Ester Groups as Effective Ligands in Chelate-Controlled Additions of Cuprates and Grignard Reagents to Chiral β-Formyl Esters

Hans-Ulrich Reissig* and Hubert Angert

Institut für Organische Chemie und Farbenchemie der Technischen Universität Dresden, Mommsenstrasse 13, D-01062 Dresden, FRG

Thomas Kunz, Agnes Janowitz, Gabriele Handke, and Emanuel Bruce-Adjei

Institut für Organische Chemie der Technischen Hochschule Darmstadt, Petersenstrasse 22, D-64287 Darmstadt, FRG

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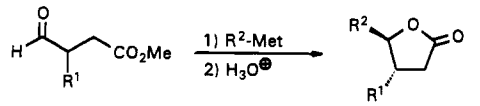
Addition of cuprates to chiral methyl β-formyl carboxylates **1a–1d** provided γ-lactones **2–7** in excellent *trans*-selectivity. The high diastereofacial selectivity was only obtained employing diethyl ether as solvent while tetrahydrofuran gave inferior results. Similar solvent effects were observed in the additions of various Grignard reagents to **1a**, which afforded γ-lactones **2, 3, 12,** and **13** in moderate *trans*-selectivity. The best solvent for these reactions was dichloromethane. The 1,3-induction of cuprate additions was studied by using aldehydes **8a–8c**. The results obtained were interpreted in terms of chelate-controlled additions with formation of seven-membered ring chelates which involve both carbonyl functions of aldehyde **1** or **8**. The function of ester groups as effective ligands of lithium or MgX cations may also be of importance for other stereoselective reactions employing organometallic reagents.

Alkoxy or amino groups[1,2] are often very effective in steering the chelate-controlled additions of Lewis acidic organometallic reagents to carbonyl compounds.[3] Much less is known about the chelate-forming ability of other bifunctional aldehydes or ketones. We could demonstrate that easily available β-formyl carboxylates[4] such as **1** react with allylsilanes/$TiCl_4$,[5] $MeTiCl_3$,[5] silyl enol ethers/$TiCl_4$ (Mukaiyama reaction),[6] and titanium enolates[7] with good to excellent *anti*-selectivities giving *trans*-γ-lactones as major diastereomers after acidic workup (*anti*-Cram selectivity if R^1 = Me). The results can be interpreted by assuming formation of seven-membered ring chelates[8] which involve both carbonyl functions of **1** and titanium as the central metal. For certain cases this chelate structure was proved unequivocally by NMR spectroscopy.[5] Thus, it was established that an ester group is a good ligand for chelation at least for titanium(IV) as the central metal[9] and that high diastereoselectivities can be achieved due to the resulting conformational rigidity.

Recent reports also demonstrate that six-membered chelates formed from certain β-dicarbonyl compounds[10] and Lewis acidic organometallics trigger the addition of the nucleophile with impressive efficiency.[11] In this paper we disclose our results on cuprate additions to chiral β-formyl carboxylates **1** which also proceed with excellent diastereofacial selectivity.[12] For comparison, several Grignard reagents were included in this study.[13]



1 *trans*-γ-lactones

Chelate-Controlled Cuprate Additions. Lithium dimethylcuprate was generated by the standard method in diethyl ether[14] and then reacted at −78 °C with aldehyde **1a** for 10 min. Workup with acid, extraction, and distillation provided γ-lactone **2** in 34% yield with an excellent *trans/cis* ratio of 95:5. The yield could be increased to 83% when the reaction was executed at −40 °C and with less excess of cuprate. We proved that in the crude products the *trans/cis* ratios were very similar or identical to those of the purified γ-lactones. Therefore, we can reasonably assume that the observed *trans/cis* ratio at the lactone stage reflects the diastereofacial selectivity of the addition step.

Similarly, aldehyde **1a** reacted at −78 °C with lithium di-*n*-butylcuprate to afford γ-lactone **3** (whisky lactone[15])

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(2) Review: Reetz, M. T. *Angew. Chem.* **1991**, *103*, 1559–1573; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.

(3) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vols. 1 and 2.

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(9) $ZrCl_4$, $HfCl_4$, and $SnCl_4$ also form chelates with **1**, but they are less effective possibly because of the longer oxygen–metal bonds which result in higher conformational flexibility and lower diastereofacial selectivity; see ref 5.

(10) For an X-ray analysis of a 1,3-diketone–$TiCl_4$ complex see: Maier, G.; Seipp, U.; Boese, R. *Tetrahedron Lett.* **1987**, *28*, 4515–4516.

(11) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1992**, *33*, 4353–4356.

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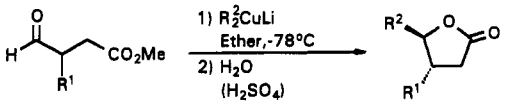


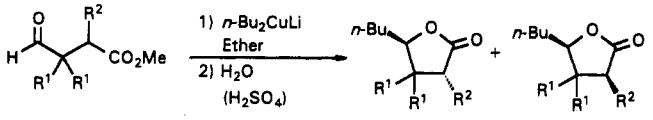
					trans : cis
1a	R^1 = Me	R^2 = Me	34%[a]	2	95 : 5
	R^1 = Me	R^2 = *n*-Bu	54%	3	95 : 5
1b	R^1 = *n*-Bu	R^2 = Me	72%	4	> 95 : 5
1c	R^1 = *i*-Prop	R^2 = *n*-Bu	82%	5	> 95 : 5
1d	R^1 = Ph	R^2 = Me	45%	6	> 95 : 5
	R^1 = Ph	R^2 = *n*-Bu	65%	7	> 95 : 5

[a] 83% yield when the reaction was performed at -40°C.

with a *trans/cis* ratio of 95:5. When the same reaction was performed in tetrahydrofuran instead of diethyl ether the yield dropped to 21% and—more remarkably—the selectivity decreased to 62:38. That THF is an inferior solvent for these reactions was also demonstrated by an experiment with Lipshutz's higher order cuprate[16] $Bu_2Cu(CN)Li_2$ which gave **3** in a 75:25 *trans/cis* ratio and in relatively low purity. Use of bromomagnesium di-*n*-butylcuprate ($Bu_2CuMgBr$) generated from the corresponding Grignard reagent in diethyl ether provided **3** with a *trans/cis* ratio of 84:16 (approximately 60% yield).

Addition of cuprates to β-formyl esters **1b–1d** which have larger substituents R^1 compared with **1a** proceed with even higher diastereoselectivities. *trans*-γ-Lactones **4**, **5** ("isowhisky lactone"), **6**, and **7** were isolated with >95:5 diastereomerical purity; no *cis*-isomers could be detected by ^1H- and ^{13}C-NMR spectroscopy (analytical limit 3–5%).

Having examined asymmetric 1,2-inductions, we studied the reactions of aldehydes **8** which have the chiral center in the β-position with respect to the reactive carbonyl group. As expected, the asymmetric 1,3-induction is considerably lower,[17] but still quite respectable. Surprisingly, reaction of lithium di-*n*-butylcuprate with aldehydes **8a** and **8b** gave γ-lactones **9** and **10** with the *cis*-isomers predominating whereas with trimethyl-substituted aldehyde **8c** compound **11** was obtained with *trans*-selectivity. This reversal of the diastereofacial selectivity has been previously observed for reactions of this aldehyde type with allylsilane/$TiCl_4$.[5] A rationale for this behavior will be presented in the discussion.



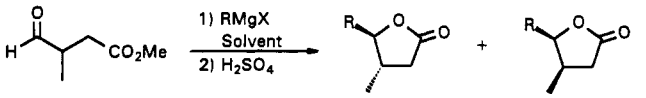
					trans : cis
8a	R^1 = H	R^2 = Me	39%	9	25 : 75
8b	R^1 = H	R^2 = Ph	32%	10	17 : 83
8c	R^1 = Me	R^2 = Me	61%	11	84 : 16

Chelate-Controlled Addition of Grignard Reagents. Since magnesium salts are considered to be effective Lewis acids we also examined a number of Grignard reagents as nucleophiles. In order to control chemoselectivity the reactions were executed at low temperature (–78 °C) and with only a very slight excess of the Grignard reagents. Nevertheless, yields were rarely very good under these conditions (Table I) which may be due to competing additions of the Grignard reagents to the ester function of **1** or to the γ-lactones produced. Later we found that the yields are higher at least with the *n*-butyl Grignard reagent when the reaction was performed at –40 °C.

Table I. Reactions of Grignard Reagents and Phenyllithium with β-Formyl Ester 1a in Diethyl Ether (–45 °C) and Tetrahydrofuran (–78 °C)

entry	reagent	solvent	γ-lactone	yield (%)	*trans:cis*
1	MeMgBr	THF	**2**	39	62:38
2	MeMgBr	Et_2O	**2**	56	69:31
3	*n*-BuMgBr	THF	**3**	24	62:38
4	*n*-BuMgCl	Et_2O	**3**	56	75:25
5	*n*-BuMgBr	Et_2O	**3**	69	79:21
6	*n*-BuMgBr	CH_2Cl_2[a]	**3**	67	84:16
7	allylMgBr	THF	**12**	25	37:63
8	allylMgBr	Et_2O	**12**	34	53:47
9	PhMgBr	THF	**13**	47	66:34
10	PhMgBr	Et_2O	**13**	58	65:35
11	PhLi	THF[b]	**13**	31	79:21
12	PhLi	Et_2O[b]	**13**	39	77:23

[a] Reaction performed at –40 °C. [b] Reaction performed at –100 °C.



1a **2** (R = Me), **3** (R = *n*-Bu)
12 (R = Allyl), **13** (R = Ph)

Reaction of **1a** with methylmagnesium bromide in diethyl ether (entry 2) provided γ-lactone **2** in a 69:31 *trans/cis* ratio (*anti*-Cram selectivity). In tetrahydrofuran the yield and diastereofacial selectivity decreased (entry 1). Similar solvent effects were observed with the *n*-butyl Grignard reagents (entries 3 and 4) and with allylmagnesium bromide (entries 7 and 8) which afforded γ-lactone **12** with the *cis*-isomer predominating (Cram selectivity) in tetrahydrofuran. Interestingly, the *trans*-selectivity in the conversion of **1a** into **3** could slightly be enhanced when the bromomagnesium Grignard reagent (entry 5) was used instead of the chloromagnesium compound (entry 4), and it could be further increased to a reasonable value of 84:16 by employing dichloromethane[18] as solvent (entry 6). On the other hand, for the additions of phenylmagnesium bromide to **1a** (entries 9 and 10), there was no difference observed between tetrahydrofuran and diethyl ether.

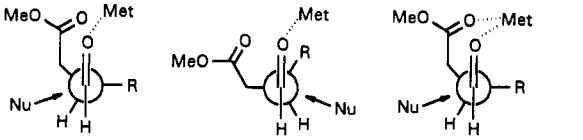
We also tried to study the reactions of organolithium compounds. However, none of the expected products could be isolated after acidic workup even when methyllithium or *n*-butyllithium were added to **13a** at –100 °C. The chemoselectivity of these highly reactive nucleophiles is apparently not sufficient to afford monoaddition products. At least we were able to include phenyllithium in our model studies. This reagent and **1a** provided γ-lactone **13** at –100 °C in poor yield (entries 11 and 12), but with slightly higher *trans*-selectivity compared to the Grignard compound. Surprisingly there was again no influence of the solvent; diethyl ether and tetrahydrofuran gave very similar *trans/cis* ratios.[19]

Discussion

Additions of nucleophiles to chiral aldehydes can be explained by application of the Felkin–Anh model.[20] For

(16) Lipshutz, B. H. *Synthesis* **1987**, 325–341.
(17) For an exception with higher 1,3-induction than 1,2-induction, see: Schmitt, A.; Reissig, H.-U. *Synlett* **1990**, 40–42.
(18) For the use of dichloromethane in reactions of Grignard compounds, see: Turner, R. M.; Lindell, S. D.; Ley, S. V. *J. Org. Chem.* **1991**, *56*, 5739–5740 and references cited therein.

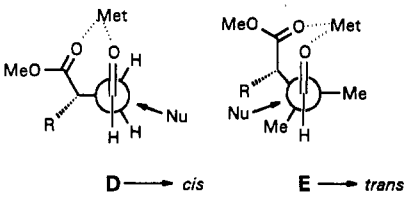
aldehydes of type 1 the conformations **A** and **B**, respectively, with R or CH_2CO_2Me in the perpendicular positions have to be considered. For large groups R **A** should clearly be the favored reactive conformation, but for R = Me **B** should be the slightly favored arrangement, since a methyl group should be sterically less demanding than a (methoxycarbonyl)methyl substituent. Thus the prediction is that additions of nucleophiles to **1a** preferentially lead to *cis*-γ-lactones or at least to low selectivities, whereas reactions of aldehydes with larger substituents give *trans*-γ-lactones. This has experimentally been demonstrated by reactions of aldehydes 1 with allyltrimethylsilane/BF_3[5] or with allyl bromide/zinc.[21]



The results obtained with cuprates are interpreted assuming again the involvement of seven-membered ring chelates **C** in which bridging of the two carbonyl functions by the Lewis-acidic metal center leads to conformational fixation and to formation of *trans*-γ-lactones regardless of the size of group R.[22] Only when R = Me could small amounts of the corresponding *cis*-γ-lactones be detected. As shown for the reactions of aldehyde **1b** this high diastereoselectivity is only observed with diethyl ether as solvent. In the better donor solvent THF this compound competes with the carbonyl functions as a ligand of the metal center and diminishes or inhibits chelate formation. Thus, the *trans*-selectivity is considerably decreased. The same effect is found for additions of most but not all Grignard reagents. *trans*-Selectivities are higher in diethyl ether compared with THF. The use of dichloromethane as solvent leads to an even increased diastereoselectivity in the reaction of butylmagnesium bromide with **1a**. The lower coordination ability of this solvent probably enhances the formation and participation of chelates. This interpretation is surely oversimplified since effects such as the Schlenk equilibria and the aggregation of the organometallic reagents involved are completely neglected. These may be responsible for the observation that clear solvent effects are found for butylmagnesium bromide but not for the phenyl Grignard reagent or phenyllithium.

For the Grignard additions it is obvious that the MgX cation has to take the role of the bridging metal cation in seven-membered chelate **C**. Less clear is the situation with cuprate reactions where the lithium cation or copper(I)[23] may be the Lewis acid. The fact that a cuprate reagent generated from the corresponding Grignard compound displays inferior selectivity compared with the corresponding lithium dialkylcuprates can be taken as evidence that the lithium cation takes the bridging position in chelate **C**. That lithium may be a better Lewis acid[24] in these reactions is also demonstrated by comparing the selectivities of phenylmagnesium bromide with that of phenyllithium (Table I). Contrary to this interpretation we have observed that additions of lithium enolates to **1a** are rather unselective.[7] Also, we have no evidence for complex formation when a solution of aldehyde **1a** in THF was treated with lithium perchlorate. The ^1H NMR and ^{13}C NMR signals of **1a** were essentially unchanged, whereas strong downfield shifts have been found with $TiCl_4$ as Lewis acid. Despite this missing spectroscopic evidence for the lithium bridged chelate we believe that it should be responsible for the diastereoselectivities observed although it may be populated in low concentrations only.

The 1,3-inductions in cuprate additions to aldehydes **8** are less impressive, but they may also be interpreted by chelate formation. Addition of di-*n*-butylcuprate to monosubstituted β-formyl esters **8a** and **8b**, respectively, giving mainly *cis*-γ-lactones can be understood if conformation **D** with the sterically most demanding substituent



in the perpendicular position and a chelate formation are proposed. Seven-membered chelates of this geometry may be not very favorable because of additional strain. Therefore, substitution of the two hydrogen atoms by methyl groups may lead to a preferential conformation such as **E** with one of the methyl substituents in the perpendicular position. Thus, attack of the nucleophile leads to the *trans*-γ-lactones as observed for the conversion of aldehyde **8c** into compound **11**. Admittedly, this interpretation is rather speculative and other possibilities to explain the results may exist. It should be noted, however, that the same reversal of diastereofacial selectivity was found for allylsilane/$TiCl_4$ additions where chelate involvement is unambiguous.[5]

Conclusion

This report demonstrates that ester substituents can be very effective ligands leading to chelate formation and thus to effective control in the addition of nucleophiles to chiral β-formyl esters. Even rather weak Lewis acids such as the lithium or halomagnesium cation lead to formation

(19) For a detailed discussion of the configurational assignments of disubstituted and tetrasubstituted γ-lactones, see ref 5. The assignments for lactones 9–11 were confirmed by NOE experiments. It was further established by equilibration experiments that the ratios obtained for 9–11 were the result of kinetic control and not of subsequent epimerization during workup.

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(21) Kunz, T.; Reissig, H.-U. *Liebigs Ann. Chem.* **1989**, 891–893.

(22) For the addition of Grignard reagents and cuprates to other aldehydes and ketones capable of chelate formation, see: Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031–1034. Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035–1038. Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *23*, 2843–2846. Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422–424. Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609–2612. Radunz, H. E.; Devant, R. M.; Eiermann, V. *Liebigs Ann. Chem.* **1988**, 1103–1105. Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417–420. Bai, X.; Eliel, E. L. *J. Org. Chem.* **1992**, *57*, 5166–5172. Burke, S. D.; Piscopio, A. D.; Marron, B. E.; Matulenko, M. A.; Pan, G. *Tetrahedron Lett.* **1991**, *32*, 857–858.

(23) For a discussion of the complexation phenomena in cuprate additions, see: Krause, N. *J. Org. Chem.* **1992**, *57*, 3509–3512 and references cited therein. Thus, a π-complex formation with one of the carbonyl groups may be conceivable; however, the formation of a seven-membered ring chelate with "soft" Cu(I) species seems rather unlikely. Also see: Kanai, M.; Koga, K.; Tomioka, K. *Tetrahedron Lett.* **1992**, *33*, 7193–7196.

(24) For complexes with lithium, see: Olsher, U.; Izatt, R. M.; Bradshaw, J. S.; Dalley, N. K. *Chem. Rev.* **1991**, *91*, 137–164. Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem.* **1990**, *102*, 273–290; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256.

Table II. Reactions of Aldehydes 1a–1d and 8a–8c with Lithium Dialkyl Cuprates

aldehyde	cuprate	γ-lactone	*trans*:*cis*	yield (%)	bp (°C) (Torr)
0.260 g of **1a** (2.00 mmol)	Me_2CuLi (5.00 mmol)	0.078 g of **2**	95:5	34	60 (2.3)
0.260 g of **1a** (2.00 mmol)	Me_2CuLi[a] (2.20 mmol)	0.190 g of **2**	96:4	83	60 (1.0)
0.325 g of **1a** (2.50 mmol)	$(n\text{-Bu})_2CuLi$ (2.63 mmol)	0.210 g of **3**	95:5	54	70 (0.01)
0.260 g of **1a** (2.00 mmol)	$(n\text{-Bu})_2CuMgBr$[a] (2.20 mmol)	0.219 g of **3**	84:16	70	70 (0.04)
0.869 g of **1b** (5.05 mmol)	Me_2CuLi (12.5 mmol)	0.572 g of **4**	>95:5	72	80–110 (0.02)
0.395 g of **1c** (2.05 mmol)	$(n\text{-Bu})_2CuLi$ (3.75 mmol)	0.377 g of **5**	>95:5	82	100 (0.5)
0.384 g of **1d** (2.00 mmol)	Me_2CuLi (4.00 mmol)	0.160 g of **6**	>95:5	45	100–120 (0.01)
0.384 g of **1d** (2.00 mmol)	$(n\text{-Bu})_2CuLi$ (5.00 mmol)	0.283 g of **7**	>95:5	65	130–140 (0.02)
0.340 g of **8a** (2.60 mmol)	$(n\text{-Bu})_2CuLi$ (4.00 mmol)	0.156 g of **9**	25:75	39	100 (0.75)[b]
1.03 g of **8b** (5.37 mmol)	$(n\text{-Bu})_2CuLi$ (8.00 mmol)	0.377 g of **10**	17:83	32	150 (0.01)[b]
0.880 g of **8c** (5.57 mmol)	$(n\text{-Bu})_2CuLi$ (8.35 mmol)	0.626 g of **11**	84:16	61	100 (0.01)

[a] Reaction performed at −40 °C. [b] Chromatographic purification.

Table III. ^{13}C NMR Data of γ-Lactones **2**, **3**, **4**, **5**, **6**, **7**, and **13**[a]

compd	δ C-2 (s)	δ C-3 (t)	δ C-4 (d)	δ C-5 (d)	δ 4-R^1	δ 5-R^2
trans-**2**	176.2	37.1	38.0	83.3		18.8, 16.5 (2q)[b]
cis-**2**	176.6	36.6	33.1	79.5		15.1, 13.6 (2q)[b]
trans-**3**	176.4	37.3	35.8	87.2	17.2, 13.6 (2q)[b]	33.5, 27.6, 22.3 (3t)
cis-**3**	176.7	36.9	32.8	83.4	13.5 (q)[c]	29.4, 27.8, 22.3 (3t)
trans-**4**	176.4	35.3	43.1	82.0	32.0, 29.6 22.4, 13.7 (3t, q)	19.7 (q)
trans-**5**	176.7	35.5	46.5	83.9	30.6, 20.3, 19.1 (d, 2q)	32.0, 27.6, 22.4, 13.8 (3t, q)
trans-**6**	175.4	37.4	49.5	83.0	138.2, 129.0 127.7, 127.2 (s, 3d)	19.1 (q)
trans-**7**	175.7	37.5	47.6	87.0	139.0, 129.0 127.6, 127.3 (s, 3d)	33.7, 22.7, 22.3, 13.8 (3t, q)
trans-**13**	176.0	37.1	35.1	88.0	16.3 (q)	137.8, 128.6, 128.5, 125.8 (s, 3d)
cis-**13**	176.6	36.9	39.7	84.0	15.0 (q)	136.8, 128.3, 127.9, 125.3 (s, 3d)

[a] Spectra are of $CDCl_3$ solutions recorded at 75.5 MHz. [b] Unambiguous assignment to 4-R^1 or 5-R^2 not possible. [c] Only one quartet observed due to signal overlap.

of chelates and as a consequence to high diastereoselectivities. The role of ester groups as ligands must therefore be considered in other reactions of Lewis acidic organometallic reagents. Beside of this general aspect, this study describes a highly diastereoselective and flexible route to *trans*-substituted γ-lactones[25] which are of interest not only as targets (e.g., whisky lactone) but also as intermediates[26] for further stereoselective transformations to more complex molecules.

Experimental Section

For general information, see ref 5. CuI was purified according to ref 27. Methyllithium (in diethyl ether, Aldrich) and *n*-butyllithium (in hexane, Aldrich) were used as received. They were titrated according to ref 28. *n*-BuMgBr was prepared according to standard procedures.[29] All other Grignard reagents were purchased (Aldrich) as solutions in the corresponding solvent and used as received. All reactions were performed in a flame-dried reaction flask under a slight pressure of dry nitrogen. Reagents were added via syringe.

Synthesis of aldehydes **1a**, **1c**, **1d**, **8a**, **8b**, and **8c** is described in ref 4. Analogously, aldehyde **1b** was prepared from *n*-hexanal via 1-(trimethylsiloxy)-1-hexene (58%, *E*/*Z* mixture) and methyl 3-*n*-butyl-2-(trimethylsiloxy)cyclopropanecarboxylate (78%, mixture of three diastereomers). After ring cleavage with $NEt_3 \cdot HF$[30] methyl 3-formylheptanoate (**1b**) was obtained as a colorless liquid (bp 90 °C, 0.02 Torr) in 90% yield: ^1H NMR δ 9.71 (s, 1 H, CHO), 3.68 (s, 3 H, OMe), 2.83 (m_c, 1 H, 3-H), 2.74, 2.42 (AB-part of ABX, J_{AX} = 5.0, J_{BX} = 8.0, J_{AB} = 16.5 Hz, 2 H, 2-H), 1.78–1.31 (3 m, 1 H, 1 H, 4 H, $CH_2CH_2CH_2$), 0.91 (m_c, 3 H, Me); ^{13}C NMR δ 202.8 (d, CHO), 172.3, 51.6 (s, q, CO_2Me), 47.5 (d, C-3), 32.7, 28.7, 28.1, 22.5 (4 t, C-2, $CH_2CH_2CH_2$), 13.6 (q, Me); IR (film) 2965, 2940, 2880, 2870 (CH), 1730 (C=O) cm^{-1}. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.50; H, 9.50.

General Procedure for the Reaction of Aldehydes 1 with Lithium Dialkylcuprates Analogous to Ref 14. A suspension of CuI in diethyl ether (2 mL/mmol of CuI) was treated at −40 °C under an atmosphere of nitrogen with 2 equiv of the corresponding alkyllithium reagent (2–3 M *n*-butyllithium solution in hexane or 1.6 M methyllithium solution in diethyl ether). For the formation of $(n\text{-Bu})_2CuLi$ the mixture was stirred for 30 min at −40 °C (black solution), while the preparation of Me_2CuLi required stirring for 30 min at 0 °C (yellow solution). The resulting cuprate solution was cooled to −78 °C, and the corresponding aldehyde **1** was added. After stirring for 10 min the mixture was quenched with water (approximately 2 mL/mmol CuI), warmed to room temperature, acidified with 50% aqueous H_2SO_4 and stirred for 16 h. The precipitate formed was removed by filtration and thoroughly washed with diethyl ether. The layers of the filtrate were separated, and the aqueous layer was three times extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and evaporated, and the residue was purified by careful Kugelrohr distillation. For exact details see individual experiments (Table II). According to ^1H

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Table IV. ^{13}C NMR Data of γ-Lactones 10 and 11[a]

compd	δ C-2 (s)	δ C-3 (d)	δ C-4	δ C-5 (d)	δ 3-R²	δ 4-R¹	δ 5-(*n*-Bu)
cis-10	176.7	47.3	38.1 (t)	78.7	136.7, 128.8 128.1, 127.6 (s, 3d)		35.1, 27.4, 22.5, 13.9 (3t, q)
trans-10	*b*	45.7	36.4 (t)	79.0	*b*, 129.0 128.6, 127.3 (3d)		35.2, 29.7, 27.5, *c* (3t)
trans-11	179.1	44.6	40.7 (s)	87.4	21.9, 9.1 (2q)		29.2, 28.3, 22.3, 13.6 (3t, q)
cis-11	*b*	47.1	42.3 (s)	87.6	23.1,T15.3, 7.7 (3q)		28.8, 28.0, *d* (2t)

[a] Spectra are of $CDCl_3$ solutions recorded at 75.5 MHz. [b] Singlet not observed due to signal overlap. [c] Quartet not observed due to signal overlap. [d] Other signals not observed due to signal overlap.

Table V. Reactions of Aldehyde 1a with Grignard Reagents and Phenyllithium

aldehyde 1a	reagent	solvent	T (°C)	γ-lactone	*trans*:*cis*	yield (%)	bp (°C) (Torr)
0.260 g (2.00 mmol)	MeMgBr (2.2 mmol)	THF	−78	0.089 g of 2	62:38	39	50 (0.1)
0.390 g (3.00 mmol)	MeMgBr (3.3 mmol)	Et_2O	−45	0.191 g of 2	69:31	56	50 (0.1)
0.650 g (5.00 mmol)	*n*-BuMgBr (5.2 mmol)	THF	−78	0.190 g of 3	62:38	24	90 (0.01)
0.650 g (5.00 mmol)	*n*-BuMgCl (5.0 mmol)	Et_2O	−45	0.437 g of 3	75:25	56	90 (0.01)
0.260 g (2.00 mmol)	*n*-BuMgBr (2.0 mmol)	Et_2O	−45	0.216 g of 3	79:21	69	80 (0.04)
0.260 g (2.00 mmol)	*n*-BuMgBr (2.0 mmol)	CH_2Cl_2	−40	0.209 g of 3	84:16	67	70 (0.04)
0.650 g (5.00 mmol)	allylMgBr (5.2 mmol)	THF	−78	0.173 g of 12	37:63	25	70 (0.02)
0.910 g (7.00 mmol)	allylMgBr (7.24 mmol)	Et_2O	−45	0.329 g[a] of 12	53:47	34	100 (0.01)
0.650 g (5.00 mmol)	PhMgBr (5.5 mmol)	THF	−78	0.131 g of 13	79:21[b]	47	120 (0.01)
0.650 g (5.00 mmol)	PhMgBr (5.0 mmol)	Et_2O	−45	0.511 g of 13	65:35[c]	58	120–140 (0.1)
0.260 g (2.00 mmol)	PhLi (2.2 mmol)	THF	−100	0.109 g of 13	79:21	31	120–140 (0.1)
0.260 g (2.00 mmol)	PhLi (2.2 mmol)	Et_2O	−100	0.139 g of 13	77:23	39	120–140 (0.1)

[a] Product of low purity (<80%). [b] *Trans*/*cis* ratio in the purified product after chromatography (crude product 66:34). [c] Workup with water and cyclization with catalytic amounts of *p*-TosOH (30 min, 120 °C).

Table VI. ^1H NMR Data for γ-Lactones[a]

compd	δ 5-H (1H)	δ 4-H	δ 3-H	δ 4-R¹	δ 5-R²
trans-2	4.15, qd (*J* = 6.1, 7.5 Hz)	2.75–2.56, 2.30–2.08, 2m (3H)		1.14, d (*J* = 6.3 Hz, 3H)	1.40, d (*J* = 6.1 Hz, 3H)
cis-2	4.68, quint (*J* = 6.5 Hz)			1.03, d (*J* = 6.8 Hz, 3H)	1.29, d (*J* = 6.5 Hz, 3H)
trans-3	4.01, dt (*J* = 4.0, 7.5 Hz)	2.64–2.58, 2.28–2.10, 2m (3H)		1.13, d (*J* = 6.5 Hz, 3H)	1.80–1.27, 0.91 (m, 6H, t, *J* = 7.0 Hz, 3H)
cis-3	4.43, ddd (*J* = 4.5, 5.8 Hz)			1.02, d (*J* = 7.0 Hz, 3H)	
trans-4[b]	4.22, qd (*J* = 6.5, 7.5 Hz)	2.08, m_c (1H)	2.68, 2.24[c] (2H)	1.54, 1.32, 0.91 (2m_c, 1H, 5H, t, *J* = 7.0 Hz, 3H)	1.40, d (*J* = 6.1 Hz, 3H)
trans-5	4.26, ddd (*J* = 4.8, 5.7, 7.8 Hz)	2.00 m_c (1H)	2.60, 2.29[d] (2H)	1.78–1.20, 1.00–0.81 (2m, 16H)	
trans-6[e]	4.55, qd (*J* = 6.2, 8.6 Hz)	3.25, td (*J* = 8.6, 11 Hz, 1H)	2.92, 2.78[f] (2H)	7.44–7.22 (m, 5H)	1.41, d (*J* = 6.2 Hz, 3H)
trans-7	4.45, td (*J* = 6.0, 8.2 Hz)	3.30, td (*J* = 8.5, 10.4 Hz, 1H)	2.94, 2.74[g] (2H)	7.41–7.15 (m, 5H)	1.74–1.16, 0.86 (m, 6H, t, *J* = 7.2 Hz, 3H)
trans-13	4.93, d (*J* = 8.3 Hz)	2.94–2.72, 2.56–2.26, 2m (3H)		1.17, d (*J* = 6.5 Hz, 3H)	7.44–7.20 (2m, 5H)
cis-13	5.58, d (*J* = 6.0 Hz)			0.68, d (*J* = 7.0 Hz, 3H)	
trans-9	4.51, qd (*J* = 5.0, 7.5 Hz)	2.12, 2.00, 2ddd[h]	2.73–2.60,[i] m (1H)		1.88–1.30, 0.97–0.87 (2m, 6H, 3H)
cis-9	4.33, dtd (*J* = 5.5, 7.5, 10 Hz)	2.50, ddd[i] (*J* = 5.5, 9.0, 12.0 Hz, 1H)			
trans-10	4.68–4.58, m	2.49, 2.37, 2ddd (*J* = 7.0, 7.5, 13.0 Hz, *J* = 6.0, 10.5, 13.0 Hz, 2H)	4.31, dd (*J* = 7.0, 10.5 Hz, 1H)[k]		1.90–1.26, 0.93 (m, t, *J* = 7.0 Hz, 6H, 3H)
cis-10	4.47, dtd (*J* = 5.5, 7.0, 10.0 Hz)	2.73–2.02, ddd, dt (*J* = 5.5, 9.0, 13.0 Hz, *J* = 10.0, 13.0 Hz, 2H)	3.86, dd (*J* = 9.0, 13.0 Hz, 1H)[k]		
trans-11	4.05, dd (*J* = 5.0, 8.0 Hz)	*l*	2.35, q (*J* = 7.5 Hz, 1H)		1.58–1.25, 1.16–0.79 (2m, 9H)
cis-11	3.95, dd (*J* = 4.0, 8.0 Hz)		2.53, q (*J* ≈ 7 Hz, 1H)		

[a] Spectra are of $CDCl_3$ solutions recorded at 300 MHz; for data for 12 see ref 5. [b] Traces of *cis*-4: δ 5-H = 4.71 (m_c). [c] AB of ABX (J_{AX} = 8.0, J_{BX} = 10.0, J_{AB} = 17.0 Hz). [d] AB of ABX (J_{BX} = 7.3, J_{AX} = 9.0, J_{AB} = 18.0 Hz). [e] Traces of *cis*-6: δ 5-H = 4.90 (m_c), δ 5-Me = 1.00 (t, *J* = 6.7 Hz). [f] AB of ABX (J_{AX} = 8.6, J_{BX} = 11.1, J_{AB} = 17.5 Hz). [g] AB of ABX (J_{AX} = 8.5, J_{BX} = 10.4, J_{AB} = 17.5 Hz). [h] *J* = 5.0, 9.0, 13.0 Hz, *J* = 7.5, 8.0, 13.0 Hz, 2H. [i] Second signal hidden. [j] δ 3-Me = 1.28, 1.25 (2d, *J* = 7 Hz, 3H). [k] δ 3-Ph = 7.39–7.23 (m, 5H). [l] δ 4-Me = 1.04, 1.00 (2 s, 6H); δ 3-Me = 1.16 (d, *J* = 7.5 Hz, 3H).

NMR the products showed a purity of 90–95%, the samples for elemental analyses were further purified by column chromatography or radial chromatography on silica gel.

General Procedure for the Reactions of Aldehyde 1a with Grignard Reagents. To a solution of aldehyde **1a** in dry tetrahydrofuran (10 mL) was slowly added at −78 °C a solution of 1.0–1.1 equiv of the Grignard reagent (the reactions in diethyl ether (10 mL) were performed at −45 °C, the reaction in dichloromethane was performed at −40 °C). The mixture was stirred under slow warming for 2 h and quenched with 50% aqueous H_2SO_4 (3 mL). After the mixture was stirred at room temperature for 16 h water (5 mL) and *tert*-butyl methyl ether (10 mL) were added. The aqueous phase was extracted three times with *tert*-butyl methyl ether (10 mL), and the combined organic phases were dried ($MgSO_4$). After evaporation of the solvent the residue was purified by Kugelrohr distillation. In

several experiments further purification by chromatography was necessary (see Table V). The reactions with phenyllithium were analogously performed but started at −100 °C.

Analytical and spectroscopic data are available in the literature for γ-lactones: **2** (ref[14]), **3** (ref[31]), **12** (ref[5]), **13** (ref[32]).

Further Spectroscopic and Analytical Data of New Compounds. 4-*n*-Butyl-5-methyl-4,5-dihydro-2(3*H*)-furanone (4): IR (film) 2950, 2920, 2865, 2850 (CH), 1775 (C=O) cm^{-1}. Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.32. Found: C, 68.78; H, 10.33.

5-*n*-Butyl-4-(2-propyl)-4,5-dihydro-2(3*H*)-furanone (5): IR (film) 2960, 2930, 2870 (CH), 1770 (C=O) cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 70.67; H, 10.81.

5-Methyl-4-phenyl-4,5-dihydro-2(3*H*)-furanone (6): IR (film) 2980, 2940 (CH), 1780 (C=O) cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.34; H, 6.88.

5-*n*-Butyl-4-phenyl-4,5-dihydro-2(3*H*)-furanone (7): IR (film) 2980, 2940, 2880 (CH), 1780 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.62; H, 8.40.

5-*n*-Butyl-3-methyl-4,5-dihydro-2(3*H*)-furanone (9): IR (film) 2940–2840 (CH), 1760 (C=O) cm^{-1}. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.15; H, 10.44.

5-*n*-Butyl-3-phenyl-4,5-dihydro-2(3*H*)-furanone (10): IR (film) 3100–3010, 2960–2860 (CH), 1765 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.76; H, 8.29.

5-*n*-Butyl-3,4,4-trimethyl-4,5-dihydro-2(3*H*)-furanone (11): IR (film) 2960–2880 (CH), 1770 (C=O) cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.56; H, 11.06.

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