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Unique Regio- and Stereoselectivity In the Allylation of Benzaldehyde with 2-Substituted Allylzincs Generated by Umpolung of π-Allylpalladium

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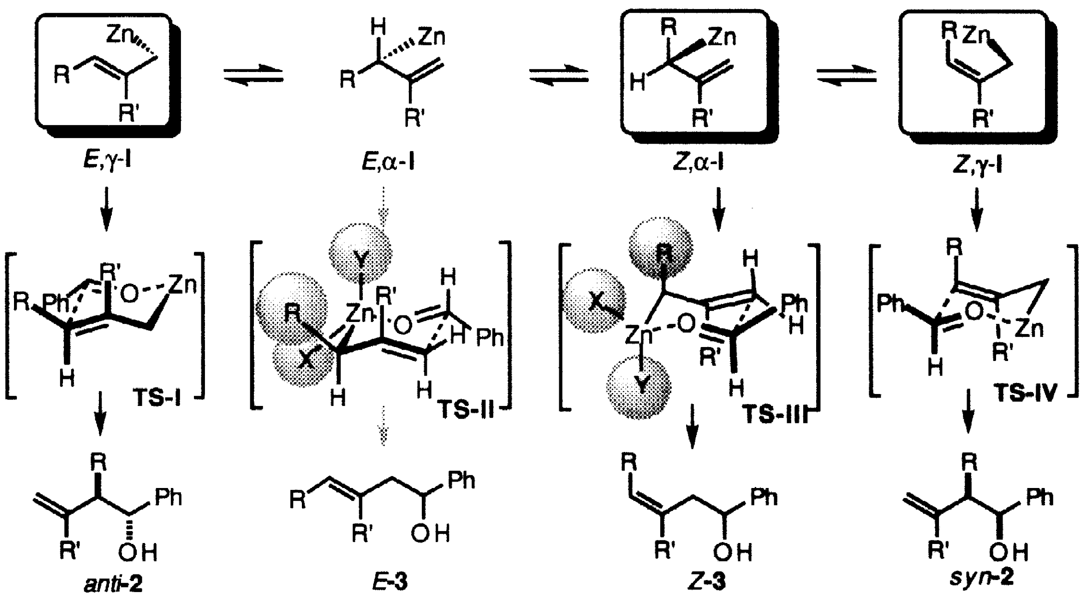
Abstract: α,β-Disubstituted allylzincs with alkoxycarbonyl as the β-substituent, generated via an umpolung of *in situ* generated π-allylpalladium by transmetallation with diethylzinc, react with benzaldehyde at the most substituted allylic terminus to provide *syn*-γ-butyrolactones **4** exclusively, while those with electron-donating Me, *i*-Pr, or OMOM as the β-substituents react at both allylic termini to give mixtures of *syn*-**2**, *anti*-**2** and *Z*-**3**. α,β,γ-Trisubstituted allylzincs provide *Z,anti*-adducts **5** exclusively.

In view of the synthetic importance of allylation of carbonyl compounds, there has been extensive development of methodology in this area.[1] Despite numerous studies on the stereo- and regioselectivities for α- or γ-monosubstituted and α,γ-disubstituted allylating agents, there have appeared surprisingly few reports concerning the same subject for the α,β-di- and α,β,γ-trisubstituted allylating agents.[2] Here we disclose that the β-substituents (R') of allylzincs, depending on their electronic nature, exert pronounced effects on their reactivity and, hence, product distributions among *syn*-**2**, *anti*-**2**, *Z*-**3**, and *E*-**3** (Scheme 1).



Scheme 1.

Recently, we have developed an efficient allylation reaction based on a unique transmetallation reaction of an *in situ* generated π-allylpalladium into allylzinc (an umpolung) with diethylzinc (eq 1 and 2, M = Pd → Zn),[3] where *trans*-γ-monosubstituted benzoates reacted regioselectively at the allylic terminus bearing the highest number of substituents, showing a modest stereoselectivity to yield mixtures of *anti*- and *syn*-adducts in 2:1 ~ 10:1 ratios (eq 1). Additional substituents on the α-position, however, caused a dramatic change in stereoselectivity, furnishing *Z,anti*-adducts exclusively (eq 2).[4]

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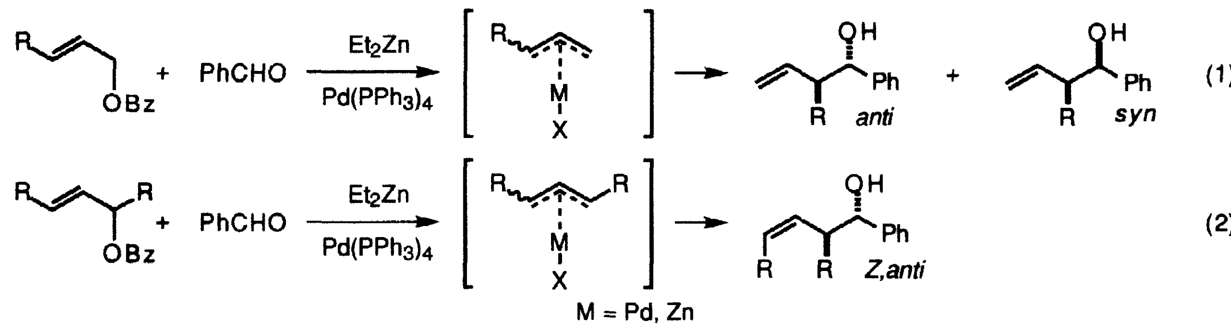


In order to address the remarkable α-substituent effects, we examined the reaction of β-substituted allyl zinc species generated from allyl benzoates **1** in detail. Results are summarized in Table 1. We selected methyl, isopropyl, and methoxymethyl (MOM) ether as the representatives of electron-donating substituents (runs 3-8) and alkoxycarbonyls as those of electron-attracting substituents (runs 9-12). For reference, the results obtained for *trans*- (**1a**)[3] and *cis*-crotyl benzoates (**1b**) are listed in runs 1 and 2.

The selective formation of *anti*-**2a** and *syn*-**2a** from *trans*-crotyl (**1a**) and *cis*-crotyl benzoates (**1b**) (runs 1,2), respectively, suggests that the allylzinc species *E*,γ-**I** and *Z*,γ-**I** (R = Me, R' = H, Scheme 1) isomerize to each other rather slowly. Comparison of two pairs of results (runs 1 and 3 and runs 2 and 4) clearly indicates that the β-methyl groups of **1c** and **1d** apparently suppress the isomerization between *E*,γ-**I** and *Z*,γ-**I** (R = R' = Me, *vide infra*). Unexpectedly, **1c** and **1d** furnished *Z*-**3a** in considerable amounts, the product being formed by the allylation at the allyic terminus with the least number of substituents via **TS-III** (Scheme 1). The structure of *Z*-**3a** was determined unequivocally by NOE experiments: 4.1%, 7.4% and 0% NOE's for $C(3)CH_3$, $C(4)CH_3$, and $C(2)H_2$, respectively, by irradiation at $C(4)H$. The corresponding *E*-isomer was not detected.

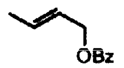
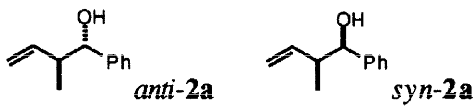
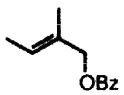
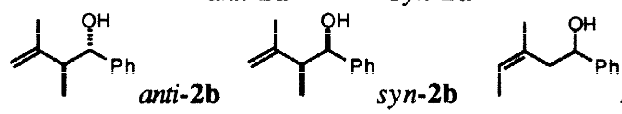
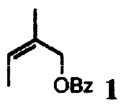
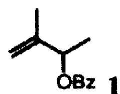
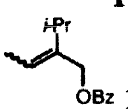
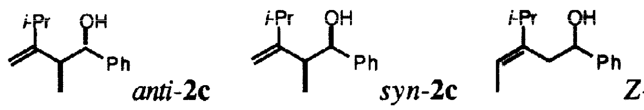
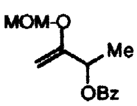
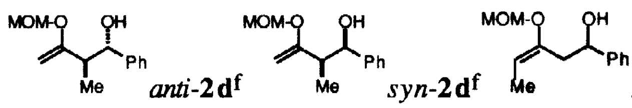
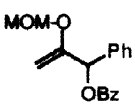
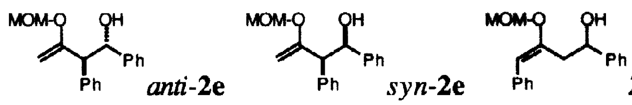
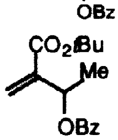
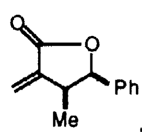
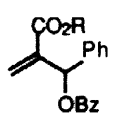
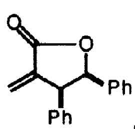
The other allylating agents with electron-donating isopropyl and MOM ether groups at the β-position showed more or less similar reactivity (runs 6-8). In these cases, however, **3b-d**, all possessing Z-stereochemistry, were obtained in much higher proportions.

β-Alkoxycarbonyl groups, on the other hand, provided *syn*-**2** exclusively which, under the reaction conditions, spontaneously cyclized to give rise to α-methylene-γ-butyrolactone derivatives (*syn*-**4a**,**b**, runs 9-12, Table 1).[7]

These contrasting β-substituent effects may be rationalized as follows. Electron-donating β-substituents may enhance the reactivity of all the allyl zinc intermediates involved, especially that of the α-substituted *Z*,α-**I** and *E*,α-**I**, since the α-substituent of *E*,γ-**I** and *Z*,γ-**I** may sterically hinder the reaction with aldehyde. The formation of *Z*-**3** as the major product (runs 6-8) or in the amounts comparable to *syn*- and *anti*-**2** (runs 3-5) may be attributed to the transition state **III**, which is free from gauche repulsion between R and the ligands X and Y on Zn that the transition state **II**, leading to *E*-**3**, suffers from.[4] The reaction of *Z*,α-**I** with benzaldehyde may interrupt the isomerization between *E*,γ-**I** and *Z*,γ-**I**; hence, a good stereochemical correlation between the starting materials and the products results, i.e., the selective formation of *anti*-**2** from *E*-**1** via **TS-I** and of *syn*-**2** from Z-**1** via **TS-IV** (runs 3,4,6). Electron-attracting β-substituents, on the other hand, render all the allylzinc intermediates less reactive and a complete equilibrium among them may have been established before the addition to benzaldehyde takes place. Hence, only the thermodynamically most stable *Z*,γ-**I** may become responsible for the allylation to provide *syn*-**2** (and hence *syn*-**4**) exclusively.

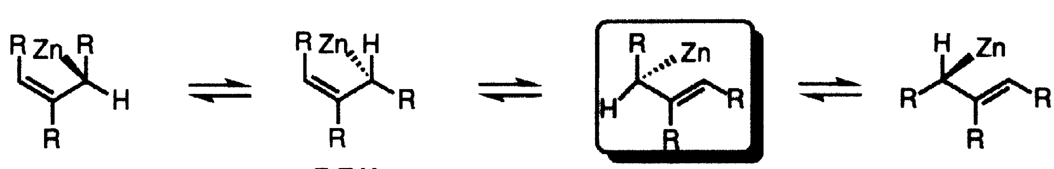
We next examined the allylation of benzaldehyde with α,β,γ-trisubstituted allyl benzoates **1m-p**. The results are summarized in Table 2. Interestingly, all the reactions, irrespective of the difference in

Table 1. Allylation of Benzaldehyde with α,β- and β,γ-Disubstituted Allylic Benzoates[a]

run	benzoate 1	time (h)	structure of products	product ratio *anti*-2:*syn*-2:*Z*-3	% yield[e]
1[b]	 **1a**	2	 *anti*-**2a** *syn*-**2a**	2.4 : 1 : 0	94
2	 **1b**	5	*anti*-**2a** *syn*-**2a**	1 : 3.6 : 0	79
3	 **1c**	72	 *anti*-**2b** *syn*-**2b** *Z*-**3a**	4.1 : 1 : 3.1	82
4	 **1d**	71	*anti*-**2b** *syn*-**2b** *Z*-**3a**	1 : 9.0 : 1.5	92
5	 **1e**	25	*anti*-**2b** *syn*-**2b** *Z*-**3a**	1.3 : 1.4 : 1	82
6	 **1f** *E* : *Z* = 3 : 1	72	 *anti*-**2c** *syn*-**2c** *Z*-**3b**	2.9 : 1 : 4.9	61
7	 **1g**[c]	24	 *anti*-**2d**[f] *syn*-**2d**[f] *Z*-**3c**	3.0 : 1 : 4.0	72
8	 **1h**[c]	24	 *anti*-**2e** *syn*-**2e** *Z*-**3d**	1 : 1 : 3.0	90
9	 **1i**[d]	4	 *syn*-**4a**	0 : 1 : 0	47
10	 **1j**[d]	3	 *syn*-**4b** R = *t*-Bu	0 : 1 : 0	57
11	**1k**[d]	3	R = Et	0 : 1 : 0	25
12	**1l**[d]	3	R = Me	0 : 1 : 0	22

a) Reaction conditions: **1** (1.2 mmol), benzaldehyde (1.0 mmol), Et_2Zn (2.4 mmol), $Pd(PPh_3)_4$ (0.05 mmol) in THF (5 ml) at rt under N_2. b) Taken from ref. 3. c) The alcohol was prepared according to the reference procedure.[5] d) The alcohol was prepared according to the reference procedure.[6] e) Yield refers to the combined isolated yield. All products were properly characterized by IR, ^1H NMR (400 MHz), ^{13}C NMR (100 MHz), and HRMS spectra (or by elemental analysis). f) Tentative assignment based on $J_{H1\text{-}H2}$ = 8.8 (*anti*-**2d**) and 2.2 Hz (*syn*-**2d**) ($CDCl_3$).

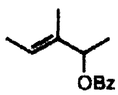
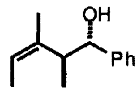
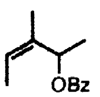
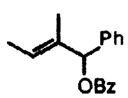
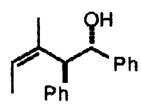
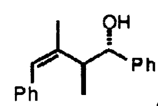
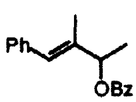
Scheme 2.



stereochemistry (runs 1,2) and substitution pattern (runs 3,4) of the starting benzoates, gave uniformly *Z,anti*-

products **5** exclusively. These results suggest that only *Z,E*-**II** (Scheme 2), among the four possible kinds of allylzinc species, is responsible for the allylation. Among these, *E,E*-**II** and *E,Z*-**II** may be excluded, since they expose the substituent R attached to the carbon bearing Zn to a gauche repulsive interaction with the X, Y ligands on Zn in a transition state for the reaction with benzaldehyde (cf. **TS-II**, Scheme 1). The allyl zinc species *Z,Z*-**II** may also be ruled out owing to a severe A(1,3)-strain between C(1)*R* and C(3)*R*.[8]

Table 2. Allylation of Benzaldehyde with α,β,γ-Trisubstituted Allylic Benzoates[a]

run	allyl benzoates	time (h)	% isolated yield of products[b]
1	 **1m**	100	 *Z,anti*-**5a**: 91
2	 **1n** (*E*:*Z* = 1:2.6)	88	*Z,anti*-**5a**: 55
3	 **1o**	6	 *Z,anti*-**5b**: 30  *Z,anti*-**5c**: 42
4	 **1p**	30	*Z,anti*-**5b**: 27 *Z,anti*-**5c**: 25

a) Reaction conditions: allyl benzoates (1.2 mmol), benzaldehyde (1.0 mmol), Et_2Zn (2.4 mmol), $Pd(PPh_3)_4$ (0.05 mmol) in THF (5 ml) at rt under N_2. b) All products were properly characterized by IR, ^1H NMR (400 MHz), ^{13}C NMR (100 MHz), and HRMS spectra (or by elemental analysis).

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