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Control of diastereofacial discrimination in the conjugate addition to 5-phenyl-1,3-dioxolan-4-yl substituted propenoate

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Abstract

The conjugate addition of methylcuprates and methyllithium to ethyl 5-phenyl-1,3-dioxolan-4-yl-2-propenoate was investigated. It was found that the stereoselectivity is highly dependent on the reagent used. In reactions with stabilized methylcuprates, the *anti*-1,4-addition product is mainly formed, whereas *syn*-diastereoselectivity is observed in the reaction with methyllithium. Additions of methyllithium were optimized with respect to solvent and additives. © 2000 Elsevier Science Ltd. All rights reserved.

The asymmetric conjugate addition of carbon nucleophiles is an important method for the formation of carbon–carbon bonds and plays an important role in the synthesis of natural products.[1] However, the divergent results regarding the diastereoselectivity of addition reactions e.g. to γ-alkoxy substituted enoates, render the interpretation and prediction of the stereochemical outcome difficult. Alkyl or silyl substituents on the γ-oxygen modulate the electron donor capability of this group and, consequently, change the reaction pathway from a chelated to a non-chelated transition state.[2,3]

A different situation may occur when the γ-alkoxy group is incorporated into a dioxolane ring.[4] We found predominant *syn*-selectivity upon addition of chiral secondary lithium amides to dioxolan-4-yl substituted *E*-configured enoates.[5] The diastereoselective conjugate addition of organolithium and organocopper reagents to glyceraldehyde-derived α,β-unsaturated ketones and esters has been examined by Leonard et al.[6] While alkyl and vinyllithium compounds yield mainly *syn*-1,4-adducts with dioxolan-4-yl substituted *E*-configured enoates, extensive decomposition is reported for additions of organocopper reagents to α,β-unsaturated esters.

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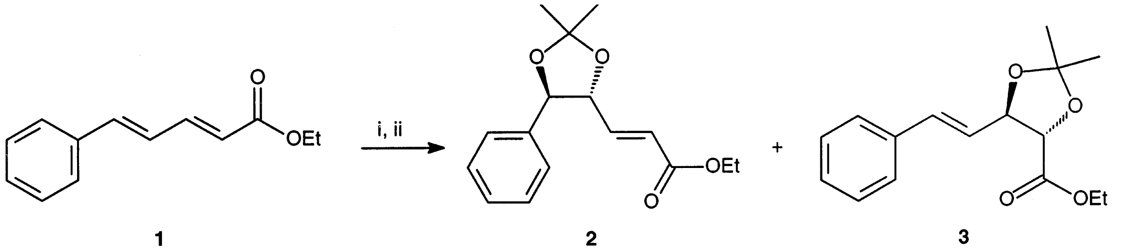
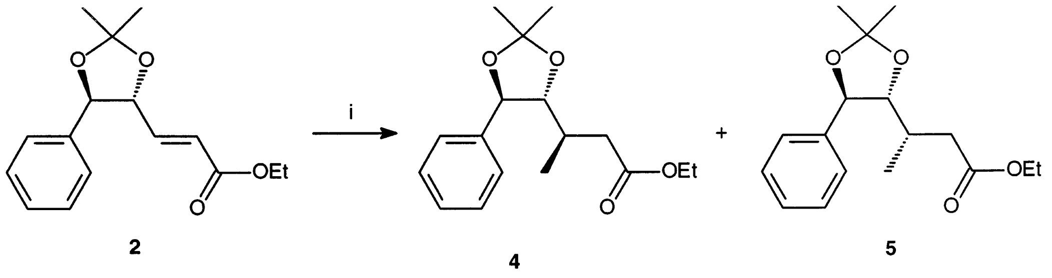
We examined the diastereoselectivity of the 1,4-addition of methyllithium and several methylcopper reagents to ethyl (2*E*)-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-2-propenoate **2** (Scheme 2) and found a profound difference in the diastereofacial discrimination among the organometallic reagents used. Enantiomerically pure **2** was prepared by asymmetric dihydroxylation[7] of dienoate **1**,[8] subsequent protection of the diol mixture and chromatographic separation of the regioisomers **2** and **3** (Scheme 1).



Scheme 1. (i) (DHQD)$_2$–PHAL (1.0 mol%), $K_2OsO_4 \cdot 2H_2O$ (1.0 mol%), $K_3[Fe(CN)_6]$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1, v:v), 0°C; (ii) $(MeO)_2CMe_2/Me_2CO$ (1:1, v:v), *p*-TosOH, rt



Scheme 2. (i) Reagents see Table 1

Initially various methylcopper reagents—reagents of choice in a similar synthesis[11]—were generated from methyllithium and reacted with enoate **2** (Table 1, entries 1–4). The relative configurations of the 1,4-addition products (**4**-*anti*, **5**-*syn*) were assigned by NOE-DIFF experiments with the corresponding γ-lactones (Scheme 3). In lactone **6**, derived from *anti*-addition product **4**, an enhancement was observed between the methyl group and H-5, and correspondingly no enhancement between methyl and benzylic protons was detected. In lactone **7**, derived from *syn*-addition product **5**, a significant enhancement between the methyl group and the benzylic proton was observed, whereas no enhancement between the methyl group and H-5 was detected.

Table 1
Selected results of enoate **2** reactions with methylcopper reagents and methyllithium

No.	Reagent	Solvent	Temperature (°C)	**4**:**5**	Yield of main isomer (%)
1	$MeCu(CN)Li/BF_3{\cdot}Et_2O$, 5 eq.	Et_2O	−78	38:1	60[a]
2[9]	Me_2CuLi/Me_3SiCl, 1.5 eq.	Et_2O	−78	7:1	72[b]
3	$Me_2CuLi{\cdot}PBu_3$, 2 eq.	Et_2O	−78	2:1	57[a]
4	Me_2CuLi, 2.5 eq.	Et_2O	−78	1.9:1	65[a]
5	MeLi, 1.1 eq.	Et_2O	−78	<1:99	29[a]
6	MeLi, 1.5 eq.	Et_2O	−78	<1:99	24[a]
7	MeLi, 1.5 eq., Me_3SiCl, 1.5 eq.[c]	Et_2O	−78	<1:99	55
8	MeLi, 1.2 eq., Me_3SiCl, 1.2 eq.[c]	Et_2O	−78	<1:99	76 (>85[a])
9	MeLi, 2.0 eq., Me_3SiCl, 3.0 eq.[d]	Et_2O	−78	<1:99	53
10	MeLi, 1.2 eq., Me_3SiCl, 2.0 eq.[d]	*t*-BuOMe:Et_2O (32:1, v/v)	−78	<1:99	46 (51[e])
11[10]	MeLi, 1.3 eq., Me_3SiCl, 2.0 eq.[d]	Hexane:Et_2O (4:1, v/v)	−90 to −80	<1:99	69 (76[e])

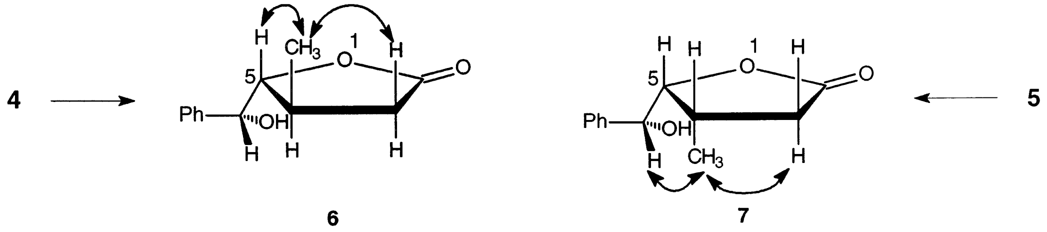
[a] According to GC–MS data.

[b] ~86% d.e.

[c] Stepwise, alternating addition of MeLi and Me_3SiCl.

[d] Me_3SiCl was added to the reaction mixture before MeLi addition.

[e] According to ^1H NMR data.



Scheme 3.

Mainly 1,4-addition products were formed with organocuprates in moderate to high *anti*-selectivity, especially when a Lewis acid or Me_3SiCl stabilized methylcopper reagent was used. The addition of 5 eq. of $MeCu(CN)Li/BF_3{\cdot}Et_2O$ leads to diastereomerically pure **4**, although a substantial amount of starting material was detected even after 20 h of reaction time. The reaction of **2** with 1.5 eq. of Me_2CuLi/Me_3SiCl proceeds smoothly with satisfactory yield. The diastereoselectivity of the reaction with PBu_3 stabilized methyl cuprate reagent (Me_2CuLi) was found to be similar to that of the reaction with Me_2CuLi, although in the presence of PBu_3 formation of 1,2-addition and double 1,2-addition products was detected.

Addition of Lewis acid stabilized methylcopper reagents leads to the *anti*-1,4-addition product and possibly proceeds due to specific coordination of the copper. In order to change the character of the coordination, we investigated the addition of methyllithium to **2**. Satisfactory results have been obtained upon addition of methyllithium to similar systems.[6] The *syn*- and the 1,4-selectivity of the methyllithium addition to (2,2-dimethyl-1,3-dioxolan-4-yl)propenoates was explained by coordination of the lithium atom to the oxygen atoms of the dioxolane ring.

Our first experiments of methyllithium addition to enoate **2** (Table 1, entries 5 and 6) showed that the reaction is completely *syn*-selective, although disappointing in terms of both regioselectivity and yield. Significant amounts of 1,2-addition, double 1,2-addition, 1,2-/1,4-addition products were formed and considerable amounts of starting material were detected. The repeated stepwise addition of MeLi and Me_3SiCl significantly increased the formation of **5** (Table 1, entry 8). In this procedure only a part (1/4) of the complete quantity of MeLi was added at once, where each addition step was followed by the addition of the equivalent quantity of Me_3SiCl. However, this procedure was too complicated for synthetic purposes. Our investigations showed that methyllithium preferably reacts with enoate **2** instead of Me_3SiCl at the reaction temperature (≤ -78°C) and nearly the same yield of **5** was obtained when Me_3SiCl was added before methyllithium. We also attempted to optimize the yield of *syn*-selective methyllithium addition to **2** by reducing the coordinative capability of the solvent and by varying the amount of Me_3SiCl (Table 1, entries 9–11). Using *t*-BuOMe (entry 10) as the solvent leads to nearly the same result as diethyl ether.[12] Compound **5** was obtained in good yield using a hexane/Et_2O-mixture as solvent in the presence of Me_3SiCl (Table 1, entry 11). Application of a non-coordinating solvent enhances the coordinating influence of the dioxolane oxygen atoms as 1,4-addition directing factor.

In conclusion, the addition of methylcopper reagents to **2** results in the formation of *anti*-1,4-addition product **4** with medium to high diastereoselectivity. The *syn*-1,4-addition product **5** was obtained exclusively by addition of MeLi to **2**.

Acknowledgements

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9. To a suspension of dry CuI (1.50 mmol, 0.29 g) in 4 ml of dry ether under Ar at −78°C, MeLi (3.00 mmol, 1.88 ml of ~1.6 M solution in ether) was added dropwise. The mixture was allowed to warm up to −10°C and stirred at this temperature for an additional 30 min. The solution of Me_2CuLi (1.50 mmol) was cooled to −78°C and Me_3SiCl (1.50 mmol, 0.16 g, 0.19 ml) was added dropwise. When ~1/3 of Me_3SiCl was added, a solution of enoate **2** (1.00 mmol, 0.28 g) in ether (2 ml) was added. After additions were completed, the reaction mixture was stirred for 1.5 h, then allowed to warm up to rt and stirred for an additional 2 h. It was quenched with satd aq. NH_4Cl/NH_4OH (20:1, v/v). The organic phase was separated, the aqueous phase extracted with ether (4×20 ml), dried over $MgSO_4$ and evaporated. The residue was chromatographed, hexanes:EtOAc (8:1, v/v) and $CHCl_3$ with 2% of EtOAc to give 0.21 g (72%) of **4** (~86% d.e.). $[\alpha]_D^{28}$ −0.95 (*c* 4.2, $CHCl_3$). ^1H NMR ($CDCl_3$): 0.86 (d, 6.8,

3H), 1.25 (t, 7.1, 3H), 1.47 (s, 3H), 1.53 (s, 3H), 2.15 (dd, 15.0, 8.8, 1H), 2.32 (m, 1H), 2.62 (dd, 15.0, 4.0, 1H), 3.77 (dd, 8.3, 5.8, 1H), 4.15 (q, 7.1, 2H), 4.68 (d, 8.2, 1H), 7.20–7.50 (m, 5H).

10. A solution of MeLi (4.43 mmol, 2.77 ml of 1.6 M solution in ether diluted with 6 ml of ether and 5 ml of *n*-hexane) was added dropwise over 2.5 h to a stirred solution of **2** (3.41 mmol, 0.94 g) and Me_3SiCl (6.81 mmol, 0.74 g, 0.86 ml) in 28 ml of *n*-hexane at −80 to −90°C. The mixture was stirred for 4 h at −78°C, slowly warmed up to rt and treated with satd NH_4Cl solution (40 ml). All precipitated salts were dissolved by dilution with water, the phases were separated and the aqueous layer was extracted with *n*-hexane (4×40 ml). Combined organic extracts were dried over a mixture of solid $NaHCO_3$ and Na_2SO_4. Evaporation of the solvent and flash chromatography (hexanes:EtOAc = 8:1, v/v) gave 0.69 g (69%) of **5**. $[\alpha]_D^{28}$ +3.3 (*c* 5.5, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.03 (d, 6.6, 3H), 1.18 (t, 7.1, 3H), 1.48 (s, 3H), 1.54 (s, 3H), 2.19 (dd, 14.8, 9.1, 1H), 2.28 (m, 1H), 2.38 (dd, 14.5, 4.4, 1H), 3.80 (dd, 8.6, 3.3, 1H), 4.07 (q, 7.1, 2H), 4.72 (d, 8.6, 1H), 7.20–7.50 (m, 5H).
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12. 1,2-Addition took place exclusively when THF was used as solvent (not presented in Table 1).