# Diastereoselectivity of Conjugate Addition to γ-Alkyl-α,β-unsaturated Esters; Stereocontrol with the Aid of Organocopper Reagents

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The conjugate addition of organo-cuprate and -copper reagents to the *trans*-ester (**1**) produced the *anti*-isomer (**4a**) predominantly, while addition of cuprates to the *cis*-esters (**2** and **3**) gave the *syn*-isomer (**5**) preferentially, and addition of organocopper compounds to (**2**) and (**3**) afforded the *anti*-isomer (**4**) predominantly; this change indicates the importance of reagent type in controlling 1,2-asymmetric induction during conjugate addition.

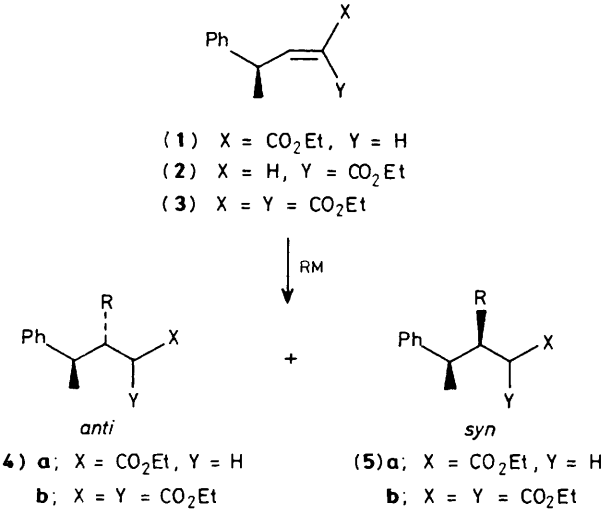
Although the diastereofacial stereoselectivity in the Michael addition to γ-alkoxy-α,β-unsaturated carbonyl compounds has been investigated widely,[1] the stereoselectivity of the conjugate addition to γ-alkyl-α,β-unsaturated derivatives has received little attention.[2] We report that the type of organocopper reagent, as well as the double bond geometry, exert a strong influence upon the diastereoselectivity. The results are summarized in Table 1.

The conjugate addition[3] to the *trans*-ester (**1**) produced the *anti*-isomer (**4a**) predominantly regardless of the reagent type (Table 1, entries 1—3; Scheme 1). To our surprise, opposite diastereoselectivity was observed with the cuprate and the copper reagents; in the addition to the *cis*-ester (**2**), butylcopper–$BF_3$ gave the *anti*-product (**4a**) predominantly (entry 5), while cuprates produced the *syn*-isomer (**5a**) preferentially (entries 4 and 6). This interesting observation was further confirmed in the addition to the diester (**3**) which also possessed a *cis*-ester group: the cuprate reagents produced the

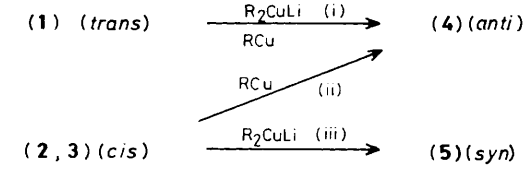
**Table 1.** Diastereoselectivity of conjugate addition to γ-alkyl-α,β-unsaturated esters.[a]

| Entry Substrate | RM | Product ratio[b] (4):(5) (*anti*):(*syn*) | Total isolated yield, % |
|---|---|---|---|
| 1 (1) | $Bu_2CuLi{\cdot}BF_3$ | 70:30 | 90 |
| 2 (1) | $BuCu{\cdot}BF_3$ | 88:12 | 82 |
| 3 (1) | $Me_3CuLi_2{\cdot}BF_3$ | 87:13 | 46 |
| 4 (2) | $Bu_2CuLi{\cdot}BF_3$ | 30:70 | 89 |
| 5 (2) | $BuCu{\cdot}BF_3$ | 74:26 | 84 |
| 6 (2) | $Me_3CuLi_2{\cdot}BF_3$ | 21:79 | 67 |
| 7 (3) | $Bu_2CuLi{\cdot}BF_3$ | 32:68 | 67 |
| 8 (3) | $BuCu{\cdot}BF_3$ | 74:26 | 90 |
| 9 (3) | $Me_3CuLi_2{\cdot}BF_3$ | 39:61 | 90 |
| 10 (3) | $Bu_2CuLi$[c] | 8:92 | 87 |
| 11 (3) | $MeCu{\cdot}BF_3$ | 79:21 | 95 |
| 12 (3) | MeMgBr | 60:40 | 89 |
| 13 (3) | $Me_4AlLi$ | 62:38 | 88 |
| 14 (3) | $CH_2{=}CHCH_2SnBu_3$[d] | 96: 4 | 93 |

[a] All reactions were carried out on a 1 mmol scale under Ar. The substrate was added to an ether solution of the organometallic compounds at −78 °C and the reaction was quenched at −20 °C, except where otherwise indicated. [b] By capillary g.l.c. (SE-30, 25 m). For entries 1, 2, 4, and 5, $^1H$ n.m.r. analysis was used. [c] 1,2-Dimethoxyethane was used as a solvent. [d] $CH_2Cl_2$ was used as a solvent and $TiCl_4$ (1 equiv.) was added.

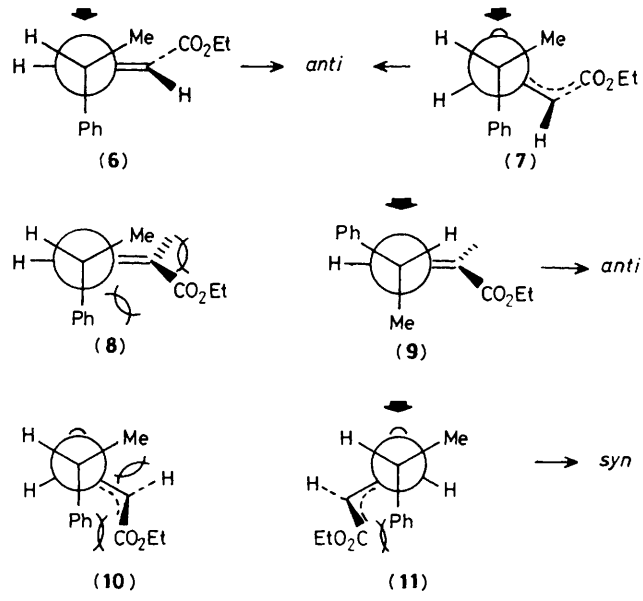



**Scheme 1**




**Scheme 2**

*syn*-isomer (**5b**) predominantly (entries 7, 9, and 10), while the copper and common organometallic reagents gave the *anti*-isomer (**4b**) preferentially (entries 8, 11—14). In conclusion, (i) the *trans*-ester (**1**) gave the *anti*-isomer (**4**) irrespective of the copper reagent type, (ii) the *cis*-esters (**2** and **3**) also produced (**4**) *via* copper reagents, and (iii) they afforded the *syn*-isomer (**5**) *via* cuprate reagents (Scheme 2). The structures of (**4**) and (**5**) were assigned unambiguously by comparison with authentic materials.†




**Scheme 3**

The diastereoselectivity can be explained as follows (Scheme 3). A modified Felkin–Anh model (**6**) is applicable to the addition of RCu to the *trans*-ester. The cuprate addition, which may proceed through an electron transfer process, presumably proceeds *via* a staggered conformation (**7**) rather than (**6**).[4] For the addition of RCu and common nucleophiles to the *cis*-esters, conformation (**8**) is destabilized owing to steric repulsion, forcing structure (**9**) to be adopted which produces the *anti*-isomer. The staggered model (**10**) of the *cis*-esters is destabilized for the same reason, and thus the cuprate addition proceeds through (**11**) to give the *syn*-isomer.

Evidence for the electron transfer process in $R_2CuLi$ addition was obtained by a trapping experiment with *p*-dinitrobenzene; $Bu_2CuLi$ addition to (**3**) in the presence of 1 equiv. of *p*-dinitrobenzene produced the *anti*-isomer predominantly. Use of 10 equiv. of *p*-dinitrobenzene completely inhibited the conjugate addition. These findings provide the first example of acyclic stereocontrol which can be directed by either a one or two electron transfer process.

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## References

1 For a recent paper on this subject see Y. Yamamoto, S. Nishii, and T. Ibuka, *J. Chem. Soc., Chem. Commun.*, 1987, 561, and references cited therein.
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4 K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y.-D. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li, and R. J. Loncharich, *Science*, 1986, **231**, 1108.

† In products (**4a**) and (**5a**) the $CHCO_2Et$ centre can also be chiral. We have not yet investigated this problem in this system. The stereoselectivity of alkylation of the related ester enolates has been reported: see Y. Yamamoto and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, 1984, 904.