Pergamon

Tetrahedron Letters 39 (1998) 6903–6906

TETRAHEDRON
LETTERS

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

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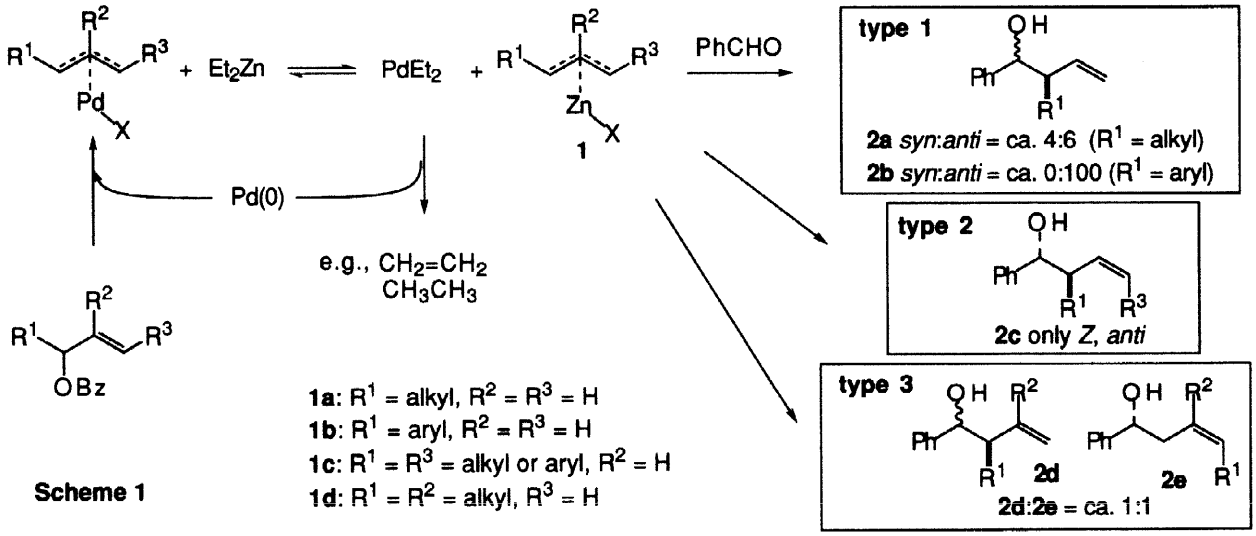
Received 6 May 1998; revised 1 July 1998; accepted 10 July 1998

***Abstract*:** Palladium-catalyzed allylation of carbonyls (1.1 - 1.5 mmol) with allylic esters **3a-d** (1 mmol) in the presence of $Pd(PPh_3)_4$ (0.05 mmol) and Et_2Zn (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.



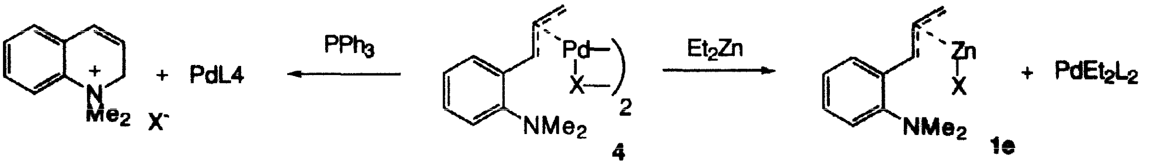
Scheme 1

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

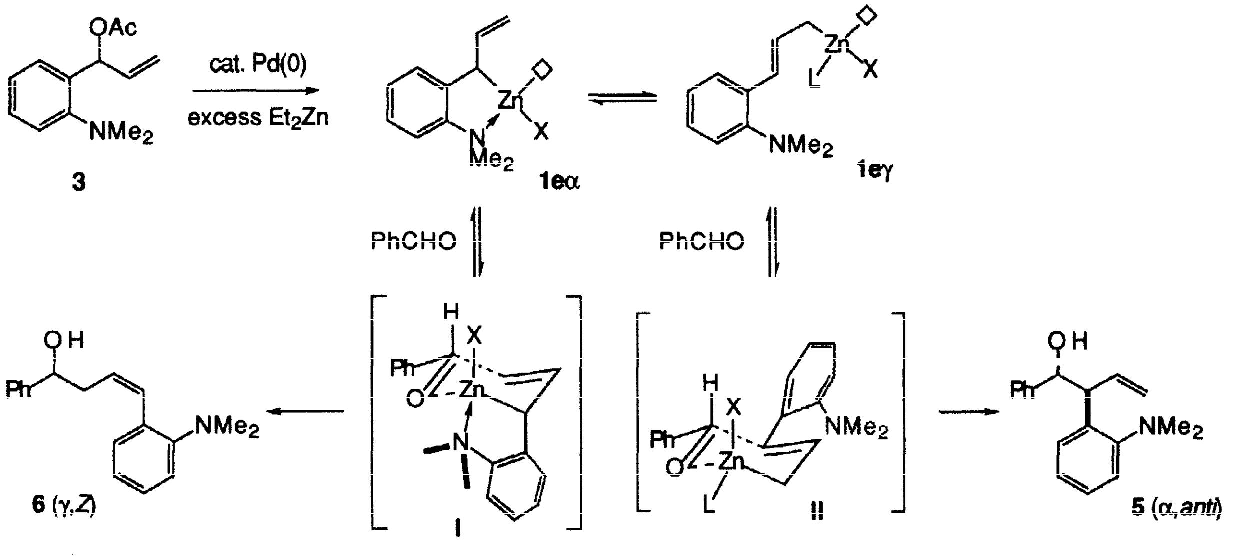
PII: S0040-4039(98)01448-8

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 stabilization[6] by the amino group, **1eα** would predominate over **1eγ** and react with carbonyls to provide **6** selectively through a transition state **I** (Scheme 2).



(1)

As is apparent from the yields of allylation products summarized in runs 1 - 10, Table 1, the diethylzinc-promoted 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.

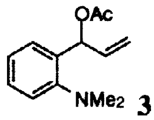
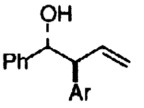
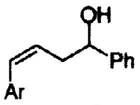
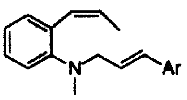
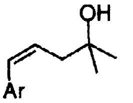
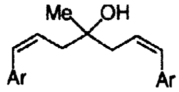
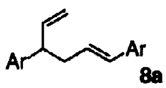
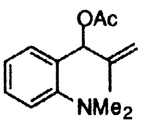
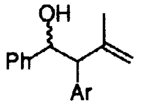
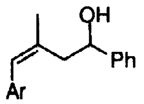
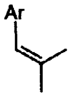
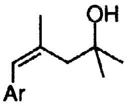
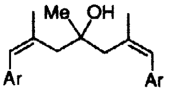
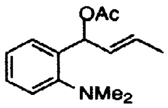
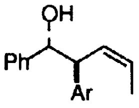
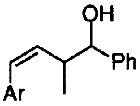
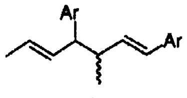
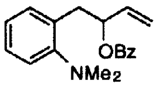
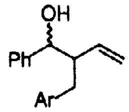
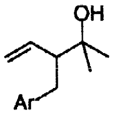
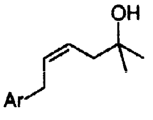
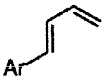
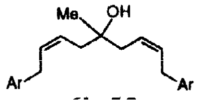
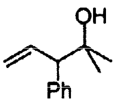


Scheme 2

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 **1eα** and **1eγ** (Scheme 2). Owing to electron donation by the amino group, the Lewis acidity of **1eα** is expected to be considerably lower than that of **1eγ**. Accordingly, **1eα** would accommodate only carbonyls of high Lewis basicity (e.g., acetone and ethyl acetate,

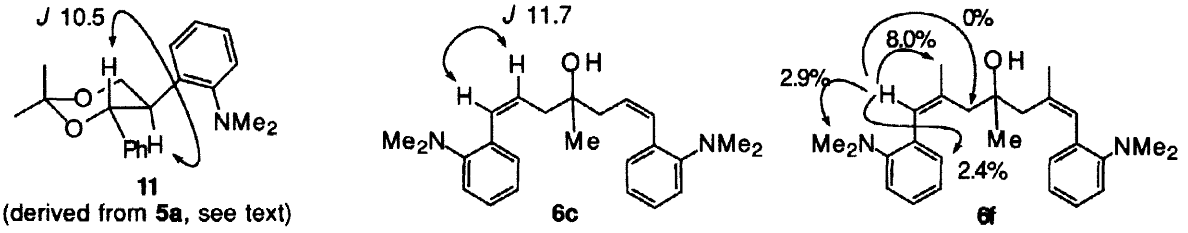
Table 1. Allylation of Carbonyl Compounds via Diethylzinc-mediated Umpolung of π-Allylpalladium[a]

run	allylic ester (1 mmol)	carbonyl (mmol)	time (h)	% isolated yield of product (isomer ratio; *syn*:*anti*)[b]		
				α-allylation product	γ-allylation product	others
1	 **3a**	PhCHO (1.2)	3	 **5a**: 78	 **6a**: 12	 **7**[c]: 5
2	**3a**	MeCOMe (1.1)	6		 **6b**: 88	**7**[c]: 6
3	**3a**	$MeCO_2Et$ (1.2)	4		 **6c**: 69	 **8a** **7**[c]: 8 + **8a**: 6
4	 **3b**	PhCHO (1.1)	24	 **5b**: 42 (1:1.1)	 **6d**: 34	 **9**: 22
5	**3b**	MeCOMe (1.5)	46		 **6e**: 51	**9**: 30
6	**3b**	$MeCO_2Et$ (1.1)	29		 **6f**: 55	**9**: 35
7	 **3c**	PhCHO (1.2)	32	 **5c**: 58	 **6g**: 2	 **8b**[d]: 24
8	 **3d**	PhCHO (1.1)	5	 **5d**: 99 (1:3)[e]		
9	**3d**	MeCOMe (1.5)	4	 **5e**: 6	 **6h**: 68	 **10**: 22
10	**3d**	$MeCO_2Et$ (1.5)	6		 **6i**: 53	**10**: 30
11	 **3e**	MeCOMe	5	 **5f**: 88		

[a] Reaction conditions: Allylic ester **3** (1 mmol), $Pd(PPh_3)_4$ (0.05 mmol), Et_2Zn (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 N_2. 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*-stereoisomers. [e] *syn*- and *anti*-structures, assigned by analogy with the reaction of *type 1*.

but not benzaldehyde)[8] into its vacant site (symbolized as ◊). That is, benzaldehyde coordinates only **1eγ** and would react selectively with it to furnish α-allylation products **5** through a transition state **II**. Acetone and ethyl acetate coordinate both **1eα** and **1eγ**; however, owing to the overwhelming predominance of **1eα** over **1eγ**, they would selectively react with **1eα** 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** (O_3 at -78 °C in the presence of an equal amount of toluenesulfonic acid in CH_2Cl_2, followed by reduction with $NaBH_4$ 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.



11
(derived from **5a**, see text)

6c

6f

Figure 1. Selected NMR data diagnostic for structure determination: *J* in Hz and percent (%) increment in NOE [^1H NMR (400 MHz, $CDCl_3$)].

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.
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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 $Pd(PPh_3)_4$ (0.05 mmol) in dry THF (8 mL) was added Et_2Zn (2.4 mmol, 1 M in hexane) via a syringe. The homogeneous mixture was stirred at ambient temperature for 3 h under N_2, during which the reaction was monitored by TLC [Kieselgel $60F_{254}$ (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 NH_4Cl-NH_3 and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$) 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.
8) Streitwieser, A.; Heathcock, C. H.; Kosower, E. M. *Introduction to Organic Chemistry*, 4th ed., Macmillan, New York, 1992, Appendix IV.