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Stereoselectivity in the 1,4-Addition Reaction of Organocopper Reagents to Ethyl 3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propenoate

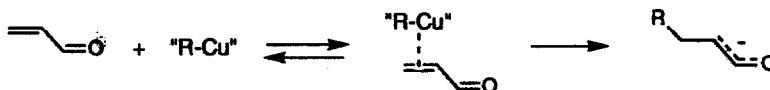
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Abstract: The chemo- and stereoselectivity in reactions with *E* and *Z* isomers of ethyl 3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]acrylate, **1** and **2**, are strongly dependent on the composition of the organocopper reagent. Synthetically useful yields and stereoselectivities are obtained with reagents of good nucleophilicity, e. g. RCu-TMSLi-LiI . A transition state model based on copper-alkene π -complex formation with intramolecular chelation of the γ -oxygen to lithium of a copper-lithium cluster can be used to rationalize the observed *anti* selectivity.

Organocopper reagents of different compositions are highly useful tools in organic synthesis for the formation of new carbon - carbon bonds.¹ Considerable effort has been spent in attempts to achieve high stereoselectivity in the bond formation. Enantioselectivity via chiral auxiliaries in the copper reagents or ligands is an elusive field with some striking examples of success.² Diastereoselectivity via chirality in the organic substrate has proved to be a more accessible route.¹

Our efforts have been directed towards a better understanding of the mechanism for the carbon - carbon bond formation between the organocopper reagent, mostly R_2CuLi , and enones or enoates.



We have shown by NMR spectroscopy that the reversible formation of a π -complex between copper in the organocopper reagent and the alkene π -orbitals of the enoate probably is an early step in the reaction leading to the carbon - carbon bond.³ It has later been shown that alkene-copper π -complex formation also takes place on addition of Me_2CuLi to enones⁴ and enynoates.⁵ Thus π -complex formation is probably a general reaction that has to be taken into account in discussions concerning the mechanism of carbon-carbon bond formation to alkenes activated by electron withdrawing groups.

Furthermore we have observed that the reactivity of the copper reagents and the chemoselectivity of the reactions are strongly influenced by the choice of solvent.⁶ Also, in a non-coordinating solvent as toluene or dichloromethane the presence of a chiral amino group can exert a strong influence on the diastereoselectivity

of the reaction.⁷ The effect of an alkoxy group is not as pronounced but it can exert some influence via chelation to lithium or copper during the reaction.

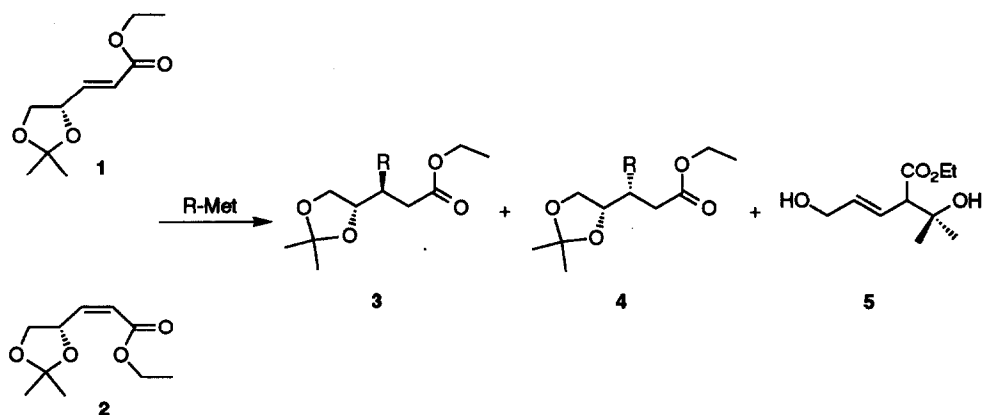
Our previous investigations have been focused on phenyl substituted acrylates. These substrates were chosen for the NMR-studies due to their simple pattern in the NMR which is favourable for interpretation. Their reactivity is also suitable for NMR-experiments. We have now attempted to test our models for the 1,4-addition reaction on compounds that are more closely related to structures of interest for synthetic applications.

Chiral γ -alkoxy substituted enones and enoates sometimes react with organocopper reagents to give good yields of the 1,4-addition products. Chirality transfer can lead to high diastereoselectivity. The presence of the oxygen in the γ -alkoxy group also provides a position for chelation to a metal atom of the organometallic reagent.⁸

It has also been observed that the γ -alkoxy group can be removed from the substrate by reduction when the γ -alkoxy substituted enone is reacted with an alkylcuprate, R_2CuLi .⁹

Results and discussion

We have studied the addition of a range of organometallic reagents to the *E* and *Z* isomers of ethyl 3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propenoate, **1** and **2** respectively.



Scheme 1

The metal composition and the structure of the organic part, R , of $R-Met$ have been varied as well as the concentration of $R-Met$. In this investigation all organocopper reagents, RCu , $RCu/TMSI$ and R_2CuLi , have been prepared by addition of RLi to copper iodide, CuI , in diethyl ether. As the lithium iodide formed in the reaction was not removed before the reactions with **1** or **2** (except in one case) the reagents should rather be written with incorporation of LiI , e.g. $RCu-LiI$. It has been demonstrated previously that this presence of LiI is important for the reactivity of the organocopper reagents.¹⁰ The effect of additives, change of the solvent and the temperature have also been studied. Some results are summarised in the Table. The *anti* and *syn* configurations of the products **3** and **4** respectively were assigned by analogy with results reported by Leonard *et al.*, who have shown the *syn* configuration to be the main product on addition of alkyl lithium reagents to **1**.¹¹

The 1,4-addition products **3** and **4** could be obtained for R = methyl, butyl or phenyl in high yields and reasonable to high stereoselectivity by a careful choice of reaction conditions and composition of the organocopper reagent " RCu ".

As seen from Table 1, dialkyl cuprates are not useful reagents for the formation of a new carbon-carbon bond to **1** or **2**. Whether the R group of the dialkylcuprate, R_2CuLi , is methyl or butyl, **5** is the only product formed. These observations are in good agreement with those of Takano *et al.* who suggested that **5** is formed via a reduction - rearrangement process where the dialkylcuprate reacts with electron transfer solely.¹² Surprisingly, Leonard *et al.* have reported that Bu_2CuLi adds with transfer of the butyl group to the methyl ketone analogues of **1** and **2**.¹³

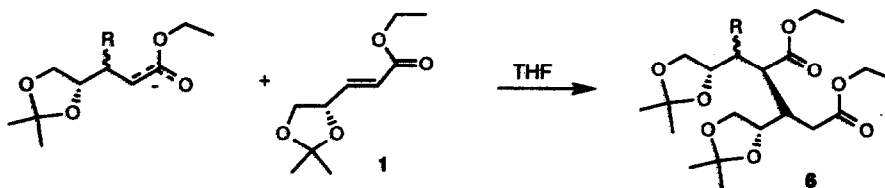
Table 1 Reactions between the *E* and *Z* isomers **1** and **2** with various organometallic reagents R-Met at temperatures and times indicated. Reactions were performed in diethyl ether unless indicated otherwise. The concentration of R-Met varied between 0.04 - 0.11 M, with a reagent : substrate ratio of 2 : 1 (R_2CuLi counted as a monomer).

Substrate	Reagent R-Met	Temp °C	Time h	Yield, % of 3 + 4 , GC	Diastereomeric
					ratio 3 : 4
1	MeCu(LiI)	0	12	no reaction	-
1	MeCu(LiI)/TMSI	-20	20	70	6.5 : 1
2	MeCu(LiI)/TMSI	-20	27	no reaction	-
1	MeCu(LiI)/TMSI	-85	23	60	11 : 1
1	MeCu/TMSI	-85	23	no reaction	-
1	BuCu(LiI)/TMSI	-85	23	83	100 : 0
1	PhCu(LiI)/TMSI	-10	24	80	9.6 : 1
1	Ph ₂ CuLi(LiI)	0	1	76	4 : 1
1	Ph ₂ CuLi (LiI) <i>a</i>	0	0.5	18 <i>c</i>	3 : 1
1	Ph ₂ CuLi (LiI) <i>b</i>	0	1	70	2.6 : 1
2	Ph ₂ CuLi(LiI)	0	5	80	182 : 1
1	MeLi	-78	3	99	1 : 210
1	BuLi	-78	5	76	0 : 100
1	Me ₂ CuLi(LiI)	-78	2	(5) <i>d</i>	
1	Me ₂ CNCuLi ₂	-78	5	(5)	
1	Bu ₂ CuLi(LiI)	-78	5	(5)	
2	Me ₂ CuLi(LiI)	-78	5	(5)	

a Reaction in THF, *b* Reaction in CH_2Cl_2 , *c* high yields of **6**,
d **5** is the only product

Contrary to the alkylcuprates Ph_2CuLi shows the normal reactivity affording high yields of the 1,4-addition products **3** and **4** in diethyl ether. Similarly, divinylcuprates have been reported to react with normal 1,4-addition affording the anti and syn products from γ -methoxyenoates.¹⁴ The addition of Ph_2CuLi to **1** affords a moderate stereoselectivity while the addition to **2** gives the anti adduct **3** only. The addition of Ph_2CuLi to **1** was repeated with tetrahydrofuran, THF, and dichloromethane, respectively, as solvents. The stereoselectivity of the reaction was not strongly affected by the change of solvent as seen from the Table. However, THF induces a considerable change in the reactivity of the cuprate as has been observed previously.^{6,7} The 1,4-addition of a cuprate to **1** is slow in THF giving a low yield of **3** and **4** while once an enolate is formed, it adds to a second molecule of **1** leading to the isolation of a high yield of three or four stereoisomers of the high molecular weight product **6**, cf. Scheme 2.

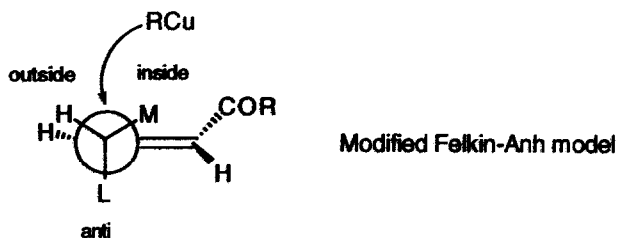
Scheme 2



It has been reported¹³ that the monoorganocopper reagent BuCu reacts with methyl ketone analogues of 1 and 2, giving the 1,4-addition products with *anti-syn*-selectivity 1 : 1.5. As expected, esters 1 and 2 exhibit lower reactivity towards organocopper reagents as demonstrated by the attempt to react 1 with methylcopper. After 12 h at 0° with MeCu(LiI) the starting material, 1, was recovered unreacted. Addition of iodo-trimethylsilane, TMSI,¹⁵ to MeCu(LiI) before addition of 1 afforded high yields of the 1,4-addition products 3 and 4 even at -85°, while the *Z* isomer 2 at -20° is still unreactive towards MeCu(LiI)/TMSI. Removal of LiI formed in the preparation renders the reagent MeCu/TMSI unreactive towards 1.

The reagents PhCu(LiI)/TMSI and BuCu(LiI)/TMSI also react with 1 to give comparable total yields of 3 and 4. The stereoselectivity obtained with MeCu(LiI)/TMSI and PhCu(LiI)/TMSI are of the same order of magnitude while only one diastereomer can be observed on GC and NMR analysis of the crude product from addition of BuCu(LiI)/TMSI to 1. This product has been assigned the *anti*-configuration after comparison with the product we obtained from addition of BuLi to 1, which has been assigned the *syn* configuration.⁸

Previous discussions of the stereoselectivity of the 1,4-addition of an alkyl or vinyl group to γ -alkoxy substituted enones or enoates have been based on a modified Felkin-Anh-model for the transition state of the reaction. The *anti* selectivity of the carbon-carbon bond formation with organocopper reagents, RCu or RCu·BF₃ has been attributed to steric effects causing bond formation *anti* to the γ -alkoxy group (L).

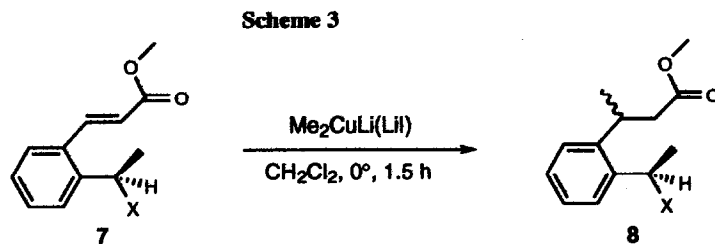


The *syn* stereoselectivities observed for R-Li has been attributed to the chelation of lithium to the γ -alkoxy oxygen atom as this is assumed to direct the nucleophile to the opposite face of the alkene.^{16,17} To increase our understanding of the relative importance of steric effects relative to chelation effects we have compared the reactions of 1 and 2 with the addition of Me₂CuLi to the chiral cinnamates 7a - d performed in dichloromethane at 0°C, Scheme 3.

Cinnamates 7a and 7c have chiral alkyl groups of similar size (steric requirements) as the hetero atom substituted side chains in 7b and 7d, Scheme 3. It is evident from the observed stereoselectivities of these reactions that steric interactions (7a and 7c) do not discriminate between the two possible transition states. The introduction of oxygen in 7b causes some increase in stereoselectivity while with nitrogen in 7d 69% d.e. is observed in the formation of 8d. This effect has been attributed to chelation of the nitrogen atom to

lithium in Me_2CuLi . The effect of oxygen is much smaller indicating that a larger share of the reaction proceeds via a competing reaction via a transition state without chelation.¹⁸

We thus conclude that the alkoxy group has a moderate chelating ability in noncoordinating solvents as dichloromethane. THF has been found to compete more favourably for coordination sites on lithium thus preventing chelation of alkoxy groups. In diethyl ether chelation of the alkoxy oxygen to lithium is a more likely event.

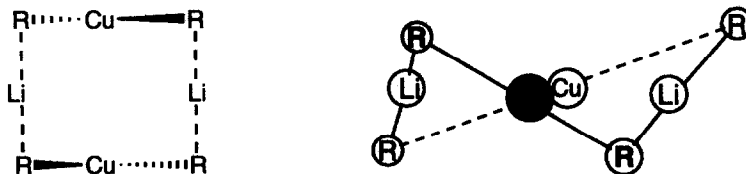


7	Substituent X	Yield, %	d.e., %
a	-CH ₂ CH ₃	88	2
b	-OCH ₃	96	15
c	-CH(CH ₃) ₂	62	2
d	-N(CH ₃) ₂	95	69

7a, 7c, 8a, 8c are new compounds. ¹H, ¹³C NMR-spectra and MS were recorded. 7b, 7c, 8b and 8a have been reported in ref. 6 and 7.

In good agreement with this, the addition of RLi to 1 and 2 and their ketone analogues has been rationalized by including chelation to lithium in the transition state model, see above. However, the corresponding transition state models for the reactions of the organocopper reagents have neither taken into account the composition and structure of "RCu", nor the likely pathway via an alkene-copper π -complex.

Based on previous work on the structure of organocopper reagents in solution and in the solid state it is reasonable to assume that the organocopper reagents RCu used in this investigation all have cluster structures. The composition and structure is likely to influence the course of the reaction, *e. g.* by introducing a site for chelation. Here we will assume that a dimeric structure based on experimental evidence for lithium diorganocuprates can serve as a model.¹⁹ The basic unit of several reported clusters is a linear R-Cu-X anion linked by lithium cations to other units. The nucleophilicity versus electron transfer ability of copper in the R-Cu-X species will depend on the character of the R and X groups on copper. In this investigation R and X can be methyl, butyl, phenyl, trimethylsilyl or iodide.



Proposed structure for the dimeric unit of the lithium diorganocuprate

Based on our previous investigations we would argue that an early step in the reaction between any organocopper reagent "RCu" and the enoates **1** and **2** is the reversible formation of a copper - alkene π -complex.³ Depending on the structure and composition of "RCu" this π -complex may also exist in equilibrium with π -complexes that also have lithium - oxygen chelation to the carbonyl oxygen or the alkoxy oxygen or both. Although it has still not been possible to prove the next step of the reaction, it is generally agreed that a copper(III) intermediate is formed by copper acting as a nucleophile towards the β -carbon. The carbon-carbon bond is then formed by reductive elimination to form an enolate and a copper(I) species. The formation of the copper(III) intermediate may be preceded by a one-electron transfer from copper to the enoate. Carbon-copper bond formation will lead to the copper(III) species and the normally observed 1,4-addition product, an enolate. The alternative route with transfer of a second electron will give reduced products as has been observed in several cases. The observed difference in chemoselectivity between RCu(Li)/TMSI, giving carbon-carbon bond formation, and the alkyl cuprates, giving the reduced product **5**, is in good agreement with the chemical scale on the electron transfer ability for organocopper reagents proposed by Yamamoto and co-workers.²⁰ The substrates **1** and **2** used in this investigation provides a sensitive tool for fine tuning of the electron transfer ability of organocopper reagents.

It is reasonable to assume chelation of oxygen to lithium also in the reactions with organocopper reagents. The opposite stereoselectivities observed for RLi and "RCu" can be related to the different steric requirements on complexation to the substrates forcing **1** and **2** to occupy different conformations on reaction with RLi and "RCu" respectively.

In Fig 1 an attempt is made to accommodate the observed *anti* stereoselectivity of the "RCu" reactions with **1** with a reaction model having copper-alkene π -complexation as the first step. In Fig 1a the γ -oxygen occupies the *anti*-position with the oxymethylene group in the outside position. This conformation allows the organocopper cluster to approach *anti* to the γ -oxygen with formation of a copper-alkene complex (Fig 1 shows only fragments of the copper-lithium cluster). In the subsequent step copper should slide towards the β -carbon causing an increased steric crowding in the transition state for the formation of the copper(III)-intermediate. The steric strain will be relieved on the carbon-carbon bond formation.

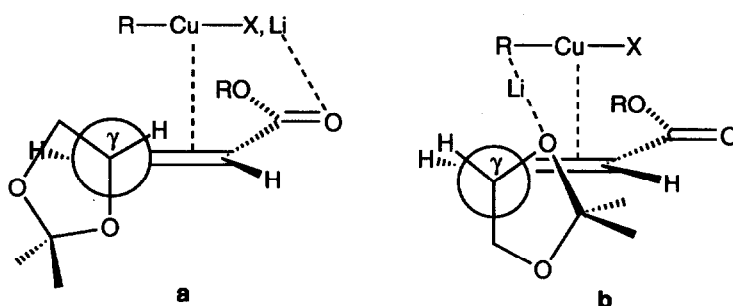


Figure 1

In Fig 1b the γ -oxygen occupies an inside position in a relatively co-planar conformation of the substrate allowing the approach of the large, dimeric cuprate. This conformation will favour interactions between copper and alkene π^* orbitals as well as γ -oxygen to lithium chelation as one of the lithium atoms of a dimeric copper-lithium aggregate will come fairly close to the oxygen. TMSI as part of the organocopper cluster (X = TMS) may participate by bridging between copper and the carbonyl oxygen, with TMS acting as a Lewis acid towards the carbonyl oxygen.

The stereoselectivity of the carbon-carbon bond formation will be determined by the relative reaction rates of this chelated and other possible π -complexes.

The much stronger *anti*-selectivity observed on addition of "RCu" to the *Z* isomer **2** can also be rationalized in terms of a π -complex with intramolecular lithium-oxygen chelation. In Fig 2 an attempt is made to visualize a π -complex where the γ -oxygen (in a pseudo-inside position) and the carbonyl oxygen are only slightly twisted out of the alkene plane bringing both oxygens into chelation to lithium.

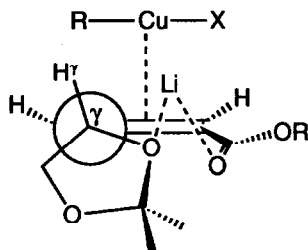


Figure 2

The lower reactivity demonstrated by the *Z* isomer may be related to steric interactions forcing the carbonyl group out of planarity, reducing the activating effect of the electron-withdrawing group. The position of the two oxygens favour chelation to lithium in the cluster, thus lowering the transition state energy relative to other transition states. The opposite *re* face is effectively blocked for approach of the copper cluster.

Conclusion

On the basis of the observed stereoselectivity in the addition of RCu-TMSI-LiI to **1** and **2** we propose a reaction sequence where the first step is the formation of a copper-alkene π -complex with intramolecular oxygen to lithium chelation. The transition state energy is lowered by chelation relative to other possible reaction paths. The high selectivity observed when R = butyl can be understood in terms of the relative steric crowding in the transition state when copper is sliding towards the β -carbon.

The esters **1** and **2** are sensitive probes for the reactivity of an organocopper reagent, as shown by the sequence: MeCu(LiI) and MeCu/TMSI unreactive; RCu(LiI)/TMSI with R = Me, Bu, or Ph, and Ph₂CuLi(LiI) normal 1,4-addition; Me₂CuLi(LiI), Me₂CNCuLi₂, Bu₂CuLi(LiI) electron transfer.

Experimental

General

All experiments with organometallic reagents were carried out under an atmosphere of argon and with dried equipment. Diethylether and THF were distilled from sodium benzophenone ketyl and dichloromethane from CaH₂. Copper(I)iodide was recrystallized using dimethylsulfide as a complexing agent in diethylether according to the method of House *et al.*²¹ Methyl lithium in diethylether, butyllithium in hexane and phenyllithium in cyclohexane/diethylether were all commercial (Aldrich and Fluka) and used with no further purification. Concentrations were determined by titration with diphenyl acetic acid. TMSI were purchased from Janssen. The *E* and *Z* isomers **1** and **2** were purchased from Fluka. ¹H and ¹³C NMR were recorded on a Varian XL 400 MHz spectrometer and gas chromatograms on a Varian 3300 chromatograph(30 m DB-1, FID). Diastereomeric ratios of **3** and **4** were determined on a chiral column(Octakis(3-O-butyl-2,6-O-pentyl- γ -cyclodextrin) for R = butyl before isolation by chromatography. High resolution mass spectra were run on a VG. ZabSpecFPD(CI, isobutane).

Typical experimental procedures.

Method I: -Addition of MeCu(LiI)/TMSI¹⁵

A slurry of 1.1 mmol CuI in 15 ml diethylether was cooled to 0°C before addition of 1 mmol (1.6M) methyl lithium. The yellow precipitate was stirred for 30 min and then cooled to -60°C. 1 mmol TMSI was added and the mixture left with stirring for 5 min. The substrate dissolved in 3 ml diethyl ether was added dropwise at the temperature indicated in Table 1 for the experiment and the mixture then left stirring for the specified time. The reaction was quenched with NH₄Cl/NH₃ and left with vigorous stirring until

the solution attained room temperature. The phases were separated and aqueous phase was extracted three times with diethyl ether. The combined organic layers was washed with saturated sodium chloride and dried over MgSO₄. The solvent was removed on a rotary evaporator.

Method II: -Addition of Ph₂CuLi(LiI)

A slurry of 2.2 mmol CuI in 15 ml diethylether was cooled to 0 °C and 4 mmol (1.6M) phenyllithium was added and stirred for 30 min before 1 mmol substrate dissolved in 3 ml diethylether was added dropwise to the clear light brown solution. The reaction was stirred at 0°C for the time specified in Table 1 and then quenched by addition of NH₄Cl/NH₃. The general work-up procedure(see above) was then followed.

Method III: - Addition of MeLi

0.5 mmol of the substrate was dissolved in 15 ml diethyl ether. The solution was cooled to -78°C before 1 mmol methylolithium was added dropwise. After stirring for 3 h at -78°C a few ml of cold water was added followed by 5 ml of 2M HCl. The mixture was stirred vigorously until room temperature was reached. After extraction with saturated NH₄Cl and NaCl, the organic layer was dried over MgSO₄. The solvent was evaporated to yield the crude product.

Acknowledgement

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References

- 1 Lipschutz, B. H.; Sengupta, S. *Organic Reactions* **1992**, *41*, 135-631
- 2 Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernandez, A. E.; Vickers, D.; Fluckiger, E.; Patterson, G.; Reddy, K. V. *Tetrahedron* **1993**, *49*, 965-986
- 3 a) Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Organomet. Chem.* **1984**, *265*, C22
b) Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Organomet. Chem.* **1985**, *285*, 133
c) Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* **1989**, *45*, 523
- 4 Bertz, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1989**, *111*, 8276
- 5 Krause, N. *J. Org. Chem.* **1992**, *57*, 3509
- 6 Hallnemo, G.; Ullenius, C. *Tetrahedron* **1983**, *39*, 1621
- 7 a) Christenson, B.; Hallnemo, G.; Ullenius, C. *Tetrahedron* **1991**, *47*, 4739
b) Christenson, B.; Ullenius, C.; Håkansson, M.; Jagner, S. *Tetrahedron* **1992**, *48*, 3623
- 8 Leonard, J.; Ryan, G.; Swain, P. *Synlett* **1990**, *1*, 613
- 9 Ibuka, T.; Yamamoto, Y. *Synlett* **1992**, *10*, 769
- 10 For example,
a) House, H. O.; Fisher, Jr., W. F. *J. Org. Chem.* **1968**, *33*, 949
b) Bertz, S. H.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425
c) Lipschutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197
d) Lipschutz, B. H.; Ellsworth, E. L.; Dimock, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 5869
- 11 Leonard, J.; Mohialdin, S.; Reed, D.; Ryan, G.; Jones, M. F. *J. Chem. Soc., Chem. Commun.* **1993**, *1*, 23
- 12 Takano, S.; Sekiguchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, *7*, 449
- 13 Leonard, J.; Ryan, G. *Tetrahedron Lett.* **1987**, *28*, 2525
- 14 Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231
- 15 a) Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1988**, *44*, 2055
b) Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *J. Organomet. Chem.* **1990**, *391*, C19
- 16 a) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, *20*, 1572
b) Hanessian, S.; Sumi, K. *Synthesis* **1991**, *12*, 1083
c) Courtemanche, G.; Alexakis, A.; Vaissermann, J.; Normant, J.-F. *J. Organomet. Chem.* **1992**, *423*, 281-305
d) Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 6524
- 17 Leonard, J.; Mohialdin, S.; Reed, D.; Jones, M. F. *Synlett* **1992**, *9*, 741
- 18 Results for **7b** and **7d** have been reported previously, reference **7a** Christenson *et al.* (10 %de for **7b** and 79/69 %de for **7d**).
- 19 a) Lorenzen, N. P.; Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 300
b) Olmstead, M. M.; Power, P. P. *J. Am. Chem. Soc.* **1990**, *112*, 8008
- 20 Yamamoto, Y. *personal communication*
- 21 House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460