

Tetrahedron Letters 39 (1998) 6903-6906

TETRAHEDRON LETTERS

Novel Carbonyl-dependent Regioselective Allylation via Diethylzinc-Mediated Umpolung of π -Allylpalladium

Masanari Kimura, Yoshimi Ogawa, Masamichi Shimizu, Masayuki Sueishi, Shuji Tanaka, and Yoshinao Tamaru*

Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunnkyo-Machi, Nagasaki 852-8521, Japan

Received 6 May 1998; revised 1 July 1998; accepted 10 July 1998

Abstract: Palladium-catalyzed allylation of carbonyls (1.1 - 1.5 mmol) with allylic esters **3a-d** (1 mmol) in the presence of Pd(PPh₃)₄ (0.05 mmol) and Et₂Zn (2.4 mmol) in THF at room temperature shows marked carbonyl-dependent regioselectivity, providing α -allylation products **5** with benzaldehyde and γ -allylation products **6** with acetone and ethyl acetate. © 1998 Elsevier Science Ltd. All rights reserved.

Allylation of carbonyl compounds is indispensable for building up desired molecules, and the development of efficient methodologies, showing high regioselectivity (at either the α - or γ -position of unsymmetrical allylic termini), stereoselectivity, and compatibility with other functionalities, has long been a subject of major interest to organic chemists.



The methodology developed by us,¹⁻³ based on diethylzinc-promoted umpolung of π -allylpalladiums, generated *in situ* by the reaction of allylic esters or halides and a catalytic amount of a palladium(0) species, has proved to display some desirable features (Scheme 1); the reaction is operationally simple and can be performed at ambient temperature. It exhibits high chemoselectivity and provides allylation products in excellent yields. The regio- and stereoselectivities depend on the structure of the allylating agents, which may be classified into three types (Scheme 1): Mono-substituted allylzincs **1a**,**b** react regioselectively at the allylic termini bearing the highest number of substituents and provide *anti*-isomers either selectively (**2a**) or exclusively (**2b**) (*type 1*).¹ 1,3-Disubstituted allylzincs **1c** exclusively furnish *Z*,*anti*-isomers **2c** (*type 2*).² Substituents at C-2 alter the regioselectivity of *type 1*, and allylzincs **1d** provide ca. 1:1 mixtures of **2d** and **2e**, the latter being unusual regiochemical products formed at the least substituted allylic termini of **1d** (*type 3*).^{3,4}

Recently, Pfeffer et al.⁵ have reported that, in the presence of triphenylphosphine, π-allylpalladium complexes with amino-substituents, e.g., **4**, readily undergo intramolecular nucleophilic displacement to give 0040-4039/98/\$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved. *Pll*: S0040-4039(98)01448-8

rise to nitrogen heterocycles (eq 1). This study led us to examine whether 4 could be converted into allylzinc species 1e by exposure to diethylzinc, since, if 1e is generated, it might become possible to reverse the regioselectivity of *type 1*; owing to chelation stabilization⁶ by the amino group, 1e α would predominate over 1e γ and react with carbonyls to provide 6 selectively through a transition state I (Scheme 2).

As is apparent from the yields of allylation products summarized in runs 1 - 10, Table 1, the diethylzincpromoted umpolung of π -allylpalladium takes place nicely for allylic substrates **3a-d**.⁷ Contrary to our expectation, however, the reactions with benzaldehyde furnished regioisomers **5** either exclusively (run 8) or with high selectivities (runs 1 and 7), that is, the *o*-dimethylamino group seemed not to influence the regioselectivity. Indeed, **3b**, bearing a C-2 substituent, reacted with benzaldehyde as usual (*type 3*) and provided an indiscriminate mixture of **5b** and **6d** (run 4). Acetone, however, reacted with **3a** in the way that we had expected and provided **6b** exclusively (run 2), which makes contrast to the exclusive formation of **5f** for the reaction with cinnamyl acetate (run 11). The Z-stereochemistry of the double bond of **6b** was confirmed by the coupling constant (J = 11.5 Hz) between the olefinic protons. Similarly, ethyl acetate reacted with **3a** to give rise to **6c**, the product being allylated doubly in the same sense of regioselectivity and stereoselectivity (run 3). It should be noted that the formation of **6c** as a single isomer attests to the high regio- and stereoselectivity of the present reaction.



Scheme 2

The reversal of regioselectivity between benzaldehyde and ethyl acetate seems to be general for other allylation substrates **3b** and **3d** (runs 4 and 6 and 8 and 10). In these cases, also, the double allylation products, **6f** and **6i**, were obtained as a single regio- and stereoisomer.

One plausible rationale for the unique dependence of regioselectivity on the kind of carbonyl compounds relies on the difference in Lewis acidity between the zinc metals of $1e\alpha$ and $1e\gamma$ (Scheme 2). Owing to electron donation by the amino group, the Lewis acidity of $1e\alpha$ is expected to be considerably lower than that of $1e\gamma$. Accordingly, $1e\alpha$ would accommodate only carbonyls of high Lewis basicity (e.g., acetone and ethyl acetate,

run	allylic ester	carbonyl	time	% isolated yield of product (isomer ratio; syn:anti) ^b		
	(I mmol)	(mmol)	(h)	α -allylation product	y-allylation product	others
1	Ac NMen a	PhCHO (1.2)	3		OH Ar Ph	N Ar
	14102 3a			5a : 78	6a : 12	7 ^c : 5
2	3a	MeCOMe (1.1)	6		ОН Аг 6b : 88	7 ¢: 6
3	3a	MeCO ₂ Et (1.2)	4		Ar Ar Ar	$Ar \xrightarrow{Ar} Ar \\ 8a \\ 7^c: 8 + 8a: 6$
4		PhCHO (1.1)	24	PH Ar	OH Ph Ar	Ar Y
	21	14 0014		5b : 42 (1:1.1)	6d: 34	9:22
5	36	MeCOMe (1.5)	46		Ar 6e: 51	9 : 30
6	3b	MeCO ₂ Et (1.1)	29		Ar Ar 6f: 55	9 : 35
7	NMe ₂ 3c	PhCHO (1.2)	32	он Рн Аг 5с: 58	OH Ar 6g: 2	$\frac{Ar}{Bbd} = 24$
8	OBz NMe2 3d	PhCHO (1.1)	5	OH Phr Ar 5d: 99 (1:3) ^e		
9	3d	MeCOMe (1.5)	4	OH Ar 5e: 6	OH Ar 6h: 68	Ar 10: 22
10	3d	MeCO ₂ Et (1.5)	6		Ar 6i: 53	10 : 30
11	PhOAc	MeCOMe	5	он		
_	3e			Ph 5f: 88		

Table 1. Allylation of Carbonyl Compounds via Diethylzinc-mediated Umpolung of π -Allylpalladium^a

^{*a*} Reaction conditions: Allylic ester 3 (1 mmol), Pd(PPh₃)₄ (0.05 mmol), Et₂Zn (2.4 mmol, 1 M in hexane), and carbonyl (indicated amount) in THF (8 mL) at ambient temperature for the period of time indicated under N₂. Ar stands for *o*-dimethylaminophenyl group. ^{*b*} All isomers 5 - 10, except for 5b and 8b, were separated by column chromatography over silica gel and characterized appropriately by ¹H NMR (400 MHz), IR, and HRMS. 5b was obtained as a non-separable diastereomeric mixture. ^{*c*} Tentatively assigned structure. ^{*d*} Mixture of 8b, composed of α , γ - and γ , γ -coupling products, each of which involves *syn*- and *anti*-structures, assigned by analogy with the reaction of *type 1*.

but not benzaldehyde)⁸ into its vacant site (symbolized as \diamond). That is, benzaldehyde coordinates only $1e\gamma$ and would react selectively with it to furnish α -allylation products 5 through a transition state II. Acetone and ethyl acetate coordinate both $1e\alpha$ and $1e\gamma$; however, owing to the overwhelming predominance of $1e\alpha$ over $1e\gamma$, they would selectively react with $1e\alpha$ to give γ -allylation products 6 through a six-membered chair-like transition state I, where a quasi-axial orientation of the *o*-dimethylaminophenyl group is suggested from the Z-structure of 6. Steric repulsion between the carbonyl substituents and the allylic terminus in a transition state II might also render this transition state unfavorable for the reactions of acetone and ethyl acetate.

The *anti*-structure of **5a** was unequivocally determined by derivatization to **11** (O₃ at -78 °C in the presence of an equal amount of toluenesulfonic acid in CH₂Cl₂, followed by reduction with NaBH₄ at -78 °C and acetalization in 2,2-dimethoxypropane at room temperature in the presence of toluenesulfonic acid). In the ¹H NMR spectrum (400 MHz) of **11**, two benzylic protons showed a diaxial relationship to each other (Fig. 1). The *anti*-structure of **5c** was assigned by analogy. Structure elucidation of **6a-g** was based on either the coupling constants of olefinic protons or NOE experiments. Some representative results are shown in Figure 1.



Figure 1. Selected NMR data diagnostic for structure determination: *J* in Hz and percent (%) increment in NOE [¹H NMR (400 MHz, CDCl₃)].

Acknowledgment. We thank Mr. Y. Ohhama, NMR Facility, Nagasaki University. Financial support from the Ministry of Education, Science, Sports and Culture, the Japanese Government, is acknowledged.

References and Notes

- 1) Yasui, K.; Goto, Y.; Yajima, T.; Taniseki, Y.; Fugami, K.; Tanaka, A.; Tamaru, Y. Tetrahedron Lett. 1993, 34, 7619 7622.
- Tamaru, Y.; Tanaka, A.; Yasui, K.; Goto, S.; Tanaka, S. Angew. Chem. Int. Ed. Engl. 1995, 34, 787 -789.
- 3) Shimizu, M.; Kimura, M.; Tanaka, S.; Tamaru, Y. Tetrahedron Lett. 1998, 39, 609 612.
- 4) Review: Tamaru, Y. J. Syn. Org. Chem. Jpn. 1995, 53, 1102 1113.
- 5) van der Schaaf, P. A.; Sutter, J.-P.; Grellier, M.; van Mier, G. P. M.; Spek, A. L.; van Koten, G.; Pfeffer, M. J. Am. Chem. Soc. 1994, 116, 5134 5144.
- 6) Krämer, T.; Hoppe, D. Tetrahedron Lett. **1987**, 28, 5149 5152. Hoppe, D.; Krämer, T. Angew. Chem. **1986**, 98, 171 173 and references cited therein.
- 7) General experimental procedure (run 1, Table 1): To a solution of 1-(o-dimethylaminophenyl)-2-propenyl acetate **3a** (1 mmol), benzaldehyde (1.2 mmol), and Pd(PPh₃)₄ (0.05 mmol) in dry THF (8 mL) was added Et₂Zn (2.4 mmol, 1 M in hexane) via a syringe. The homogeneous mixture was stirred at ambient temperature for 3 h under N₂, during which the reaction was monitored by TLC [Kieselgel 60F₂₅₄ (Merck), hexane:ethyl acetate = 4/1 v/v, Rf = 0.63 (**3a**), 0.45 (**5a**), 0.30 (**6a**), 0.68 (**7**)]. During the reaction, a facile rearrangement of **3a** to 3-(o-dimethylaminophenyl)-2-propenyl acetate (Rf = 0.57) was observed. The mixture was diluted with aqueous NH₄Cl-NH₃ and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried (MgSO₄) and filtered and the solvents were removed *in vacuo*. The residue was purified by column chromatography over silica gel to provide spectroscopically homogeneous **5a**, **6a**, and **7** in 78, 12, and 5% yields, respectively.
- Streitwieser, A.; Heathcock, C. H.; Kosower, E. M. Introduction to Organic Chemistry, 4th ed., Macmillan, New York, 1992, Appendix IV.