Around and beyond Cram's Rule†

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I. Introduction

The influence of a chiral center on a prochiral reaction center within the same molecule is one of the fundamental stereochemical issues addressed in organic synthesis. Ever since D. J. Cram[1] outlined almost 50 years ago an edifice to explain the stereoselectivity in the addition of nucleophiles to α-chiral carbonyl compounds, which became known as the Cram rule,[2] a fabric was created which proved to be most fruitful in understanding, predicting, and controlling diastereoselectivity induced by a remote stereocenter. The aim of this review is the analysis and comparison of the various models having evolved on the basis of Cram's rule and their application toward diastereoselective synthesis.

Throughout this review, we employ the following abbreviations: Ac = acetyl, 9-BBN = 9-borobicyclo-[3.3.1]nonane, Bn = benzyl, Boc = *tert*-butoxycarbonyl, BOM = benzyloxymethyl, Bz = benzoyl,

† Dedicated to Professor Armin de Meijere on the occasion of his 60th birthday.

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DIBAL-H = diisobutylaluminum hydride, E = electrophile, EWG = electron-withdrawing group, HMPT = hexamethylphosphortriamide, L = large-sized substituent, M = medium-sized substituent, Met = metal, MAT = methylaluminum bis(2,4,6-tri-*tert*-butylphenoxide), MEM = 2-methoxyethoxymethyl, MOM = methoxymethyl, Nu = nucleophile, PMB = *p*-methoxybenzyl, S = small-sized substituent, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid, THP = tetrahydropyran, TIPS = triisopropylsilyl, TMEDA = *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine, TMS = trimethylsilyl, Ts = *p*-toluenesulfonyl, Z = benzyloxycarbonyl.

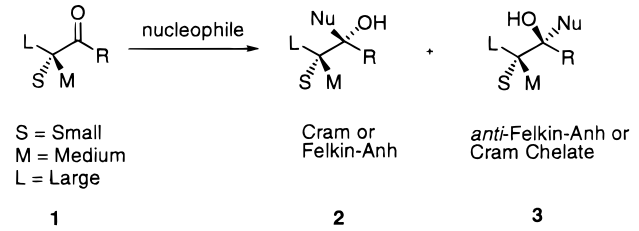
II. Models for 1,2-Induction

Since it can be expected that a chiral center being in close proximity to a prochiral reaction center will exhibit the strongest influence, there is an overwhelming number of examples for 1,2-induction, and consequently, models to explain such diastereoselectivity have been most prominent in the literature. The fundamental models such as the Cram and the Felkin−Anh rule can be found today in almost every organic textbook; nevertheless, the underlying concepts still form the basis for further modifications, and extensions are applied to current research problems.

A. Nucleophilic Attack to α-Chiral Carbonyl Compounds

The addition of nucleophiles to α-chiral carbonyl compounds **1** can lead to two diastereomeric products **2** and **3** (Scheme 1).

Scheme 1. 1,2-Induction in α-Chiral Carbonyl Compounds

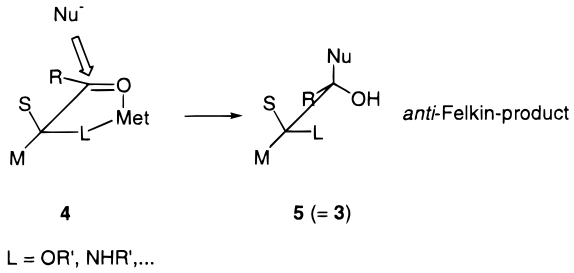


1 **2** **3**

In 1952, the seminal publication by D. J. Cram and F. A. Abd Elhafez[1b] appeared in which a model was introduced—since then known as the Cram rule—which allowed the analysis of the stereochemical outcome of such reactions. On the basis of the nature of the substituents at the chiral center, two different conformations of the substrate **1** were proposed together with the favored trajectory of the attacking nucleophile to explain the preferential formation of **2** or **3**, respectively.

(1) Cram-chelate Rule:[1b,3,4] If chelation between the carbonyl group and one of the substituents[5] of the α-stereocenter facilitated by a metal cation can occur, the substrate will be locked into the conformation **4** (Scheme 2). This will place the remaining two substituents, here S and M, on different sides of the carbonyl group. A nucleophile will now preferentially

Scheme 2. Cram-Chelate Model

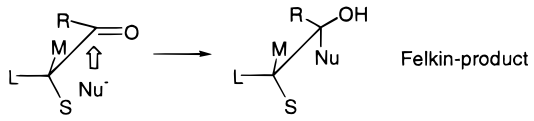


4 **5 (= 3)**

attack the carbonyl group from the side of the small substituent S and not from the side of the medium substituent M, leading to **5** (which corresponds to **3**) as the major product, which is generally called the Cram-chelate product. The Cram-chelate rule has been shown to be most reliable in its predictive power for numerous examples (e.g., Scheme 9, Table 1, entries 72−73, 80−93, 99−100, 106−111, 113−117, 119−123) in organic synthesis, and no amendments have been necessary to correct the assumptions described here.

(2) Cram Rule:[1b] If chelation cannot occur, **6** was proposed to be the preferred reactive conformation based on steric reasons (Scheme 3): the decisive

Scheme 3. Cram Model



6 **7 (= 2)**

steric interaction to be avoided was thought to be between the large substituent L and the carbonyl group. Consequently, L is oriented *anti* to the carbonyl group, placing S and M on different sides of the carbonyl group. A nucleophile will now preferentially attack from the side of the small substituent S, leading to **7** as the major product, the so-called Cram or Felkin−Anh product.[6]

The Cram rule proved to be a reliable tool to explain the preferred diastereoselection in carbonyl addition reactions if no polar substituents were present on the α-stereocenter. However, if the α-stereocenter contained acceptor groups such as chlorine or trimethylsiloxyl, they took on the role of L even though sterically more demanding substituents could be present. This behavior could not be explained under the assumptions made for **6**. Conforth[7] therefore modified the Cram rule in that electron-withdrawing substituents (EWG) assume the role of L in order to minimize the dipole moment (Figure 1). However, for various reasons **6**, (or **8**) did not seem to be a good choice for representing the reactive conformation for nucleophilic addition by a nonchelation pathway: The steric bulk of the carbonyl group was overestimated, resulting in an unfavorable alignment of L and R in **6**, especially in ketones (R ≠ H).

As the reaction center is rehybridizing from sp^2 to sp^3 under the influence of the approaching nucleophile, unfavorable interactions occur due to the

Table 1. Reactions between α-Chiral Aldehydes 1 and Nucleophiles (cf. Scheme 9)

entry	L	M	S	R	Met−Nu	**2:3**	ref
1	Ph	Me	H	H	MeLi	80:20	14a,b
2	Ph	Me	H	H	MeLi/$Yb(Otf)_3$	91:09	14c
3	Ph	Me	H	H	$MeCeCl_2$	88:12	14d
4	Ph	Me	H	H	MeMgOTf	90:10	14e
5	Ph	Me	H	H	MeMgOTs	92:08	14e
6	Ph	Me	H	H	$MeMgOSO_2C_6H_2Me_3$	94:06	14e
7	Ph	Me	H	H	MeMgOAc	91:09	14e
8	Ph	Me	H	H	$MeMgOCO^tBu$	94:06	14e
9	Ph	Me	H	H	$MeTi(OPh)_3$	93:07	14f−h
10	Ph	Me	H	H	$MeTiCl_3$	81:19	14h
11	Ph	Me	H	H	$MeTi(O^iPr)_3$	88:12	14i
12	Ph	Me	H	H	Me_2TiCl_2	81:19	14h
13	Ph	Me	H	H	Me_2Zn, $AlCl_3$	66:34	14i
14	Ph	Me	H	H	PhMg(OTs)	93:07	14e
15	Ph	Me	H	H	Ph_2TiCl_2	80:20	14i
16	Ph	Me	H	H	BuLi, 18-crown-6	91:09	14a
17	Ph	Me	H	H	BuLi, 15-crown-5	>97:03	14a
18	Ph	Me	H	H	Bu_2CuLi	76:24	14j
19	Ph	Me	H	H	Ph(CN)(OTMS)CuLi	95:05	14k
20	Ph	Me	H	H	$Bu[NBu_4]$	98:11	14l
21	Ph	Me	H	H	Bu_2CuNBu_4	34:66	14l
22	Ph	Me	H	H	Bu_2CuLi/18-crown-6	19:81	14a
23	Ph	Me	H	H	MAT/BuMgBr	33:67	14f,g
24	Ph	Me	H	H	PhCCLi	84:16	14m
25	Ph	Me	H	Me	$LiAlH_4$	74:26	8, 14n
26	Ph	Et	H	H	EtMgBr	75:25	14o
27	Ph	Et	H	H	MeMgI	70:30	14p
28	Ph	Et	H	H	$MeTi(O^iPr)_3$	87:13	14p
29	Ph	^{i}Pr	H	H	^{i}PrLi	50:50	14r
30	Ph	^{i}Pr	H	H	^{i}PrMgBr	66:34	14r
31	Ph	Me	H	TMS	MeLi	98:02	14b
32	Ph	Me	H	TMS	BuLi	>99:01	14b
33	Ph	Et	H	Me	$LiAlH_4$	75:25	1b
34	Ph	^{i}Pr	H	^{i}Pr	$LiAlH_4$	91:09	14s
35	Ph	Me	H	Me	Li^sBu_3BH	>99:01	14n
36	Ph	Me	H	Me	$LiNH_3$	24:76	14n
37	Ph	Me	H	Me	$^cHex_2BH$	26:74	14t
38	Ph	Me	H	Me	disiamylborane	20:80	14t
39	Ph	CH_2CO_2Me	H	H	allylBr/Zn	77:23	14u
40	Ph	CH_2CO_2Me	H	H	$allylSiMe_3/BF_3$	70:30	14u
41	Ph	CH_2CO_2Me	H	H	$allylSiMe_3/TiCl_4$	93:07	14u
42	Ph	Me	H	H	$allylSiMe_3/TiCl_4$	70:30	14v
43	Ph	Me	H	H	$allylSiMe_3/SnCl_4$	73:27	14v
44	Ph	Me	H	H	$allylSnMe_3/TiCl_4$	69:31	14v
45	Ph	Me	H	H	$allylSnMe_3/BF_3$	80:20	14v
46	Ph	Me	H	H	$allylSnMe_3$/10 kbar	67:33	14v
47	Ph	Me	H	H	allyl-9-BBN	55:45	14v
48	Et	Me	H	H	MeMgBr	60:40	14w
49	Et	Me	H	H	$MeTi(O^iPr)_3$	68:32	14w
50	Bn	Me	H	H	BuMgI	50:50	14g
51	Bn	Me	H	H	BuLi	55:45	14a
52	^{i}Pr	CH_2CO_2Me	H	H	allylBr/Zn	68:32	14u
53	^{c}Hex	Me	H	H	BuMgBr	89:11	14g
54	^{c}Hex	Me	H	H	BuLi	78:22	14b
55	^{c}Hex	Me	H	H	MeMgI	82:18	14f,g
56	^{c}Hex	Me	H	H	MeLi	66:34	14b
57	^{c}Hex	Me	H	Me	$LiAlH_4$	62:38	8
58	^{c}Hex	Me	H	Et	$LiAlH_4$	67:33	8
59	^{c}Hex	Me	H	^{i}Pr	$LiAlH_4$	80:20	8
60	^{c}Hex	Me	H	^{t}Bu	$LiAlH_4$	62:38	8
61	CH_2CO_2Me	Me	H	H	allylBr/Zn	48:52	14u
62	Cl	Me	H	Ph	$LiAlH_4$	75:25	14x
63	Cl	Et	H	Bu	$NaBH_4$	80:20	14x
64	Cl	Ph	H	Ph	$LiAlH_4$	50:50	14x
65	Cl	Me	H	Ph	HC≡CMgBr	89:11	14y
66	Cl	Ph	H	Ph	HC≡CMgBr	20:80	14y
67	Cl	Me	H	H	MeMgCl	88:12	14z
68	Cl	Me	H	H	$BuTi(O^iPr)_3$	80:20	14z
69	OTBS	^{c}Hex	H	H	$allylSnBu_3$, BF_3	95:05	15a
70	OTBS	^{c}Hex	H	H	$allylSnMe_3$, $LiClO_4$	45:55	15b
71	OTBS	^{c}Hex	H	H	allylBr/In	81:19	15c,d
72	OBn	^{c}Hex	H	H	$allylSnMe_3$, $LiClO_4$	04:96	15b
73	OBn	^{c}Hex	H	H	$allylSnBu_3$, $LiClO_4$	04:96	15b

Table 1 (Continued)

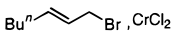
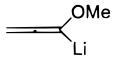
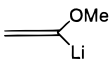
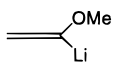
entry	L	M	S	R	Met−Nu	**2:3**	ref
74	OBn	^{c}Hex	H	H	allylBr/In	69:31	15c,d
75	OBzl	CH_2OBzl	H	H	MeMgBr	55:45	15e
76	OBzl	CH_2OBzl	H	H	MeLi/LiBr	55:45	15e
77	OBzl	CH_2OBzl	H	H	Me_2CuLi	53:47	15e
78	OBzl	CH_2OBzl	H	H	$MeTi(O^iPr)_3$	93:07	15e
79	OCH_2OMe	^{c}Hex	H	H	allylBr/In	37:63	15c,d
80	OCH_2OMe	Me	H	H	$allylSnMe_3/TiCl_4$	0:100	14v
81	OCH_2OMe	Me	H	H	$allylSnMe_3$/10 kbar	61:39	14v
82	OCH_2OMe	Me	H	H	allyl-9-BBN	48:52	14v
83	OCH_2OBn	Me	H	H	MeMgBr	50:50	15f
84	OCH_2OBn	Me	H	H	Me_2CuLi	03:97	15f
85	OCH_2OBn	Me	H	H	BuLi	37:63	15f
86	OCH_2OBn	Me	H	H	Bu_2CuLi	06:94	15f
87	OMEM	C_7H_{15}	H	Me	BuMgBr	<01:99	15g
88	OMOM	C_7H_{15}	H	Me	BuMgBr	<01:99	15g
89	OCH_2SMe	C_7H_{15}	H	Me	BuMgBr	<01:99	15g
90	OCH_2OBn	C_7H_{15}	H	Me	BuMgBr	<01:99	15g
91	OBn	C_7H_{15}	H	Me	BuMgBr	<01:99	15g
92	OTHP	C_7H_{15}	H	Me	BuMgBr	25:75	15g
93	O-2-OMe-Ph	Me	H	Ph	$Zn(BH_4)_2$	<01:99	15h
94	OPh	Me	H	Ph	$Zn(BH_4)_2$	>99:01	15h
95	O-2-^{t}Bu-Ph	Me	H	Ph	$Zn(BH_4)_2$	>99:01	15h
96	O-2-OMe-Ph	Me	H	Ph	$NaBH_4$	11:89	15h
97	OPh	Me	H	Ph	$NaBH_4$	58:42	15h
98	O-2-^{t}Bu-Ph	Me	H	Ph	$NaBH_4$	>99:01	15h
99	O-2-OMe-Ph	Me	H	Ph	$LiAlH_4$	10:90	15h
100	OPh	Me	H	Ph	$LiAlH_4$	28:72	15h
101	O-2-^{t}Bu-Ph	Me	H	Ph	$LiAlH_4$	>99:01	15h
102	OTBDPS	^{n}Pent	H	Me	$NaAlH_2(OCH_2OCH_2CH_2OMe)_2$	98:02	15i
103	OTBDPS	Me	H	^{n}Pent	$NaAlH_2(OCH_2OCH_2CH_2OMe)_2$	61:39	15i
104	OMe	Me	H	Ph	Bu_3SnH, Bu_4NF	100:0	15j
105	OMe	Me	H	Ph	Bu_2SnClH	10:90	15j
106	OMe	Me	H	Ph	Me_2Mg	<01:99	15k,l
107	OTMS	Me	H	Ph	Me_2Mg	01:99	15k,l
108	OTES	Me	H	Ph	Me_2Mg	04:96	15k,l
109	OTBS	Me	H	Ph	Me_2Mg	12:88	15k,l
110	OTBDPS	Me	H	Ph	Me_2Mg	37:63	15k,l
111	OTIPS	Me	H	Ph	Me_2Mg	58:42	15k,l
112	OTBS	Me	H	H		99:01	15m
113	OBn	Me	H	Et	MeMgCl	<01:99	15n
114	OBn	Me	H	Et	MeLi	40:60	15n
115	OBn	Me	H	Et	$MeLi/TiCl_4$	05:95	15n
116	OTBS	Me	H	Et	MeMgCl	40:60	15n
117	OTBS	Me	H	Et	$MeLi/TiCl_4$	15:85	15n
118	OTBS	Me	H	Et	$MeTi(O^iPr)_3$	>99:01	15n
119	OTMS	Me	H	Et	$MeTi(O^iPr)_3$	22:78	15n
120	OTMS	Me	H	Et	$MeLi/TiCl_4$	19:81	15n
121	OAc	Ph	H	Ph	4-Me-PhMgBr	03:97	15o
122	NBn_2	Me	H	H	MeMgI	95:05	15p
123	NBn_2	Me	H	H	$MeTiCl_3$	06:94	15p
124	NMe_2	Me	H	Ph	$HSiMe_2Ph$/TBAF	>99:1	15q
125	NMe_2	Me	H	Ph	$HSiMe_2Ph$/TFA	<1:99	15r
126	NH^{t}Bu	Me	H	Ph	$NaBH_4$	21:79	15s
127	$NHCO_2Et$	Me	H	Ph	$NaBH_4$	20:80	15s
128	$NHCO_2Et$	Me	H	Ph	$LiAlH_4$	20:80	15s
129	$NHCO_2Et$	Me	H	Ph	$Li(^{s}Bu)_3BH$	50:50	15s
130	$NHCO_2Et$	Me	H	Ph	$Pd/C/H_2$	33:67	15s
131	NHBoc	CH_2Ph	H	H	$allylSiMe_3$/9 kbar	12:88	15t
132	NHBoc	^{i}Bu	H	H		86:14	15u
133	NHBoc	CH_2Ph	H	H		62:38	15u
134	NHBoc	Me	H	H		89:11	15u
135	SMe	Et	H	Ph	$Li(^{s}Bu)_3BH$	>99:01	15v
136	SMe	Et	H	Ph	$Zn(BH_4)_2$	06:94	15v
137	SMe	^{n}Pentyl	H	^{c}Hex	$Li(^{s}Bu)_3BH$	81:19	15v
138	CO_2Me	Me	H	Ph	$Zn(BH_4)_2$	01:99	15w
139	CO_2Me	Me	H	Ph	MeLi	78:22	15x
140	CO_2Et	Me	H	Ph	$NaBH_4$	75:25	15y

Table 1 (Continued)

entry	L	M	S	R	Met−Nu	**2:3**	ref
141	CO_2Et	Me	H	Ph	$NaBH_4 + CeCl_3$	39:61	15y
142	CO_2Et	Me	H	Ph	$NaBH_4 + CaCl_2$	20:80	15y
143	CO_2Et	Me	H	Ph	$NaBH_4 + ZnCl_2$	14:86	15y
144	CO_2Et	Me	H	Ph	$NaBH_4 + MnCl_2$	10:90	15y
145	CO_2Et	Me	H	Ph	Me_3Al	<01:99	15x
146	CO_2tBu	Me	H	Ph	$NaBH_4$	88:12	15y
147	CO_2tBu	Me	H	Ph	$NaBH_4 + MnCl_2$	22:78	15y
148	$CONMe_2$	Me	H	Ph	MeMnCl	<01:99	15x
149	$CONMe_2$	Me	H	Ph	Me_3Al	<01:99	15x
150	$CONMe_2$	Me	H	Ph	$MeTiCl_3$	<01:99	15x
151	$CONMe_2$	Me	H	Ph	Et_2AlCl	<01:99	15x
152	OH	Ph	Me	Ph	MeMgI	34:66	14x
153	OH	Ph	H	Me	$NaBH_4$	30:70	15z
154	OH	Ph	H	Me	$Zn(BH_4)_2$	13:87	15z
155	OH	Me	H	^{n}Pent	$Zn(BH_4)_2$	23:77	15z
156	OH	Et	H	^{n}Bu	$Zn(BH_4)_2$	11:89	15z
157	OH	^{n}Pr	H	^{n}Pr	$Zn(BH_4)_2$	<01:99	15z
158	OH	^{n}Pent	H	Me	$Zn(BH_4)_2$	15:85	15z
159	OH	^{n}Pent	H	Me	$LiAlH_4$	30:70	15z
160	OH	Ph	H	Ph	Me_4Ti	<01:99	16a
161	OH	Ph	H	Ph	$MeTi(O^iPr)_3$	<01:99	16a
162	OH	Me	H	H	allylBr/In	12:88	16b,c
163	OH	^{c}Hex	H	H	allylBr/In	09:91	15c

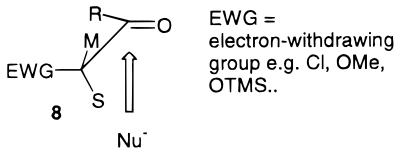


Figure 1. Conforth model.

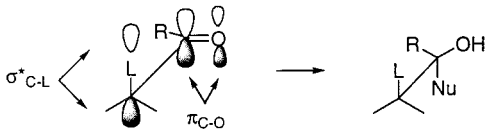
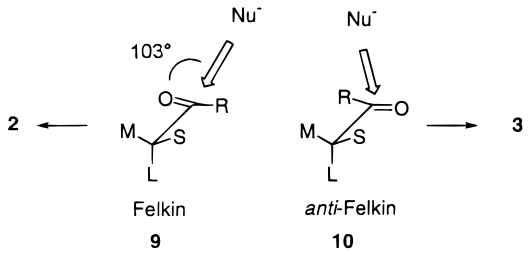


Figure 2. Orbital orientation in the transition state of the Felkin−Anh model.

nearly eclipsed conformation **7**, which is obtained via this reaction pathway.

Consequently, several contributions by Felkin,[8] Anh, and Eisenstein[9] evolved into a new model, which became subsequently known by the names of its main developers as the Felkin−Anh rule (Scheme 4). The key idea was that the substituent L is placed

Scheme 4. Felkin−Anh Model

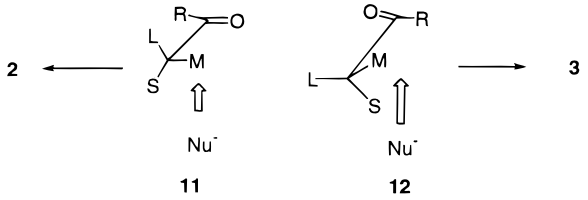


orthogonal to the carbonyl group, allowing the nucleophile to attack *anti* to L, thus most effectively avoiding steric repulsion. Moreover, the definition of L was broadened in that electronic factors were recognized to play a pivotal role in stabilizing the transition state with the incoming nucleophile. Substituents exhibiting an electron-withdrawing effect are regarded as L independent of their steric bulk. In this way, the low-lying σ^*_{C-L} orbital is aligned parallel with the π- and π^*-orbital of the carbonyl group, allowing delocalization of electron density by hyperconjugation from the reaction center toward L (Figure 2). Moreover, the reaction pathway is advantageous compared to the one starting from the Cram conformation since it leads directly to a staggered conformation in the product.

With the prerequisite of L being orthogonal to the carbonyl group, the two conformations **9** and **10** remain possible. **9**, leading to the preferred Cram or Felkin−Anh product **2**, is apparently favored according to this model. When calculations by Bürgi/Dunitz[10] and Anh/Eisenstein[11,12] showed that the attack of the nucleophile onto the carbonyl group does not occur in a 90° but rather in a 103° angle with respect to the carbonyl group, a conclusive argument had been found pointing toward **9** as the decisive reactive conformation. This way the nucleophile attacks from the side of the small substituent S, i.e., it is experiencing the least steric repulsion by the chiral center.

The analysis by Karabatsos[13] emphasized the importance that attack of the nucleophile should occur via the least hindered pathway (Scheme 5).

Scheme 5. Karabatsos Model

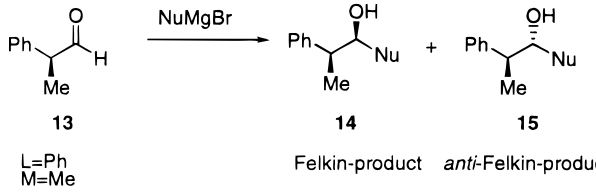


Such an attack is realized in both conformations **11** (being almost identical to the Felkin−Anh conformation **9**) and **12**, with the latter being disfavored because of eclipsing L with the carbonyl group rather than M as seen in **11**. Therefore, the Karabatsos model also predicts **2** as the preferred product.

On the basis of the Felkin−Anh model, trends of selectivities obtained in a large number of nucleo-

philic additions to α-chiral aldehydes can be convincingly explained (Table 1).[14−16] An increase in the steric bulk of the nucleophile renders its addition more selective toward the Felkin product, as depicted in the reaction of **13** with various Grignard reagents (Scheme 6), since the nucleophile is "more aware" of

Scheme 6. Dependence of Selectivity on the Size of the Nucleophile

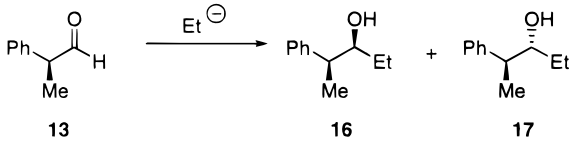


Nu	14:15	Ref.
Me	72:28	14b,f
Et	80:20	14a,f,g
Bu	87:13	14b,f
Ph	72:28	14e
^{t}Bu	98:02	17

the difference of S and M upon attacking the carbonyl group.[17] It is important to note that the phenyl group must be regarded quite similar in its steric size to a methyl group, as seen by comparison of the selectivities obtained with phenyl- and methylmagnesium bromide. The fact that the phenyl group is regarded in **13** as the substituent L and the methyl group as M might be due to stereoelectronic reasons with phenyl being a weak electron acceptor. However, the balance of the factors seems to be quite delicate, and examples in which methyl rather than phenyl takes the role of L are also encountered.

From the previous analysis it becomes clear that an important trick to increase the selectivity in the addition of a given nucleophile is to use a sterically more demanding metal as the counterion (Scheme 7).[18]

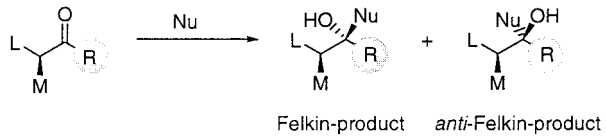
Scheme 7. Increasing the Size of the Nucleophile by Larger Countercations



Et⊖	16:17	Ref.
EtMgBr	80:20	14a,g,f
Et_2Mg, 15-crown-5	93:07	14a
Et[NBu_4]	91:09	18a
Et_4Pb, $TiCl_4$	93:07	18b
Et_2Zn, $Me_2N(CH_2)_2OH$	93:07	18c

Sterically demanding substituents R in **18** cause higher ratios in favor of the Felkin product **19**, since in order to avoid interactions between R and the nucleophile its trajectory bends more toward the chiral center, enhancing the influence of the latter (Scheme 8).

Scheme 8. Dependence of Selectivity on the Steric Bulk of R



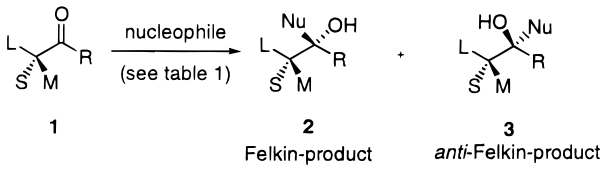
Nu = $LiAlH_4$

L	M	R	19:20	Ref.
Ph	Me	Et	67:33	1b
			76:24	8
Ph	Me	^{i}Pr	83:17	8
Ph	Me	Ph	80:20	1b
Ph	Me	^{t}Bu	98:02	8

Nu = MeMgBr

L	M	R	19:20	Ref.
Ph	Me	Et	86:14	17a
Ph	Me	^{i}Pr	90:10	17a
Ph	Me	Ph	87:13	13a
Ph	Me	^{t}Bu	96:04	17a

Scheme 9. Reactions between α-Chiral Aldehydes and Nucleophiles



Chlorine being a relatively weak electron acceptor assumes the role of L; however, as the size of M increases, the stereoelectronic effect of the acceptor is counteracted by the steric effect, resulting in a loss of selectivity (Scheme 9, Table 1, entries 62−68). When the acceptor substituent becomes stronger, e.g., OTBS, even highly sterically demanding substituents such as cyclohexyl are seemingly unable to override the stereoelectronic control (Table 1, entries 69−71). However, if chelation is not effectively precluded or more than one possibility for chelation exists, diastereomeric mixtures of **2** and **3** are usually obtained (Table 1, entries 74, 79).

Some substrates can react either according to Felkin−Anh or Cram-chelate control by appropriately choosing the reagent (Scheme 9, Table 1, entries 122−123, 124−125, 135−136, or 146−147). Moreover, a simple switch in the steric bulk of a protecting group can also be responsible for a turnover in selectivity (Table 1, entries 107−111). In general, heteroatoms such as oxygen, nitrogen, and sulfur are amenable toward chelation. These atoms might be attached directly to the stereocenter, giving rise to a five-membered chelate (Scheme 9, Table 1, entries 72, 73, 106, 113−115, 119−120, 126, 131, 136, 137, 152−163) or be one atom further away (Table 1, entries 138, 141−145, 147−151), resulting in a six-membered chelate.

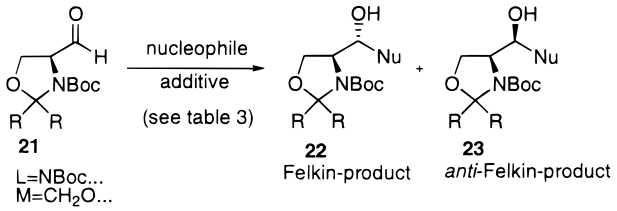
It has also been noted that the selectivities obtained are dependent on the solvent used in the reaction (Table 2). In some cases correlations with solvent polarity (ET_{30} value) have been successful (entries 1−5), suggesting that dipole considerations of **1** in its reactive conformation cannot be neglected.[19]

Of great synthetic potential is the so-called Garner aldehyde **21** which has been widely used in nucelophilic addition reactions (Scheme 10, Table 3).[20,21]

Table 2. Solvent Effects on Reactions between α-Chiral Aldehydes 1 and different Nucleophiles

entry	L	M	R	nucleophile	solvent	**2:3**	ref
1	Ph	Me	Me	PhMgBr	DME	73:27	19a
2	Ph	Me	Me	PhMgBr	THF	61:39	19a
3	Ph	Me	Me	PhMgBr	dioxane	51:49	19a
4	Ph	Me	Me	PhMgBr	Et_2O	36:64	19a
5	Ph	Me	Me	PhMgBr	Et_3N	26:74	19a
6	CH_2CO_2Me	Me	H	$^nBu_2CuLi$	THF	38:62	19b
7	CH_2CO_2Me	Me	H	$^nBu_2CuLi$	Et_2O	05:95	19b
8	OBn	Me	H	PhCCZnBr	THF	19:81	19c
9	OBn	Me	H	PhCCZnBr	Et_2O	05:95	19c
10	OMEM	C_7H_{15}	Me	BuLi	CH_2Cl_2	25:75	15 g
11	OMEM	C_7H_{15}	Me	BuLi	THF	59:41	15 g
12	OMEM	C_7H_{15}	Me	BuMgBr	pentane	10:90	15 g
13	OMEM	C_7H_{15}	Me	BuMgBr	Et_2O	10:90	15 g
14	OMEM	C_7H_{15}	Me	BuMgBr	THF	<01:99	15 g
15	OMEM	C_7H_{15}	Me	BuMgBr	CH_2Cl_2	07:93	15 g

Scheme 10. Addition of Nucleophiles to the Garner Aldehyde 21



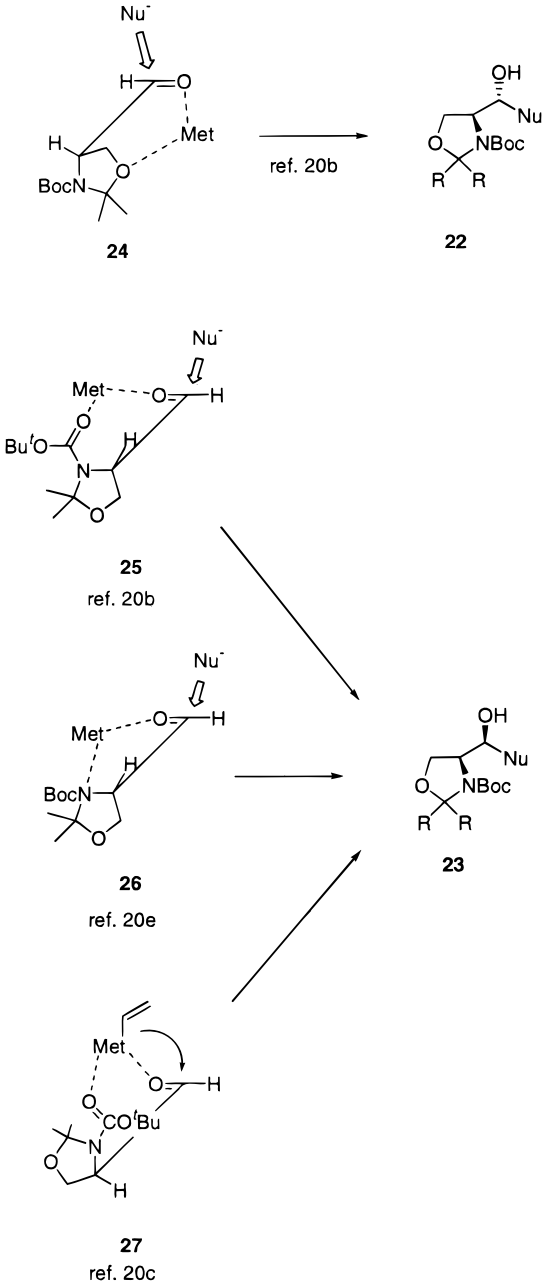
Good Felkin control leading to **22** is observed under conditions in which chelation is precluded; however, if chelation between the carbonyl and the *β*-alkoxy group is preferred by highly oxophilic metals, again the Felkin adduct **22** is preferentially formed via **24** (Scheme 11). Nevertheless, chelation with the *N*-Boc group via the nitrogen or the carbonyl of the *tert*-butyl ester group can also occur, leading via **25**, **26**, or **27** to the *anti*-Felkin adduct **23**. An X-ray structure analysis of **23** (Table 3, entry 10) shows a hydrogen bond from the hydroxyl to the carbonyl group of *N*-Boc, suggesting that **25** or **27** is particularly important. The preferred atoms to be chelated seem to be dependent on the metal and/or on the nucleophile, as well as on conformational constraints due to the choice of the groups R in **21**.

Similarly, selectivities obtained with the glyceraldehyde **28** can be explained (Scheme 12, Table 4).[22] However, as the only mild preference in the formation of **29** indicates, competitive chelation between the α-oxygen group, leading to **30**, and the *β*-oxygen group, leading to **29**, must occur for many nucleophiles (Scheme 13).

The relatively low tendency of an α-oxygen substituent being incorporated in a cyclic structure to participate in chelation also becomes apparent in reactions of the acrolein dimer **33** with nucleophiles (Scheme 14, Table 5).[23] Only metals forming out exceptionally facile chelates such as titanium or zinc gave rise mainly to the *anti*-Felkin product **35**, while even with alkyllithium reagents the Felkin product **34** was still preferred.

Conformational effects allowing or precluding chelation with oxygen or sulfur of a thioketal also must play a pivotal role in nucleophilic additions to **36** (Scheme 15, Table 6).[24] Small differences in the side

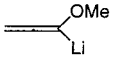
Scheme 11. Transition States for Reactions with the Garner Aldehyde 21



chain or in the nucleophile can have a dramatic effect on the selectivity in this system. It is especially striking to note the opposite selectivities when changing the nucleophile from phenyllithium to phenylmagnesium bromide (entries 5−6, 11−12). It has been argued that Grignard compounds act as hard acids and are therefore—in contrast to lithium—not able to coordinate with the soft sulfur atom. However, invoking a six-membered lithium chelate between the thioketal oxygen and the side chain oxygen atom as in **40** might be another rationalization for the observed stereochemical results (Scheme 16).

An ideal setup of a substrate for obtaining high diastereoselectivity was found with the *N*-tosyl-1,3-oxazine **41** (Table 7).[25] While the *N*-tosyl group acts as L both for steric and electronic reasons, the ring oxygen assumes M but is likewise able to be chelated. Consequently, excellent selectivity for **42** is obtained

Table 3. Addition of Nucleophiles to the Garner-Aldehyde 21

entry	R	nucleophile	additive	22:23	ref
1	Me	Li—≡—$SiMe_3$	HMPT	95:05	20a
2	Me	Li—≡—$SiMe_3$	18-crown-6	93:07	20a
3	Me	Li—≡—$SiMe_3$	$ClZr(OBu)_3$	92:08	20a
4	Me	Li—≡—$SiMe_3$	TMEDA	91:09	20a
5	Me	Li—≡—$SiMe_3$		89:11	20a
6	Me	BrMg—≡—$SiMe_3$		87:13	20a
7	Me	Li—≡—$SiMe_3$	$TiCl(O^iPr)_3$	75:25	20a
8	Me	Li—≡—$SiMe_3$	$ZnBr_2$	09:91	20a
9	Me	BrMg—≡—$SiMe_3$	CuI	05:95	20a
10	Me		$Ti(O^iPr)_4$	40:60	20b
11	Me	vinylMgBr		75:25	20c
12	Me	vinylMgBr	$BF_3.OEt_2$	80:20	20c
13	Me	vinylMgBr	$ZnCl_2$	50:50	20c
14	Me	vinylLi		83:17	20c
15	Me	vinylLi	$TiCl_4$	83:17	20c
16	Me	$vinyl_2CuLi$		60:40	20c
17	Me	$vinylAlEt_2$		40:60	20c
18	Me	vinylZnCl	$ZnCl_2$	14:86	20c
19	Me	vinylZnCl		14:86	20c
20	Me	allylLi	HMPA	80:20	20d
21	Me	allylMgBr		60:40	20d
22	Me	allylMgBr	CuI	25:75	20d
23	Me	EtMgBr		10:90	20e
24	Me	EtLi		77:23	20e
25	Me	EtMgBr	$CeCl_3$	40:60	20e
26	Me	MeMgCl		06:94	20e
27	Me	MeMgCl	$CeCl_3$	88:12	20e
28	Me	PhMgBr		83:17	20f
29	Me	^iPrMgCl		14:86	20f
30	$(CH_2)_5$	PhMgBr		89:11	20f
31	$(CH_2)_6$	MeMgCl		67:33	20f
32	$(CH_2)_6$	EtMgBr		10:90	20f
33	$(CH_2)_6$	^iPrMgCl		10:90	20f
34	$(CH_2)_6$	^{t}BuMgBr		07:93	20f
35	$(CH_2)_6$	^{c}HexMgBr		06:94	20f
36	$(CH_2)_6$	PhMgBr		89:11	20f
37	Me			83:17	15u

with chelating reducing agents; however, nonchelating hydrides, while still favoring **42**, exerted only modest stereocontrol.

Instead to carbonyl compounds,[26] the Felkin−Anh model has also been successfully applied to thioketones[27] or imines.[28,29] It is interesting to note that imines **44** (X = N^{i}Pr) consistently gave better results

Scheme 12. Addition of Nucleophiles to 2,3-Isopropylideneglyceraldehyde 28

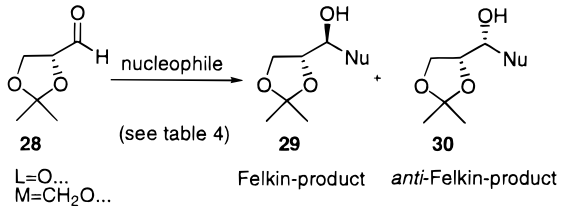
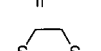
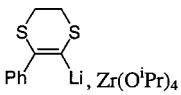
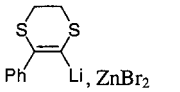
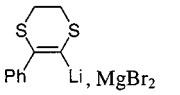
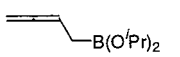


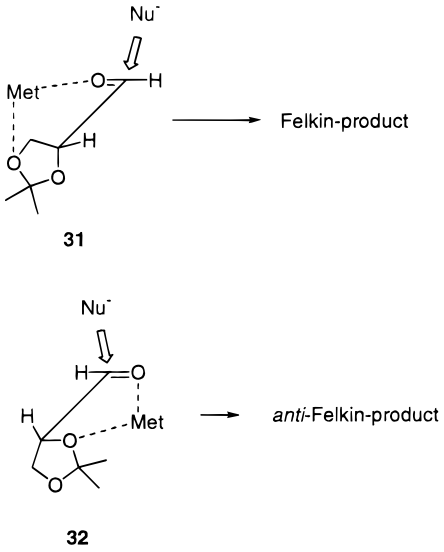
Table 4. Addition of Nucleophiles to 2,3-Isopropylideneglyceraldehyde 28

entry	nucleophile	29:30	ref
1	allylMgBr	60:40	22a
2	$allylTi(O^iPr)_3$	71:29	22a
3	$(allyl)_2Zn$	90:10	22b
4	PhLi	48:52	22a
5	PhMgBr	48:52	22a
6	$PhTi(O^iPr)_3$	09:91	22a
7	MeLi	60:40	22a
8	MeMgBr	67:33	22a
9	^{n}BuLi	69:31	22a
10	^{n}BuMgBr	75:25	22a
11	^{i}BuMgBr	75:25	22c
12	^{n}BuTi(O^{i}Pr)$_3$	90:10	22a
13	≡—Li	50:50	22d,e
14	—≡—Li	50:50	22d,e
15		70:30	22f
16		70:30	20b
17		78:22	20b
18		55:45	20b
19		47:53	20b
20		92:08	22g

compared to the corresponding aldehydes in favor of the Felkin product **46** (Scheme 18, Table 8).

The addition of nucleophiles to 3-substituted cyclohexanones has also been analyzed by Felkin and Anh. The underlying concepts in these cases are, however, the distinction between axial attack due to torsional strain and equatorial attack due to the lower steric hindrance of the nucleophile on its incoming trajectory. Since there is no issue of conformational flexibility as found in acyclic α-chiral or β-chiral substrates, such cases should not be considered in the context of Cram's rule.[30]

Scheme 13. Reactive Conformation for Reactions with 28



Scheme 14. Addition of Nucleophiles to the Acroleindimer 33

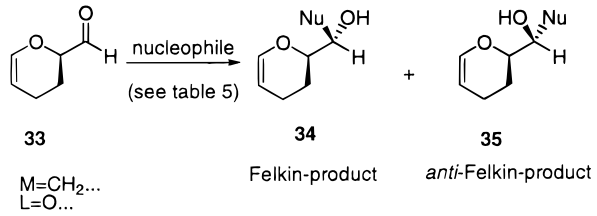


Table 5. Addition of Nucleophiles to Acroleindimer 33

entry	M−Nu	**34**:**35**	ref
1	Et_2TiCl_2	24:76	23a
2	$EtCu^{(1)}Li$	50:50	23a
3	$EtCu^{(1)}MgBr$	12:88	23a
4	Et_2Zn	15:85	23b
5	EtLi	72:28	23a,b
6	EtLi/TMEDA	80:20	23c,b

B. Nucleophilic Attack to Cyclopropyl-Substituted Carbonyl Compounds—Conflicting Models

Due to stereoelectronic reasons, cyclopropyl-substituted carbonyl compounds are most stable in bisected conformations. On the basis of this preference, a model was postulated for the nucleophilic attack to α-chiral cyclopropyl carbaldehydes and ketones:[31a] of the two possible bisected conformations, the *s-cis* conformation **49** is disfavored in cyclopropyl carbaldehydes because of steric interactions with the cyclopropyl moiety (Scheme 19). The attack of the nucleophile is therefore thought to occur in the preferred *s-trans* conformation **51** of the cyclopropyl compound from the sterically less shielded side, predicting **53** as the major diastereomer. However, in this case, the trajectory of the nucleophile is interfering with the cyclopropane ring (substituent M) corresponding to an *anti*-Felkin−Anh attack. In accordance with the Felkin−Anh rule, one would therefore postulate a transition state resulting from the conformation **50** as most favorable, giving rise to **48** as the major diastereomer.[31b]

Scheme 15. Addition of Nucleophiles to Substituted Benzoxathiin 36

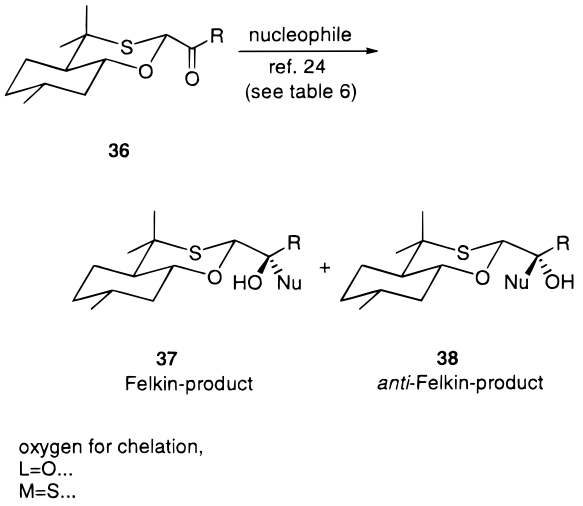


Table 6. Addition of Nucleophiles to Substituted Benzoxathiin 36[24]

entry	R	nucleophile	**37**:**38**
1	Me	PhMgBr	22:78
2	Me	PhLi	50:50
3	CH_2OTIPS	PhMgBr	0:100
4	CH_2OMe	PhMgBr	84:16
5	CH_2SMe	PhMgBr	13:87
6	CH_2SMe	PhLi	77:23
7	CHMeOMe (*S*)	PhMgBr	21:79
8	CHMeOMe (*R*)	PhMgBr	100:0
9	CHMeOTIPS (*S*)	PhMgBr	0:100
10	CHMeOTIPS (*R*)	PhMgBr	0:100
11	CHEtSMe (*S*)	PhMgBr	0:100
12	CHEtSMe (*S*)	PhLi	91:09
13	CHEtSMe (*R*)	PhMgBr	0:100
14	CHEtSMe (*R*)	PhLi	47:53

Scheme 16. Transition State for Reactions of 36 and Nucleophiles

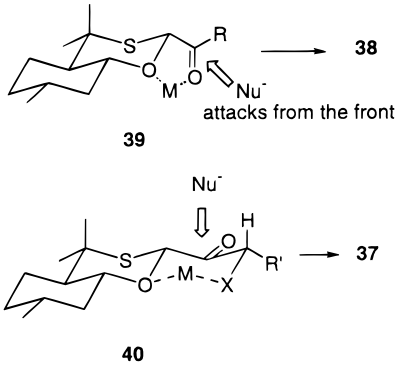
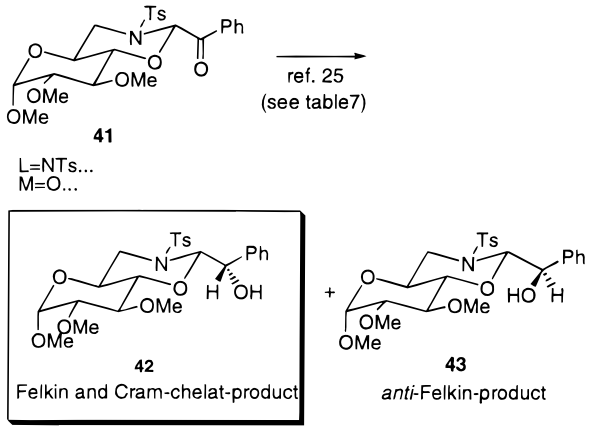


Table 7. Addition of Nucleophiles to *N*-Tosyl-2-benzoyl-1,3-oxazines (41)[25]

entry	reagent	**42**:**43**
1	$NaBH_4$	85:15
2	$LiAlH_4$	99:01
3	L-Selectride	99:01
4	L-Selectride/12-crown-4	70:30
5	DIBAL-H	80:20

Indeed, cyclopropyl carbaldehydes **54** are known to yield, with high selectivity, both the Felkin adduct **55** or the *anti*-Felkin adduct **56** depending on the

Scheme 17. Addition of Nucleophiles to N-Tosyl-2-benzoyl-1,3-oxazines (41)



Scheme 18. Addition of Nucleophiles to α-Chiral Imines in Comparison with α-Chiral Aldehydes

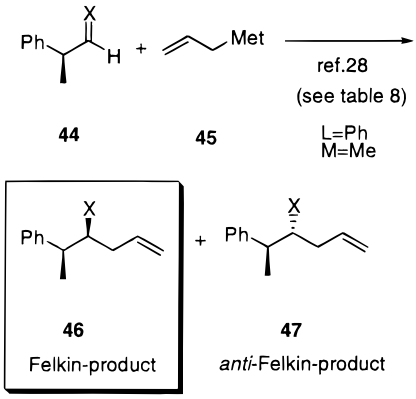


Table 8. Addition of Nucleophiles to α-Chiral Imines in Comparison with α-Chiral Aldehydes[28,29]

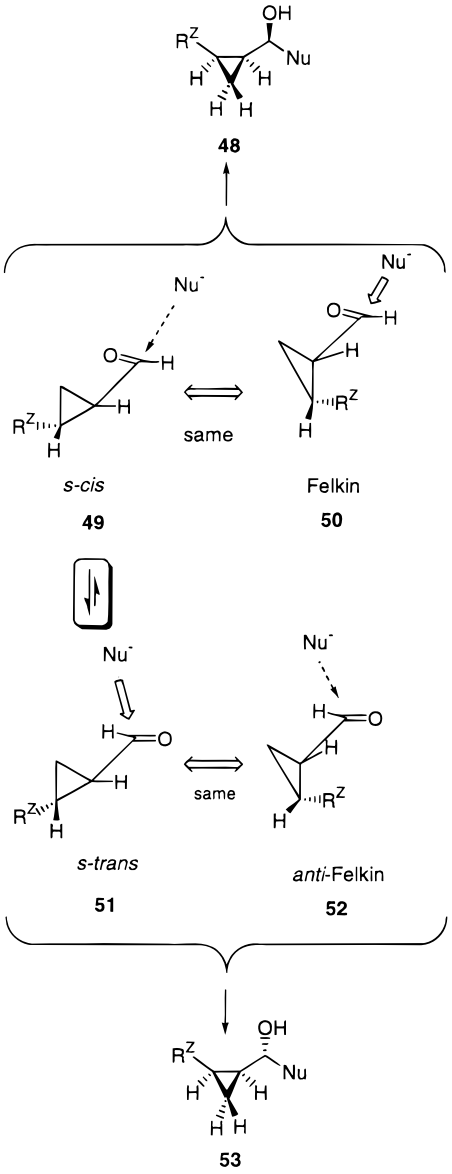
entry	X	Met	**46**:**47**
1	O	9-BBN	55:45
2	N^{i}Pr	9-BBN	100:0
3	O	$SnBu_3/TiCl_4$	69:31
4	N^{i}Pr	$SnBu_3/TiCl_4$	92:08
5	O	MgCl	60:40
6	N^{i}Pr	MgCl	70:30

substrate and the nucleophile (Scheme 20, Table 9).[31,32] However, the high preference for the formation of **56** (entries 1−2) might also be explained by chelation with the carbamide group in the β-position. In cases in which chelation can be conclusively ruled out, high selectivity toward the Felkin diastereomer **55** was observed.

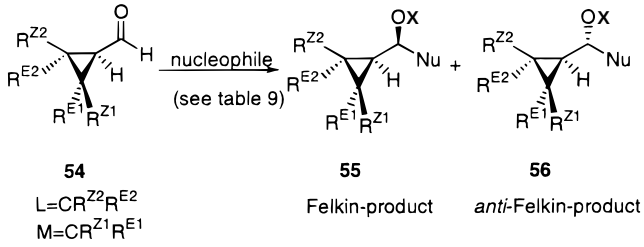
In cyclopropyl ketones, the substituent R becomes sterically more demanding than the carbonyl group, consequently the *s-cis* conformation **58** is preferred (Scheme 21). Therefore, the analysis based on preferential attack of the *s-cis* conformation[31a] **58** or of the Felkin−Anh conformation[33] **59** leads to the same prediction that the favored diastereomer should be **57**.

Concurrent with this analysis, various cyclopropyl ketones **63** have been reduced with hydride reagents to yield the Felkin product **64** predominately (Scheme 22, Table 10).[31a,33] By switching the

Scheme 19. Transition States of the Nucleophilic Attack to Cyclopropyl-Substituted Carbaldehydes



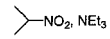
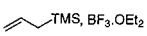
Scheme 20. Addition of Nucleophiles to Cyclopropyl Carbaldehydes



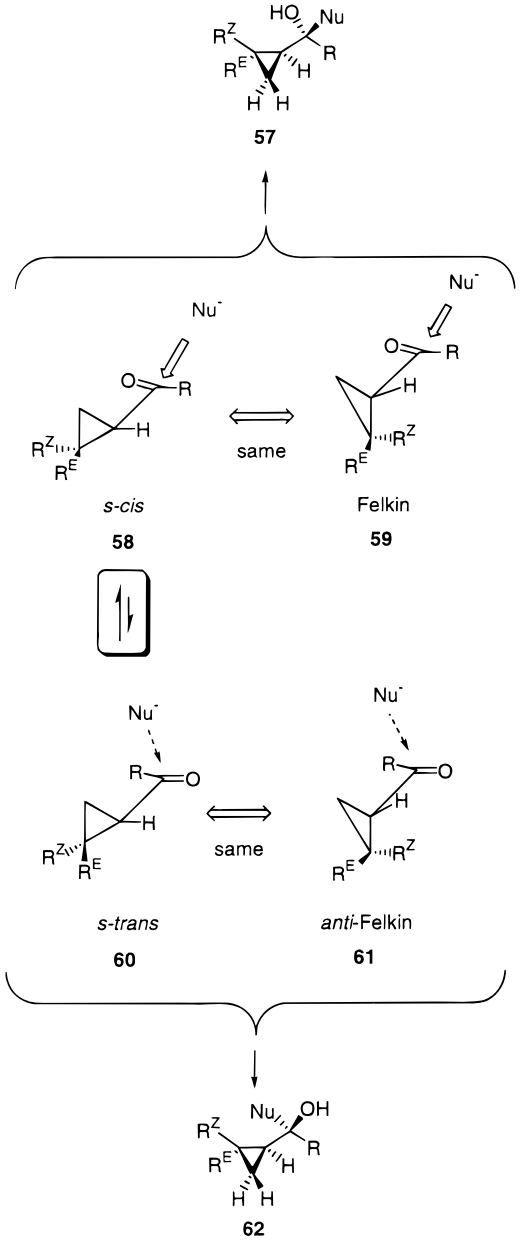
reducing reagent, an impressive change of selectivity was accomplished in one case (entries 7 and 8). This was explained by precoordination of DIBAL-H to the carbonyl group, thus disfavoring **58** or **59** for steric reasons.[31a]

A similar picture is obtained when analyzing nucleophilic additions to α-chiral epoxyaldehydes and ketones (Scheme 23, Table 11).[34] Again, there seems to be quite a delicate balance between chelation

Table 9. Addition of Nucleophiles to Cyclopropylcarbaldehydes 54

entry	R^{E2}	R^{Z2}	R^{E1}	R^{Z1}	X	nucleophile	55:56	ref
1	Ph	$CONEt_2$	H	H	H	MeMgBr	04:96	31a
2	Ph	$CONEt_2$	H	H	H	EtMgBr	04:96	31a
3	H	NBocCHO	CO_2Me	H	H		>99:01	31b
4	H	NBocCHO	CO_2Me	H	CHO	TMSCN	91:09	31b
5	H	NBocCHO	CO_2Me	H	H		>99:01	31b
6	H	allyl	Me	Me	H	$CH_3CO(CH_2)_3OTBS$	76:14	32

Scheme 21. Transition States of the Nucleophilic Attack to Cyclopropyl Substituted Ketones



control by invoking the oxygen of the epoxide and Felkin control. Alkoxy groups in the β-position being placed *cis* to the carbonyl group seem to be able to effectively compete with the ring oxygen for chelation, thus explaining the preference for the Felkin product **67** (entries 6−8). Further examples have been reported.[35]

Scheme 22. Addition of Nucleophiles to Substituted Cyclopropyl Ketones

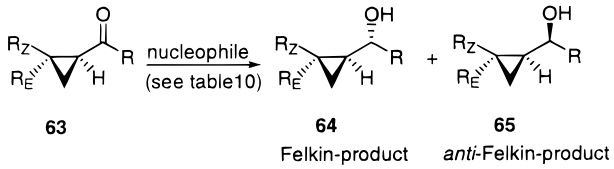


Table 10. Addition of Nucleophiles to Substituted Cyclopropylketones 63

entry	R^E	R^Z	nucleophile	**64**:**65**	ref
1	TMS	H	$LiAlH_4$	71:29	33a,b
2	^{n}Bu	H	$LiAlH_4$	50:50	33a,b
3	$SnBu_3$	^{n}Bu	$LiAlH_4$	94:06	33a,b
4	TMS	$SnBu_3$	$LiAlH_4$	95:05	33a,b
5	$SnBu_3$	$SnBu_3$	$LiAlH_4$	94:06	33a,b
6	Ph	$CONEt_2$	$NaBH_4$	80:20	31a
7	Ph	$CONEt_2$	$Li(^sBu)_3BH$	98:02	31a
8	Ph	$CONEt_2$	DIBAL-H	02:98	31a

Scheme 23. Addition of Nucleophiles to Epoxyketone 66

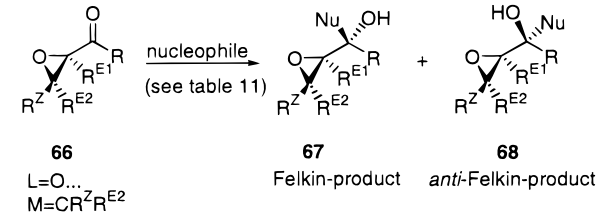


Table 11. Addition of Nucleophiles to Epoxyketone 66

entry	R^{E1}	R^{E2}	R^Z	R	nucleophile	**67**:**68**	ref
1	H	^{n}Am	H	H	EtMgBr	50:50	34a
2	TMS	^{n}Am	H	H	EtMgBr	96:04	34a
3	H	TMS	H	^{n}Bu	MeMgI	20:80	34b
4	H	TMS	H	^{n}Bu	MeMgI/HMPA	<01:99	34b
5	H	TMS	H	Me	^{n}BuMgBr/ HMPA	17:83	34b
6	H	H	CH_2OBn	H	MeLi	80:20	34c
7	H	H	CH_2OBn	H	MeMgCl	75:25	34c
8	H	H	CH_2OTBS	H	MeLi	73:27	34c

C. Combination of the Felkin–Anh Rule and the Zimmerman–Traxler Model

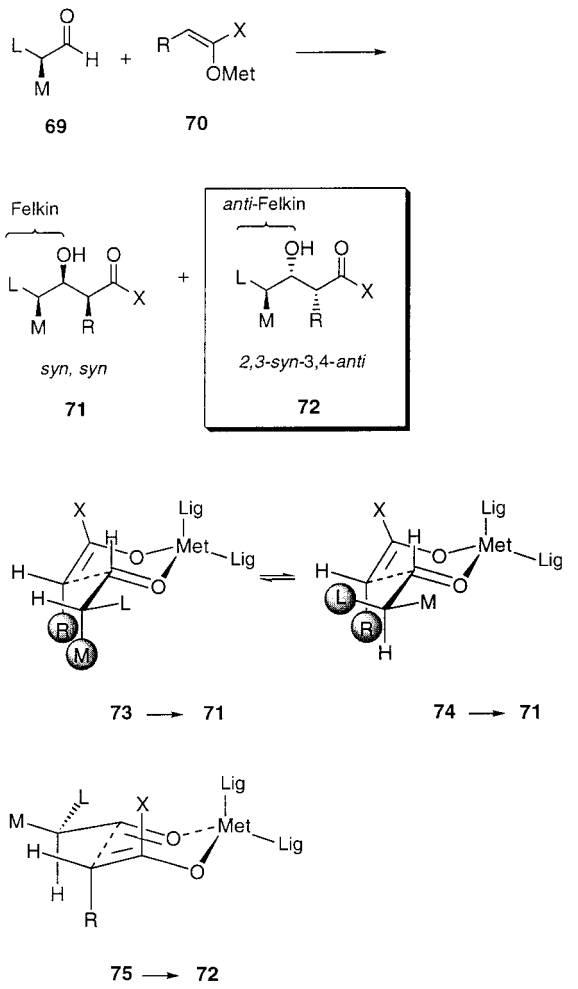
Many addition reactions to carbonyl compounds proceed via cyclic six-membered transition states. The course of such reactions can be understood by the Zimmerman−Traxler model,[36] which requires the arrangement of the reaction partners in a chairlike transition state, placing the large substituents equatorially if possible. This model is usually strictly followed in ene,[37] allylation,[38] and aldol reactions.[39]

1. Aldol Reactions

The reaction of α-chiral aldehydes **69** with enolates calls for the combination of the Zimmerman−Traxler model and the Felkin−Anh rule, which was thoroughly analyzed by Roush[40a] and Gennari.[40b]

In agreement with the Zimmerman−Traxler model, the reaction of aldehydes with *Z*(O)-enolates affords predominantly *syn*-aldol adducts while *E*(O)-enolates give rise to *anti*-aldol adducts. The *Z*(O)-enolate **70** should therefore give rise to the *syn*,*syn* diastereomer

Scheme 24. Models for Aldol Reactions between α-Chiral Aldehydes and *Z*(O)-Enolates

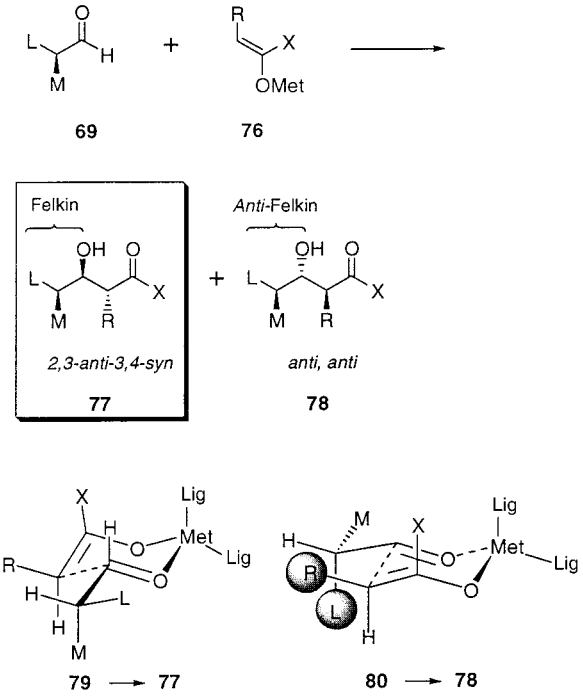


71 by abiding both the Felkin−Anh rule and the Zimmerman−Traxler model (Scheme 24). However, the Felkin-type transition states leading to **71** suffer from severe 1,3-*syn*-pentane (cf. **73**) or gauche (cf. **74**) interactions. In contrast, the *anti*-Felkin transition state **75** minimizes both 1,3-*syn*-pentane and gauche interactions, leading to **72** as the preferred diastereomer.

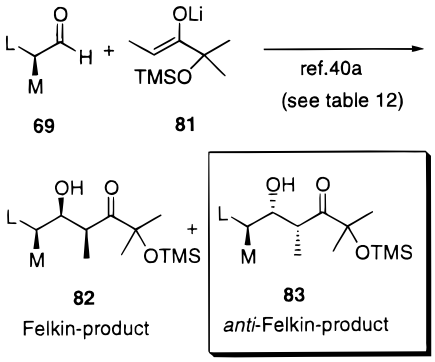
In contrast, *E*(O)-enolates **76** should preferentially give rise to the Felkin adduct **77** (Scheme 25). The transition state **80** leading to the *anti*-Felkin adduct **78** suffers from a gauche interaction between R and L compared to the Felkin transition state **79**, in which only a gauche interaction between R and M is evident.

Experimental evidence and theoretical calculations seem to support these models, although in many cases the selectivities obtained in favor of one diastereomer are not particularly high (Scheme 26, Table 12[40a] and Scheme 27[41]). Moreover, the assignment of L and M is not straightforward: Substituents such as phenyl or vinyl groups must apparently be regarded as smaller than a methyl group (Table 12, entries 1−3). Due to their flat, sterically undemanding π-surface, these substituents seem to experience very little of the decisive gauche interaction between M (π-substituent) and R (Me) in **75**.[42,43]

Scheme 25. Models for Aldol Reactions between α-Chiral Aldehydes and *E*(O)-Enolates



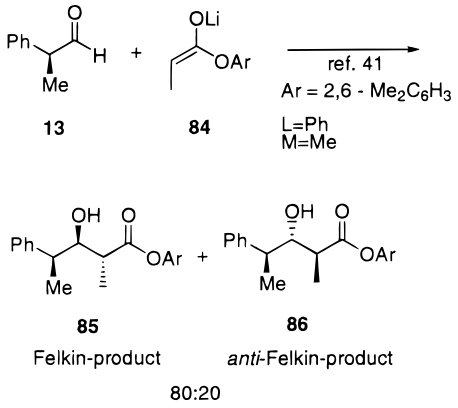
Scheme 26. Aldol Reactions of *Z*(O)-Enolates and α-Chiral Aldehydes



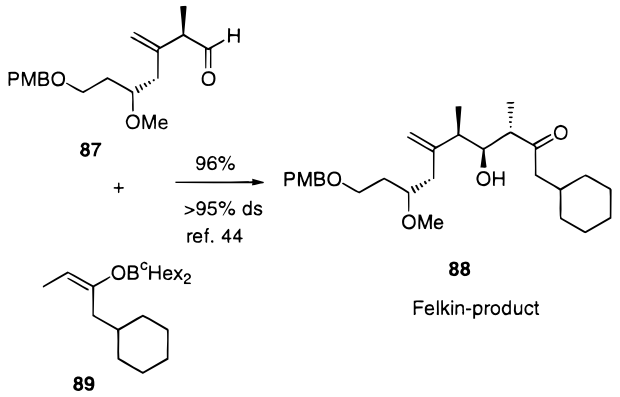
If there is sufficient steric differentiation between L and M, high selectivities can nevertheless be accomplished. In the synthesis of a subunit of Songistatin 1, the key step consists of a boron-mediated *anti*-aldol coupling reaction between **87** and **89**, which has led to the Felkin product **88** with perfect stereocontrol (Scheme 28).[44]

The situation changes if enolate **90** bearing no substituent at the β-carbon reacts with α-chiral aldehydes. Since *syn*-pentane and gauche interactions being encountered in **73** and **74** are now negligible, preference for the Felkin diastereomer **91** is found in a very similar way, as observed in the reaction of **1** with simple nucleophiles (Scheme 29 and Table 13).[45] In particular, the stereoelectronic control exerted by electron acceptors outweighs the influence of sterically demanding substituents (Table 13, entries 1−5). The increase in selectivity with the steric bulk of M can be understood as disfavoring the *anti*-Felkin attack (cf. **75**). Again, the phenyl group being a weak acceptor assumes the role of L; however, a conflict arises with sterically demanding

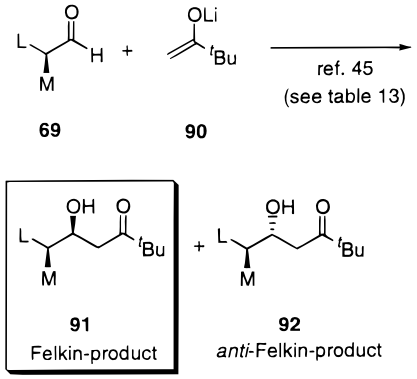
Scheme 27. Aldol Reaction of the *E*(O)-Enolate 84 and α-Chiral Aldehyde



Scheme 28. Key step in the Synthesis of 88



Scheme 29. Aldol Reactions with β-Unsubstituted Enolates



groups such as *i*-Pr or *t*-Bu, resulting in a loss of selectivity (Table 13, entries 6−9).[46−48]

2. Allylboration Reactions

The same analysis as for the aldol reactions can be applied for the addition of crotylboranates to α-chiral aldehydes, since the allyl transfer also proceeds via six-membered chairlike transition states. *Z*-boronates **93** should therefore yield as the major diastereomer the *anti*-Felkin adduct **95**, while with *E*-boronates **96** one would expect the Felkin adduct **97** to be preferred (Scheme 30). While this analysis seems to hold in most cases using **96** as the starting boronate (Table 14, entries 1−4), there seems to be no clear picture for the corresponding *Z*-boronate **93** (entries 5−8).[40a,49]

Table 12. Aldol Reactions of *Z*(O)-Enolates 81 and α-Chiral Aldehydes[40a]

entry	L	M	82:83
1	Me	Ph	19:81
2	Me	Vinyl	25:75
3	Me		06:94
4	^{c}Hex	Me	27:73
5	$PhCH_2OCH_2$	Me	33:67
6	$AcOCH_2$	Me	23:77
7	$TBSOCH_2$	Me	21:79

Table 13. Aldol Reactions with β-Unsubstituted Enolate 90[45]

entry	L	M	91:92
1	OMe	Me	58:42
2	OMe	Et	76:24
3	OMe	^{i}Pr	92:08
4	OMe	^{t}Bu	93:07
5	OMe	Ph	83:17
6	Ph	Me	78:22
7	Ph	Et	86:14
8	Ph	^{i}Pr	70:30
9	Ph	^{t}Bu	37:63

Scheme 30. Aldol Reactions of Crotylboronates and α-Chiral Aldehydes

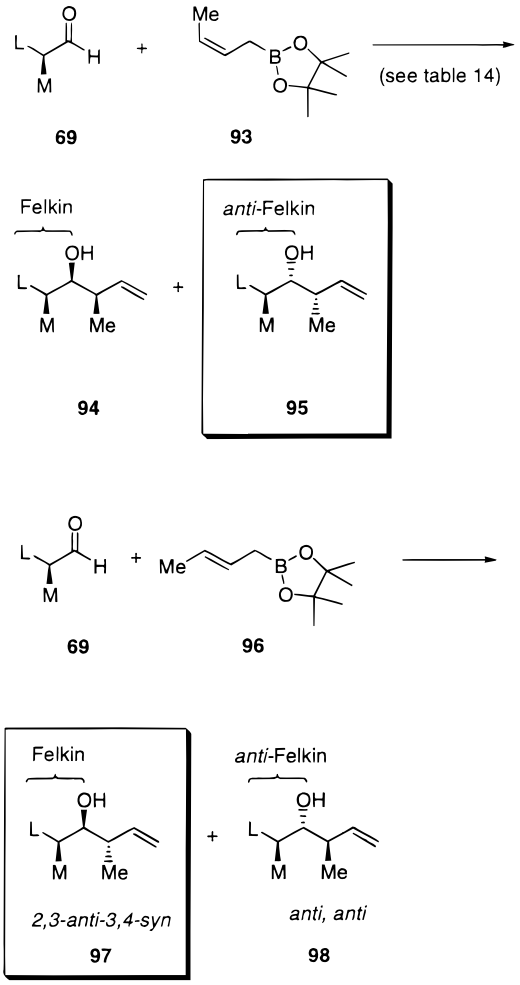


Table 14. Aldol Reaction of Crotylboronates 93 and 96 and α-Chiral Aldehydes 69

entry	L	M	*E*/*Z*-Boranat	**94**:**95** or **97**:**98**	ref
1	Et	Me	*E*	83:17	40a
2	^{t}Bu	Me	*E*	>97:03	49
3	OBn	Me	*E*	47:53	49
4	CHMeOTBS	Me	*E*	95:05	49
5	Et	Me	*Z*	30:70	40a
6	^{t}Bu	Me	*Z*	60:40	49
7	OBn	Me	*Z*	88:12	49
8	CHMeOTBS	Me	*Z*	09:91	49

D. Double Stereodifferentiation

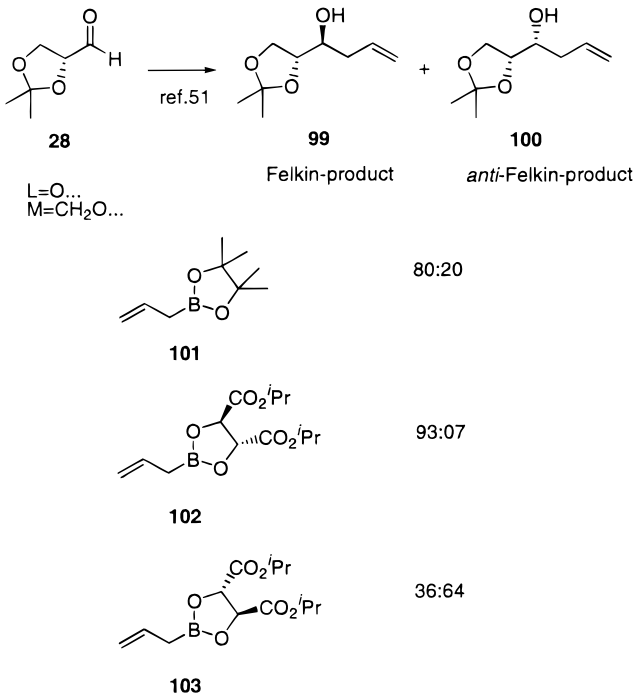
If α-chiral carbonyl compounds are reacted with chiral nucleophiles, the issue of double sterecontrol[50] arises. The analysis of such cases becomes therefore more complicated since it is very often not unambiguously possible to attribute the induced stereoselection to the α-chiral carbonyl substrate or to the nucleophile, respectively. Many situations are encountered in which the nucleophile is rendered chiral by an auxiliary or a catalyst, which efficiently overrides the influence of the α-stereocenter in the substrate. A typical example (Scheme 31) is the allylation of the aldehyde **28** with the achiral allylborane **101** to yield **99** with moderate Felkin control as expected.[51a] Using the chiral allylborane **102**, the selectivity is dramatically increased in favor of **99** (matched case), while with the enantiomeric **103**, the *anti*-Felkin product **100** is mainly formed (mismatched case) (Scheme 31). Ideally, an auxiliary-based reagent would completely control the outcome of a reaction independent of the chirality of the substrate. The most successful auxiliaries, such as the oxazolidinones developed by Evans, give indeed generally excellent selectivities also for the mismatched cases.

Mulzer[52] demonstrated the combination of Felkin and Cram-chelate control with an ingenious set of experiments. The α-stereocenter in the α,α′-chiral ketone **104** having an appropriate protected oxygen group exhibits Felkin control, while the α′-center is amenable toward chelation (Scheme 32, Table 15). As shown in **107**, these two control elements are reinforcing; consequently, **104** gives rise predominately to **105** with especially high selectivity if PG is chosen in a way that chelation with the α-center is efficiently precluded (Table 15, entries 6−9).

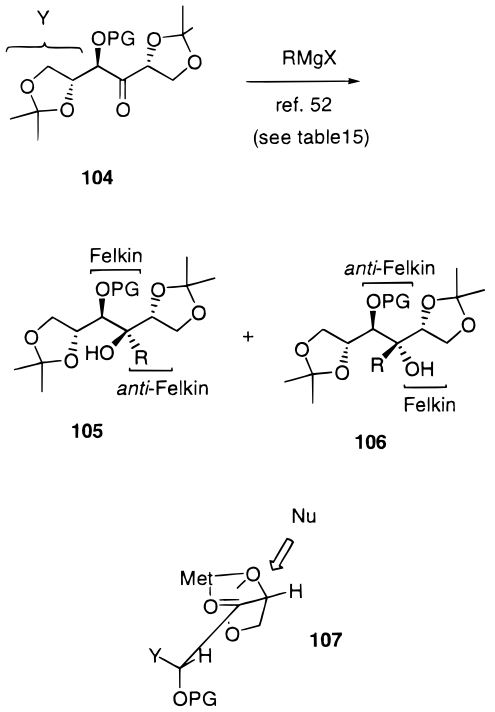
In contrast, with diastereomer **108**, a conflict arises between the preferred conformation of the α-stereocenter for Felkin control and of the α′-stereocenter for Cram-chelate control, the two control elements are nonreinforcing (Scheme 33, Table 16). Nevertheless, high selectivities in favor of **109** have been achieved, indicating that Cram-chelate control through the α′-center has been the decisive factor.

There are also a number of examples for the reaction of α-chiral nucleophiles with α-chiral aldehydes. In general, the stereochemical control of the

Scheme 31. Double Stereodifferentiation in the Allylation of Aldehyde 28



Scheme 32. Grignard Additions to α- and α′-Chiral Ketones (reinforcing)



carbonyl compound seems to be the decisive factor, consequently the reaction of **113** and **114** lead predominantly to the Felkin product **115** (Scheme 34).[53]

The preference of a substrate to yield preferentially the Felkin−Anh or the Cram-chelate adduct can be used as a selection criteria in kinetic and dynamic kinetic resolutions.[54] Thus, racemic α-alkoxyaldehydes and α-aminoaldehydes can be resolved with high diastereoselectivity to alkenes when reacted

Table 15. Grignard Additions to α- and α′-Chiral Ketones (reinforcing)[52]

entry	PG	RMgX	**105**:**106**
1	Bn	^{i}propenylMgBr	>98:02
2	Bn	EtMgBr	91:09
3	Bn	vinylMgCl	96:04
4	Bn	allylMgBr	67:33
5	TBS	^{i}propenylMgBr	95:05
6	Bzl	^{i}propenylMgBr	>98:02
7	Piv	^{i}propenylMgBr	>98:02
8	2,6-Cl_2−Bn	^{i}propenylMgBr	>98:02
9	TBDPS	^{i}propenylMgBr	>98:02
10	Me	^{i}propenylMgBr	65:44

Scheme 33. Grignard Additions to α- and α′-Chiral Ketones (nonreinforcing)

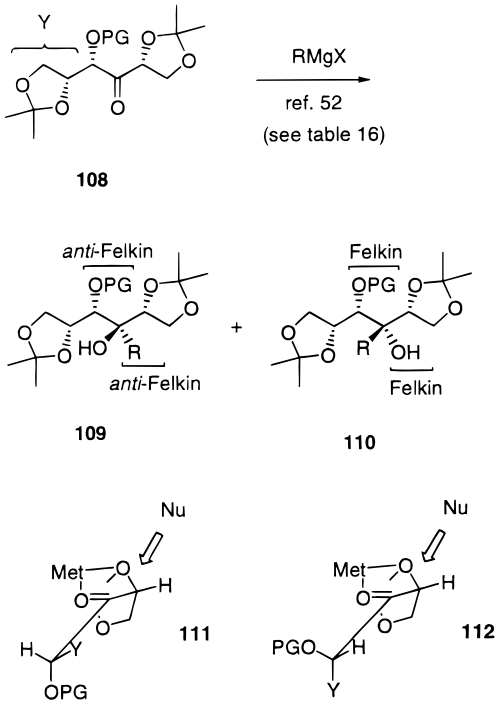
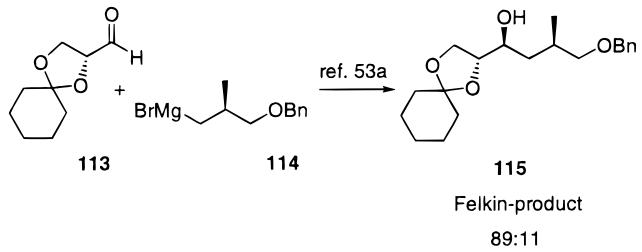


Table 16. Grignard Additions to α- and α′-Chiral Ketones (nonreinforcing)[52]

entry	PG	RMgX	**109**:**110**
1	2,6-Cl_2-Bn	^{i}propenylMgBr	>90:10
2	2,6-Cl_2-Bn	vinylMgCl	75:25
3	Bzl	^{i}propenylMgBr	>98:02
4	Bzl	EtMgBr	95:05
5	Bzl	vinylMgCl	90:10

Scheme 34. Reaction between α-Chiral Aldehyde and α-Chiral Nucleophile



with chiral phosphonates using nonchelating conditions. In particular, starting from racemic **116**, either the Felkin diastereomer **118** or the *anti*-Felkin

Scheme 35. Felkin−Anh Model in Kinetic Resolution

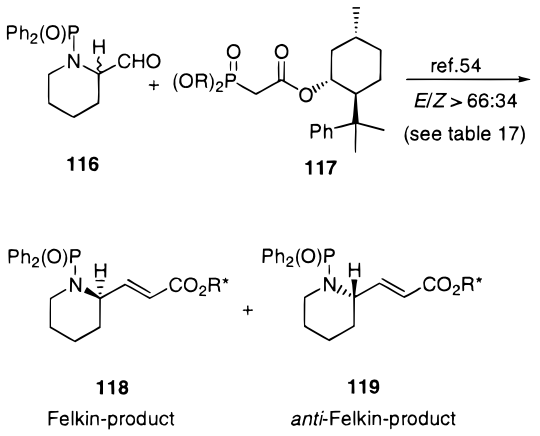
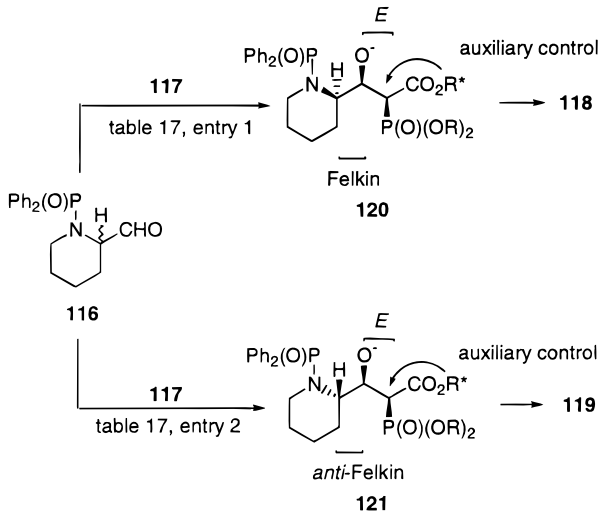


Table 17. Felkin−Anh Model in Kinetic Resolution of 116[54a]

entry	R	base, solvent	**118**:**119**
1	*o*-Tol	KHMDS/18-crown-6,THF	93:07
2	CF_3CH_2	KHMDS, DCM	03:97

Scheme 36. Application of the Felkin−Anh Model in Kinetic Resolution of 116



diastereomer **119** can be obtained selectively only by switching from nonchelating to chelating conditions using the same chiral auxiliary (Scheme 35, Table 17).[54a] The observed selectivity can be explained by control of the stereocenter adjacent to the ester group by the chiral auxiliary, which is relayed via the geometric control to the *β*-stereocenter. Finally, the aldehyde enantiomer of **116** will react preferentially that will allow the formation of the Felkin or the *anti*-Felkin diastereomer depending on the reaction conditions applied (Scheme 36).

The reaction of the α-chiral aldehyde **13** and the chiral carbanion **122** has been shown to proceed with high diastereoselectivity.[55] In a mutual kinetic resolution, high Felkin control was achieved along with high *syn*-selectivity if an appropriate metal as countercation is chosen (Scheme 37, Table 18).

Scheme 37. Addition of Chiral Carbanions to α-Chiral Aldehydes

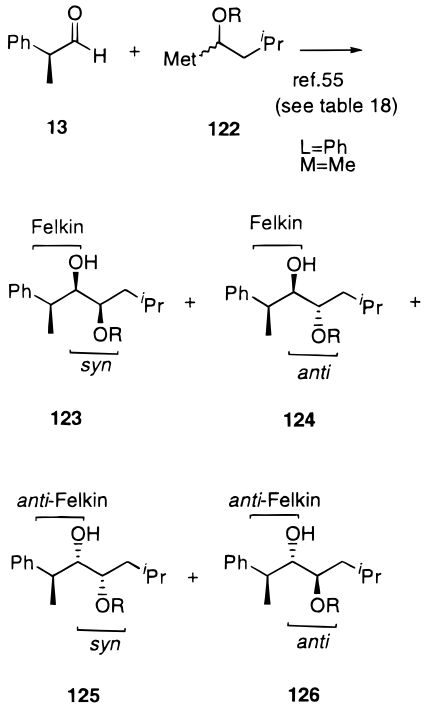


Table 18. Addition of Chiral Carbanions to α-Chiral Aldehydes[55]

entry	R	Met	**123**:**124**: **125**:**126**	Felkin: *anti*-Felkin	*syn*: *anti*
1	Me	$PbBu_3$, $TiCl_4$	95:0:5:0	95:05	100:0
2	Me	$SnBu_3$, $TiCl_4$	90:0:10:0	90:10	100:0
3	MOM	Li	49:43:4:4	92:08	53:47

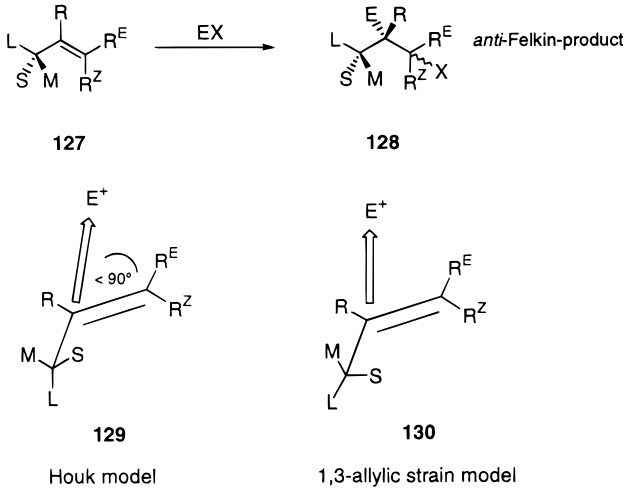
III. Addition to α-Chiral C–C Double Bonds

The great success of the Felkin−Anh rule to provide an understanding for addition reactions to α-chiral C−O double bonds called for the extension of this concept to C−C double bonds. However, the analysis of addition reactions to α-chiral alkenes is more complicated: depending on the electronic nature of the alkene, both electrophiles or nucleophiles can be added. This has implications on the kind of stereoelectronic effects that might be executed from substituents of the chiral α-center as well as on the trajectory of the incoming reagent. To further complicate the situation, some nucleophiles having countercations such as zinc can behave like electrophilic reagents due to the initial interaction of the alkene double bond with the metal acting as a Lewis acid. Consequently, the definition of the substituents L, M, and S at the chiral center is dependent on the type of reaction under the premises that L should always be orthogonal to the double bond. Last but not least, the *E*/*Z*-geometry of the alkene can play a significant role for the selectivity. Especially in *Z*-alkenes the terminal substituent of the double bond can interact with the α-stereocenter, bringing in the issue of 1,3-allylic strain[56] as another important control element for the reactive conformation. With all additional factors to be taken into account, it becomes questionable if and to what extent the Felkin−Anh model can be applied to such reactions. Nevertheless, we will examine additions to carbon−carbon double bonds within the boundaries of the Felkin−Anh rule in comparison with the concept of 1,3-allylic strain, which also often plays a pivotal role in such reactions.

A. Electrophilic Additions

A model for the addition of electrophiles to α-chiral C−C double bonds was developed by Houk.[57] The basis again is found in the Felkin−Anh rule; however, there are two important differences: since electrophiles attack a double bond at the center, its trajectory is 90° or smaller, contrary to the addition of nucleophiles. Consequently, on this trajectory the electrophile feels the least steric influence of the α-center if the small substituent S orients onto the side of the double bond as shown in **129** (Scheme 38).

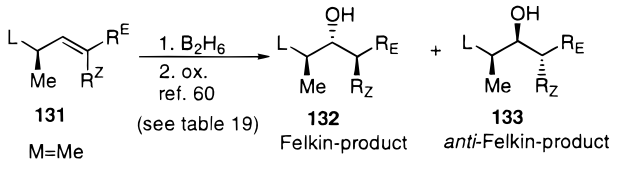
Scheme 38. Houk Model for Electrophilic Additions to Alkenes



As an additional benefit, the 1,3-allylic strain between R^Z and S is minimized; therefore, the *anti*-Felkin[58] adduct **128** should be the preferred one. Furthermore, the stereoelectronic influence of electron acceptors being orthogonal to the double bond would destabilize the transition state as electron density would be delocalized toward this group. Therefore, acceptors are not regarded as L, while electron donors when placed orthogonal make the double bond more electron rich and therefore assume the role of L.[59]

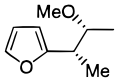
In agreement with this model, the hydroboration of **131** gives rise via **129** to the *anti*-Felkin product **133** (Scheme 39, Table 19).[60] However, the same

Scheme 39. Hydroboration of α-Chiral Alkenes 131

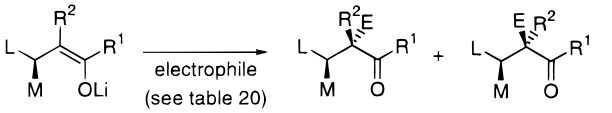


conclusion is reached via the transition state **130** which calls for eclipsing the small substituent with R^Z to minimize 1,3-allylic strain and electrophilic attack from the less sterically hindered side.

Table 19. Hydroboration of α-Chiral Alkenes 131[60]

entry	L	R_Z	R_E	132:133
1	$BzOCH_2$	Me	CH_2OCH_2OMe	29:71
2	$BzOCH_2$	CH_2OCH_2OMe	Me	25:75
3		Me	CH_2OBz	08:92
4		CH_2OH	Me	11:89

Scheme 40. Addition of Electophiles to α-Chiral Enolates



134 **135** Felkin-product **136** *anti*-Felkin-product

Table 20. Addition of Electophilies to α-Chiral Enolates 134

entry	R^1	R^2	M	L	electrophile	**135:136**	ref
1	OMe	Me	Bn	NHZ	EtI	16:84	61a
2	OMe	Me	Bn	NHZ	allylBr	0:100	61a
3	OEt	H	Me	NHCOPh	MeI	20:80	61b
4	OEt	H	Me	NHCOPh	EtI	07:93	61b
5	OEt	H	Me	NHCOPh	PhCHO	25:75	61b
6	OMe	H	Me	NHCOPh	MeI	20:80	61b
7	OMe	H	Me	NHCOPh	EtI	06:94	61b
8	OMe	Et	Me	NHCOPh	$PhCH_2Br$	<01:99	61b
9	OMe	H	Me	$PhCH_2OCONH$	MeI	12:88	61b
10	OMe	H	Me	$PhCH_2OCONH$	$PhCH_2Br$	<09:91	61b
11	OMe	H	Me	$PhCH_2OCONH$	PhCHOH	33:67	61b
12	Me	H	Me	Ph	MeI	40:60	61c
13	Me	H	Me	^{i}Pr	MeI	25:75	61c
14	Me	Me	Me	Ph	TFA	15:85	61c
15	Me	Me	Me	^{i}Pr	TFA	20:80	61c

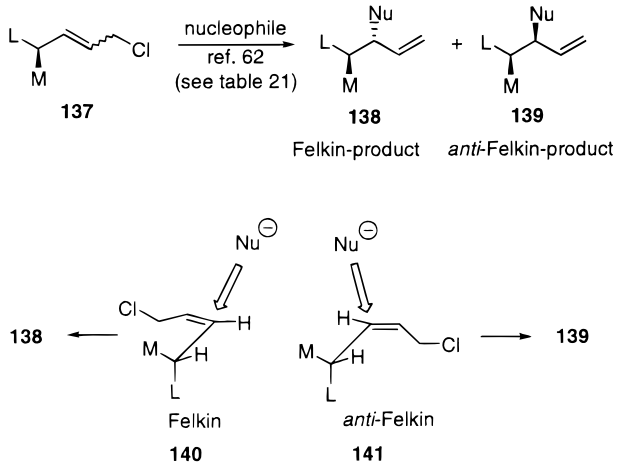
Likewise, α-chiral enolates **134** are trapped by various electrophiles yielding the *anti*-Felkin products **136** predominantly (Scheme 40, Table 20).[61]

B. Nucleophilic Additions

1. S_N2' Reactions

The addition of nucleophiles to α-chiral allyl chlorides via a S_N2' mechanism also follows, in principle, the Felkin−Anh rule as discussed for the addition of nucleophiles to α-chiral carbonyl compounds; however, some important differences again apply. Accordingly, the Felkin conformation **140** leading to the adduct **138** should be favored; however, in the case of (*Z*)-configurated alkenes **137**, the *anti*-Felkin conformation **141** increases in importance in order to minimize 1,3-allylic strain (Scheme 41). Therefore, excellent Felkin diastereoselectivity is found for the addition of cuprates to (*E*)-**137** (Table 21, entries 1−8)[62] while with (*Z*)-**137** the stereoselectivity is somewhat diminished (entries 9−10). Surprisingly, alkoxy substituents do not seem to exert the stereoelectronic effect seen earlier by the addition to carbonyl compounds. High Felkin selectivity is generally displayed by such substrates; however, the alkoxy substituent plays the role of M rather than of L (entries 11−19). An explanation for this "inside alkoxy effect", being discussed for the first time by Houk for 1,3-dipolar cycloadditions of nitriloxides to alkenes (vide infra),[59] might be found in the fact that the addition of zinc(II) chloride acting as a Lewis acid was required in the cuprate additions. The Lewis acid might withdraw electron density by coordination of the alkene, therefore making it disadvantageous for an α-alkoxy group to align orthogonal to the double bond. Again, selectivities with (*Z*)-alkenes (entries 18−19) are lower, probably due to competing 1,3-allyl strain favoring the *anti*-Felkin diastereomer **139**.

Scheme 41. 1,2-Induction in S_N2' Reactions



137 **138** Felkin-product **139** *anti*-Felkin-product

140 **141**

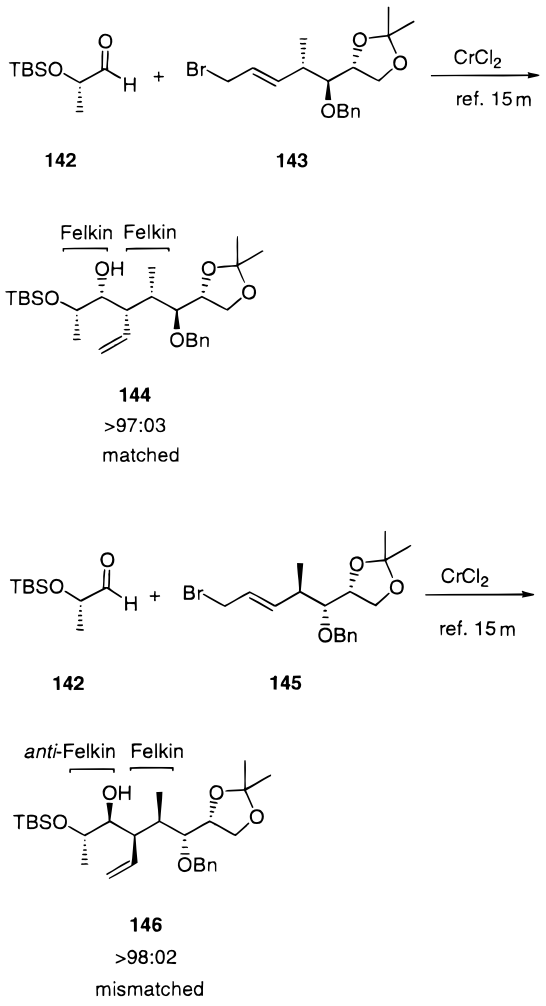
Table 21. 1,2-Induction in S_N2'-Reactions

entry	L	M	nucleophile	*E*/*Z*-olefin	**138:139**
1	Ph	Me	Bu_2CuLi	*E*	96:04
2	Ph	Me	$Bu_2CuLi{\cdot}ZnCl_2$	*E*	95:05
3	Ph	Me	$Me_2CuLi{\cdot}ZnCl_2$	*E*	95:05
4	Ph	Me	$Bu_2Ti(O^iPr)_3Li/CuI_{cat}$	*E*	95:05
5	Ph	Me	$BuCu{\cdot}BF_3$	*E*	96:04
6	Ph	Me	$Me_2CuLi/ZnCl_2$	*E*	95:05
7	^{c}Hex	Me	$Bu_2CuLi{\cdot}ZnCl_2$	*E*	100:0
8	^{c}Hex	Me	$Me_2CuLi{\cdot}ZnCl_2$	*E*	100:0
9	Ph	Me	$Bu_2CuLi{\cdot}ZnCl_2$	*Z*	78:22
10	Ph	Me	$Me_2CuLi{\cdot}ZnCl_2$	*Z*	88:12
11	Me	OMOM	$Bu_2CuLi{\cdot}ZnCl_2$	*E*	65:35
12	^{i}Pr	OTIPS	$Bu_2CuLi{\cdot}ZnCl_2$	*E*	100:0
13	^{i}Pr	OBn	$Bu_2CuLi{\cdot}ZnCl_2$	*E*	100:0
14	^{i}Pr	OMOM	$Bu_2CuLi{\cdot}ZnCl_2$	*E*	100:0
15	^{c}Hex	OMOM	$Bu_2CuLi{\cdot}ZnCl_2$	*E*	100:0
16	^{n}Pent	OMOM	$Bu_2CuLi{\cdot}ZnCl_2$	*E*	75:25
17	^{t}Bu	OMOM	$Bu_2CuLi{\cdot}ZnCl_2$	*E*	100:0
18	^{i}Pr	OBn	$Bu_2CuLi{\cdot}ZnCl_2$	*Z*	90:10
19	^{t}Bu	OMOM	$Bu_2CuLi{\cdot}ZnCl_2$	*Z*	40:60

A particularly impressive case combining the nucleophilic addition to an α-chiral aldehyde and the electrophilic addition to an α-chiral alkene was reported by Mulzer with the chromium-mediated reactions of **142** and the allyl bromides **143** and **145** (Scheme 42).[15m] The exclusive formation of **144** is rationalized with both an attack to the aldehyde **142** and to the alkene **143** according to the Felkin−Anh model and has consequently been labeled as the matched case. The reaction of **142** with **145** also proceeded with excellent stereochemistry, resulting in the diastereomer **146** in which attack of the alkene

according to the Felkin−Anh model has completely overridden the preference of the aldehyde to also yield the Felkin−Anh product.

Scheme 42. Addition of Chiral Nucleophiles to α-Chiral Carbonyl Compounds



2. Conjugated 1,4-Additions (Michael Additions)

In a very similar way to the S_N2' reactions, the addition of nucleophiles to γ-chiral-α,β-unsaturated carbonyl compounds can be analyzed (Scheme 43). Again, (*E*)-alkenes (*E*)-**147** preferentially give rise to diastereomer **148** following the Felkin paradigm,

Scheme 43. Addition of Nucleophiles to 147

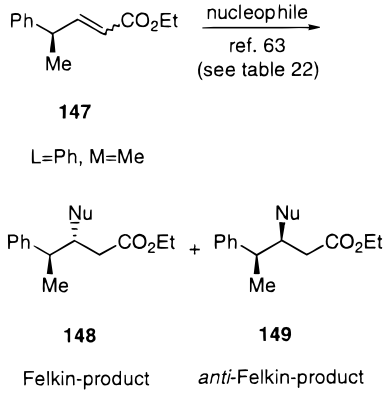
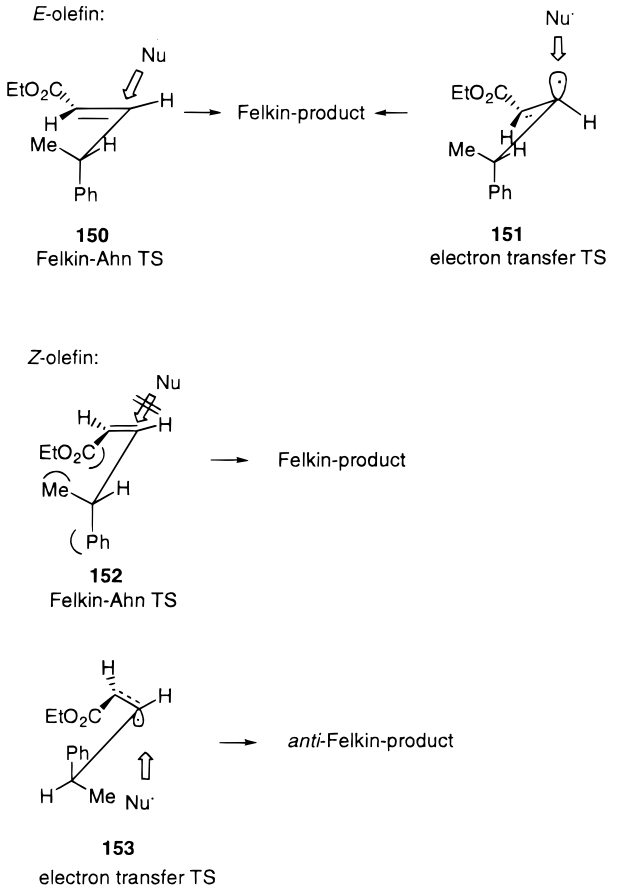


Table 22. Addition of Nucleophiles to 147[63]

entry	nucleophile	*E*/*Z*-olefin	**148**:**149**
1	$Bu_2CuLi{\cdot}BF_3$	*E*	70:30
2	$BuCu{\cdot}BF_3$	*E*	88:12
3	$Me_3CuLi_2{\cdot}BF_3$	*E*	87:13
4	$Bu_2CuLi{\cdot}BF_3$	*Z*	30:70
5	$BuCu{\cdot}BF_3$	*Z*	74:26
6	$Me_3CuLi_2{\cdot}BF_3$	*Z*	21:79

Scheme 44. Models for the Addition of Cuprates to γ-Chiral-α,β-unsaturated Acrylates



while with (*Z*)-alkenes (*Z*)-**147** 1,3-allylic strain is the dominating control element leading to the *anti*-Felkin diastereomer **149**.[63,64]

However, it is interesting to note that the nature of the nucleophile can also determine the stereochemical course of the reaction in the case of (*Z*)-alkenes as substrates. Low-order cuprates displayed Felkin selectivity for both (*E*) and (*Z*)-**147** (Table 22, entries 2, 5), while high-order cuprates predominantly yield the Felkin adduct **148** starting from (*E*)-**147** (entries 1 and 3) but favor the *anti*-Felkin adduct **149** starting from (*Z*)-**147** (entries 4 and 6). It has been argued that such reagents initially transfer an electron to the Michael acceptor, rendering the staggered conformation **153** decisive for the stereochemical outcome of the reaction (Scheme 44).

Disubstituted olefins show the same tendency discussed for (*Z*)-alkenes (Scheme 45, Table 23).[63]

Lithium amides generally display moderate to high Felkin selectivity in the 1,4-addition to γ-alkoxy-substituted acrylates, assigning the alkoxy group the

Scheme 45. Addtion of Cuprates to 154

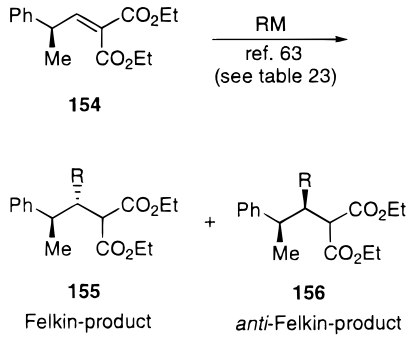
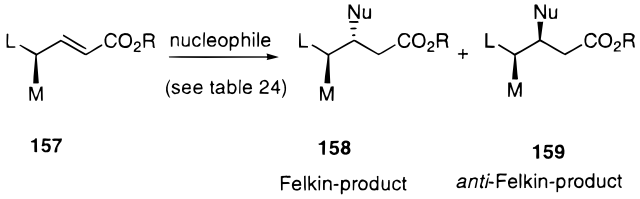


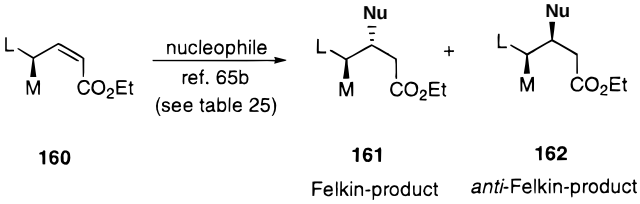
Table 23. Addition of Cuprates to 154[63]

entry	R−M	**155**:**156**
1	Bu_2CuLi	32:68
2	$BuCu{\cdot}BF_3$	74:26
3	$Me_3CuLi_2{\cdot}BF_3$	39:61
4	Bu_2CuLi	08:92
5	MeMgBr	60:40
6	Me_4AlLi	62:38
7	$allylSnBu_3$	96:04
8	$MeCu{\cdot}BF_3$	79:21

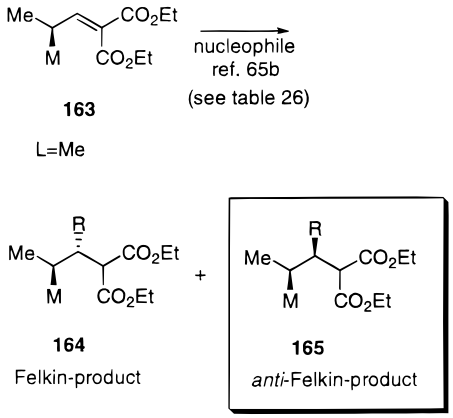
Scheme 46. Addition of Nucleophiles to 157



Scheme 47. Addition of Nucleophiles to 160



Scheme 48. Addition of Nucleophiles to 163



role of L based on the stereoelectronic argument discussed earlier (Scheme 46, Table 26, entries 1−6).[65] In the analogous addition of cuprates, however, alkoxy groups again must be viewed as M because of the electrophilic nature of the nucleophile

Table 24. Addition of Nucleophiles to 157

entry	L	M	R	nucleophile	**158**:**159**	ref
1	OTBS	Me	^{t}Bu	LiNBnTMS	54:46	65a
2	OTBDPS	Me	^{t}Bu	LiNBnTMS	89:11	65a
3	OTIPS	Me	^{t}Bu	LiNBnTMS	90:10	65a
4	OTIPS	Me	^{t}Bu	$LiNBn_2$	30:70	65a
5	$OCPh_3$	Me	^{t}Bu	LiNBnTMS	100:0	65a
6	OMe	Me	^{t}Bu	$LiNBn_2$	63:37	65a
7	Me	OBn	Et	$(methallyl)_2CuLi$	42:58	65b
8	Me	OBn	Et	(methallyl)Cu	40:60	65b
9	Me	OBn	Et	$(vinyl)_2CuLi$	72:28	65b
10	Me	OBn	Et	$(vinyl)_2CuLi{\cdot}BF_3$	94:06	65b
11	Me	OBn	Et	$(vinyl)_2Cu(CN)Li_2$	72:28	65b
12	Me	OBn	Et	$(vinyl)_2Cu(CN)Li_2{\cdot}BF_3$	95:05	65b
13	Me	OBn	Et	$MeCu{\cdot}BF_3$	69:31	65b
14	Me	OBn	Et	$MeCu(CN)Li{\cdot}BF_3$	95:05	65b
15	Me	OBn	Et	$BuCu{\cdot}BF_3$	92:08	65b
16	Me	OTBS	Et	$MeCu{\cdot}BF_3$	68:32	65b
17	Me	OTBS	Et	$Me_2CuLi{\cdot}BF_3$	73:27	65b
18	Me	OTBS	Et	$Me_2Cu(CN)Li_2{\cdot}BF_3$	92:08	65b

Table 25. Addition of Nucleophiles to 160[65b]

entry	L	M	nucleophile	**161**:**162**
1	Me	OBn	$(2\text{-methallyl})_2CuLi$	20:80
2	Me	OBn	$(vinyl)_2CuLi$	>99:01
3	Me	OBn	$(vinyl)_2CuLi{\cdot}BF_3$	52:48
4	Me	OBn	$(vinyl)_2Cu(CN)Li_2$	96:04
5	Me	OBn	$(vinyl)_2Cu(CN)Li_2{\cdot}BF_3$	21:79
6	Me	OBn	$MeCu{\cdot}BF_3$	22:78
7	Me	OBn	$MeCu(CN)Li{\cdot}BF_3$	26:74
8	Me	OBn	$BuCu{\cdot}BF_3$	22:78
9	Me	OTBS	$MeCu{\cdot}BF_3$	14:86
10	Me	OTBS	$Me_2CuLi{\cdot}BF_3$	13:87
11	Me	OTBS	$Me_2Cu(CN)Li_2{\cdot}BF_3$	18:82

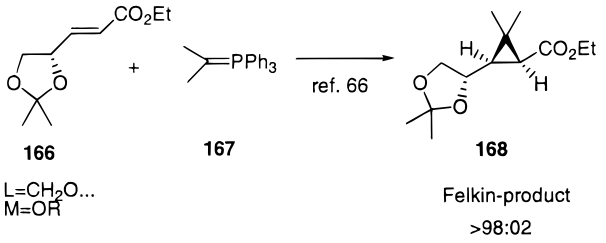
Table 26. Addition of Nucleophiles to 163[65b]

entry	M	nucleophile	**164**:**165**
1	OBn	$(2\text{-methallyl})_2CuLi$	10:90
2	OBn	$(vinyl)_2CuLi$	38:62
3	OBn	$(vinyl)_2CuLiiBF_3$	39:61
4	OBn	$(vinyl)_2Cu(CN)Li_2$	29:71
5	OBn	$(vinyl)_2Cu(CN)Li_2{\cdot}BF_3$	31:69
6	OBn	$MeCu{\cdot}BF_3$	06:94
7	OBn	MeCu	11:89
8	OBn	$BuCu{\cdot}BF_3$	05:95
9	OTBS	$MeCu{\cdot}BF_3$	16:84
10	OTBS	MeCu(CN)Li	08:92
11	OTBS	$MeCu(CN)Li{\cdot}BF_3$	09:91

(Scheme 46, Table 24, entries 7−18). The decisive control element for (*Z*)-alkenes **160** (Scheme 47, Table 25) and disubstituted alkenes **163** (Scheme 48, Table 26) seems to be again the minimization of 1,3-allylic strain, as the general turnover of selectivity in comparison to **157** suggests. However, a comparison of entries 1 and 2 in Tables 25 and 26 clearly shows the limits in trying to rationalize the stereochemical outcome in cuprate additions as described here.

The high Felkin selectivity obtained in the cyclopropanation[66] of **166** by the ylide **167** serves as another example for the ambiguity of a nucleophilic reagent being capable of electrophilic activation of a double bond, thus dictating for stereoelectronic reasons an alkoxy group to be positioned inside rather perpendicular to the incoming reagent (Scheme 49).

Scheme 49. Cyclopropanation of 166



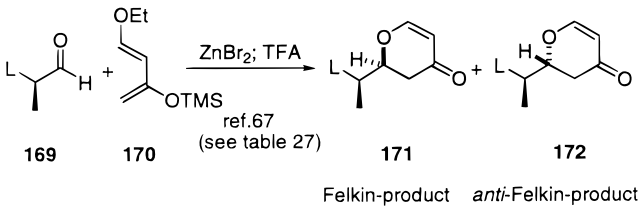
C. Pericyclic Reactions

1. [4+2]-Cycloadditions

The Felkin−Anh rule does not seem to be applicable in general for Diels−Alder reactions of dienes to α-chiral dienophiles. Electrostatic interactions such as dipole−dipole interactions play an important role in the transition-state geometries. Nevertheless, the Felkin−Anh rule can be taken as a good starting point for the analysis of such reactions. In the Lewis acid-catalyzed hetero-Diels−Alder reaction of α-amino aldehydes **169** with the diene **170**, selectivity can be controlled by the protecting group on nitrogen. Increasing the steric size of L prevents chelation, and the Felkin diastereomer **171** becomes preferred via **173** against **172**, which is formed via **174** (Schemes 50 and 51, Table 27).[67−69]

The [4+2]-cycloaddition between the (*E*)- and (*Z*)-acrylates **175** and 1,3-butadiene (**176**)[70] illustrates nicely the possible models which can be applied to explain product distributions (Scheme 52). In both cases the main diastereomers formed are the *anti*-Felkin cycloadducts **178** and **180**, respectively. Since

Scheme 50. Hetero-Diels−Alder Reactions with α-Chiral Aldehydes



Scheme 51. Models for the Hetero-Diels−Alder Reactions with α-Chiral Aldehydes

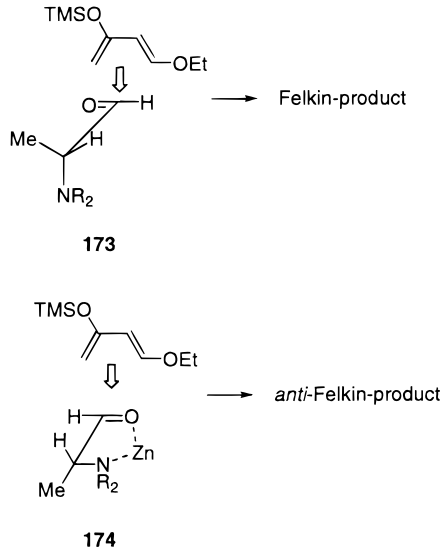
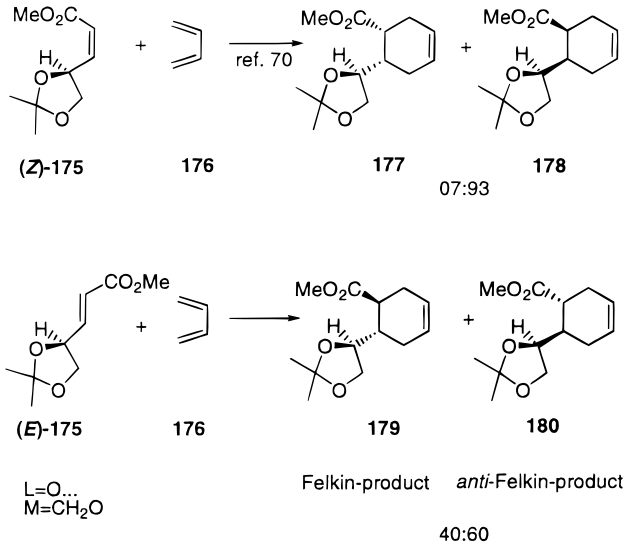


Table 27. Hetero-Diels−Alder Reactions with α-Chiral Aldehydes[67]

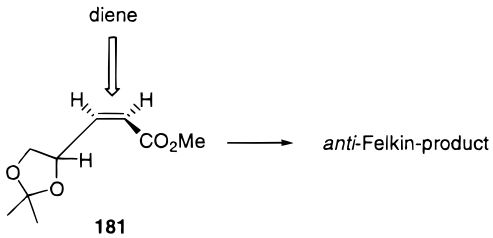
entry	L	**171**:**172**
1	NHBoc	25:75
2	NHZ	33:67
3	NHTs	50:50
4	NBn_2	90:10
5	NBnTs	91:09
6	NBnBoc	93:07

the selectivity for **178**, resulting from (*Z*)-**175**, is considerably higher than that of **180**, resulting from (*E*)-**175**, it is obvious that 1,3-allylic strain is again a decisive control element. The transition state **181** should therefore be preferred by reason of minimizing 1,3-allylic strain but also by reason of placing the acceptor *anti* to the incoming diene (nucleophile; Scheme 53). The direction of the incoming diene can also be explained by the Kahn−Here proposal[71] which states that the selectivity should be mainly influenced by electrostatic interactions. Therefore, cycloadditions involving electron-rich dienes and electron-poor dienophiles should occur preferentially onto the diene face which is more nucleophilic, i.e., having an electron donor on this face, and onto the dienophile face which is more electrophilic, i.e., having an electron donor *anti* to this face. In this proposal alkoxy groups are viewed as donors rather than as acceptors in contrast to the definition used for the Felkin−Anh model. Keeping this discrepancy in mind, the predictions of the Kahn−Here proposal and the Felkin−Anh model are the same for the example described here.

Scheme 52. Diels−Alder Reaction of 175 with 1,3-Butadiene



Scheme 53. Model for the Diels−Alder Reaction with (*Z*)-175



With (*E*)-**175** no selectivity is observed, which can be explained by the lack of conformational control due to the absence of 1,3-allylic strain and by the symmetrical trajectory of the incoming diene, resulting in no differentiation between the Felkin and *anti*-Felkin conformations.

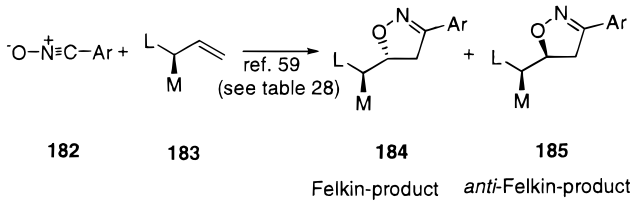
2. [3+2]-Cycloadditions

The cycloaddition of nitriloxides **182** to α-chiral alkenes **183**[59,72] must be considered as an electrophilic attack onto the dipolarophile; consequently, acceptor substituents are not placed orthogonal but rather parallel to the double bond. Moreover, since the attack of **182** occurs in an angle of >90°, alkoxy groups prefer the inside position (M) with regard to the double bond (Scheme 55). This so-called inside alkoxy effect has been analyzed thoroughly by Houk[59] experimentally and theoretically in the context of extending the Felkin−Anh model toward carbon−carbon double bonds. Accordingly, **184** is the preferred product (Scheme 54, Table 28, entries 2−10); however, if the possibility of hydrogen bonding with the oxygen atom in **182** exists (M = OH, entry 1), the outside position also becomes populated, resulting in a loss of selectivity.

The palladium-catalyzed [3+2]-cycloaddition of **188** to the acrylate **187** was investigated by Trost.[73] This example clearly demonstrates the limits of the analysis of such reactions with the Felkin−Anh paradigm. Stereoelectronic arguments would suggest **191** to be preferred, similar to the cases discussed for electrophilic additions to double bonds by the Houk model (inside alkoxy effect), which would lead to the Felkin product **189**. However, it has been argued that both steric effects due to the cyclic structure of the α-stereocenter and minimization of the dipole moment would favor **192**, leading to the *anti*-Felkin product **190**, as is indeed observed with moderate selectivity.

Kishi has thoroughly analyzed the osmium-catalyzed dihydroxylation to α-alkoxy-substituted alkenes

Scheme 54. 1,3-Dipolar cycloaddition of Nitriloxides and α-Chiral Alkenes



Scheme 55. Inside Alkoxy Effect in the Cycloaddition Reactions of Nitriloxides to α-Chiral Alkenes 183

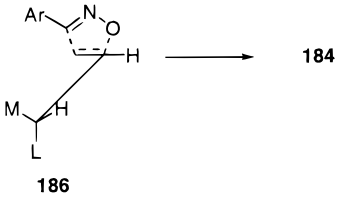
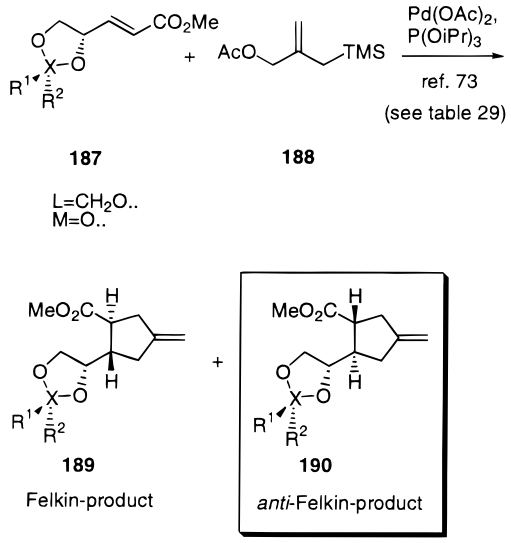


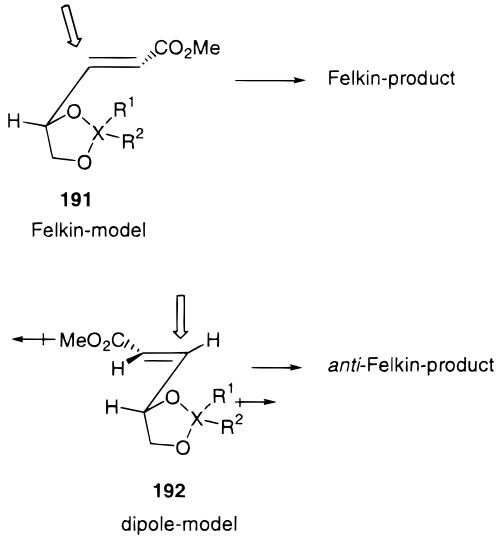
Table 28. 1,3-Dipole-Cycloaddition of Nitriloxides and α-Chiral Alkenes 183

entry	Ar	L	M	**184**:**185**
1	Ph	Me	OH	40:60
2	Ph	Me	OCH_2Ph	64:36
3	Ph	Me	OTHP	63:37
4	Ph	Me	OTMS	71:29
5	Ph	Me	OTBS	72:28
6	*p*-NO_2Ph	Me	$OSiMe_2Ph$	65:35
7	*p*-NO_2Ph	Ph	OTMS	69:31
8	*p*-NO_2Ph	Et	$OSiMe_2Ph$	80:20
9	*p*-NO_2Ph	^{i}Pr	$OSiMe_2Ph$	91:09
10	*p*-NO_2Ph	^{t}Bu	OTMS	>95:05

Scheme 56. Palladium-Catalyzed [3+2]-Cycloaddition Reaction of 187



Scheme 57. Models for the [3+2]-Cycloaddition Reaction with 187

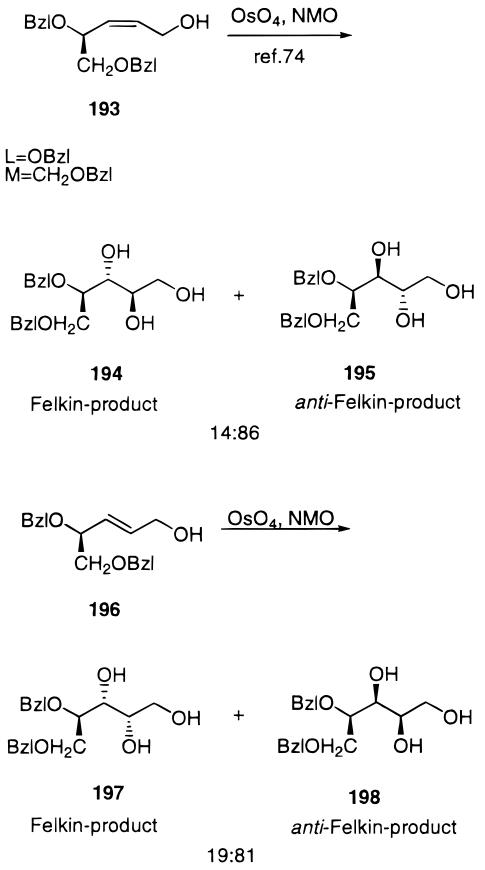


(Scheme 58).[74] Analogously to the arguments put forward in the Diels−Alder reaction of **175** (Scheme 52), (*Z*)-alkenes such as **193** consistently gave better selectivities compared to (*E*)-alkenes. Nevertheless, some (*E*)-alkenes such as **196** also displayed surprisingly high *anti*-Felkin selectivity, although 1,3-allylic strain should not be a decisive factor any longer in such cases.

Table 29. Models for the [3+2]-Cycloaddition Reaction with 187

entry	X	R^1	R^2	**189:190**
1	C	Me	Me	25:75
2	C	BOM	H	28:72
3	C	H	BOM	28:72
4	Si	^{t}Bu	^{t}Bu	12:88

Scheme 58. 1,3-Allylic Strain Model (Kishi's model) in Dihydroxylations of Alkenes

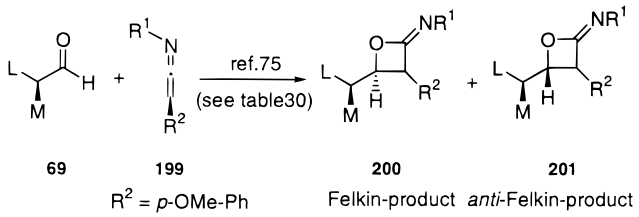


3. [2+2]-Cycloadditions

Lewis acid-catalyzed [2+2]-cycloadditions of ketene imines and α-alkoxy aldehydes also do not seem to follow a clear trend. Depending on the Lewis acid there can be a competition between chelated and nonchelated pathways (Schemes 59 and 60), which only in some cases resulted in high selectivities (Table 30).[75]

Remarkable selectivites, however, have been achieved in Paterno−Büchi reactions. 1,3-Allylic strain again seems to be the governing principle to explain the outcome of these reactions (Scheme 61).[76]

Scheme 59. [2+2]-Cycloadditions of Keteneimines 199 and α-Chiral Aldehydes



Scheme 60. Models for the [2+2]-Cycloaddition of 69 and 199

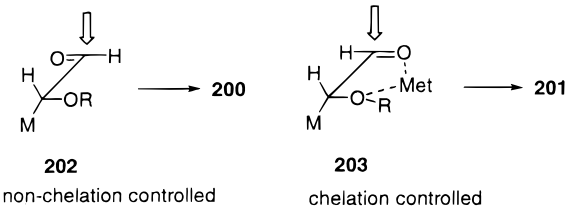
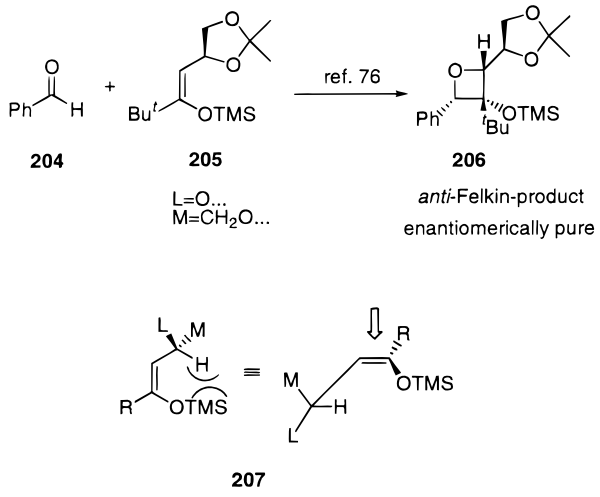


Table 30. [2+2]-Cycloaddtions of Keteneimines 199 and α-Chiral Aldehydes[75]

entry	L	M	R^1	cat.[a]	**200:201**
1	OTBS	Me	Me	Yt(fod)$_3$	60:40
2	OCPh$_3$	Me	Me	Yt(fod)$_3$	66:34
3	OCPh$_3$	Me	Me	Eu(fod)$_3$	65:35
4	OCPh$_3$	Me	Et	Yt(fod)$_3$	70:30
5	OCPh$_3$	Me	Et	Yt(hfc)$_3$	56:44
6	OCPh$_3$	Me	Et	Eu(fod)$_3$	55:45
7	OCPh$_3$	Me	Et	Eu(tfc)$_3$	57:43
8	OCPh$_3$	Me	Et	Cr(acac)$_3$	57:43
9	OTBS	Me	Et	Yt(fod)$_3$	52:48
10	OTBS	Ph	Et	Yt(fod)$_3$	36:64
11	OTBS	Ph	^{t}Bu	Yt(fod)$_3$	17:83
12	OMe	MEM	MEM	Yt(fod)$_3$	58:42
13	OMe	MEM	MEM	Yt(hfc)$_3$	44:56
14	OMEM	Me	^{t}Bu	Yt(fod)$_3$	0:100
15	OCPh$_3$	Me	^{t}Bu	MgBr$_2$	41:59
16	OCPh$_3$	Me	Me	ZnCl$_2$	78:22
17	OCPh$_3$	Me	Me	BF$_3$	83:17
18	OCPh$_3$	Me	Et	ZnCl$_2$	90:10
19	OCPh$_3$	Me	Et	BF$_3$	89:11

[a] fod: tris(6,6,7,7,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato). tfc: tris-[-3-[trifluoromethylhydroxymethylene]-(+)-camphorato]. hfc: tris-[-3-(heptafluoropropyl)hydroxymethylene]-(+)-camphorato].

Scheme 61. Diastereoselective Paterno−Büchi reactions

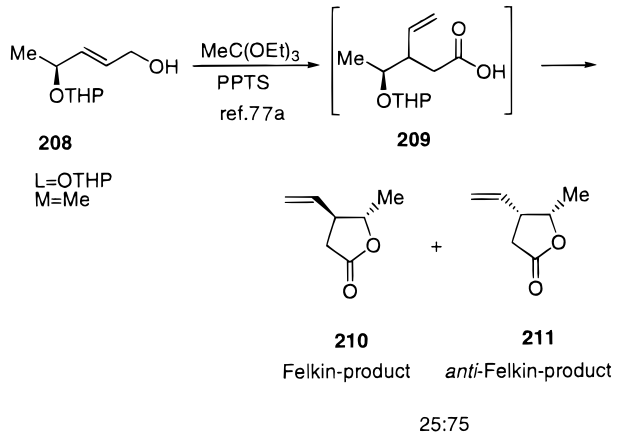


D. Sigmatropic Rearrangements

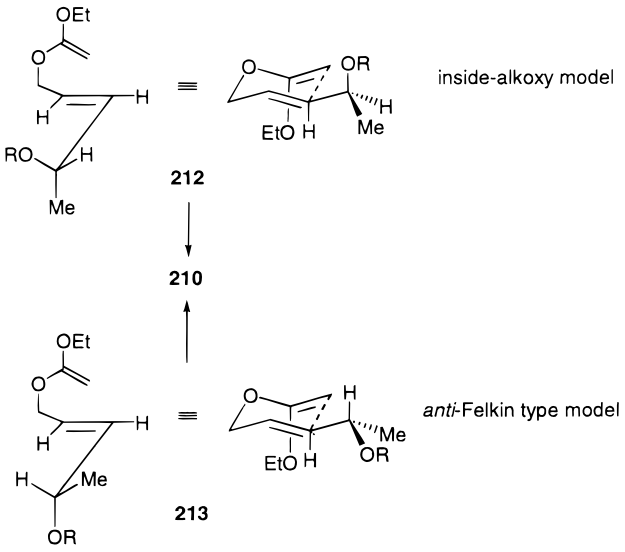
1. Claisen Rearrangement

Sigmatropic rearrangements occur via cyclic transition states; therefore, the Claisen rearrangement of **208**[77] in accordance with a Zimmerman−Traxler transition state can be analyzed in an analogous way as discussed earlier for aldol reactions. *Anti*-Felkin transition states **213** leading to **210** were proposed

Scheme 62. 1,2-Induction in the Claisen Rearrangement (1)



Scheme 63. Transition State of the Claisen Rearrangement of 208



in order to minimize *syn*-pentane interactions most effectively and taking into account that the trajectory of the incoming nucleophile is smaller 90° (Schemes 62 and 63). The same prediction would be made if the inside alkoxy model is applied, thus considering the rearrangement as being electrophilic and **212** being the important conformation for the course of the reaction. Likewise, the preferred formation of **216** from **214** (Scheme 64, Table 31) and of **220** from **217** (Scheme 65, Table 32) can be understood.[78]

2. [2,3]-Wittig Rearrangements

[2,3]-Wittig rearrangements display high *anti*-Felkin selectivity already for the *E*-configurated olefin **221**, in which 1,3-allylic strain cannot be a controlling factor (Scheme 66). However, applying the Felkin−Anh model taking into account that the attack of the carbanion occurs in an angle <90° explains conclusively the observed results (Scheme 67). Even better selectivity is found for the

Scheme 64. 1,2-Induction in the Claisen Rearrangement (2)

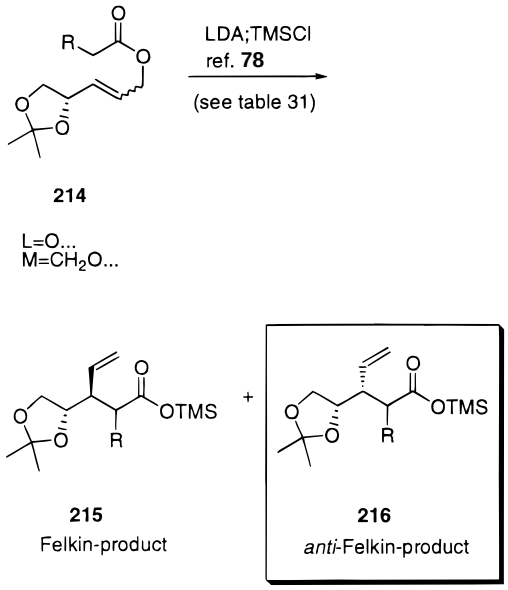


Table 31. 1,2-Induction in the Claisen rearrangement (2) of 214

entry	*Z*/*E*	R	**215**:**216**
1	*E*	H	57:43
2	*E*	OMe	22:78
3	*E*	OMOM	27:73
4	*E*	OBn	25:75
5	*Z*	H	58:42
6	*Z*	OMe	12:88
7	*Z*	OMOM	27:73
8	*Z*	OBn	20:80

Scheme 65. 1,2-Induction in the Claisen rearrangement (3)

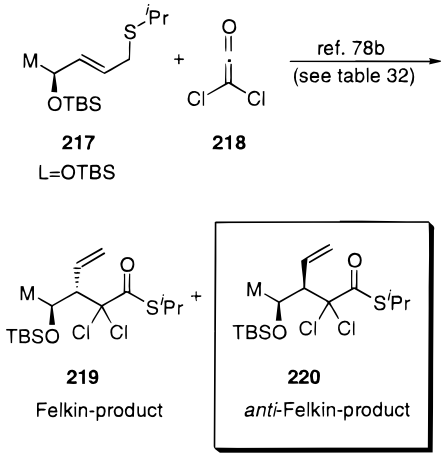
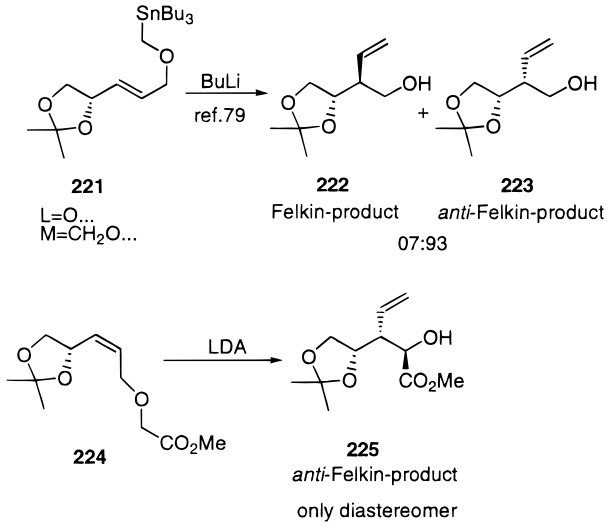


Table 32. 1,2-Induction in the Claisen rearrangement (3)

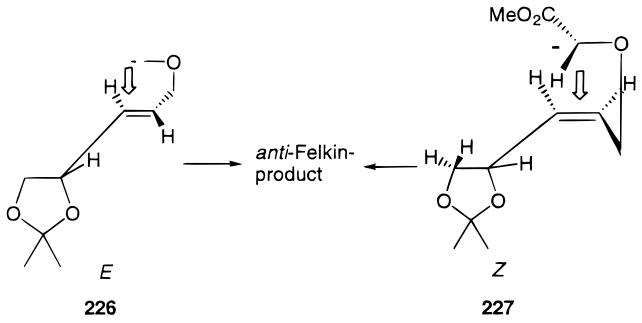
entry	M	**219**:**220**
1	Me	<03:97
2	^{i}Pr	<05:95
3	EtOTBS	<05:95

rearrangement of **224**, in which in addition the minimization of 1,3-allylic strain works in concert with the control factors discussed above.[79]

Scheme 66. 1,2-Induction in the [2,3]-Wittig Rearrangement



Scheme 67. Transition State of the [2,3]-Wittig Rearrangement



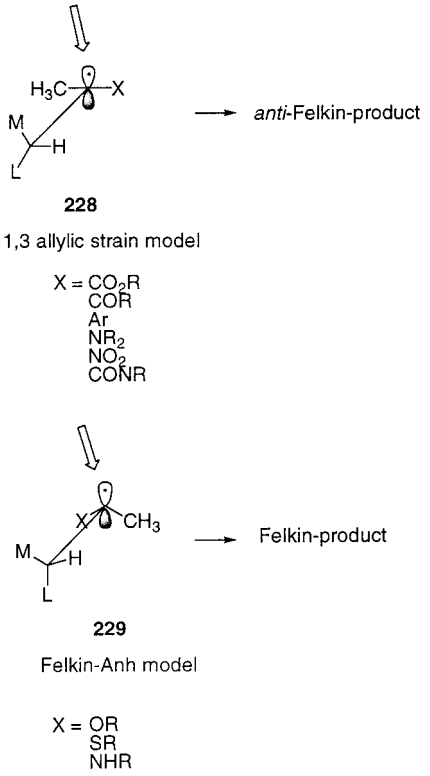
E. Radical Reactions

The Felkin−Anh model can also be applied to radical reactions; however, the type of substrate will determine if 1,3-allylic strain is the more important control element.[16a,80,81] If X in **228** is a carbonyl, phenyl, nitro, or dialkylamino substituent, a radical is considered to be sp^2-hybridized and allylic strain between X and the α-stereocenter becomes an issue (Scheme 68). In contrast, with X being OR, SR or NHR, ESR studies suggest that the radical center has considerable tetrahedral character as depicted in **229**, making the Felkin−Anh model applicable for such cases.

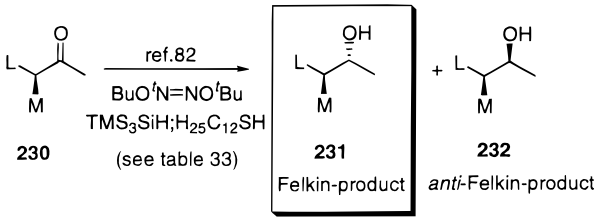
Thus, Giese demonstrated in the reduction of **230** that high selectivites for the Felkin product **231** can be obtained by using sterically demanding trapping reagents which deliver a hydrogen atom to the initially formed radical **233**. Stereoelectronic factors seem to be an important factor in the control of the conformation of **233**. The phenyl substituent assumes, as already discussed for the hydride reactions, the role of the substituent L even in the case of bulky substituents such as *tert*-butyl (Schemes 69 and 70, Table 33).[82] Likewise, alkoxy groups are able to stabilize the transition states in such radical reactions in the same way as that discussed for ionic reactions (Scheme 71, Table 34).[83]

Interestingly, the radical addition of 2-iodopropane to **237** (Table 35, entry 2) also yielded the Felkin

Scheme 68. 1,2-Induction in Radical Reactions



Scheme 69. Addition of Radicals to α-Chiral Aldehydes



Scheme 70. Model for 1,2-Induction in Radical Reactions

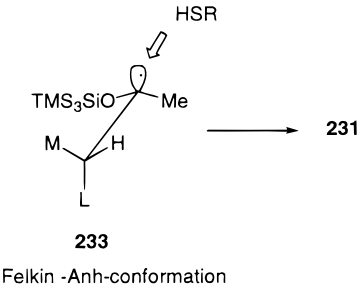


Table 33. Addition of Radicals to α-Chiral Aldehydes 230

entry	L	M	reagent	231:232
1	Ph	Me	TMS_3SiH; $H_{25}C_{12}SH$	74:26
2	Ph	^{i}Pr	TMS_3SiH; $H_{25}C_{12}SH$	93:07
3	Ph	^{t}Bu	TMS_3SiH; $H_{25}C_{12}SH$	84:16

product **238** with excellent selectivity, although one would have expected that the reaction leads to the *anti*-Felkin product by minimizing 1,3-allylic strain via **240** (Scheme 72, Table 35). It has been argued that in such a conformation attack from both sides is hindered on steric reasons, causing the Felkin

Scheme 71. Addition of Radicals to 234

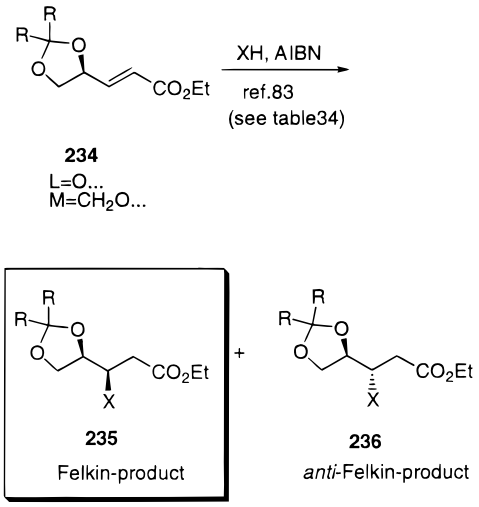


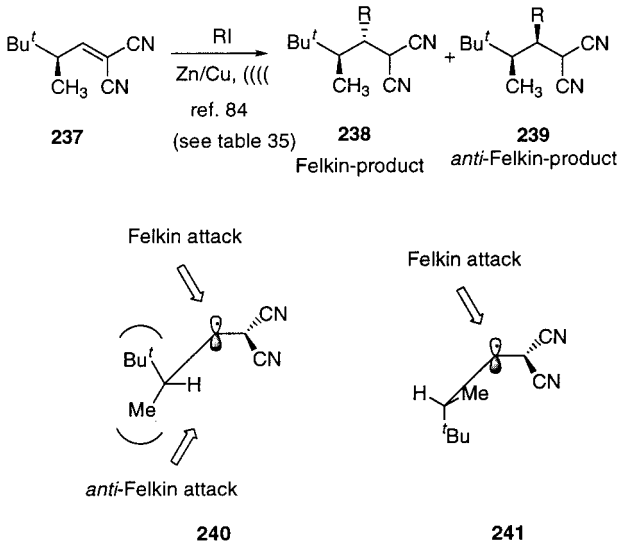
Table 34. Addition of Radicals to 234

entry	R	XH	**235:236**
1	Me	TMS_3SiH	100:0
2	H	TMS_3SiH	85:15
3	Me	$^nBu_3SnH$	70:30

Table 35. Additions of Radicals to 237

entry	RI	**238:239**
1	^{t}Bu	>99:01
2	^{i}Pr	80:20
3	Et	50:50
4	Me	39:61

Scheme 72. Additions of Radicals to 237



conformation **241** to be determining the course of the reaction because of the sterically least hindered trajectory of the nucleophile.[84]

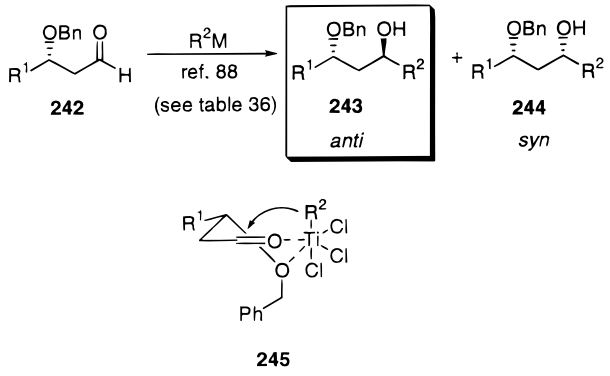
IV. 1,3-Induction

Moving the chiral center to the β-position of the reaction center naturally should diminish its influence unless communication through a tether becomes possible. Therefore, in most studies of 1,3-induction the chiral center was chosen in a way that one substituent would offer the possibility of chelation with the reaction center by an appropriate reagent.[85] Only recently some principles have been demonstrated for 1,3-inductions in nonchelated processes.[86]

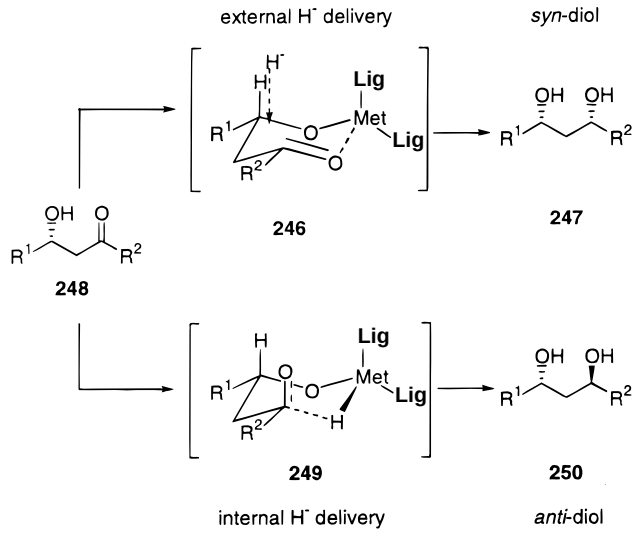
A. Chelation-Controlled 1,3-Induction

There are two complimentary modes possible for chelate-controlled reactions occurring with 1,3-induction.[87] Either the reaction center and the chiral center are tethered together and the nucleophile is delivered externally of the chelate or the nucleophile becomes part of the chelate itself (internal delivery of the nucleophile). Both modes can be effectively demonstrated for the addition of nucleophiles to β-hydroxycarbonyl compounds **242** and **248** (Schemes 73 and 74). The analogous analysis to the Cram-chelate model for 1,2-inductions (cf. Chapter I.A.) according to Reetz leads to the chelate **245** in which attack of the nucleophile occurs from the sterically less hindered side, i.e., *anti* to the substituent R^1, predicting **243** as the major product.[88] The prerequisites to form such chelates are again that the metal center must have at least two free coordination sites[89] and the protecting group P must permit effective bidentate complexation of the Lewis acid.[90]

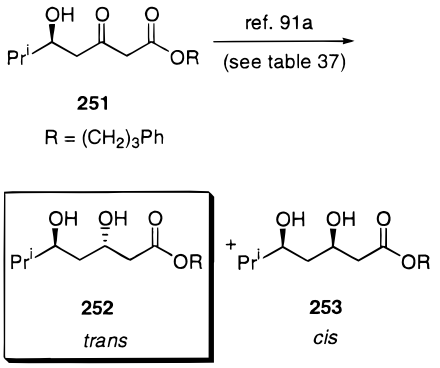
Scheme 73. Chelation-Controlled 1,3-Induction (Reetz model)



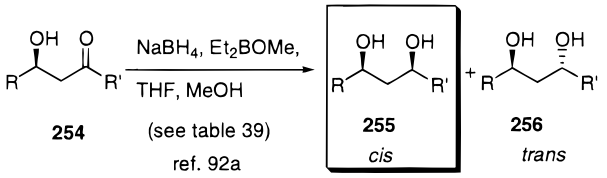
Scheme 74. Chelation Controlled 1,3-Induction by External and Internal Delivery of Hydride (Evans model)



Scheme 75. 1,3-Reduction of 251



Scheme 76. Chelation-Controlled 1,3-Induction for the Reduction to *cis*-1,3-diols



The same conclusion is obtained by considering a chairlike transition state **246**, placing R^1 and R^2 as the large substituents into equatorial positions (Scheme 74). Nucleophilic attack occurs axial with a minimal reorganization of the chelate structure to give **247** as the preferred product.

Alternatively, the transition state **249** is encountered in which the nucleophile might be delivered internally, requiring the axial position of the carbonyl group to lead to **250**. These two models have been proposed by Evans[87,91,92] for hydride reduction of β-hydroxyketones (Schemes 75, 76) along with the successful development of reagents which would effectively differentiate between the two possible reaction modes.

An interesting application demonstrating the complimentary strategies was reported by Brückner[93] with the stereoselective synthesis of the butyrolactones **260** and **261** starting from the common precursor **257**.

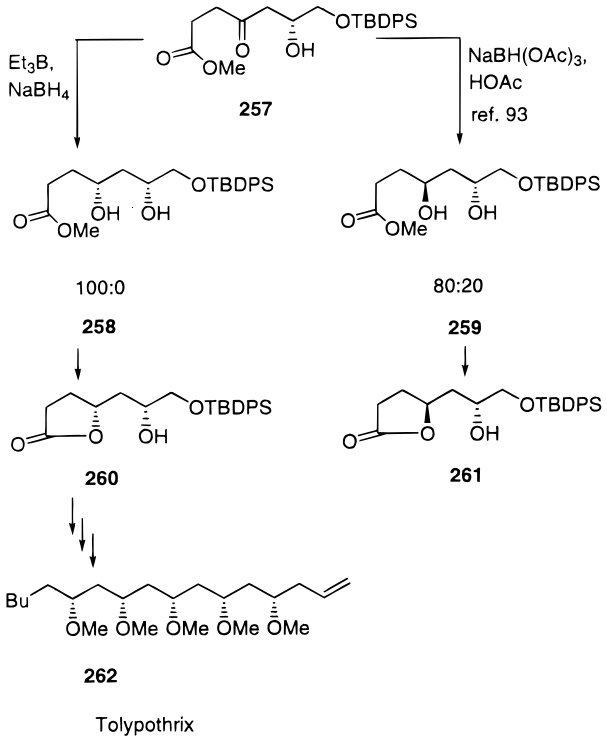
Very recently, Hanessian[94] could demonstrate that the electrophilic addition to enolates derived from γ-amino esters proceeds highly stereoselectively to the *anti*-configurated products **264**. The chairlike transition state **266** involving a seven-membered chelate was proposed to explain the results obtained (Scheme 78).

B. Nonchelation-Controlled 1,3-Induction

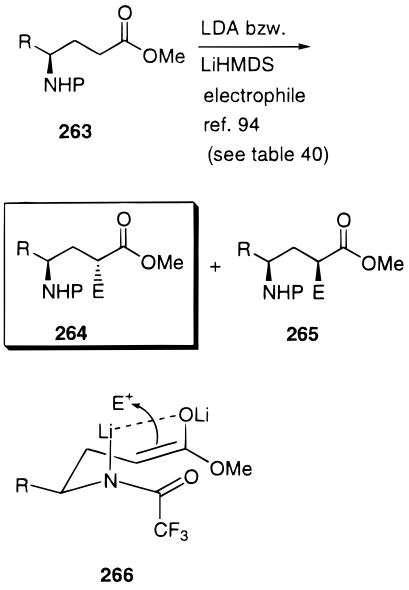
1. Cram–Reetz Model

Early studies by Cram[95a,b] and Reetz[95c] demonstrated that 1,3-stereocontrol can also be possible if only acyclic transition states are involved. The reaction of **267** with allyltrimethylsilane resulted with good selectivity in the *anti*-1,3-diol **268**, which was explained by the analysis of polar effects in the transition state (Scheme 79). Thus, **270** should be the

Scheme 77. Key Steps in the Synthesis of 1,3-Polyols



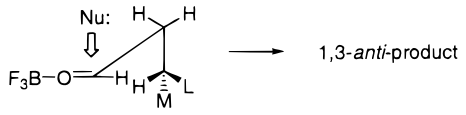
Scheme 78. Electrophilic 1,3-Induction



decisive conformation in which the β-stereocenter being the large substituent is placed *anti* to the carbonyl group. The benzyloxy group adopts the conformation in which the dipole moment is minimized most effectively, and attack of the nucleophile occurs *anti* to the bulkier of the remaining two substituents on the β-stereocenter, which bisect the carbonyl group.

2. Evans Model

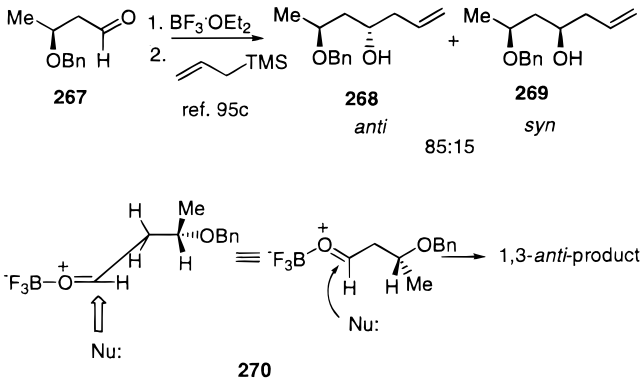
Only recently, Evans presented a different model for nonchelate 1,3-inductions based on some carefully



271

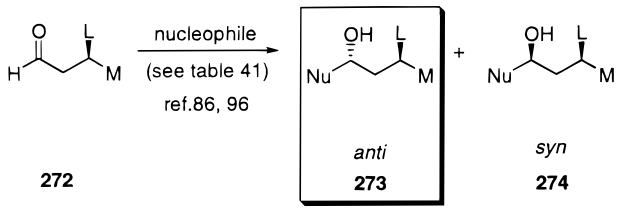
Figure 3. 1,3-Stereocontrol with Acyclic Transition States (Evans model).

Scheme 79. 1,3-Stereocontrol with Acyclic Transition States (Cram and Reetz Model)



270

Scheme 80. 1,3-Induction in β-Chiral Carbonyl Compounds



orchestrated experimental evidence and by taking the successful concepts of the Felkin−Anh model into account.[96] Also in this model the presence of a polar substituent is important as one control element in the reaction. In the proposed transition state **271** (Figure 3), the β-stereogenic center being the large substituent is oriented *anti* to the incoming nucleophile in analogy to the Felkin−Anh model. This way a staggered relationship between the forming bond and the α-substituents is also achieved. The polar substituent L is placed *anti* to the carbonyl group in order to minimize dipole−dipole interactions. Last but not least, the substituent M is placed *anti* to the aldehyde group, allowing minimization of steric effects of the β-stereocenter and the carbonyl group by aligning the smallest substituent H with the carbonyl oxygen. Consequently, the 1,3-*anti*-diol would be predicted again as the major product, which is indeed obtained in many cases with high selectivity (Scheme 80, Table 41).[96−98]

If the substrate contains an α- and a β-stereocenter, the Felkin−Anh rule for 1,2-induction and the Evans model for 1,3-induction must be analyzed in concert. If these two stereocenters have an *anti* relationship as in **278** (Scheme 82), both models predict the diastereomer **279** rather than **280** as the preferred one. The two stereocenters are called to be reinforcing in difference to the terminus matched, which should be reserved for stereocenters interacting intermolecularly with each other. Indeed, high selectivities were achieved in such cases for a variety of aldol reactions (Table 43). In the *syn*-substrate **275** (Scheme 81, Table 42), the Felkin−Anh and the Evans model

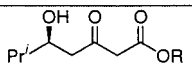
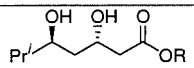
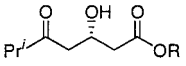
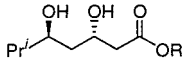
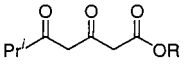
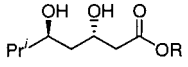
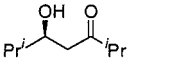
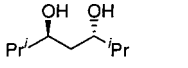
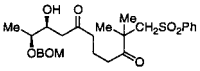
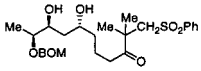
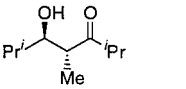
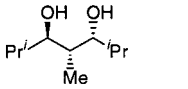
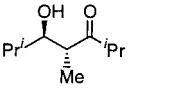
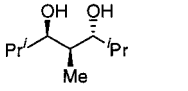
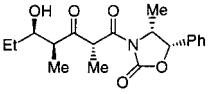
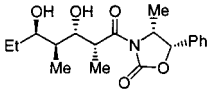
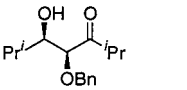
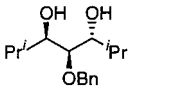
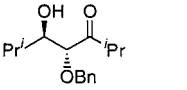
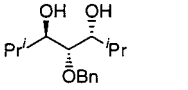
Table 36. Chelation-Controlled 1,3-Induction (Reetz model)

entry	reagent	R^1	R^2	**243:244**
1	$MeTiCl_3$	Me	Me	90:10
2	$TiCl_4$/AllylTMS	Me	allyl	95:05
3	$TiCl_4/Zn^nBu_2$	Me	^{n}Bu	90:10
4	$MeTiCl_3$	^{n}Bu	Me	91:09
5	$TiCl_4$/AllylTMS	^{n}Bu	allyl	95:05
6	$TiCl_4/CH_2C(Me)CH_2TMS$	Me	$CH_2C(Me)CH_2$	95:05
7	$TiCl_4/CH_2C(Me)CH_2TMS$	^{n}Bu	$CH_2C(Me)CH_2$	95:05

Table 37. 1,3-Reduciton of 251

entry	reagent	**252:253**
1	$NaBH_4$/HOAc	80:20
2	Me_4NBH_4/HOAc	92:08
3	$Me_4NHB(OAc)_3$/HOAc	92:08
4	$NaHB(OAc)_3$/HOAc	84:14
5	$NaHB(OAc)_3$/THF	77:23
6	$Me_4NHB(OAc)_3$/THF	69:31
7	$NaHB(OAc)_3$/THF,$HOAc_{cat}$	82:18
8	$Me_4NHB(OAc)_3$/THF,$HOAc_{cat}$	79:21
9	$Me_4NHB(OAc)_3/CH_3CN$/HOAc	92:08
10	$Me_4NHB(OAc)_3$/acetone/HOAc	92:08

Table 38. *trans*-1,3-Diols by Reduction with $Me_4NHB(OAc)_3$[a]

entry	substrate	product	*trans*:*cis*
1			95:05
2			95:05
3			92:08
4			96:04
5			94:06
6			98:02
7			98:02
8			>98:02
9			93:07
10			79:21

[a] R=$(CH_2)_3Ph$).[91a]

Table 39. Chelation-Controlled 1,3-Induction for Reduction to *cis*-1,3-Diol 255

entry	R	R′	255:256
1	^{n}Bu	^{n}Bu	99:01
2	Ph	Ph	99:01
3	Ph	CH_2CO_2Et	98:02
4	^{i}Pr	CH_2CO_2Et	98:02

Table 40. Electrophilic 1,3-Induction

entry	P	R	electrophile	264:265
1	TFA	Bn	allylBr	>95:05
2	TFA	Bn	BnBr	>95:05
3	TFA	Bn	MeI	>95:05
4	TFA	Bn	cinnamylBr	>95:05
5	TFA	^{i}Pr	allylBr	>95:05
6	TFA	Me	allylBr	>95:05
7	TFA	^{i}Bu	allylBr	>95:05
8	Boc	Me	allylBr	>95:05
9	Boc	Me	cinnamylBr	>95:05
10	Boc	^{i}Pr	allylBr	>95:05
11	Boc	^{i}Pr	cinnamylBr	>95:05

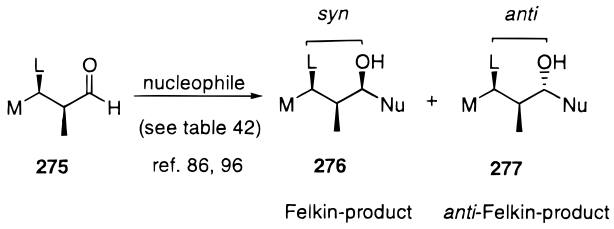
Table 41. 1,3-Induction in β-Chiral Carbonyl Compounds 272

entry	L	M	nucleophile	273:274
1	OPMB	^{i}Pr	OLi	71:29
2	OPMB	^{i}Pr	$OTiCl_n$ ^{i}PrNEt$_2$	60:40
3	OPMB	^{i}Pr	OBR_2 ^{i}PrNEt$_2$	42:58
4	OPMB	^{i}Pr	OTMS $BF_3.EtO_2$	92:08
5	OTBS	^{i}Pr	OLi	76:24
6	OTBS	^{i}Pr	$OTiCl_n$ ^{i}PrNEt$_2$	58:42
7	OTBS	^{i}Pr	OBR_2 ^{i}PrNEt$_2$	52:48
8	OTBS	^{i}Pr	OTMS $BF_3.EtO_2$	80:20
9	OAc	CH_2Bn	OLi	59:41

lead to different predictions since the two stereocenters are not reinforcing. Interestingly, it seems that the stereocenter exerting the decisive control in the reaction is dependent on the size of the nucleophile. If it is large, high Felkin control is observed, indicating the interaction of the α-stereocenter with the incoming nucleophile is the determining factor. However, as the steric demand of the enolsilane decreases, the β-center becomes the dominant control element despite its larger distance to the reaction center.[99,100]

The principles discovered here could be taken one step further by reaction of β-substituted enolates with

Scheme 81. 1,3- and 1,2-Induction in β-Chiral Carbonyl Compounds (1)



Scheme 82. 1,3- and 1,2-Induction in β-Chiral Carbonyl Compounds (2)

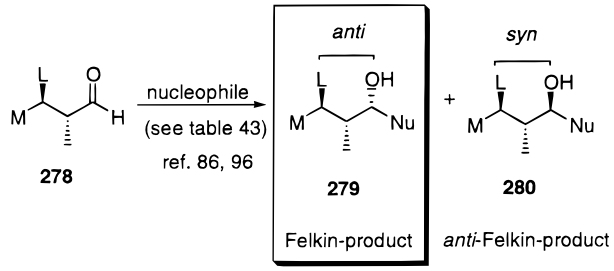


Table 42. 1,3- and 1,2-Induction in β-Chiral Carbonyl Compounds 275

entry	L	M	R	nucleophile	276:277
1	OPMB	^{i}Pr	H	OTMS, $BF_3.OEt_2$, CH_2Cl_2	96:04
2	OPMB	^{i}Pr	H	OTMS, $BF_3.OEt_2$, CH_2Cl_2	56:44
3	OPMB	^{i}Pr	H	OTMS, $BF_3.OEt_2$, CH_2Cl_2	83:17
4	OTBS	^{i}Pr	H	OTMS, $BF_3.OEt_2$, CH_2Cl_2	96:04
5	OTBS	^{i}Pr	H	OTMS, $BF_3.OEt_2$, CH_2Cl_2	87:13
6	OTBS	^{i}Pr	H	OTMS, $BF_3.OEt_2$, CH_2Cl_2	58:42
7	OPMB	^{i}Pr	H	OTMS, $BF_3.OEt_2$, toluene	06:94
8	OPMB	^{i}Pr	H	OTMS, Ph_3CClO_4, CH_2Cl_2	89:11
9	OPMB	^{i}Pr	H	$SnBu_3$, $BF_3.OEt_2$, toluene	20:80
10	OPMB	^{i}Pr	H	$SnBu_3$, $BF_3.OEt_2$, toluene	13:87
11	OPMB	^{i}Pr	H	$SnBu_3$, Ph_3CClO_4, CH_2Cl_2	62:38
12	OPMB	^{i}Pr	H	LDA, THF	11:89
13	OPMB	^{i}Pr	H	LDA, THF	14:86
14	OPMB	^{i}Pr	H	LDA, THF	22:78

Table 43. 1,3- and 1,2-Induction in β-Chiral Carbonyl Compounds 278

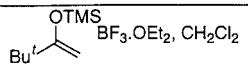
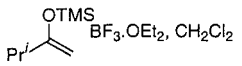
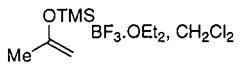
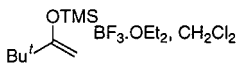
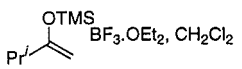
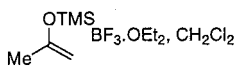
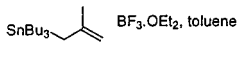
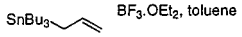
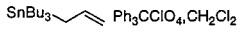
entry	L	M	R	nucleophile	279:280
1	OPMB	^{i}Pr	H		99:01
2	OPMB	^{i}Pr	H		98:02
3	OPMB	^{i}Pr	H		97:03
4	OTBS	^{i}Pr	H		99:01
5	OTBS	^{i}Pr	H		95:05
6	OTBS	^{i}Pr	H		71:29
7	OPMB	^{i}Pr	H		>99:01
8	OPMB	^{i}Pr	H		>99:01
9	OPMB	^{i}Pr	H		>99:01
10	OPMB	^{i}Pr	H		67:33
11	OPMB	^{i}Pr	H		72:28
12	OPMB	^{i}Pr	H		84:16

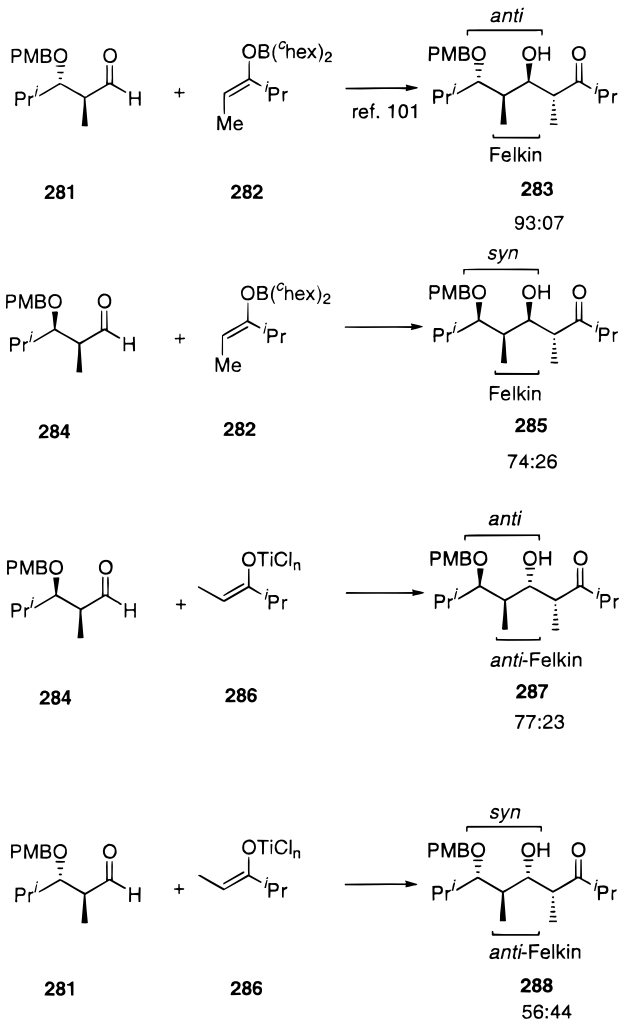
Table 44. 1,3-Induction of β-Chiral Ketones

entry	L	M	R	nucleophile	299:300	ref
1	OPMB	^{i}Pr	^{i}Pr	Li(^{s}Bu)$_3$BH	81:19	102d
2	OPMB	^{i}Pr	^{i}Pr	Li(^{t}BuO)$_3$AlH	77:23	102d
3	OPMB	^{i}Pr	^{i}Pr	DIBAL-H	78:22	102d
4	OPMB	^{i}Pr	^{i}Pr	9-BBN	58:42	102d
5	OTBS	^{i}Pr	^{i}Pr	Li(^{s}Bu)$_3$BH	94:06	102d
6	OTBS	^{i}Pr	^{i}Pr	Li(^{t}BuO)$_3$AlH	87:13	102d
7	OTBS	^{i}Pr	^{i}Pr	DIBAL-H	73:27	102d
8	OTBS	^{i}Pr	^{i}Pr	9-BBN	50:50	102d
9	^{c}Hex	Me	TMS	BuLi/THF	25:75	102a
10	^{c}Hex	Me	TMS	allylTMS/CH_2Cl_2	67:33	102a
11	^{c}Hex	Me	TMS	allylSnMe$_3$/CH_2Cl_2	67:33	102a
12	^{c}Hex	Me	TMS	methallylTMS/CH_2Cl_2	83:17	102a
13	^{c}Hex	Me	TMS	methallylSnMe$_3$/CH_2Cl_2	83:17	102a
14	^{t}Bu	Me	TMS	BuLi/THF	58:42	102a
15	^{t}Bu	Me	TMS	allylTMS/CH_2Cl_2	92:08	102a
16	^{t}Bu	Me	TMS	allylSnMe$_3$/CH_2Cl_2	86:14	102a
17	^{t}Bu	Me	TMS	methallylTMS/CH_2Cl_2	93:07	102a
18	^{t}Bu	Me	TMS	methallylSnMe$_3$/CH_2Cl_2	90:10	102a

α,β-chiral aldehydes (Schemes 83 and 84), thus creating another stereocenter in the products.[101] Since the Lewis acids used for generating the enolates have another open coordination site, these reactions should proceed via a Zimmermann−Traxler transition state. As discussed for the aldol reactions in chapter II.C.1, the geometry of the enolate explains the observed preference for the Felkin or the *anti*-Felkin product in addition to the bias of the β-stereocenter toward the 1,3-anti product.

The reaction of β-chiral ketones **298** with hydride reagents under nonchelation control leads

Scheme 83. Addition of Enolates to α- and β-Chiral Carbonyl Compounds



predominantly to 1,3-*syn*-products **299**, indicating that the attack of the nucleophile occurs from the same carbonyl face as that observed for aldehydes **272** (Scheme 85). However, the transition state **303** being analogous to **271** is disfavored due to steric interactions between R and L of the β-stereocenter. Likewise, **306** suffers from such steric hindrance between R and M, while in **304** an unfavorable dipole moment is encountered.[102] Therefore, **301** seems to be the best possibility to explain the stereoselectivity observed (Scheme 86).

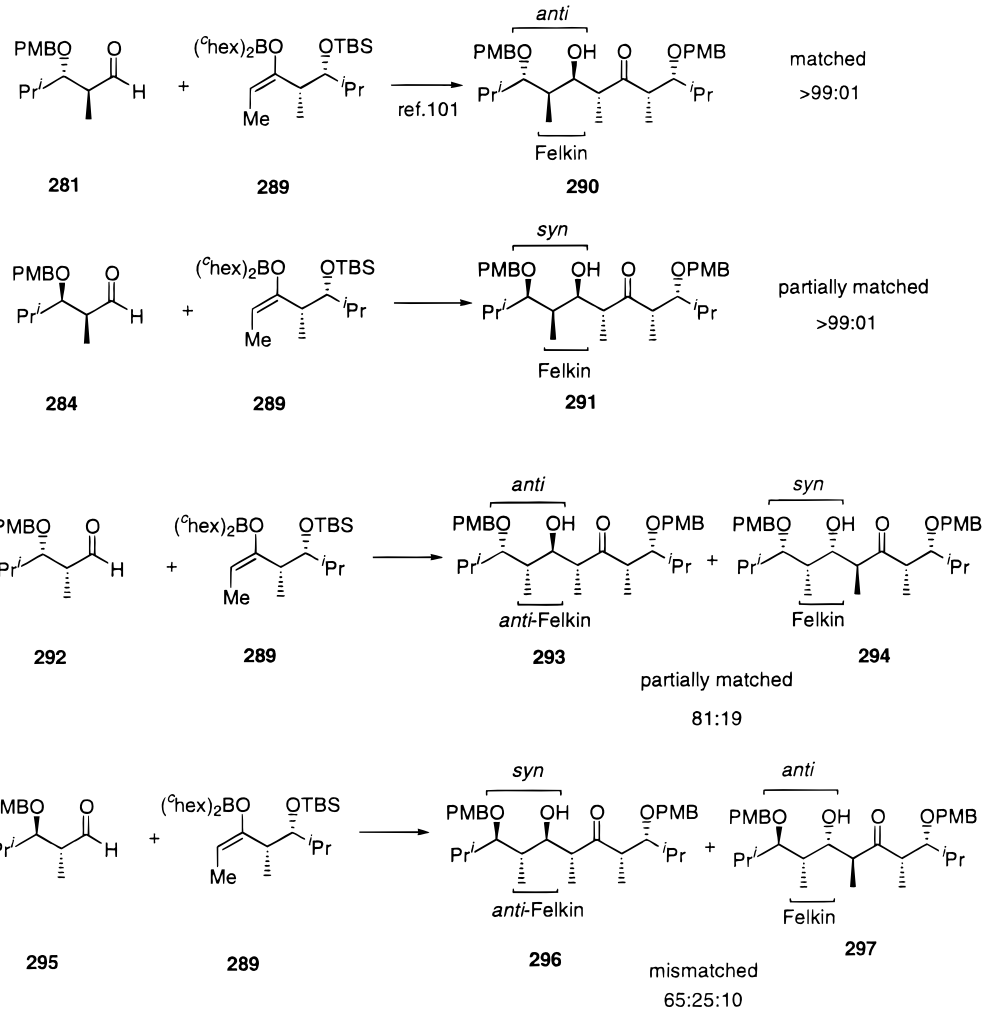
C. 1,4-Induction

There have been few examples for 1,4-inductions which are only successful when effective organization of the substrate by chelation can take place. Therefore, application of models of the Felkin−Anh type have no meaning at the present time.[16a,103]

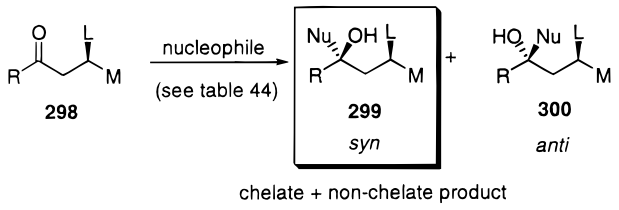
V. Conclusion

Together with the concept of 1,3-allylic strain, the initially proposed models by Cram, Felkin, and Anh are still the most powerful tools for explaining and

Scheme 84. Addition of Enolates to α- and *β*-Chiral Carbonyl Compounds



Scheme 85. 1,3-Induction of *β*-Chiral Ketones



predicting the asymmetric induction of a chiral center to adjacent prochiral centers. In particular, the 1,2-inductions in nucleophilic additions to carbonyl groups provide a consistent picture for a great variety of reaction types. Despite several shortcomings, extension of the underlying concepts of the original models to electrophilic and radical additions as well as to alkenes has proved to be most useful. There are many more examples which can be considered in the realm of this topic but were beyond the scope of this review. Moreover, the recently proposed models for 1,3-inductions via acyclic transition states giving new impulses for stereoselective synthesis show that the Felkin−Anh rule still forms a formidable basis for future developments.

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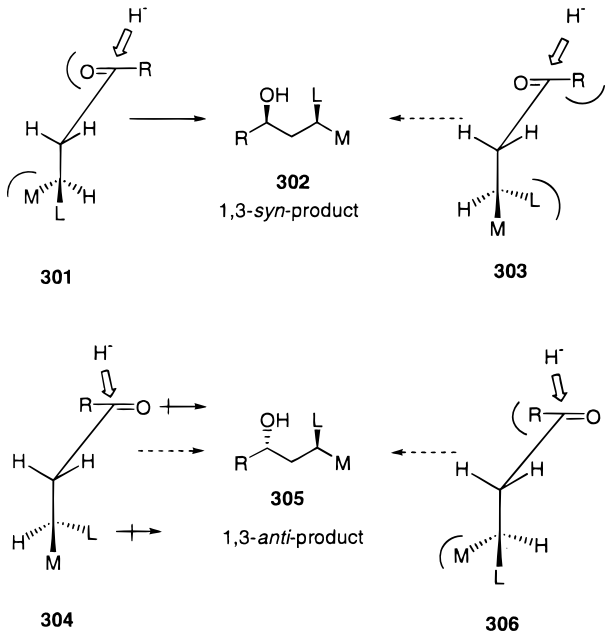
Scheme 86. Transition State for 1,3-Induction of *β*-Chiral Ketones



VI. References

(1) (1) (a) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245−1249. (b) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828−5835. (c) Cram, D. J.; Greene, F. D. *J. Am. Chem. Soc.* **1953**, *75*, 6004−6010.

(2) Reviews: (a) Vögtle, F.; Franke, J.; Aigner, A.; Worsch, D. *Chem. Unserer Zeit* **1984**, *18*, 203−212. (b) Mulzer, J. *Nachr. Chem. Technol. Lab.* **1984**, *32*, 16−18. (c) Mulzer, J. *Organic Synthesis Highlights*; VCH: Weinheim, 1991; pp 3−8. (d) Devant, R. M.; Radunz, H.-E. *Formation of C−C Bonds by Addition to Carbonyl Groups*; Houben-Weyl, Georg Thieme: Stuttgart/New York, 1995; E21, pp 1151−1235. (e) Mulzer, J. *Diastereoface Selection (Differentiation) 1, n-Induction*; Houben-Weyl, Georg Thieme: Stuttgart/New York, 1995; E21, pp 121−140. (f) Yamaguchi, M. Lewis Acid Promoted Addition Reactions of Organometallic Compounds. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon Press: Oxford/New York, 1991; Vol. 1, pp 325−353.

(3) First direct observation of Cram-Chelate transition states, see: (a) Reetz, M. T.; Huellmann, M.; Seitz, T. *Angew. Chem.* **1987**, *99*, 478−480; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 477. (b) Reetz, M. T.; Raguse, B.; Seitz, T. *Tetrahedron* **1993**, *49*, 8561−8568.

(4) Review: Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468.

(5) Substituents being able to form attractive interactions to other groups, e.g., OH, OMe, have been called *active volume*, while substituents being repulsive to other groups, e.g., OTBS, alkyl, etc., have been called *passive volume*. Winterfeldt, E. *Stereoselektive Synthese. Prinzipien und Methoden*; Friedr. Vieweg & Sohn: Braunschweig/Wiesbaden, 1988.

(6) We use "Felkin product" to refer to the Cram− or Felkin−Anh product and "*anti*-Felkin product" to refer to the Cram-chelate or *anti*-Felkin−Anh product.

(7) Cornforth, J. W.; Cornforth, M. R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112−127.

(8) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199−2204.

(9) (a) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145−162. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70. (c) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, *3*, 155−158.

(10) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065−5067. (b) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1561−1572. (c) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153−161.

(11) (a) Eisenstein, O.; Hoffmann, R. *J. Am. Chem. Soc.* **1980**, *102*, 6148−6149. (b) Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Dâu, M.-E. T. H. *J. Am. Chem. Soc.* **1973**, *95*, 6146−6147.

(12) Similar results: Fraser, R. R.; Stanciulescu, M. *J. Am. Chem. Soc.* **1987**, *109*, 1580−1581.

(13) (a) Karabotsos, G. J. *Tetrahedron Lett.* **1972**, *52*, 5289−5292. (b) Karabatsos, G. J.; Althuis, T. H. *Tetrahedron Lett.* **1967**, *49*, 4911−4914. (c) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367−1371.

(14) (a) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1985**, *107*, 6411−6413. (b) Nakada, M.; Urano, Y.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1988**, *110*, 4826−27. (c) Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990−91. (d) Greeves, N.; Lyford, L.; Pease, J. E. *Tetrahedron Lett.* **1994**, *35*, 285−288. (e) Reetz, M. T.; Harmat, N.; Mahrwald, R. *Angew. Chem.* **1992**, *104*, 333−334; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 342. (f) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573−4576. (g) Maruoka, K.; Ttoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588−3597. (h) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441−1454. (i) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R. *Angew. Chem.* **1980**, *92*, 1044−45. (j) Matsuzawa, S.; Isaka, M.; Nakamura, E. *Tetrahedron Lett.* **1989**, *30*, 1975−1978. (k) Huenig, S.; Marschner, C. *Chem. Ber.* **1989**, *122*, 1329−1340. (l) Yamamoto, Y.; Matsuoka, K. *J. Chem. Soc., Chem. Commun.* **1987**, 923−924. (m) Krause, N.; Seebach, D. *Chem. Ber.* **1987**, *120*, 1845−51. (n) Yamamoto, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4475−4476. (o) Cram, D. J.; Elhafez, F. A. A.; Weingartner, H. *J. Am. Chem. Soc.* **1953**, *75*, 2293−97. (p) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441−54. (r) Cram, D. J.; Elhafez, F. A. A.; Nyquist, H. L. *J. Am. Chem. Soc.* **1954**, *76*, 22−28. (s) Cram, D. J.; Ejhafez, F. A. A.; Nyquist, H. L. *J. Am. Chem. Soc.* **1954**, *76*, 22−28. (t) Midland, M. M.; Kwon, Y. C. *J. Am. Chem. Soc.* **1983**, *105*, 3725−3727. (u) Kunz, T.; Reissig, H.-U. *Liebigs Ann. Chem.* **1989**, 891−894. (v) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Organomet. Chem.* **1985**, *285*, 31−42. (w) Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem.* **1982**, *94*, 133−134; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 135. (x) Rahman, A. U.; Shah, Z. In *Stereoselective Synthesis in Organic Chemistry*; Springer-Verlag: New York, 1993; pp 168−169. (y) Toda, F.; Tanaka, K.; Mori, K. *Chem. Lett.* **1983**, 827−830. (z) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 9005−18.

(15) (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265−268. (b) Henry, K. J.; Grieco, P. A.; Jagoe, C. T. *Tetrahedron Lett.* **1992**, *33*, 1817−1820. (c) Paquette, L. A.; Mitzel, T. M. *Tetrahedron Lett.* **1995**, *36*, 6863−6866. (d) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1995**, *118*, 1931−1937. (e) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422−24 (f) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035−38. (g) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1031−34. (h) Samuels, W. D.; Nelson, D. A.; Hallen, R. T. *Tetrahedron Lett.* **1986**, *27*, 3091−3094. (i) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653−2656. (j) Shibata, I.; Yoshida, T.; Kawakami, T.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 4049−4051. (k) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130−6131. (l) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778−1784. (m) Mulzer, J.; Kattner, L.; Strecker, A. R.; Schröder, C.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 4218−29. (n) Reetz, M. T.; Huellmann, M. *J. Chem. Soc., Chem. Commun.* **1986**, *21*, 1600−1602. (o) Stocker, J. H.; Sidisunthorn, P.; Benjamin, B. M.; Collins, C. J. *J. Am. Chem. Soc.* **1960**, *82*, 3913−18. (p) Reetz, M. T.; Drewer, M. W.; Schmitz, A. *Angew. Chem.* **1987**, *99*, 1186−1188; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. (q) Barbaro, G.; Battaglia, A.; Giorgianni, P. *Tetrahedron* **1993**, *49*, 4293−4306. (r) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5415−5421. (s) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157−6163. (t) Cokley, T. M.; Isaacs, N. S.; McCluskey, A.; Young, D. J. *Main Group Metal Chem.* **1997**, *20*, 581−582. (u) Hormuth, S.; Reissig, H.-U.; Dorsch, D. *Liebigs Ann. Chem.* **1994**, 121−128. (v) Shimagaki, M.; Maeda, T.; Matsuzaki, Y.; Hori, I.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, *25*, 4775−4778. (w) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641−1644. (x) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1992**, *33*, 4353−4356. (y) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron* **1993**, *49*, 11169−11182. (z) Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 2045−2062.

(16) (a) Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem.* **1982**, *94*, 133−134; *Angew. Chem., Int. Ed.* **1982**, *21*, 135. (b) Paquette, L. A.; Mitzel, T. M. *J. Org. Chem.* **1996**, *61*, 8799−8804. (c) Paquette, L. A.; Bennett, G. D.; Isaac, M. B.; Chhatriwalla, A. *J. Org. Chem.* **1998**, *63*, 1836−1845.

(17) Alvarez-Ibarra, C.; Arjona, O.; Perez-Ossorio, R.; Perez-Rubalcaba, A.; Quiroga, M. L.; Santesmases, M. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1645−1648.

(18) (a) Yamamoto, Y.; Matsuoka, K. *J. Chem. Soc., Chem. Commun.* **1987**, 923−924. (b) Yamamoto, Y.; Yamada, J. *J. Am. Chem. Soc.* **1987**, *109*, 4395−96. (c) Soai, K.; Niwa, S.; Hatanaka, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2129−30.

(19) (a) Perez-Ossorio, R.; Perez-Rubalca, A.; Quiroga, M. L. *Tetrahedron Lett.* **1980**, *21*, 1565−1566. (b) Janowitz, A.; Kunz, T.; Handke, G.; Reissig, H.-U. *Synlett* **1989**, 24−25. (c) Mead, K. T. *Tetrahedron Lett.* **1987**, *28*, 1019−1022.

(20) (a) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354−362. (b) Caputo, R.; Longobardo, L.; Palumbo, G.; Pedaella, S.; Giordano, F. *Tetrahedron* **1996**, *52*, 11857−11866. (c) Coleman, R. S. *Tetrahedron Lett.* **1992**, *33*, 1697−1700. (d) Bayquen, A. V.; Read, R. W. *Tetrahedron* **1996**, *52*, 13467−13482. (e) Ageno, G.; Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Riva, R.; Rocca, V. *Tetrahedron* **1995**, *51*, 8121−8134. (f) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullie, M. M. *Tetrahedron* **1996**, *52*, 11673−11694.

(21) Similar to the Garner aldehyde: Poli, G.; Maccagni, E.; Manzoni, L.; Pilati, T.; Scolastico, C. *Tetrahedron* **1997**, *53*, 1759−1776.

(22) (a) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843−2846. (b) Mulzer, J.; Kappert, M.; Huttner, G.; Jibril, I. *Angew. Chem.* **1984**, *96*, 726−727; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 704. (c) Mulzer, J.; Buettelmann, B.; Muench, W. *Liebigs Ann. Chem.* **1988**, 445−448. (d) Mulzer, J.; Greifenberg, S.; Beckstett, A.; Gottwald, M. *Liebigs Ann. Chem.* **1992**, *11*, 1131−1136. (e) Mulzer, J.; Funk, G. *Synthesis* **1995**, 101−112. (f) Paquette, L. A.; Montgomery, F. J.; Wang, T.-Z. *J. Org. Chem.* **1995**, *60*, 7857−7864. (g) Ramachandran, P. V.; Li, G.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 100−104.

(23) (a) Singh, S. M.; Oehlschlager, A. C. *Can. J. Chem.* **1988**, *66*, 209−213. (b) Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* **1985**, *26*, 2619−2622. (c) Cohen, T.; Bhupathy, M. *Tetrahedron Lett.* **1983**, *24*, 4163−64.

(24) Bai, X.; Eliel, E. L. *J. Org. Chem.* **1992**, *57*, 5166−5172.

(25) Ko, K.-Y.; Park, J.-Y. *Tetrahedron Lett.* **1997**, *38*, 407−410.

(26) Further examples for the application of the Felkin−Anh model to cyclohexancarbaldehydes: Krafft, M. E.; Chirico, X. *Tetrahedron Lett.* **1994**, *35*, 4511−4514.

(27) Felkin−Anh model in thioketone chemistry: Mori, I.; Barlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5966−5977.

(28) Yamamoto, Y.; Nishii, S.; Maruyama, K. *J. Am. Chem. Soc.* **1986**, *108*, 7778−7786.
(29) Further examples for the application of the Felkin−Anh model in imine chemistry: (a) Stojanovic, A.; Renaud, P. *Helv. Chim. Acta* **1998**, *81*, 268−285. (b) Yamada, J.-I.; Sato, H.; Yamamoto, Y. *Tetrahedron Lett.* **1989**, *30*, 5611−5614. (c) Williams, D. R.; Osterhout, M. H.; Reddy, J. P. *Tetrahedron Lett.* **1993**, *34*, 3271−3274. (d) Cowling, M. P.; Jenkins, P. R.; Cooper, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1503−1504. (e) Wuts, P. G. M.; Jung, Y.-W. *J. Org. Chem.* **1991**, *56*, 365−372.
(30) (a) Chérest, M.; Felkin, H.; Frajerman, C. *Tetrahedron Lett.* **1971**, 379−82. (b) Huet, J.; Maroni-Barnaud, Y.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron Lett.* **1976**, 159−62. (c) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447−62. (d) Li, H.; Noble le, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199−210.
(31) (a) Ono, S.; Shuto, S.; Matsuda, A. *Tetrahedron Lett.* **1996**, *37*, 221−224. (b) Bubert, C.; Reiser, O. *Tetrahedron Lett.* **1997**, *38*, 4985−4988.
(32) Dauben, W. G.; Dinges, J.; Smith, T. C.; Timothy, C. *J. Org. Chem.* **1993**, *58*, 7635−7637.
(33) (a) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1995**, *60*, 2474−2487. (b) Delanghe, P. H. M.; Lautens, M. *Tetrahedron Lett.* **1994**, *35*, 9513−9516.
(34) (a) Takeda, Y.; Matsumoto, T.; Sato, F. *J. Org. Chem.* **1986**, *51*, 4728−31. (b) Okamoto, S.; Tsujiyama, H.; Yoshino, T.; Sato, F. *Tetrahedron Lett.* **1991**, *32*, 5789−92. (c) Howe, G. P.; Wang, S.; Procter, G. *Tetrahedron Lett.* **1987**, *28*, 2629−32.
(35) Further examples in epoxid chemistry: (a) Escudier, J.-M.; Baltas, M.; Gorrichon, L. *Tetrahedron Lett.* **1991**, *32*, 5345−5348. (b) Escudier, J.-M.; Baltas, M.; Gorrichon, L. *Tetrahedron* **1993**, *49*, 5253−5266.
(36) (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920−1923. (b) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 2177−2194.
(37) (a) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639−644. (b) Whitesell, J. K. *Formation of C−C Bonds by Pericyclic Reactions, Ene Reaction*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21c, pp 3271−3297.
(38) (a) Cozzi, P. G.; Tagliavini, E.; UmaniRonchi, A. *Gazz. Chim. Ital.* **1997**, *127*, 247−254. (b) Duthaler, R. O.; Hafner, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 43−45.
(39) Reviews: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Heathcock, C. H. In *Asymmetric Synthesis. Stereodifferentiating Reactions, Part B*; Morrison, J. D., Ed.; AP: New York, 1984; Vol. 3, p 111. (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.
(40) (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151−4157. (b) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J. M. *Tetrahedron* **1992**, *48*, 4439−4458.
(41) (a) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087−4095. (b) Woodward, R. B.; et al. *J. Am. Chem. Soc.* **1981**, *103*, 3210−3213. (c) Tschamber, T.; Waespe-Sarcevic, N.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 621−625.
(42) Further examples with *E*(O)-enolates: (a) Aggarwal, V. K.; Stuart, S. *Tetrahedron Lett.* **1987**, *28*, 1925−1928. (b) Ahmar, M.; Bloch, R.; Mandville, G.; Romain, I. *Tetrahedron Lett.* **1992**, *33*, 2501−2504.
(43) Further examples with *Z*(O)-enolates: (a) Heathcock, C. H.; White, C. T.; Morrison, J. J.; VanDerveer, D. *J. Org. Chem.* **1981**, *46*, 1296−1309. (b) Heathcock, C. H.; Young, S. D.; Hagen, J. P. *J. Org. Chem.* **1980**, *45*, 3846−3856.
(44) Paterson, I.; Oballa, R. M. *Tetrahedron Lett.* **1997**, *38*, 8241−8244.
(45) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353−3361.
(46) Further examples for Aldol reactions: (a) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129−6132. (b) Dondoni, A.; Merino, P. *J. Org. Chem.* **1991**, *56*, 5294−5301.
(47) Further examples for Mukayama-Aldol reactions: (a) Davis, A. P.; Plunkett, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, 2173−2174. (b) Saigo, K.; Kudo, K.; Hashimoto, Y.; Kimoto, H.; Hasegawa, M. *Chem. Lett.* **1990**, 941−944.
(48) Example of nitro aldol reactions: Borrachero, P.; Dianez, M. J.; Estrada, M. D.; Gomez-Guillen, M.; Gomez-Sanchez, A. *Carbohydr. Res.* **1995**, *271*, 79−100.
(49) Gennari, C.; Fioravanzo, E.; Bernardi, A.; Vulpetti, A. *Tetrahedron* **1994**, *50*, 8815−8826.
(50) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem.* **1985**, *97*, 1−78; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) Heathcock, C. H.; White, C. T.; Morrison, J. J.; VanDerveer, D. *J. Org. Chem.* **1981**, *46*, 1296−1309.
(51) (a) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422−34. (b) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109−17.
(52) Mulzer, J.; Pietschmann, C.; Buschmann, J.; Luger, P. *J. Org. Chem.* **1997**, *62*, 3938−43.
(53) (a) Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1988**, *53*, 4643−4644. (b) Hollady, M. W.; Rich, D. H. *Tetrahedron Lett.* **1983**, *24*, 4401−4404. (c) Jones, D. M.; Nilsson, B.; Szelke, M. *J. Org. Chem.* **1993**, *58*, 2286−2290. (d) Karlsson, J. O.; Lundblad, A.; Malm, B.; Nilsson, I.; Nitenberg, T.; Starke, I. *Tetrahedron Lett.* **1989**, *30*, 2653−2656.
(54) (a) Kreuder, R.; Rein, T.; Reiser, O. *Tetrahedron Lett.* **1997**, *38*, 9035−9038. (b) Rein, T.; Anvelt, J.; Soone, A.; Kreuder, R.; Wulff, C.; Reiser, O. *Tetrahedron Lett.* **1995**, *36*, 2302−2305. (c) Rein, T.; Kreuder, R.; Zezschwitz, P. v.; Wulff, C.; Reiser, O. *Angew. Chem.* **1995**, *107*, 1099−1102. (d) Rein, T.; Kann, N.; Kreuder, R.; Gangloff, B.; Reiser, O. *Angew. Chem.* **1994**, *106*, 597−599.
(55) Furuta, T.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1992**, 863−864.
(56) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.
(57) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162−7166.
(58) Although the analysis according to the Houk model is distinctively different from the Felkin−Anh model, we will nevertheless—in an attempt to create a unified picture—refer to adducts such as **132** as the Felkin and to adducts such as **133** as the *anti*-Felkin product, treating the alkene double bond analogously to a carbonyl double bond. Thus, once L, M, and S have been defined on the steric and stereoelectronic prerequisites of the reaction under investigation, the Felkin product always arises upon placing L orthogonal to and M on the same side of the double bond with the double bond being attacked *anti* to L (cf. Scheme 4, **9** and **10**).
(59) Houk, K. N.; Moses, S. R.; Wu, Y. D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880−3882.
(60) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257−2274.
(61) (a) Podlech, J.; Seebach, D. *Liebigs Ann. Org. Bioorg. Chem.* **1995**, *7*, 1217−1228. (b) Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824−1840. (c) Fleming, I.; Lewis, J. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3257−3266.
(62) Arai, M.; Kawasuji, T.; Nakamura, E. *J. Org. Chem.* **1993**, *58*, 5121−5129.
(63) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1572−1573.
(64) Further examples: (a) Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231−2234. (b) Ibarra, C. A.; Perez, M. S. A.; Castro, I. D.; Fernandez, M. J. *J. Chem. Soc., Perkin Trans. 2* **1991**, 467−470. (c) Mulzer, J.; Graske, K.-D.; Shanyoor, M. *Liebigs Ann. Org. Bioorg. Chem.* **1995**, 593−598. (d) Dorigo, A. E.; Morokuma, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1884−1886.
(65) (a) Asao, N.; Shimada, T.; Sudo, T.; Taukada, N.; Yazawa, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274−6282. (b) Yamamoto, Y.; Chouman, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652−7660.
(66) Mulzer, J.; Kappert, M. *Angew. Chem.* **1983**, *95*, 60; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 63.
(67) Jurczak, J.; Golebiowski, A.; Raczko, J. *J. Org. Chem.* **1989**, *54*, 2495−2496.
(68) Similar results: (a) Midland, M. M.; Afonso, M. M. *J. Am. Chem. Soc.* **1989**, *111*, 4368−4371. (b) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1990**, *55*, 5058−5065. (c) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609−2612.
(69) Application in total synthesis: (a) Danishefsky, S. J.; De Ninno, M. P.; Chen, S.-H. *J. Am. Chem. Soc.* **1988**, *110*, 3929−3940. (b) Danishefsky, S. J.; Myles, D. C.; Harvey, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 862−867. (c) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 1981−1983.
(70) Casas, R.; Parella, T.; Branchadell, V.; Olivia, A.; Ortuno, R. M.; Guingant, A. *Tetrahedron* **1992**, *48*, 2659−2680.
(71) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663−666.
(72) Similar results: (a) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762−2772. (b) Jäger, V.; Schohe, R. *Tetrahedron Lett.* **1983**, *24*, 5501−5504.
(73) Trost, B. M.; Lynch, J.; Renaut, P. *Tetrahedron Lett.* **1985**, *26*, 6313−6316.
(74) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943−3946.
(75) Barbaro, G.; Battaglia, A.; Giorgianni, P. *Tetrahedron* **1993**, *49*, 4293−4306.
(76) Bach, T. *Synthesis* **1998**, 683−703.
(77) (a) Takano, S.; Hatakeyama, S.; Saijo, K. *Tetrahedron Lett.* **1985**, *26*, 865−868. (b) Nubbemeyer, U.; Öhrlem, R.; Gonda, J.; Ernst, B.; Bellus, D. *Angew. Chem.* **1991**, *103*, 1533−1534; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1465.
(78) Cha, J. K.; Lewis, S. C. *Tetrahedron Lett.* **1984**, *25*, 5263−5266.
(79) Brückner, R.; Priepke, H. *Angew. Chem.* **1988**, *100*, 285−286; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 278.

(80) Review on 1,2-stereocontrol in radical chemistry: (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996; pp 164−177. (b) Linker, T.; Schmittel, M. *Diastereoselektive Reaktionen acyclischer Verbindungen*; Wiley-VCH: Weinheim, 1998.
(81) Examples of 1,2-stereocontrol in radical chemistry: (a) Roth, M.; Damm, W.; Giese, B. *Tetrahedron Lett.* **1996**, *37*, 351−354. (b) Curran, D. P.; Sun, S. *Tetrahedron* **1993**, *34*, 6181−6184. (c) Renaud, P.; Carrupt, P.-A.; Gerster, M.; Schenk, K. *Tetrahedron Lett.* **1994**, *35*, 1703−1706. (d) Angelaud, R.; Landais, Y. *Tetrahedron Lett.* **1997**, *38*, 233−236. (e) Haraguchi, K.; Tanaka, H.; Saito, S.; Yamaguchi, K.; Miyasaka, T. *Tetrahedron Lett.* **1994**, *35*, 9721−9724. (f) Renaud, P.; Gerster, M. *J. Am. Chem. Soc.* **1995**, *117*, 6607−6608.
(82) Giese, B.; Damm, W.; Dickhaut, J.; Wetterich, F.; Sun, S.; Curran, D. P. *Tetrahedron Lett.* **1991**, *32*, 6097−6100.
(83) Smadja, W.; Zahouily, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 5511−5514.
(84) Roth, M.; Damm, W.; Giese, B. *Tetrahedron Lett.* **1996**, ***37***, 351−354.
(85) Reetz, M. T. *Angew. Chem.* **1984**, *96*, 542−555; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.
(86) Evans, D. A.; Dart, M. J.; Duffy, J. l.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.
(87) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190−5192.
(88) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833−4835.
(89) Shambayati, S.; Schreiber, S. L. *Comprehensive Organic Synthesis: Addition to C−X-Bonds, Part 1*; Pergamon Press: New York, 1991; Vol. 10.
(90) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847−3849.
(91) Further examples leading to *trans*-1,3-diols: (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578. (b) Anwar, S.; Davis, A. P. *Tetrahedron* **1988**, *44*, 3761−3770. (c) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449.
(92) Further examples leading to *cis*-1,3-diols: (a) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158. (b) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233−2238. (c) Hanamoto, T.; Hiyama, T. *Tetrahedron Lett.* **1988**, *29*, 6467−6470. (d) Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem Lett.* **1987**, 1923−1926. (e) Bonadies, F.; DiFabio, R.; Gubioti, A.; Mecozzi, S.; Bonini, C. *Tetrahedron Lett.* **1987**, *28*, 703−706. (f) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009−3012. (g) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803−805. (h) Narasaka, K.; Pai, F.-C. *Chem. Lett.* **1980**, 1415−1418.
(93) Priepke, H.; Weigand, S.; Brueckner, R. *Liebigs Ann.* **1997**, *8*, 1635−1644.
(94) Hanessian, S.; Schaum, R. *Tetrahedron Lett.* **1997**, *38*, 163−166.
(95) (a) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011−4018. (b) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4019−4026. (c) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729−732.
(96) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537−8540.
(97) Further 1,3-inductions with aldehydes: Mulzer, J.; Pietschmann, C. *J. Org. Chem.* **1997**, *62*, 3938−3943.
(98) 1,3-Induction in total synthesis: (a) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583−5601. (b) Yamamoto, Y.; Chouman, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652−7660.
(99) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619−6620.
(100) Further combinations of 1,2- and 1,3-induction: (a) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 3769−3771. (b) Cirillo, P. F.; Panek, J. S. *J. Org. Chem.* **1990**, *55*, 6071−6073.
(101) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073−74.
(102) 1,3-Inductions with ketones: (a) Nakada, M.; Urano, Y.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1994**, *35*, 741−744. (b) Evans, D. A.; Bartroli, O.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4577−4580. (c) Fleming, I.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3309−3326. (d) Evans, D. A.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1994**, *35*, 8541−8544.
(103) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *Tetrahedron* **1990**, *46*, 6167−6184. (b) Reetz, M. T.; Kessler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem.* **1983**, *95*, 1007−1008; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989.

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