3[b]	**70**	**11**	**90**	**0**	**64**	**15/85**
4[a]	90	4	74	29	27	55/45

[a] Rapid addition of the substrate/catalyst solution to the nucleophile solution.
[b] Slow addition of the nucleophile solution to the substrate/catalyst solution.

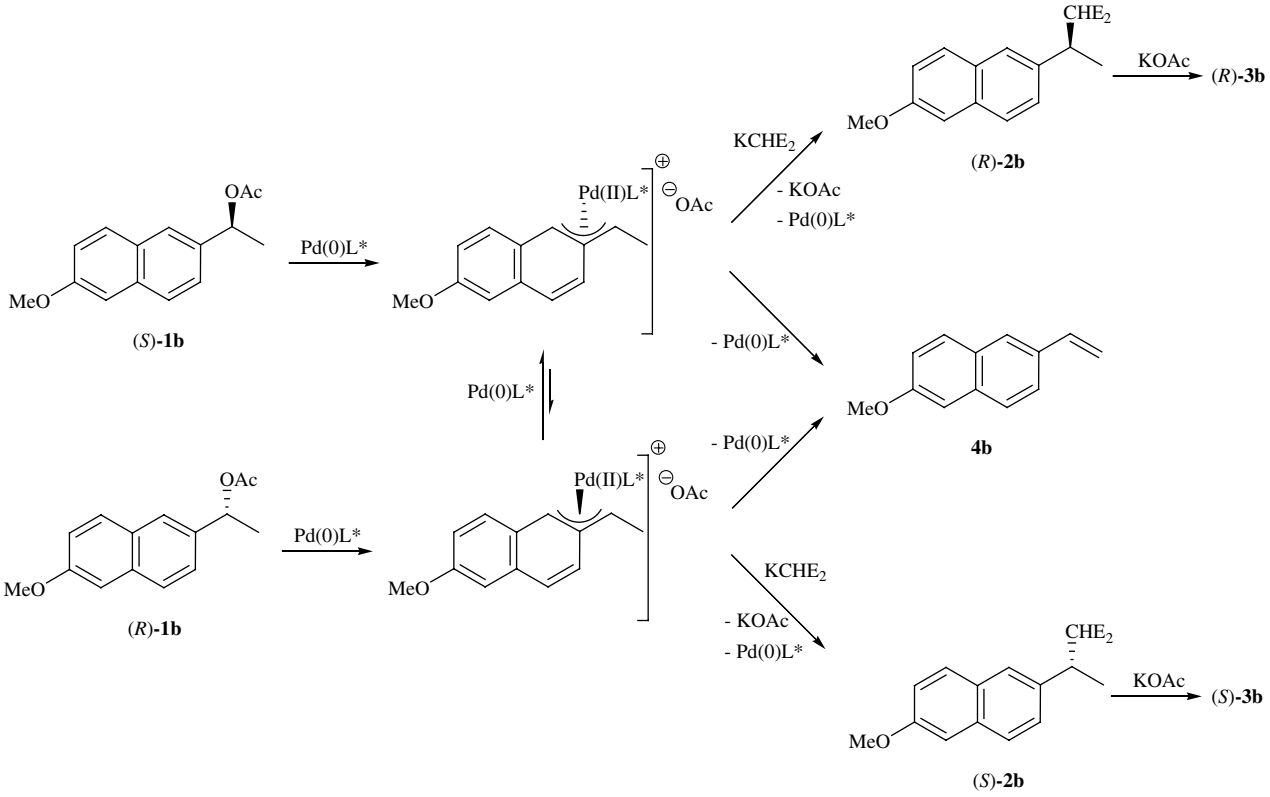


Figure 2. Asymmetric induction process.

A typical experimental procedure is as follows (Table 1, entry 8): acetate **1b** (244 mg, 1 mmol) in 1 mL of DMSO was added under an argon to a mixture of $Pd(dba)_2$ (11.5 mg, 0.02 mmol) and (*R*,*R*)-*i*Pr-DUPHOS (12.6 mg, 0.03 mmol) in 1 mL of DMSO. After 0.25 h stirring, this solution was added to a suspension of potassium dimethylmalonate (340 mg, 2 mmol, from *t*BuOK and dimethylmalonate) in 2 mL of DMSO. The reaction mixture was stirred at 70 °C for 48 h, then diluted with ethyl acetate (20 mL) and the organic phase washed with 2×10 mL of water. The aqueous phases were extracted with ethyl acetate (2×10 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate: 90/10 then 80/20) to give **2b** (75 mg, 24%, ee = 87%), **3b** (17 mg, 7%) and **4b** (78 mg, 42%). The two enantiomers of **2b** were resolved by HPLC analysis with a chiral stationary-phase column Chiracel OD-H [hexane/isopropanol 99/1, 0.5 mL min^{-1}, t = 34.4 min (enantiomer *R*), 37.2 min (enantiomer *S*)].

Compounds **2a** and **2b** have already been characterized.[2] 2-Vinylnaphthalene **4a** and 6-methoxy-2-vinylnaphthalene **4b** are commercially available products.

Methyl 3-naphthalen-2-ylbutanoate **3a** was obtained as a colourless oil. R_f 0.32 (heptane/EtOAc 90/10). IR ($CHCl_3$): ν_{max} 1732 cm^{-1}. HRMS: calcd for $C_{15}H_{16}O_3$ 228.1145. Found: 228.1133. ^1H NMR: 1.38 (d, 3H, ^3J = 6.7 Hz, CH_3–CH); 2.62 (dd, 1H, ^2J = 15.2 Hz and ^3J = 7.9 Hz, CH_2–CO_2CH_3); 2.73 (dd, 1H, ^2J = 15.2 Hz and ^3J = 7.3 Hz, CH_2–CO_2CH_3); 3.38–3.52 (m, 1H, CH_3–CH); 3.60 (s, 3H, OCH_3); 7.34–7.48 (m, 3H, Ar); 7.65 (s, 1H, Ar); 7.76–7.80 (m, 3H, Ar). ^{13}C NMR ($CDCl_3$, 62.9 MHz): 172.9, 143.2, 133.7, 132.4, 128.3, 127.8, 127.7, 126.1, 125.6, 125.5, 125.0, 51.7, 42.7, 36.7, 21.9.

Methyl 3-(6-methoxy-naphthalen-2-yl)butanoate **3b** was obtained as a white solid. Mp: 69 °C. R_f 0.28 (heptane/EtOAc 90/10). IR ($CHCl_3$): ν_{max} 1732 cm^{-1}; mp: 69 °C. HRMS: calcd for $C_{16}H_{18}O_3$ 258.1250. Found: 258.1249. ^1H NMR ($CDCl_3$, 250 MHz): 1,37 (d, 3H, ^3J = 6.8 Hz, CH_3–CH); 2.61 (dd, H, ^2J = 15.1 Hz and ^3J = 8.3 Hz, CH_2–CO_2CH_3); 2.71 (dd, H, ^2J = 15.1 Hz and ^3J = 6.8 Hz, CH_2–CO_2CH_3); 3.31–3.49 (m, 1H, CH_3–CH); 3.61 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 7.10–7.15 (m, 2H, Ar); 7.32 (d, 1H, Ar, ^3J = 8.3 Hz); 7.57 (s, 1H, Ar); 7.68 (d, 2H, Ar, ^3J = 8.3 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz): 173.0, 157.4, 140.9, 133.4, 129.2, 129.1, 127.1, 126.0, 124.8, 118.8, 105.6, 55.3, 51.6, 42.8, 36.4, 21.9.

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