Pergamon

Tetrahedron Letters, Vol. 38, No. 1, pp. 77-80, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02219-8

DMF as a Dimethylamine Equivalent in the Palladium-Catalyzed Nucleophilic Substitution of Naphthylmethyl and Allyl Acetates.

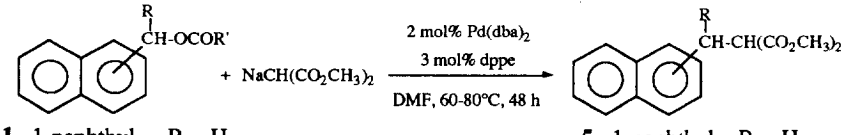
Martial Toffano, Jean-Yves Legros* and Jean-Claude Fiaud*

Laboratoire de Synthèse Asymétrique Associé au C.N.R.S.
Institut de Chimie Moléculaire d'Orsay, Bâtiment 420, Université de Paris-Sud, 91405 Orsay, France.
Fax: (33) 01 69 15 46 80. E-mail: jylegros@icmo.u-psud.fr or fiaud@icmo.u-psud.fr

Abstract: *Naphthylmethyl acetates* ***1a*** *and* ***2a*** *were substituted by morpholine in DMPU in the presence of 2 mol% of [Pd(dba)$_2$ + 1.5 dppe] to give products* ***9-10*** *in 66-70% isolated yield. In DMF in the presence of benzylamine, N,N-dimethylnaphthylmethylamines* ***11-12*** *were produced in 78-85% isolated yield.* Copyright © 1996 Elsevier Science Ltd

We recently described the palladium-catalyzed substitution of esters **1-4** by sodium dimethylmalonate (Scheme 1). [1] On the observation of: i) the inertness of benzyl acetate under the same conditions, and ii) the overall retention of the configuration in the case of optically active substrates, we suggested that the substitution takes place through the formation of a cationic η^3-benzylic palladium intermediate complex **I** or **II**, similarly to the palladium-catalyzed allylation of nucleophiles (Tsuji-Trost reaction). [2]

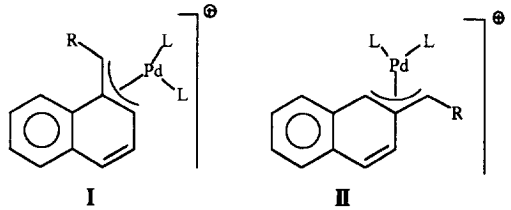
Scheme 1



1 1-naphthyl R = H
2 2-naphthyl R = H
3 1-naphthyl R = Me
4 2-naphthyl R = Me
a: R' = Me **b**: R' = OMe

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

dba = dibenzylideneacetone; dppe = 1,2-bis(diphenylphosphino)ethane

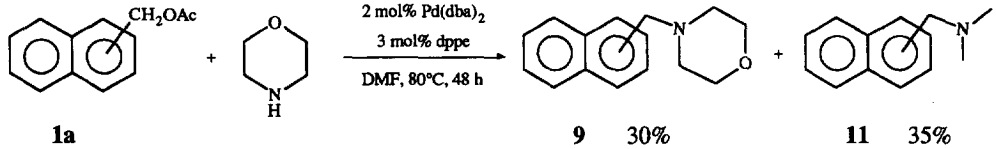


I **II**

We wish to report in this letter our preliminary results concerning the study of the palladium-catalyzed amination of acetates **1a** and **2a**.

We examined first the reaction of 1-naphthylmethyl acetate **1a** with morpholine (Scheme 2). This amination was performed under the optimal conditions determined for the substitution by a carbonucleophile (see Scheme 1). To our surprise, two amine products were obtained. Beside the expected N-(1-naphthylmethyl)-morpholine **9** isolated in 30% yield, the major product (35%) was N,N-dimethyl-1-naphthylmethylamine **11**, resulting from the formal substitution of **1a** by dimethylamine. A similar result was obtained starting from regioisomer **2a**, although the ratio of the two products was inverted. N-formylmorpholine **13** was also detected in the reaction mixtures.

Scheme 2



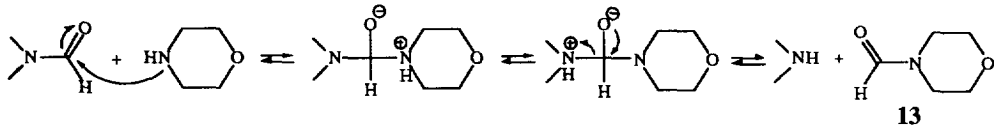
1a
2a

9 30%
10 35%

11 35%
12 25%

It is well known that DMF decomposes into carbon monoxide and dimethylamine. However, neither **11** nor **12** were detected on submitting **1a** or **2a** to the same reaction conditions but in the absence of morpholine. The formation of N-formylmorpholine **13** in reactions of Scheme 2 can be rationalized by the mechanism depicted in Scheme 3 involving formylation of morpholine by DMF. The liberated dimethylamine then reacts with the cationic η^3-benzylic palladium intermediate complex to give product **11** or **12**. [3]

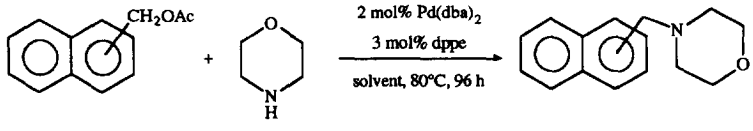
Scheme 3



13

In order to suppress the dimethylamine formation and to obtain selectively the substitution products **9** and **10**, the reactions of **1a** and **2a** with morpholine were conducted in others solvents (Scheme 4): THF gave incomplete conversion and poor reaction yields of **9**-**10** whereas the use of DMPU (N,N'-dimethylpropylene-urea) allowed the isolation of N-(naphthylmethyl)morpholines **9** and **10** in 70 and 66% yield respectively.

Scheme 4

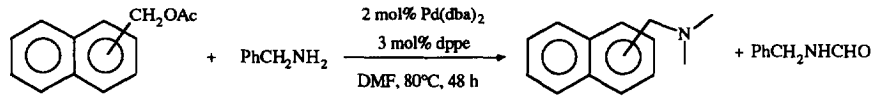


	solvent	THF	DMPU
1a	**9**	30%	70%
2a	**10**	30%	66%

The chemoselectivity in favour of N,N-dimethylnaphthylmethylamines **11**-**12** was also greatly improved by a proper choice of the amine (Scheme 5). In fact, since benzylamine did not react at all with the palladium(II)

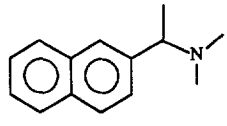
intermediate, clean reactions and good yields in **11** and **12** could be recorded, with N-benzylformamide **14** as the only by-product. Since dimethylamine is a gaseous reagent (or available as aqueous or THF solution), this reaction represents a convenient method to introduce a dimethylamino group in the benzylic position of a naphthyl ring.

Scheme 5



1a **2a** **11** 85% **12** 78% **14**

2-Naphthylethyl esters **4a** and **4b** were also tested, but the results were less satisfactory: in the presence of morpholine or benzylamine, the major product was 2-vinylnaphthalene, produced via a base-promoted elimination on the cationic intermediate. In the conditions of Scheme 5, the product **15** was isolated in 30% yield starting from acetate **4a** and 40% from carbonate **4b**.



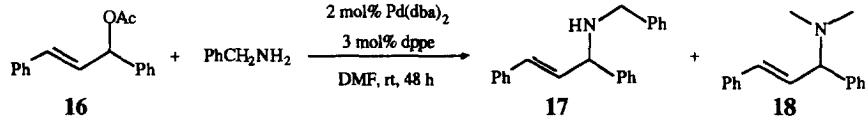
15

Finally, we tried to extend this dimethylamination to an allylic system. N-nucleophiles and especially amines are frequently described in the Tsuji-Trost reaction, [2,4] but dimethylamine was rarely used. [5] To our knowledge, allylic amination has never been conducted in DMF.

We chose (*E*)-1,3-diphenylprop-2-enyl acetate **16** as a test substrate in two sets of experimental conditions, both employing benzylamine in DMF in the presence of 2 mol% of [$Pd(dba)_2$ + 1.5 dppe] (Scheme 6). In a first experiment, substrate **16** and benzylamine were successively added under an argon atmosphere to a solution of the catalyst in DMF at room temperature; the main product was **17** (53%) and N,N-dimethylamino compound **18** was produced in only 9% yield.

In order to favour the formation of dimethylamine according to Scheme 3, benzylamine was first placed in DMF at 80°C during 72 h, and after cooling at room temperature, the catalyst and the substrate were successively added. These conditions increased the yield of product **18** to 39%, but **17** was also obtained (28%). Conducting the reaction at 80°C did not improve this result.

Scheme 6



16 **17** **18**

In summary, naphthylmethyl acetates are efficiently substituted by an amine (morpholine) if the palladium-catalyzed reaction is conducted in DMPU, and by dimethylamine if the presence of benzylamine in N,N-

dimethylformamide. Work is actually in progress to extend this methodology to other volatile amines (as methylamine) and to improve the results concerning naphthylethyl substrates (prone to elimination) and allylic substrates (more sensitive to the direct substitution by benzylamine).

Typical procedure: A solution of acetate **1a** (200 mg, 1 mmol) in 1 mL of DMPU was transferred under an argon atmosphere onto 11.5 mg (0.02 mmol) of $Pd(dba)_2$ and 12 mg (0.03 mmol) of dppe in 1 mL of DMPU. After 0.25 h stirring, morpholine (0.22 mL, 2.5 mmol) was added and the reaction mixture was heated to 80°C during 96 h. After cooling, ether (20 mL) was added and the solution was extracted twice with 20 mL HCl M. Tha aqueous phase was neutralized ($NaHCO_3$) and extracted twice with 20 mL ether. The combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica, hexane / ethyl acetate / triethylamine 20 / 80 / 1) to give **9** (160 mg, 70%).

The same procedure with DMF rather than DMPU and benzylamine (0.5 mL, 4.5 mmol) instead of morpholine gave **11** (157 mg, 85%) after 48 h of reaction.

Acknowledgement: One of us (M.T.) thanks the Ministère de l'Enseignement Supérieur et de la Recherche for a Grant.

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. c) Legros, J.Y.; Toffano, M.; Fiaud, J.C. *Tetrahedron: Asymmetry* **1995**, *6*, 1899-1902.

2- For recent reports, see: a) Godleski, S.A. in "Comprehensive Organic Synthesis", Trost, B.M.; Fleming, I.; Semmelhack, M.F. Eds., Pergamon Press: Oxford, **1991**, *4*, 585-661. b) Tsuji, J. " Palladium Reagents and Catalysts. Innovations in Organic Synthesis", John Wiley & Sons: Chichester, **1995**, 290-422. c) Trost, B.M.; Van Vranken, D.L. *Chem. Rev.* **1996**, *96*, 395-422.

3- Although DMF is a common formylating agent, the dimethylamine liberated by this process is to our knowledge rarely used: see Comins, D.L.; Joseph, S.P. in "Encyclopedia of Reagents for Organic Synthesis", Paquette, L.A. Ed., John Wiley & Sons: Chichester, **1995**, *3*, 2072-2075.

4- For some recent examples: a) Kuo, D.L. *Heterocycles* **1993**, *36*, 1463-1469. b) Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 6826-6832. c) Yamazaki, A.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1021-1024. d) Thorey, C.; Wilken, J.; Hénin, F.; Martens, J.; Mehler, T.; Muzart J. *Tetrahedron Lett.* **1995**, *36*, 5527-5530. e) Yamazaki, A.; Achiwa, I.; Achiwa, K. *Tetrahedron: Asymmetry* **1996**, *7*, 403-406. f) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P.S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031-1037. g) Jin, Z.; Fuchs, P.L. *Tetrahedron Lett* **1996**, *37*, 5253-5256.

5- a) Bäckvall, J.E.; Nordberg, R.E.; Nyström, J.E.; Högberg, T.; Ulff, B. *J.Org.Chem.* **1981**, *46*, 3479-3483. b) Genêt, J.P.; Balabane, M.; Bäckvall, J.E.; Nyström, J.E. *Tetrahedron Lett.* **1983**, *24*, 2745-2748. c) Nikaido, M.; Aslanian, R.; Scavo, F.; Helquist, P.; Akermark, B.; Bäckvall, J.E. *J.Org.Chem.*, **1984**, *49*, 4738-4740. d) Bäckvall, J.E.; Juntunsen, S.K. *J. Am. Chem. Soc.* **1987**, *109*, 6396-6403. e) Genêt, J.P.; Thorimbert, S.; Mallart, S.; Kardos, N. *Synthesis* **1993**, 321-324.

(*Received in France* 10 *October* 1996; *accepted* 12 *November* 1996)