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Asymmetric palladium-catalyzed nucleophilic substitution of 1-(2-naphthyl)ethyl acetate by dimethyl malonate anion

Jean-Yves Legros*, André Boutros, Jean-Claude Fiaud[1], Martial Toffano

Laboratoire de Catalyse Moléculaire associé au C.N.R.S., UPRESA 8075, Institut de Chimie Moléculaire et des Matériaux d'Orsay, Bâtiment 420, Université de Paris-Sud, F91405 Orsay Cedex, France

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Abstract

The asymmetric palladium-catalyzed nucleophilic substitution of 1-(2-naphthyl)ethyl acetate (**1**) by dimethyl malonate anion was realized and led to dimethyl 2-[1-(2-naphthyl)ethyl]propanedioate (**2**) with up to 74% ee. The analysis of the course of the reaction gave some information on the behaviour of the intermediate complexes.

Keywords: Palladium; Asymmetric catalysis; Benzylic nucleophilic substitution; C–C bond formation; Elimination

1. Introduction

In transition metal-catalyzed reactions, the knowledge of the different steps of the transformation (especially the enantiodetermining one) and of the behaviour of the different intermediates is crucial for applications in asymmetric synthesis. This is illustrated by two classical examples in rhodium-catalyzed hydrogenation [1] and palladium-catalyzed allylic substitution (Tsuji–Trost reaction) [2] using the same chiral ligand, namely CHIRAPHOS.[2] In the hydrogenation reaction, the predominant intermediate diastereomer in solution was isolated and did not give the major enantiomer of the product. In the nucleophilic substitution of allyl acetates, the stereochemistry of the product corresponded to the major diastereomer. Both cases are under Curtin–Hammett conditions, but the former is under reactant control whereas the latter is under product control.

We have described in the last 10 years a novel palladium-catalyzed nucleophilic substitution on esters of 1-arylethanols [3–9] (where aryl is a naphthyl, quinolyl or isoquinolyl moiety) in Tsuji–Trost reaction conditions. Although we never isolated nor characterized the reaction intermediates, we postulated a mechanism similar to the palladium-catalyzed substitution on allylic esters. We presented here some results concerning the asymmetric induction and the analysis

* Corresponding author. Tel.: +33-169-154736; fax: +33-169-154680.
E-mail addresses: jylegros@icmo.u-psud.fr (J.-Y. Legros), fiaud@icmo.u-psud.fr (J.-C. Fiaud).

[1] Co-corresponding author.

[2] CHIRAPHOS = 2,3-bis(diphenylphosphino)butane. BDPP = 2,4-bis(diphenylphosphino)pentane. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. PROPHOS = 1,2-bis(diphenylphosphino)propane. DIOP = O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane. Me-DUPHOS = 1,2-bis(2,5-dimethylphospholano)benzene.

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Table 1
Solvent effects in the palladium-catalyzed nucleophilic substitution of 1-(2-naphthyl)ethyl acetate (**1**)

Entry	Solvent	Remaining **1**	Substitution **2**		Elimination **3**
		(%)	(%)	ee (%)	
1	1,4-Dioxane	15	75	15	10
2	THF	6	85	26	9
3	MeCN	16	50	40	34
4	NMP	50	8	53	42
5	DMF	4	26	56	70
6	DMA	21	26	62	53
7	DMSO	0	67	64	33
8	DMPU	15	15	74	70

Conditions: Pd(dba)2 (0.02 mmol, 2 mol%), Me-DUPHOS (0.03 mmol, 3 mol%), acetate (**1**) (1 mmol), sodium dimethylmalonate (2 mmol, 2 eq.), solvent (3 ml), 70 °C, 48 h.

of the course of this transformation, including the behaviour of the diastereomeric intermediates.

2. Experimental

A typical experimental procedure is as follow (Table 1, entry **7**): acetate (**1**) (214 mg, 1 mmol) in 1 ml of DMSO was added under argon to a mixture of Pd(dba)2 (11.5 mg, 0.02 mmol) and Me-DUPHOS (9 mg, 0.03 mmol) in 1 ml of DMSO. After 0.25 h stirring, this solution was added to a suspension of sodium dimethylmalonate (308 mg, 2 mmol, from NaH and dimethylmalonate) in 1 ml of DMSO. The reaction mixture was stirred at 70 °C for 48 h, then diluted with ether (15 ml) and the organic phase washed with 2 × 10 ml of water. The aqueous phases were extracted with ether (2 × 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 2 (186 mg, 65%). The two enantiomers are resolved by HPLC analysis with chiral stationary-phase column Chiracel OD-H [hexane/isopropanol 99/1, 0.5 ml min^{-1}, $t = 23.6$ min (enantiomer R), 26.6 min (enantiomer S)].

3. Results and discussion

We already reported the enantioselective substitution of 1-(2-naphthyl)ethyl acetate (**1**) by dimethyl malonate anion using a Pd/BDPP complex as the chiral catalyst [5]. The product **2** was obtained in 30% ee (Fig. 1). A rapid screening of some available chiral enantiopure diphosphine ligands showed that BINAP, PROPHOS, DIOP and CHIRAPHOS were less effective in this reaction.

We found that Me-DUPHOS gave a more enantioselective catalyst and the substitution product **2** was obtained in 56% ee in the same conditions (Fig. 1). But this increase of the enantiomeric excess was realized in the detriment of the yield. Only 25% of **2** were isolated and the major product was 2-vinylnaphthalene **3** obtained in 67% yield. Alkene **3** resulted from an elimination reaction and was only marginal in the Pd/BDPP-catalyzed substitution. A possible explanation is the different reactivity of the two intermediate cationic complexes **4** which are structurally and electronically different: with the Me-DUPHOS ligand, the hydrogen abstraction by a base (acetate or malonate anion) is favoured over the nucleophilic attack at the benzylic position (Fig. 2).

An elevation of the reaction temperature led to an increase of the yield of the substitution product. Since the enantioselectivity was unchanged at 70 °C but dropped to 48% at 80 °C, we choose to conduct the rest of this study at 70 °C. A reaction time of 48 h was selected because of the deactivation of the catalytic system at prolonged time.

DMF solvent was originally selected because it gave the best result on an achiral substrate, 1-naphthylmethyl acetate [4] We studied the influence of the nature of the solvent on the chemo- and enantioselectivities of the Pd/Me-DUPHOS catalyzed-reaction. Our results are collected in the following Table 1. Yields were evaluated from ^1H NMR spectra and ee were determined by HPLC.

1,4-Dioxane and THF gave the better yields of product **2**, but with a low ee (entries 1 and 2). An ee value of 40% was obtained in acetonitrile (entry 3), whereas in NMP elimination was the major evolution process: only 8% of substitution product **2** in 53% ee was obtained at 50% conversion (entry 4). For the others solvents, conversion and enantioselectivity were better (entries 5–8) but an increase of ee was correlated to a higher tendency to elimination, with the notable exception of DMSO (entry 7). Not only did it give a total conversion in 48 h in contrast to all other solvents tested, but it was the best compromise in terms

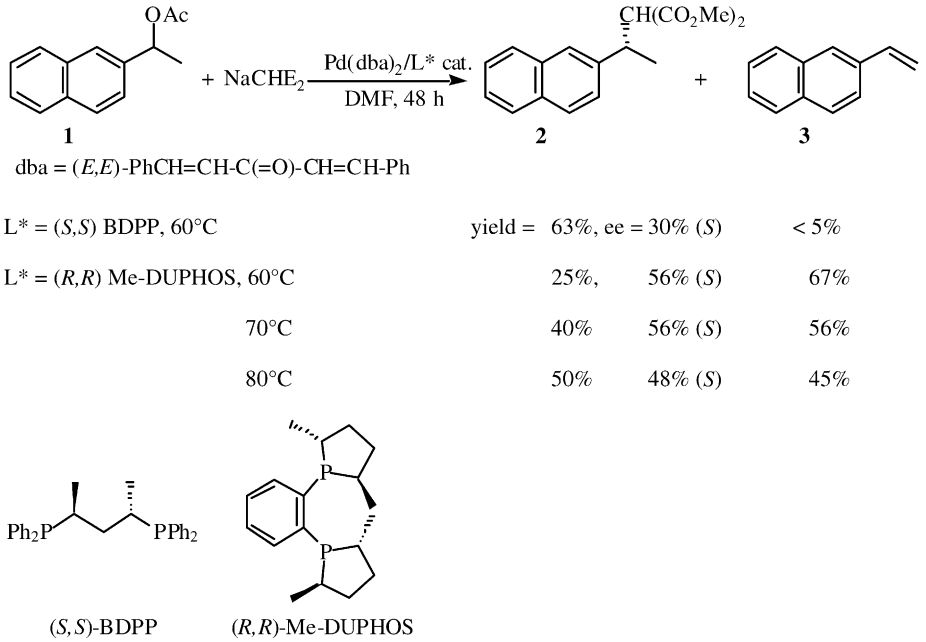


Fig. 1. Enantioselective palladium-catalyzed substitution of acetate (**1**).

of selectivity in favor of substitution (**2**/**3** ≈2) and enantioselectivity of the reaction (ee = 64%). The product was isolated in 65% yield. DMPU gave the best ee but with a very poor yield. It should be noticed that the solvent influence on the enantioselectivity is strongly ligand-dependent since the substitution reaction with the Pd/BDPP catalyst conducted in DMPU gave 93% of isolated compound **2** with only 16% ee.

The following scheme (Fig. 3) illustrates the course of the benzylic palladium-catalyzed nucleophilic substitution which occurs stereospecifically with global retention of configuration [4] (note that the modification of *R*, *S* descriptors is only the consequence of different sequences in **1** and in **2** according to the CIP priority rules). The observed stereochemistry results more likely from a double inversion of configuration like in the Tsuji–Trost reaction [10].

In order to obtain an excess of one enantiomer of product **2** from racemic substrate **1**, an efficient interconversion of the two diastereomeric cationic intermediates complexes (*S*) **4** and (*R*) **4** must occur (the configuration of intermediate complex **4** refers to

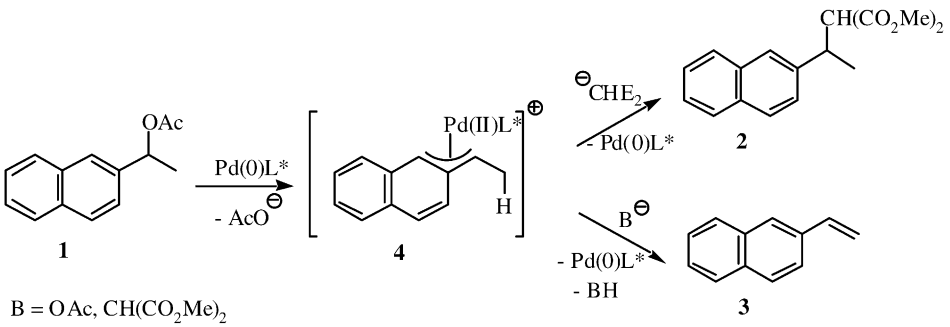


Fig. 2. Substitution and elimination pathways.

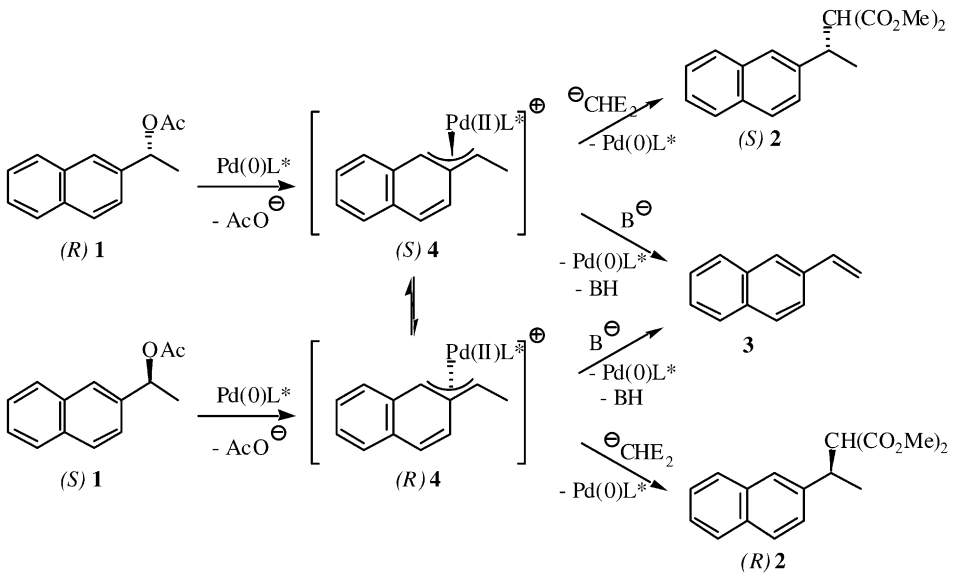
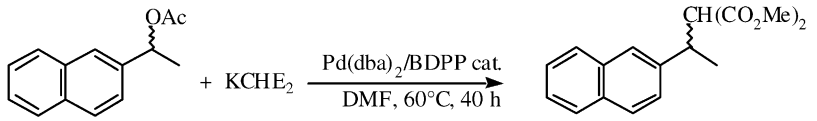


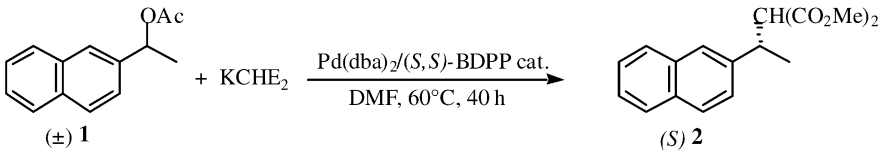
Fig. 3. Stereochemical course of the reaction.



(*R*) **1** c = 100% (*S*) **2** ee = 81%

(*S*) **1** c = 85% (*R*) **2** ee = 68%

Fig. 4. Substitution from enantiomerically pure acetate (**1**).



c = 0	ee = 0	
c = 23%	ee = 10% (*S*)	ee = 38% ± 2%
c = 53%	ee = 27% (*S*)	
c = 76%	ee = 56% (*S*)	

Fig. 5. Partial kinetic resolution of racemic acetate (**1**).

exocyclic asymetric carbon atom). We decided to study the reactivity of the two enantiomers (*R*) **1** and (*S*) **1** independently to obtain some information on the behaviour of the intermediates **4** (Fig. 4). The reaction conditions were slightly modified: potassium dimethyl malonate was employed for solubility reasons and BDPP was used as chiral ligand since it gave little elimination, and consequently determinations of conversions and ee's were easier by HPLC.

After 40 h of reaction, (*R*) **1** gave a total reaction and the product (*S*) **2** was obtained in 81% ee. For (*S*) **1**, the conversion was only 85% in the same time and ee of (*R*) **2** was 68%. (*R*) **1** is hence more reactive in this reaction and this is verified by the observation off a slight kinetic resolution ($E = k_R/k_S \approx 2$–3) of racemic acetate (**1**) (Fig. 5).

This phenomenon is not responsible of the asymmetric induction of the reaction since ee of the product (*S*) **2** is constant with time in this run (ee $= 38 \pm 2\%$). The ee of the isolated product was 37% employing the potassium salt of dimethylmalonate, it was better than the result obtained with its sodium counterpart (30% ee).

4. Conclusion

From these results, it is possible to deduce that this the used BDPP ligand of (*S*,*S*) configuration: (1) (*S*) **4** is produced more rapidly than (*R*) **4** (kinetic resolution of acetate (**1**)); (2) a slow interconversion between (*S*) **4** and (*R*) **4** exists (if rapid, the same results should be obtained from racemic, (*R*) and (*S*) **1**; without equilibrium, no asymmetric synthesis from racemic substrate **1** should be possible); (3) (*S*) **4** is more stable and/or more reactive towards nucleophilic attack than (*R*) **4** (obtention of (*S*) **2** as major enantiomer in asymmetric synthesis and better asymmetry transfer from (*R*) **1** compared to (*S*) **1**).

The same situation exists in the case of MeDUPHOS ligand but is probably complicated by the elimination pathway. The hydrogen abstractions from (*S*) **4** and (*R*) **4** could operate at different rates and could give a second kinetic resolution phenomenon which enhance asymmetric induction of the substitution in detriment of the yield.

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