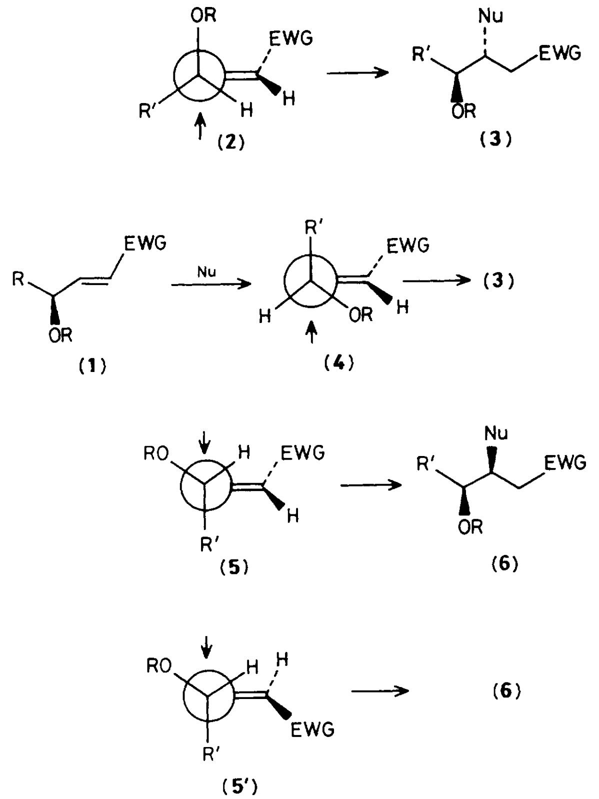
# Diastereoselectivity of Conjugate Addition to γ-Alkoxy-α,β-unsaturated Esters *via* Organocopper–Lewis Acids and Related Reagents. Importance of the Double Bond Geometry in Controlling the Selectivity

**Yoshinori Yamamoto,*[a] Shinji Nishii,[a] and Toshiro Ibuka[b]**

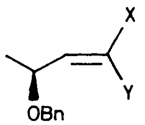
[a] *Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan*
[b] *Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto 606, Japan*

The Lewis acid mediated addition of organocopper reagents to the *trans*-ester (**7a**) produced the *anti*-isomer (**8a**) predominantly, while addition to the *cis*-derivative (**7b**) gave the *syn*-isomer (**9a**) preferentially, and addition of organometallic compounds to the diester (**7c**) also afforded the *syn*-isomer (**9b**) predominantly; this change in diastereoselectivity indicates the importance of the double bond geometry in controlling the 1,2-asymmetric induction of γ-alkoxy-α,β-unsaturated carbonyl compounds.

The diastereoselectivity of nucleophilic addition to γ-alkoxy-α,β-unsaturated carbonyl derivatives (**1**) is puzzling. Some additions have been interpreted in terms of a modified Felkin–Anh model (**2**), which produces the *anti*-isomer (**3**) (Scheme 1).[1] $^1$H N.m.r. analyses[2] and calculations[3] suggest that conformer (**4**), which would also give (**3**) as the major product, would be preferred in the ground state. It has not so far been possible to determine whether (**2**) or (**4**) is the more reactive conformer. Further, in some cases the opposite diastereoselectivity is observed; the *syn*-isomer (**6**) is pro-

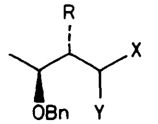


**Scheme 1.** EWG = electron withdrawing group.



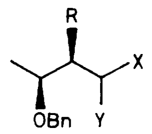
(7)

a; X = $CO_2Et$, Y = H
b; X = H, Y = $CO_2Et$
c; X = Y = $CO_2Et$



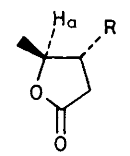
(8)

a; X = H, Y = $CO_2Et$
b; X = Y = $CO_2Et$

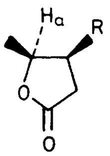


(9)

a; X = H, Y = $CO_2Et$
b; X = Y = $CO_2Et$



(10)



(11)

Bn = $PhCH_2$

**Table 1.** Diastereoselectivity of conjugate addition to γ-alkoxy-α,β-unsaturated esters.[a]

| Entry | Substrate | RM | Product ratio (**8**)(*anti*) : (**9**)(*syn*) | Total isolated yield, % |
|---|---|---|---|---|
| 1 | (**7a**) | MeCu–$BF_3$ | 69 : 31[b] | 60 |
| 2 | (**7a**) | BuCu–$BF_3$ | 92 : 8[c] | 64 |
| 3 | (**7b**) | MeCu–$BF_3$ | 22 : 78[b] | 30 |
| 4 | (**7b**) | BuCu–$BF_3$ | 22 : 78[c] | 56 |
| 5 | (**7c**) | MeCu–$BF_3$ | 6 : 94[d]<br>(4 : 96)[e] | 54 |
| 6 | (**7c**) | $Me_2CuLi$ | 37 : 63[d]<br>(23 : 77)[e] | 75 |
| 7 | (**7c**) | MeMgBr | 5 : 95[e] | 83 |
| 8 | (**7c**) | MeLi | 2 : 98[e] | 78 |
| 9 | (**7c**) | BuCu–$BF_3$ | 5 : 95[d] | 52 |
| 10 | (**7c**) | $Bu_2CuLi$–$BF_3$ | 19 : 81[e] | 51 |
| 11 | (**7c**) | $Bu_2CuLi$ | 32 : 68[d]<br>(23 : 77)[e] | 63 |
| 12 | (**7c**) | BuCu | 30 : 70[e] | 75 |
| 13 | (**7c**) | BuLi | 28 : 72[e] | 67 |

[a] All reactions were carried out on a 1 mmol scale under $N_2$. The reagents were added at −78 °C and the reactions were quenched at room temperature. The stereochemistry of (**8**) and (**9**) was determined as follows. Treatment of (**8a**) and (**9a**) with $H_2$–Pd/C in ethanol gave (**10**) and (**11**), respectively. $H_a$ of (**10**) resonated at higher field than $H_a$ of (**11**) owing to the shielding effect of R: (**10**), $H_a$ δ 4.05 for R = Me and Bu; (**11**), $H_a$ δ 4.55 for R = Me and 4.58 for R = Bu. Decarboxylation of (**8b**) and (**9b**) upon heating in $Me_2SO$–$H_2O$–NaCl produced (**8a**) and (**9a**), respectively, and thus the stereochemistry of (**8b**) and (**9b**) could be correlated with that of (**8a**) and (**9a**). [b] By capillary g.l.c. (SE-30; 25 m). [c] By 400 MHz $^1$H n.m.r. spectroscopy. [d] By capillary g.l.c. after decarboxylation. [e] By 90 MHz $^1$H n.m.r. spectroscopy.

duced predominantly which may be interpreted as being formed *via* addition to the conformer (**5**).[4]

We now report that the double bond geometry plays an important role in controlling the diastereoselectivity of conjugate addition to γ-alkoxy-α,β-unsaturated esters. The results are summarized in Table 1.

The reaction of the *trans*-ester (**7a**) with RCu–$BF_3$ produced the *anti*-isomer (**8a**) predominantly (entries 1 and 2), whereas the *cis*-ester (**7b**) gave the *syn*-isomer (**9a**) preferentially (entries 3 and 4).[5] The reaction of (**7a**) and (**7b**) with $R_2CuLi$ or $R_2CuLi$–$BF_3$ did not give the conjugate addition product, but afforded the product of allylic substitution at the α-position as the major product; $S_N2'$ type substitution took place.[6] The conjugate addition to (**7c**) produced the *syn*-isomer (**9b**) with very high to good selectivity (entries 5—13). The diastereoselectivity in the reactions of (**7c**) is thus identical to that of the *cis*-derivative (**7b**). Conjugate addition to (**7c**) proceeded smoothly with normal copper reagents, or even with the lithium and magnesium reagents.

It is noteworthy that the diastereoselectivity depends upon the geometry of double bond. Most previous results for conjugate additions indicate that the selectivity does not depend on the geometry.[1a,4b,g] Only two papers, on $OsO_4$ catalysed hydroxylation,[1j,l] and one, on conjugate addition,[1e] indicate the importance of the geometry.

The stereochemical outcome of the reactions of (**7a**) is in good agreement with predictions *via* the modified Felkin model (**2**). The diastereoselectivity with (**7b**) and (**7c**) may be interpreted as arising *via* addition to conformer (**5'**). However, an important question arises concerning both models (**2**) and (**5'**). Is there any logical reason why the *trans*-isomer (**7a**) reacts *via* (**2**), and the *cis*-isomer (**7b**) and (**7c**) react *via* (**5'**)? The answer is no. The present results can be explained as follows.

The *trans*-isomer (**7a**) would adopt a conformation similar to (**4**) in the ground state as verified by $^1$H n.m.r. studies,[2] and in conformity with a favourable interaction between the p orbital of the double bond and the lone electron pair on the oxygen.[11] Although the ground state and the reactive conformer are not necessarily the same, it seems that the addition takes place *via* (**4**). In (**7b**), the *cis*-geometry of the electron withdrawing substituent destabilizes this conformer, forcing structure (**5′**) to be adopted in order to minimize the steric repulsion between the electron withdrawing group and the allylic substituent.

In conclusion, we propose that (**4**) is the reactive conformer for the addition to (**7a**), although (**2**) is generally believed to be the reactive conformer.† Further, the present development provides a synthetically useful method for preparing both diastereoisomers (**3**) and (**6**) selectively.

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† Stork also proposed (**4**) in the hydroxylation reaction [ref. 1(l)].