Crystal Structures – A *Manifesto* for the Superiority of the Valine-Derived 5,5-Diphenyloxazolidinone as an Auxiliary in Enantioselective Organic Synthesis

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Dedicated to Professor *David Evans* on the occasion of his 60th birthday

The crystal structures of 32 derivatives of 4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one (**A** and **1**–**31**) are presented (*Fig. 2* and *Tables 1–3*). In all but four structures, the Me_2CH group is in a disposition that mimick a Me_3C group (*Figs. 3–5*). The five-membered ring shows conformations from an envelope form with the Ph_2C group out of the plane containing the other four atoms to the twist form with the twofold axis through the C=O group (*Fig. 6*, and *Table 2*). In the entire series, the Me_2CH and the neighboring *trans* Ph group are approximately antiperiplanar (average torsion angle 155°). The structural features are used to interpret the previously observed reactivity behavior of the diphenyl-oxazolidinone derivatives. The practical advantages of the title compound over classical *Evans* auxiliaries are outlined (*Figs. 1* and *7*, and *Scheme 2*): high crystallinity of all derivatives, steric protection of the C=O group in the ring, excellent stereoselectivities in reactions of its derivatives, and safe preparation and easy recovery of the auxiliary.

The use of covalently attached chiral auxiliaries for overall enantioselective and, less frequently, diastereoselective[2]) transformations is of enormous importance in organic synthesis, as demonstrated by a recent compendium consisting of three volumes and containing 2700 references and 13000 entries [1]. In the era of catalytic enantioselective reactions [2] – *cf.* the 2001 *Nobel* prize in chemistry – such a statement seems questionable, but every practitioner in a research laboratory or in a pharmaceutical early-development division will agree that it is more convenient to take an auxiliary approach than to use a sometimes capricious catalytic reaction[3]) to *quickly* prepare a sample of an enantiomerically pure compound. The principle of auxiliary-based enantioselective transformations is simple (*Scheme 1*), and the properties of an ideal chiral auxiliary have been defined many times: inexpensive, of low molecular weight, available in both enantiomeric forms, easy to introduce, efficient in generating diastereotopic-face or -group bias, and easy to remove and to recover[4]).

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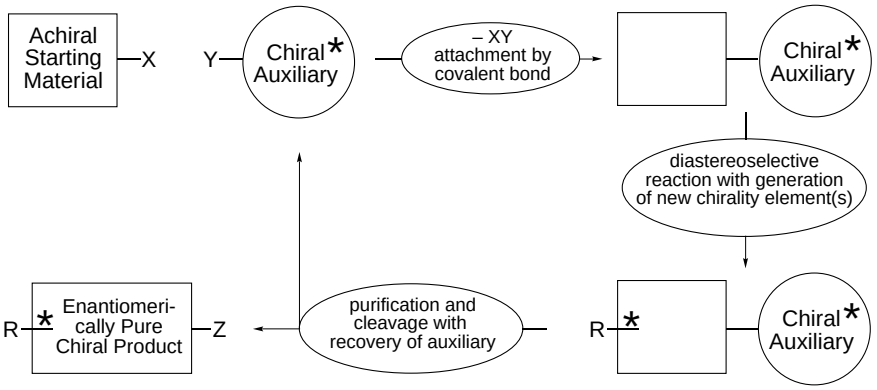
[1]) Part of the Ph.D. Thesis of *C. G.*, Dissertation No. 14516, ETH-Zürich, 2002.

[2]) If the auxiliary group is 'dictating' the stereochemical course of reaction with a chiral enantiomerically pure reactant, either one of two diastereoisomeric products may be obtained after removal of the corresponding auxiliary.

[3]) Many of the most attractive catalytic methods require carefully controlled reaction conditions (*e.g.*, inert atmospheres, high pressures) and skilled and experienced experimentalists; catalytic methods are usually much more effective on large scale, after – sometimes – laborious optimization.

[4]) Some of us would add that the ideal auxiliary should also be C_2-symmetrical [3].

Scheme 1. *The Principle of Overall Enantioselective Transformations with the Help of Chiral Auxiliaries Temporarily Attached through Covalent Bonds.* In so-called 'reagent-controlled' reactions, the chiral auxiliary may also be used for overall diastereoselective processes involving chiral starting materials.



Among the most important auxiliary groups are the chiral oxazolidinones (*Evans* auxiliaries; *Fig. 1*, *top*)[5]), *N*-acyl and *N*-enoyl derivatives of which are widely used for overall enantioselective enolate alkylations, aldol additions, *Michael* additions, and *Diels-Alder* reactions, considering the synthetic equivalence of the carboxylic acid-functional group with the aldehyde-, the primary-alcohol-, and thus the $X-CH_2$-alkylating-functional group, the central role of this methodology in organic synthesis can hardly be overestimated.

Guided by our experience with the TADDOL system [7], where we had learned that the diarylmethanol moiety with its two geminal aryl groups greatly favors ring formation[6])[7]) and also increases ring stability, we have prepared [9][10][8]) 4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **A** (*Fig. 1*, *bottom*), and tested it as a chiral auxiliary [10–18]. The compound had been described before [19–21] (both enantiomeric forms are offered commercially as DIOZ by a Japanese company)[9])[10]), but its virtues have

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[5]) For review articles, see [4], and for early recognition of the advantages of S-containing analogs of the *N*-acyl-oxazolidinones, see the discussion in [5]. For references to the seminal contributions by *Meyers* in the use of chiral heterocycles for synthetic transformations, see [1][6].

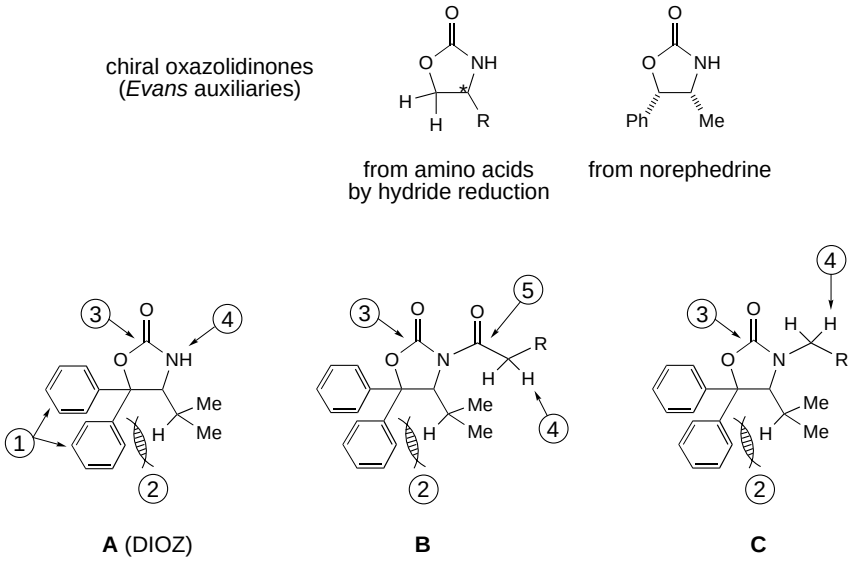
[6]) See the discussions in Sect. 11 of a review article on TADDOLs [7b] and references 103 and 104 to the *Thorpe-Ingold* or geminal-dimethyl effect in Sect. 4 (structures of TADDOLs) and 11 (auxiliaries and catalyst ligands containing $(Arl)_2C-O$ moieties), therein.

[7]) The use of geminal-dimethyl-substituted oxazolidinones (dubbed 'SuperQuats') has been investigated by *Davies* and co-workers [8].

[8]) The preparation of **A** by reaction of $RO-CO-NH-CH(CHMe_2)-CO_2R$ (protected valine esters) with phenyl *Grignard* reagent is practically more convenient than the preparation of the parent oxazolidinone (with CH_2 instead of CPh_2), requiring hydride reagents, which can be hazardous on a large scale. An *Organic Syntheses* procedure has been submitted (by *M. Brenner*, *L. La Vecchia*, *T. Leutert*, *D. Seebach*) for checking by one of the editors. A copy of the manuscript can be obtained by request from the correspondence author of the present paper.

[9]) (+)-DIOZ and (−)-DIOZ, *Shiratori Pharmaceutical Co., Ltd*. Japan. DIOZ is also offered by *Onyx Scientific, Ltd.*, UK.

[10]) For other diphenyl-oxazolidinones of this type, derived from phenylalanine, phenylglycine, and *tert*-leucine, see, *e.g.*, [9][10][13][17][22][23].



(1) Ph groups introduced by reaction of (*S*)- or (*R*)-valine ester with commercial phenyl *Grignard* reagent
geminal diphenyl substitution leads to high crystallinity of all derivatives – DIOZ itself (m.p. 251°) precipitates from reaction mixtures, is filtered, washed, dried, and reused

(2) Ph group in *cis* position to the i-Pr group has a buttressing effect, fixing the conformation around the CH–CHMe$_2$ bond to mimic a *t*-Bu group's effect upon substituents on the N-atom

(3) nucleophile attack on the C=O group (*Bürgi-Dunitz* trajectory) is sterically blocked by a Ph group on one face and by an i-Pr group on the other face of the ring plane

(4) deprotonation on the N-atom or on groups attached to it can be achieved directly with BuLi, due to steric protection of the C=O group, to give amine- and salt-free solutions of Li derivatives; low temperatures are not always required

(5) the exocyclic C=O group is much more reactive than the endocyclic one, which allows for simple cleavage of *N*-acyl groups

Fig. 1. *Chiral oxazolidinone auxiliaries and derivatives.* The classical *Evans* auxiliaries (*top*) and the valine-derived 5,5-diphenyl-substituted analog **A** with *N*-acyl (**B**) and *N*-alkyl (**C**) groups; (1–5) are important issues justifying the use of the diphenyl-oxazolidinone auxiliary (sold under the name DIOZ, *cf. Footnote 9*), in spite of its higher molecular weight, as compared to the parent compound (281 *vs.* 129). For references, see the accompanying paragraphs.

become evident only recently, as we [9–18][11]) and others [24–28] have employed it in an ever increasing number of different types of reactions[12]). Some of the most prominent features of the oxazolidinone **A** and its derivatives **B** and **C** are listed in *Fig. 1*.

It is the aim of this paper *i*) to demonstrate the high crystallinity of products obtained from oxazolidinone **A**, and *ii*) to show what conclusions can be drawn about the reactivity of its derivatives – from crystal structures. The great tendency of these compounds to crystallize is useful for their purification by recrystallization, so that the minor diastereoisomeric products and other impurities can be removed without having to resort to chromatographic methods. The auxiliary itself is essentially insoluble in all common solvents (see crystal-packing pattern of **A** in *Fig. 2*); it precipitates upon removal from the desired enantiomerically pure products.

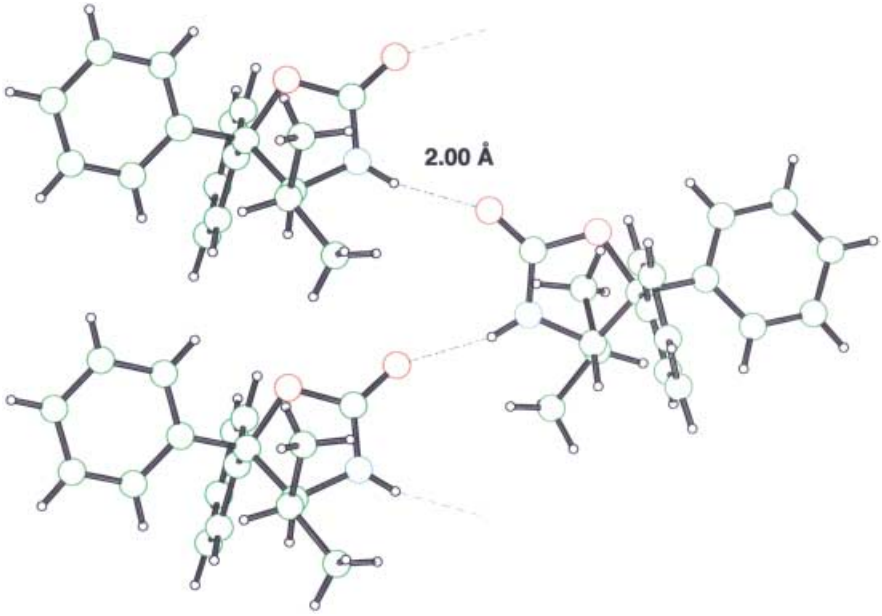


Fig. 2. *Crystal-packing pattern in the X-ray structure of the auxiliary* **A**. The H-bonded chains of molecules cause the high melting point (251°) and low solubility of **A**. The derivatives of **A** (*Table 1*) are soluble in common organic solvents. On a laboratory scale, substituents on the N-atom of **A** are best introduced by addition of BuLi at 0° to a slurry of **A** in THF, producing a colorless solution, which is combined with an acid chloride or alkylating reagent. Alternatively, a mixed anhydride R–CO–O–COCMe$_3$ is generated *in situ*, **A** is added, and acylation with dissolution of **A** is mediated by LiCl at room temperature [29][30].

The crystallinity of the well-soluble products derived from **A** has rendered structure determination by single-crystal X-ray diffraction, and thus configurational

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11) For a short review article containing a section on the use of **A**, see [18].

12) These do not only include the transformations, in which *Evans* auxiliaries are usually employed [1][4], but, *e.g.*, also metallations with BuLi, which would not be possible without the geminal-diphenyl substitution on the oxazolidinone ring [13–17].

Table 1. *Crystal Structures, Formulae, and Melting Points of* **A** *and Its Derivatives* **1**–**31**, *with References to Publications in Which the Preparation of the Compounds Has Been Described*. The presentation of the structures was produced with the program MOLMOL [31]. Color code: N: blue, O: red, S: yellow, Si: magenta, Br: green, C and bonds: gray. Most of the structures were obtained in the course of the Ph.D. Thesis of *Gaul* [17]. The ordering was chosen after the types of reactions by which the compounds have been prepared. All structures are derived from (*S*)-valine. Crystal structures of 5,5-diphenyloxazolidinones with substituents other than i-Pr at C(4) have also been published [9][10][17].

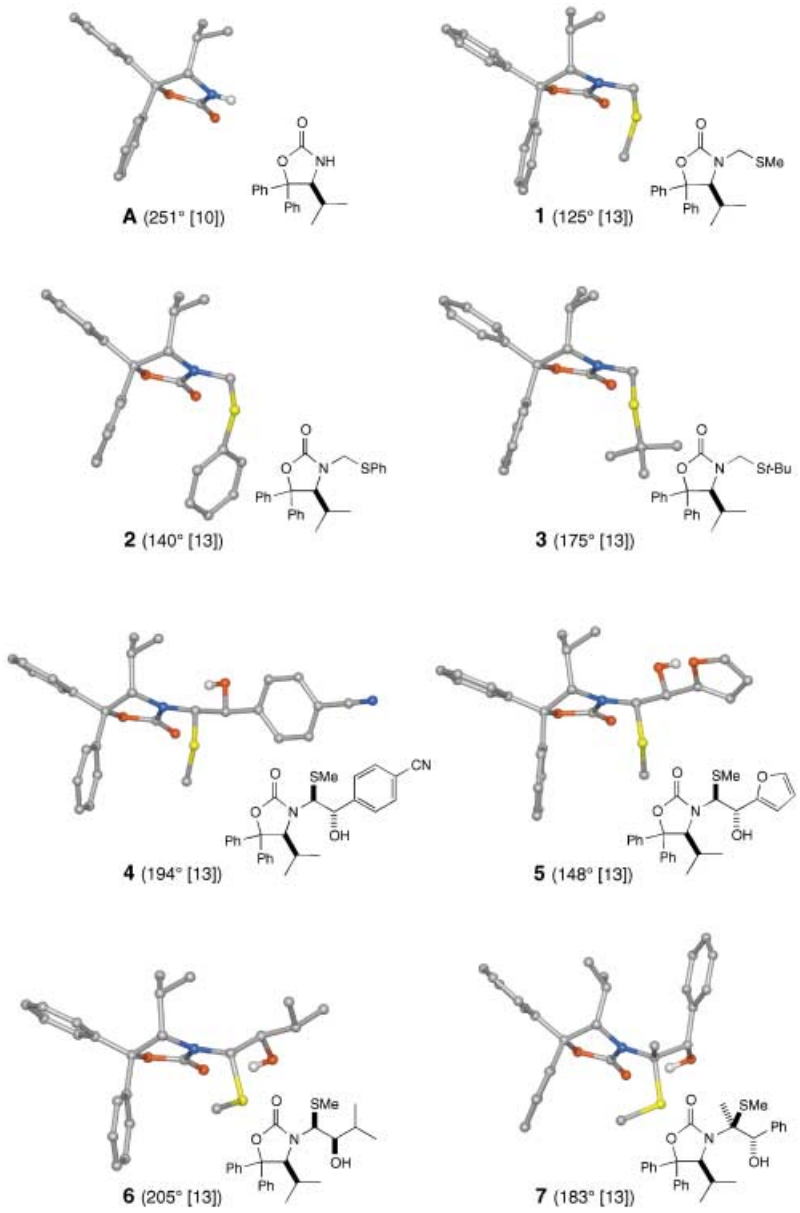


Table 1 (cont.)

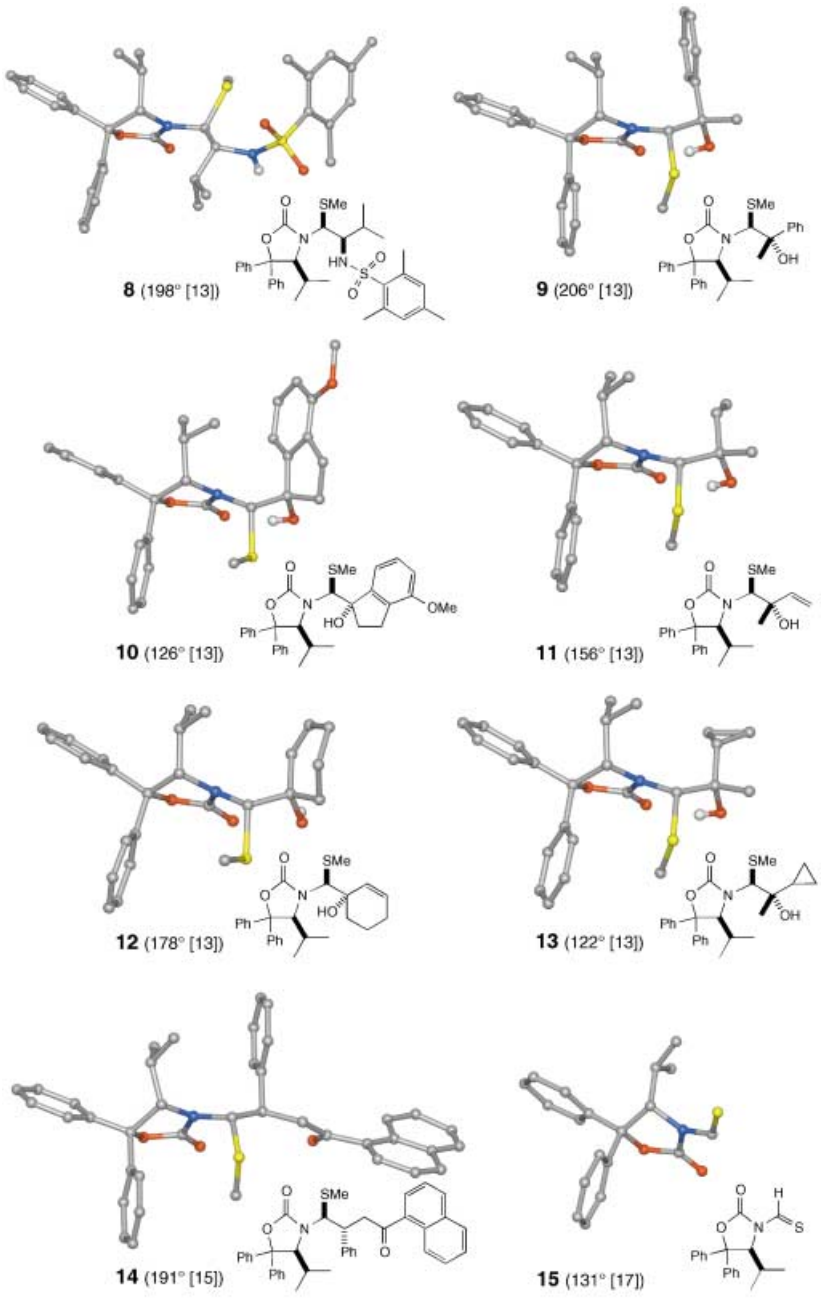

8 (198° [13])
9 (206° [13])
10 (126° [13])
11 (156° [13])
12 (178° [13])
13 (122° [13])
14 (191° [15])
15 (131° [17])

Table 1 (cont.)

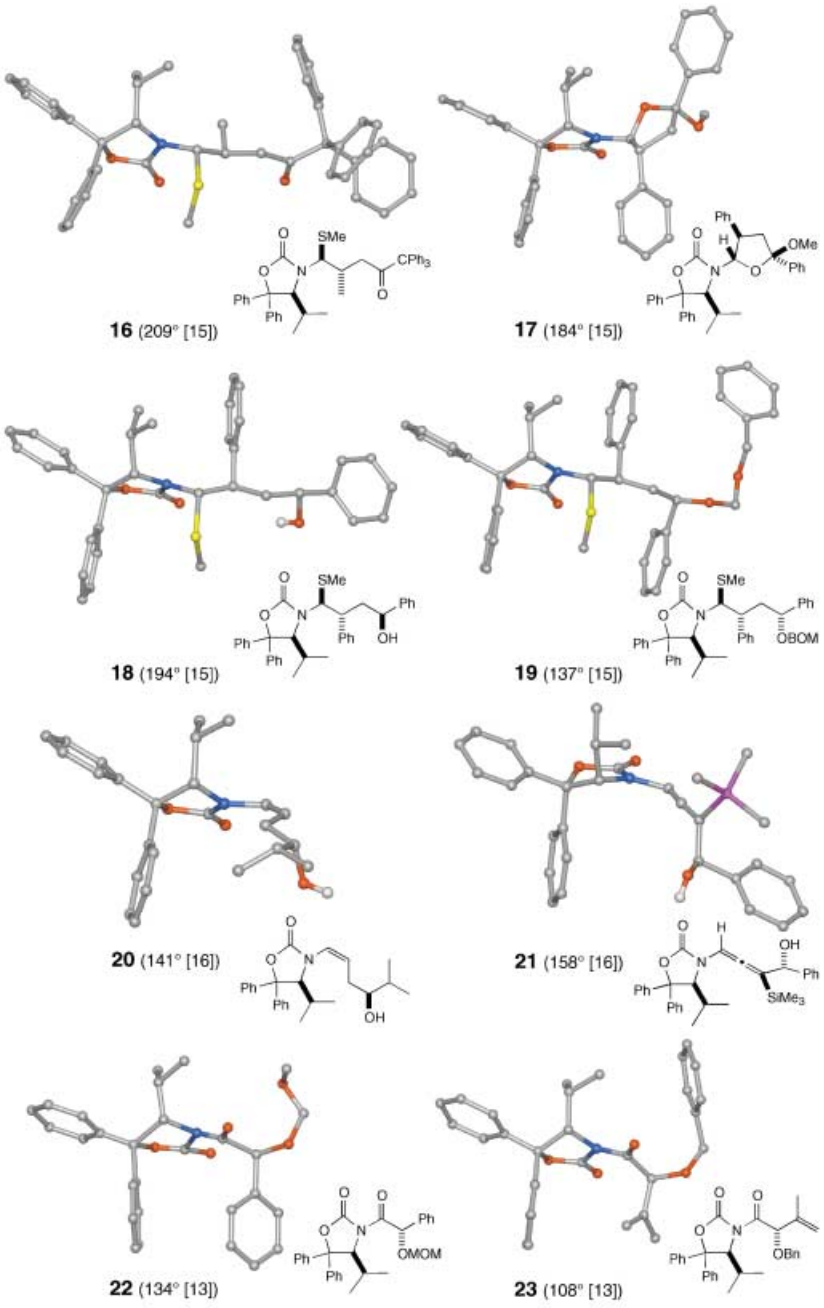

16 (209° [15])
17 (184° [15])
18 (194° [15])
19 (137° [15])
20 (141° [16])
21 (158° [16])
22 (134° [13])
23 (108° [13])

Table 1 (cont.)

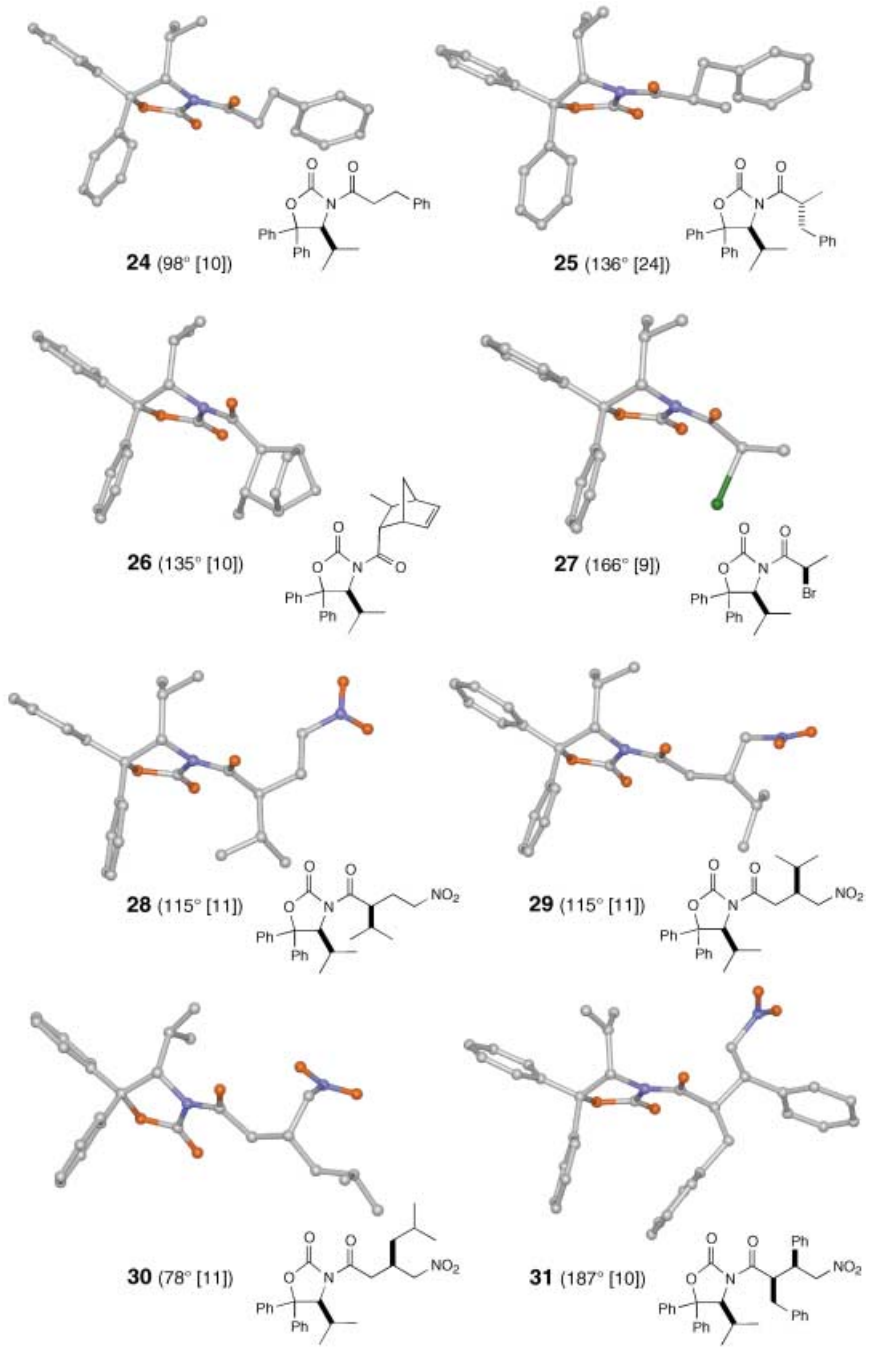

24 (98° [10])
25 (136° [24])
26 (135° [10])
27 (166° [9])
28 (115° [11])
29 (115° [11])
30 (78° [11])
31 (187° [10])

Table 2. *Geometric Deformation of the Amide Group and Puckering Coordinates of 37 Oxazolidinone Fragments from* **A** *and Its Derivatives* **1**–**31**. Ring puckering for five-membered rings can be described with two coordinates [36]: amplitude q shows total derivation of the ring atoms relative to its mean plane, phase ϕ describes kind of puckering (envelope, twist, see *Fig. 6*), and t is the torsion angle R–N–C=O. The last two columns show the out-of-plane distance of N- and of the carbonyl-C-atoms from their substituents (pyramidalization).

Fragment	Compound	q [Å]	ϕ [°]	t [°]	N···P1 [Å]	C···P2 [Å]
1	**A**	0.32	23.64			
2	**1**	0.31	6.85	– 12.428	0.054	– 0.007
3	**2**	0.281	9.32	– 8.522	0.014	– 0.01
4	**3**	0.328	13.32	– 4.399	– 0.026	0.006
5	**4**	0.324	12.05	– 15.96	0.045	– 0.015
6	**4**	0.295	0.58	– 11.234	0.071	0.013
7	**5**	0.325	8.31	– 18.387	0.08	0.015
8	**6**	0.315	7.37	– 11.604	– 0.046	0.007
9	**7**	0.333	15.98	– 14.879	0.026	– 0.008
10	**8**	0.296	11.11	– 4.148	– 0.021	– 0.002
11	**9**	0.355	7.14	– 12.652	– 0.049	0.008
12	**10**	0.316	7.69	– 25.631	0.16	– 0.003
13	**11**	0.344	5.94	– 19.272	0.106	– 0.008
14	**12**	0.32	6.53	– 21.747	– 0.145	– 0.005
15	**13**	0.334	5.01	– 22.854	– 0.13	0.014
16	**14**	0.312	4.51	– 20.568	0.12	– 0.009
17	**14**	0.33	6.89	– 25.515	– 0.16	0.002
18	**15**	0.349	15.65	– 17.477	0.042	– 0.01
19	**15**	0.36	8.29	– 12.493	– 0.062	– 0.007
20	**15**	0.351	15.45	– 16.734	– 0.055	– 0.005
21	**15**	0.362	19.47	– 23.83	0.071	– 0.007
22	**16**	0.262	4.43	– 19.959	– 0.12	0.01
23	**17**	0.322	17.46	– 3.854	– 0.04	0.013
24	**18**	0.293	– 1.15	– 17.226	– 0.126	0.008
25	**19**	0.319	0.72	– 20.672	– 0.14	0.012
26	**20**	0.351	17.55	2.461	0.12	0.004
27	**20**	0.342	16.85	2.325	0.11	0.002
28	**21**	0.321	8.10	– 12.421	0.034	– 0.015
29	**23**	0.368	17.90	– 25.92	0.087	– 0.016
30	**24**	0.314	21.35	– 18.227	– 0.026	0.011
31	**25**	0.326	16.14	– 15.733	0.035	– 0.005
32	**26**	0.368	17.48	– 24.956	0.07	– 0.018
33	**27**	0.345	20.26	– 33.252	– 0.122	0.019
34	**28**	0.347	15.51	– 25.33	– 0.096	0.01
35	**29**	0.326	13.46	– 17.814	0.069	0.001
36	**31**	0.335	17.95	– 21.326	– 0.043	0.024
37	**31**	0.304	18.29	– 16.145	0.019	– 0.017

Table 3. *Crystallographic Data of the Oxazolidinones* **A** *and of* **1**–**23**. For the methods used in the structure determination, see *Exper. Part*. The crystallographic data of oxazolidinones **24**–**31** have been published previously [9][10][11][24].

Data	**A**	**1**	**2**	**3**	**4**
Formula	$C_{18}H_{19}NO_2$	$C_{20}H_{23}NO_2S$	$C_{25}H_{25}NO_2S$	$C_{23}H_{29}NO_2S$	$C_{28}H_{28}N_2O_3S$
Formula weight [g mol^{-1}]	281.34	341.45	403.16	383.53	472.58
T [K]	293(2)	293(2)	293(2)	213(2)	103(2)
Wavelength [Å]	1.54184	0.71069	1.54184	1.54184	1.54184
Source	CuK_α	MoK_α	CuK_α	CuK_α	CuK_α
Crystal	0.35 × 0.25	0.35 × 0.30	0.50 × 0.10	0.15 × 0.10	0.30 × 0.25
Dimensions [mm]	× 0.005	× 0.20	× 0.10	× 0.10	× 0.25
Crystal system	orthorhombic	monoclinic	orthorhombic	monoclinic	triclinic
Space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$C2$	$P1$
θ Range [°]	$4.1 < \theta < 64.8$	$2.0 < \theta < 28.0$	$1.6 < \theta < 24.9$	$2.7 < \theta < 55.0$	$3.7 < \theta < 55.0$
a [Å]	6.277(2)	10.356(5)	6.787(1)	20.616(5)	8.885(2)
b [Å]	15.020(1)	8.802(4)	15.858(4)	6.411(1)	12.413(2)
c [Å]	15.677(1)	10.824(3)	20.218(8)	18.301(4)	13.302(2)
α [°]	90	90	90	90	63.94(1)
β [°]	90	109.57(3)	90	114.56(2)	80.41(2)
γ [°]	90	90	90	90	69.03(2)
V [Å^3]	1478.0(5)	929.7(7)	2176.0(11)	2200.0(8)	1230.6(4)
Z	4	2	4	4	2[a])
$\rho_{calc.}$ [g cm^{-3}]	1.264	1.220	1.232	1.158	1.275
μ [mm^{-1}]	0.653	0.185	0.169	1.425	1.424
Refl. measured	2777	2492	2214	1787	3331
Independent refl.	1511	2375	2189	1551	3331
Refl. observed	366	1848	1124	1536	3086
Restraints	0	1	0	1	3
No. of variables	85[b])	217	262	274	670
Criterion	$I > 3\sigma(I)$	$I > 3\sigma(I)$	$I > 3\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
Final R [%]	8.40	4.09	4.40	4.02	3.28
wR_2 [%]	14.29	12.47	10.87	11.08	8.72
Goodness-of-fit	0.789	1.129	0.960	1.167	1.039
$\Delta\rho$ (max, min) [e Å^{-3}]	0.139, −0.175	0.329, −0.323	0.156, −0.229	0.194, −0.251	0.426, −0.203

[a]) The structure contains two symmetrically independent molecules in the unit cell ($Z' = 2$). [b]) The small size and the poor quality of the crystal did not allow normal refinement. The Ph groups were refined as rigid bodies with assumed ideal geometry and the other non-H-atoms were refined isotropically with SHELXL-97.

Data	**5**	**6**	**7**[a])	**8**	**9**
Formula	$C_{25}H_{27}NO_4S + CH_3OH$	$C_{24\,H31}NO_3S$	$C_{28}H_{31}NO_3S$	$C_{33}H_{42}N_2O_4S_2$	$C_{28}H_{31}NO_3S$
Formula weight [g mol^{-1}]	469.58	413.56	461.60	594.81	461.60
T [K]	173(2)	173(2)	200(2)	293(2)	173(2)
Wavelength [Å]	1.54184	1.54184	1.54184	0.71069	1.54184
Source	CuK_α	CuK_α	Cu	MoK_α	CuK_α
Crystal	0.25 × 0.25	0.20 × 0.20	0.30 × 0.20	0.40 × 0.15	0.20 × 0.15
Dimensions [mm]	× 0.25	× 0.15	× 0.15	× 0.10	× 0.15
Crystal system	orthorhombic	orthorhombic	monoclinic	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$

Table 3 (cont.)

Data	**5**	**6**	**7**[a])	**8**	**9**
θ Range [°]	$4.4 < \theta < 64.9$	$3.4 < \theta < 64.9$	$4.4 < \theta < 66.9$	$1.3 < \theta < 25.0$	$3.2 < \theta < 64.9$
a [Å]	10.551(1)	6.492(1)	8.404(2)	6.448(6)	6.214(1)
b [Å]	11.978(2)	16.019(1)	14.063(4)	15.465(4)	18.515(3)
c [Å]	19.048(2)	21.564(2)	9.969(2)	32.102(9)	20.802(4)
α [°]	90	90	90	90	90
β [°]	90	90	91.27(2)	90	90
γ [°]	90	90	90	90	90
V [Å^3]	2407.3(5)	2242.6(4)	1177.9(5)	3201(3)	2393.3(7)
Z	4	4	2	4	4
$\rho_{calc.}$ [g cm^{-3}]	1.296	1.225	1.301	1.234	1.281
μ [mm^{-1}]	1.499	1.468	1.459	0.205	1.436
Refl. measured	2363	2240	2270	3239	2380
Independent refl.	2337	2214	2178	3239	2354
Refl. observed	2281	2007	2133	1883	2079
Restraints	0	0	2	0	0
No. of variables	340	294	307	374	330
Criterion	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 3\sigma(I)$	$I > 3\sigma(I)$	$I > 2\sigma(I)$
Final R [%]	3.10	3.11	3.37	4.57	3.32
wR_2 [%]	8.56	8.04	9.19	13.31	8.85
Goodness-of-fit	1.089	1.048	0.942	1.233	0.985
$\Delta\rho$ (max, min) [e Å^{-3}]	0.401, −0.195	0.258, −0.151	0.608, −0.300	0.407, −0.233	0.213, −0.223

[a]) The position of the H(O) atom was found from a difference *Fourier* map and was refined with fixed isotropic displacement parameters.

Data	**10**[a])	**11**	**12**[b])	**13**	**14**
Formula	$C_{30}H_{33}NO_4S + CH_3OH$	$C_{24}H_{29}NO_3S$	$C_{26}H_{31}NO_3S$	$C_{25}H_{31}NO_3S$	$C_{39}H_{37}NO_3S$
Formula weight [g mol^{-1}]	535.68	411.54	437.58	425.57	599.25
T [K]	220(2)	113(2)	293(2)	173(2)	180(2)
Wavelength [Å]	1.54184	1.54184	1.54184	1.54184	1.54184
Source	CuK_α	CuK_α	CuK_α	CuK_α	CuK_α
Crystal Dimensions [mm]	$0.35 \times 0.30 \times 0.25$	$0.20 \times 0.15 \times 0.15$	$0.30 \times 0.30 \times 0.15$	$0.40 \times 0.40 \times 0.20$	$0.15 \times 0.10 \times 0.08$
Crystal system	triclinic	monoclinic	triclinic	monoclinic	triclinic
Space group	$P1$	$P2_1$	$P1$	$P2_1$	$P1$
θ Range [°]	$3.6 < \theta < 66.9$	$3.8 < \theta < 59.9$	$5.3 < \theta < 54.9$	$3.6 < \theta < 59.9$	$3.0 < \theta < 66.9$
a [Å]	6.308(2)	6.103(1)	6.416(7)	6.114(1)	9.332(3)
b [Å]	9.124(2)	15.021(5)	9.010(8)	14.923(1)	12.117(4)
c [Å]	12.388(3)	11.969(5)	11.535(6)	12.327(1)	15.698(4)
α [°]	87.480(15)	90	105.46(6)	90	68.04(2)
β [°]	86.538(15)	100.47(29	97.75(7)	91.68(1)	87.95(3)
γ [°]	77.906(15)	90	103.69(8)	90	78.48(3)
V [Å^3]	695.5(3)	1079.0(6)	610.3(9)	1124.2(2)	1611.7(8)
Z	1	2	1	2	2[c])
$\rho_{calc.}$ [g cm^{-3}]	1.279	1.267	1.191	1.257	1.236
μ [mm^{-1}]	1.362	1.526	1.378	1.481	1.189

Table 3 (cont.)

Data	**10**[a])	**11**	**12**[b])	**13**	**14**
Refl. measured	2401	1855	1520	1813	5576
Independent refl.	2401	1671	1520	1725	5576
Refl. observed	2393	1370	1405	1704	2709
Restraints	3	1	3	1	3
No. of variables	354	292	280	302	799
Criterion	$I > 3\sigma(I)$	$I > 2\sigma(I)$	$I > 3\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
Final R [%]	4.29	3.39	7.35	3.04	3.83
wR_2 [%]	12.36	8.40	18.04	8.47	9.90
Goodness-of-fit	1.324	1.232	1.777	1.111	0.882
$\Delta\rho$ (max, min) [e Å^{-3}]	0.477, −0.467	0.250, −0.217	0.423, −0.505	0.145, −0.350	0.140, −0.184

[a]) The position of the H(O) atom was found from a difference *Fourier* map and was refined with fixed isotropic displacement parameters. [b]) The structure contains an unresolved, disordered MeOH molecule. [c]) The structure contains two symmetrically independent molecules in the unit cell ($Z' = 2$).

Data	**15**	**16**	**17**	**18**	**19**
Formula	$C_{19}H_{19}NO_2S$	$C_{43}H_{43}NO_3S$	$C_{35}H_{35}NO_4$	$C_{35}H_{37}NO_3S$	$C_{43}H_{45}NO_4S$
Formula weight [g mol^{-1}]	325.41	653.84	533.64	551.72	671.86
T [K]	100(2)	293(2)	293(2)	293(2)	293(2)
Wavelength [Å]	1.54184	1.54184	0.71069	1.54184	1.54184
Source	CuK_α	CuK_α	MoK_α	CuK_α	CuK_α
Crystal Dimensions [mm]	0.20 × 0.18 × 0.16	0.25 × 0.25 × 0.20	0.30 × 0.10 × 0.10	0.30 × 0.30 × 0.10	0.35 × 0.30 × 0.25
Crystal system	monoclinic	triclinic	orthorhombic	monoclinic	orthorhombic
Space group	$P2_1$	$P1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
θ Range [°]	$2.6 < \theta < 64.9$	$3.7 < \theta < 68.9$	$1.8 < \theta < 23.0$	$2.5 < \theta < 66.0$	$3.3 < \theta < 69.9$
a [Å]	15.282(2)	8.643(2)	12.286(15)	10.352(5)	10.813(3)
b [Å]	12.881(2)	8.875(3)	14.276(4)	8.271(4)	12.848(2)
c [Å]	17.324(2)	12.594(3)	17.559(5)	17.789(8)	26.757(8)
α [°]	90	71.51(2)	90	90	90
β [°]	89.99(1)	87.90(2)	90	98.29(4)	90
γ [°]	90	80.10(2)	90	90	90
V [Å^3]	3410.2(8)	902.4(4)	3080(4)	1507.2(12)	3717.2(16)
Z	8[a])	1	4	2	4
$\rho_{calc.}$ [g cm^{-3}]	1.268	1.203	1.151	1.216	1.201
μ [mm^{-1}]	1.753	1.103	0.075	1.224	1.103
Refl. measured	6340	3266	2434	2976	7936
Independent refl.	6072	3266	2434	2826	7035
Refl. observed	5488	3146	966	2518	6003
Restraints	1	3	0	1	0
No. of variables	831	438	341[b])	364	446
Criterion	$I > 2\sigma(I)$	$I > 3\sigma(I)$	$I > 3\sigma(I)$	$I > 3\sigma(I)$	$I > 2\sigma(I)$
Final R [%]	3.79	2.99	5.36	4.13	3.86
wR_2 [%]	10.20	9.99	13.22	12.76	10.74
Goodness-of-fit	1.058	0.994	1.205	1.208	0.948
$\Delta\rho$ (max, min) [e Å^{-3}]	0.789, −0.304	0.152, −0.198	0.159, −0.182	0.409, −0.248	0.294, −0.202

[a]) The structure contains four symmetrically independent molecules in the unit cell ($Z' = 4$). [b]) The poor quality of the crystal did not allow normal refinement. Some of the non-H-atoms were refined isotropically with SHELXL-97.

Table 3 (cont.)

Data	**20**	**21**[a])	**22**	**23**
Formula	$C_{25}H_{31}NO_3$	$C_{31}H_{35}NO_3Si$	$C_{28}H_{29}NO_5$	$C_{30}H_{31}NO_4$
Formula weight [g mol^{-1}]	393.51	497.69	459.52	469.56
T [K]	170(2)	200(2)	293(2)	293(2)
Wavelength [Å]	1.54184	1.54184	1.54184	1.54184
Source	CuK_α	CuK_α	CuK_α	CuK_α
Crystal	0.45 × 0.35	0.45 × 0.08	0.35 × 0.05	0.50 × 0.05
Dimensions [mm]	× 0.30	× 0.08	× 0.05	× 0.05
Crystal system	triclinic	monoclinic	orthorhombic	monoclinic
Space group	$P1$	$P2_1$	$P2_12_12_1$	$P2_1$
θ Range [°]	$3.4 < \theta < 65.9$	$2.5 < \theta < 70.4$	$3.3 < \theta < 59.2$	$2.6 < \theta < 62.0$
a [Å]	13.242(10)	11.932(5)	6.620(3)	11.642(2)
b [Å]	8.767(5)	6.571(2)	17.368(3)	6.660(7)
c [Å]	9.825(5)	18.590(6)	21.936(8)	17.423(5)
α [°]	88.88(3)	90	90	90
β [°]	83.71(4)	107.54(3)	90	102.80(2)
γ [°]	78.40(5)	90	90	90
V [Å^3]	1110.6(12)	1389.8(8)	2522.1(15)	1317.3(14)
Z	2[b])	2	4	2
$\rho_{calc.}$ [g cm^{-3}]	1.177	1.189	1.210	1.184
μ [mm^{-1}]	0.604	0.988	0.671	0.623
Refl. measured	3407	2431	2296	3127
Independent refl.	3407	2306	2296	3013
Refl. observed	3390	1669	585	1053
Restraints	3	1	0	1
No. of variables	537	327	101[c])	316
Criterion	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 3\sigma(I)$	$I > 3\sigma(I)$
Final R [%]	4.91	8.14	16.30	5.69
wR_2 [%]	13.78	21.73	36.53	12.93
Goodness-of-fit	1.465	1.961	3.005	1.121
$\Delta\rho$ (max, min) [e Å^{-3}]	0.204, −0.441	0.543, −0.461	0.528, −0.569	0.191, −0.280

[a]) The determination of the structure was difficult, since, despite cooling, more than 50% of the crystal decomposed during the measurement. [b]) The structure contains two symmetrically independent molecules in the unit cell ($Z' = 2$). [c]) The poor quality of the crystal did not allow normal refinement. The Ph groups were refined as rigid bodies with assumed ideal geometry and the other non-H-atoms were refined isotropically with SHELXL-97.

assignments, easy, so that we have a collection of more than 30 structures, only a few of which have previously been published, with data deposition in the *Cambridge Crystallographic Data File*; this statistically relevant number of structures is now enabling us to interpret the reactivity observed experimentally with the derivatives of oxazolidinone **A**.

In *Table 1*, we have listed the crystal structures of **A** and of all known[13]) derivatives **1**–**31**, together with the corresponding formulae, melting points, and references. *Tables 2* and *3* contain the hitherto unpublished crystallographic and structural data of

[13]) Literature and *Cambridge Crystallographic Data File* search as of February 6, 2002. Only one conformer is shown in *Table 1* of structures with several symmetrically independent molecules (up to four, *cf.* **15**).

24 of the 32 compounds shown in *Table 1*. Clearly, most melting points are well above 100°, the average of the 32 values in *Table 1* is actually 157°!

Inspection of the structures in *Table 1* reveals immediately that the conformation around the CH–$CHMe_2$ bond is such that the methine H-atom of the i-Pr group points towards the Ph group in *cis* position (**a** in *Fig. 3*), with only four exceptions, where the i-Pr H-atom is in a (–)-*synclinal* (*sc*) position with respect to the N-atom of the heterocycle (**b** in *Fig. 3*); the third possible conformer **c**, with this H-atom above the ring, is not observed.

Thus, geminal diphenyl substitution causes the i-Pr group to present itself to the substituent on the N-atom of the oxazolidinone ring, where steric hindrance is desired for face-selective reactions, as if it were a *t*-Bu group (buttressing effect [32]; for a reaction in which this effect is borne out, see *Scheme 2*); the small coupling constant ($J \leq 2$ Hz) between H–C(4) and *H*CMe_2 in the NMR spectra of most of the 32

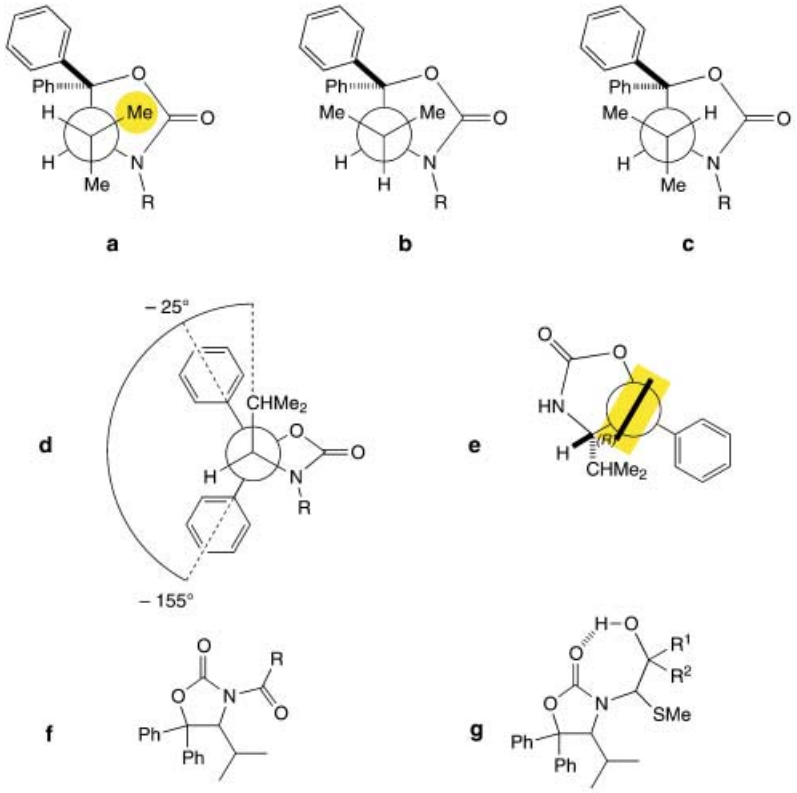
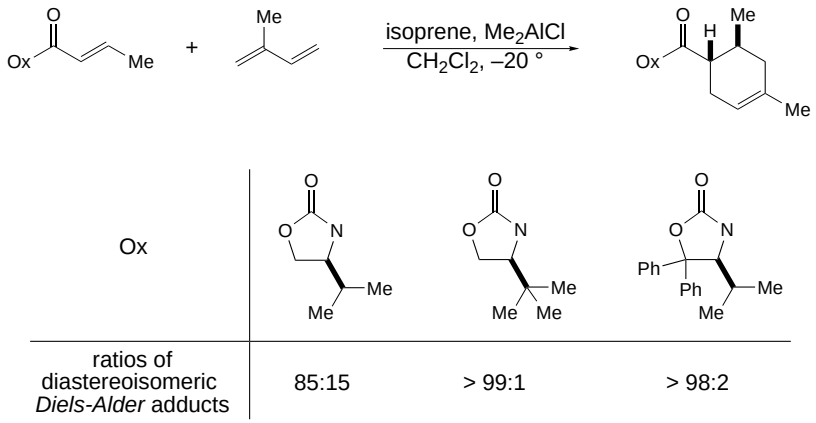


Fig. 3. *Prominent conformations* **a**–**g** *in the structures of* **A** *and its derivatives* (*cf. Table 1* and *Figs. 4* and *5*; for comments, see accompanying paragraph). Conformation **a** is present in *ca.* 90%, and **b** in *ca.* 10% of the structures shown in *Table 1*, and **c** is not found at all; in **a** and **e**, it is demonstrated that both faces of the ring are sterically blocked (by Me and Ph groups); in **d**, we illustrate the small dihedral angle between the Me_2CH and the *cis* Ph group; **f** shows the *anti* arrangement of the two C=O dipoles in *N*-acyl derivatives, and, in **g**, the H-bond between the oxazolidinone C=O and the OH group in hydroxy compounds is depicted (these are formed by addition of the lithiated N–CHLi–SMe derivative to aldehydes and ketones [13]).

Scheme 2. *Stereoselectivities of the* Diels-Alder *Additions of (*E*)-3-Butenoyl-oxazolidinones to Isoprene*. A second diastereoisomer is not present within routine NMR-spectroscopic detection limits, when the *tert*-leucine-derived and the diphenyl-substituted valine-derived oxazolidinones are used as auxiliaries (hitherto unpublished results, described in the dissertation of *Gaul* [17]).



compounds (with the conformation **a** or **b** (*Fig. 3*) in the crystalline state) is proof that the preferred conformation around the CH–CHMe$_2$ bond is the same in solution.

In all structures, a conformation is observed in which the Me$_2$CH and the *trans*-Ph group are as close to an *antiperiplanar* arrangement as possible. Average dihedral angles of *ca.* –25° and –155° between the i-Pr group and the neighboring Ph groups (**d** in *Fig. 3*) are probably a maximum that can be achieved in a five-membered ring containing two trigonal centers and a carbamate O-atom. Steric protection[14]) from nucleophilic attack on the oxazolidinone C=C group is evident from the *Newman* projections **a** (*Si* face of the C=O plane) and **e** (*Re* face of the C=O plane) in *Fig. 3*. As in all other known *N*-acyl-oxazolidinones, the two C=O groups of the O=C–N–C=O moiety are arranged in an *anti* orientation (**f** in *Fig. 3*; minimalization of $A^{1,3}$ strain [34] and dipole–dipole repulsion).

Especially informative are the overlays of 27 structures with the preferred conformation around the CH–CHMe$_2$ bond in *Fig. 4* and of the four unusual structures in *Fig. 5*. The conformation of the five-membered ring ranges from an envelope form with the Ph$_2$C atom out of the plane to the twist form with the two fold axis through the C=O group (*Fig. 6* and *Table 2*). There is a slight-to-moderate torsion around the amide bond in the ring (O=C–N–R torsion angle, 0 to –33°), with varying pyramidalization of the two trigonal centers (*Table 2*). The structure of the ethane moiety Ph$_2$C–C(4)H in the heterocycle appears to be extremely rigid, like a solid scaffold, to which the substituents on the N-atom are attached in seemingly chaotic arrangement, except that the exocyclic C=O bond[15]) is always *anti* to the endocyclic

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[14]) For examples of previous preparative exploitations of 'sterically protected but electronically effective functional groups', see [33].

[15]) ··· and also the C=S bond in compound **15**!

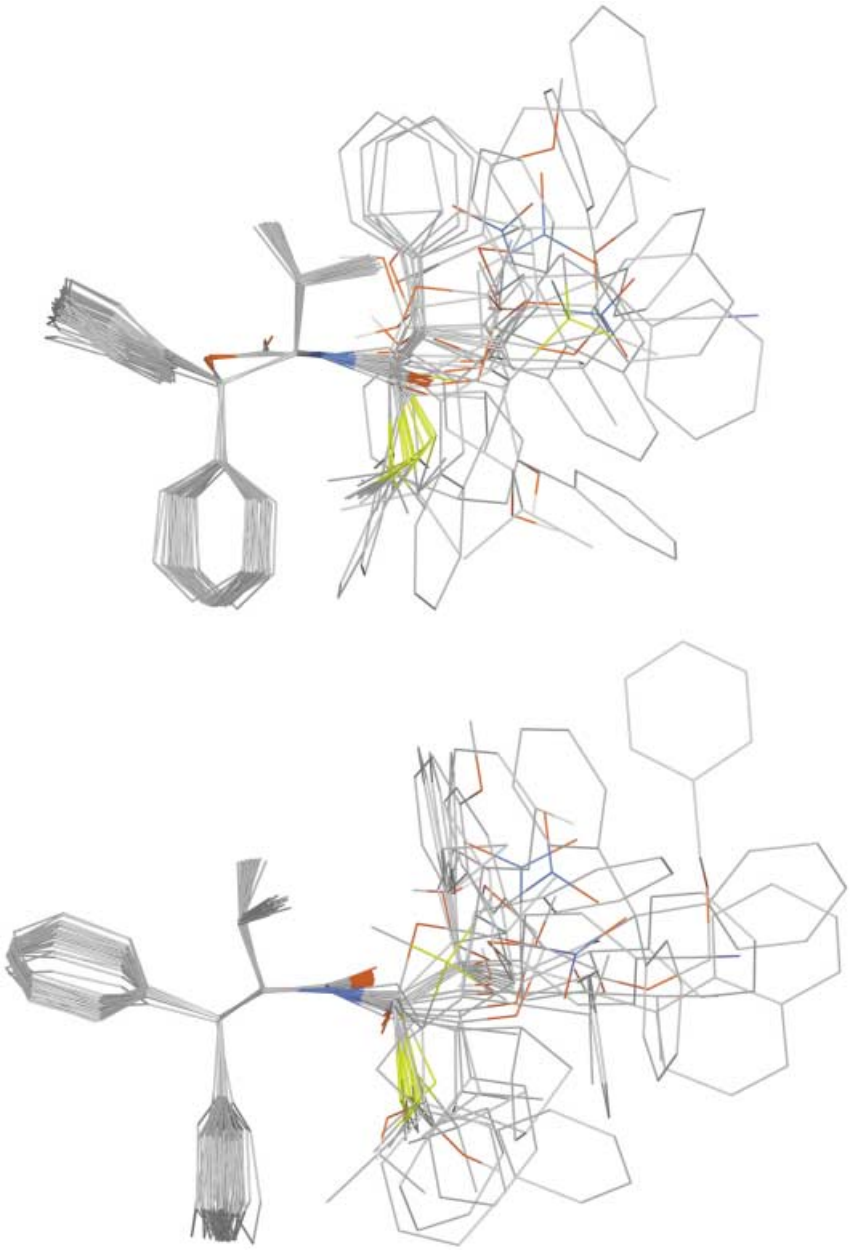

Fig. 4. *Two views of the overlay of 27 structures of* **A** *and its derivatives with the preferred conformation of the CH−CHMe$_2$ bond. Top:* view along the main ring plane and the oxazolidinone C=O bond axis; *bottom:* view along the approximate planes containing the atoms C−N−C−O and the atoms O−C−C of the heterocycle, with best fits of the five ring atoms. Color coding as in *Table 1*. The programs INSIGHT [35] and MOLMOL [31] were used to produce the overlay.

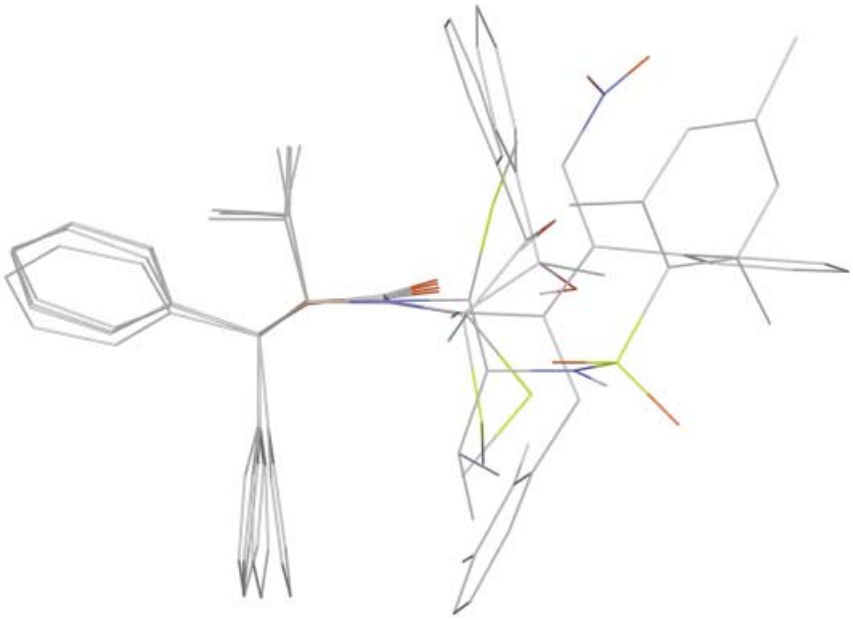

Fig. 5. *Overlay of four 'runaway' structures of 4-isopropyl-5,5-diphenyloxazolidinone derivatives* **7**–**9** *and* **31** *with an unusual conformation of the i-Pr group.* For details, see caption of *Fig. 4*.

one (*cf.* **f** in *Fig. 3*), and that, in the N–CH–SR derivatives, the C–S bond is in an *anti* arrangement with respect to the CH–$CHMe_2$ bond, in most cases. In the less common structures of *Fig. 5*, it looks as if there are large groups in the exocyclic position on the same side of the ring on which the i-Pr group resides. Note that, in two of these unusual structures, there is a H-bond between an OH group in the *N*-substituent and the oxazolidinone carbonyl O-atom (as in many other structures shown in *Table 1*, *cf.* **g** in *Fig. 3*). In structures **7** and **9**, a Ph group on the resulting seven-membered H-bonded ring is forced into a position in which the i-Pr group winds up sandwiched between two Ph groups. Such sandwiching may (**7** and **9**) or may not (**10**, **14**, **18**, and **19**), lead to a conformational switch.

The atoms of the 4-isopropyl-5,5-diphenyloxazolidinon-3-yl group, as seen in so many crystal structures, are held like a template in a vise. There is no doubt in our minds that this arrangement is also present in solution[16]). The template provides the proper environment for diastereoselective reactions on substituents attached to the oxazolidinone N-atom. Approach to one of the diastereotopic faces of trigonal centers on the N-atom of the heterocycle is sterically hindered by the i-Pr group, as depicted in **a** and **b** of *Fig. 7* for metal-chelated derivatives[17]). Similarly, the results of reactions of lithiated (methylthiomethyl)- and allyl-oxazolidinones can be interpreted [13–16] as occurring on this template (see **c** and **d** in *Fig. 7*).

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[16]) *Cf.* the CH–$CHMe_2$ NMR conformation alluded to above.

[17]) For the crystal structure of a Ti derivative of an *N*-acyl-oxazolidinone, see, *e.g.*, [10].

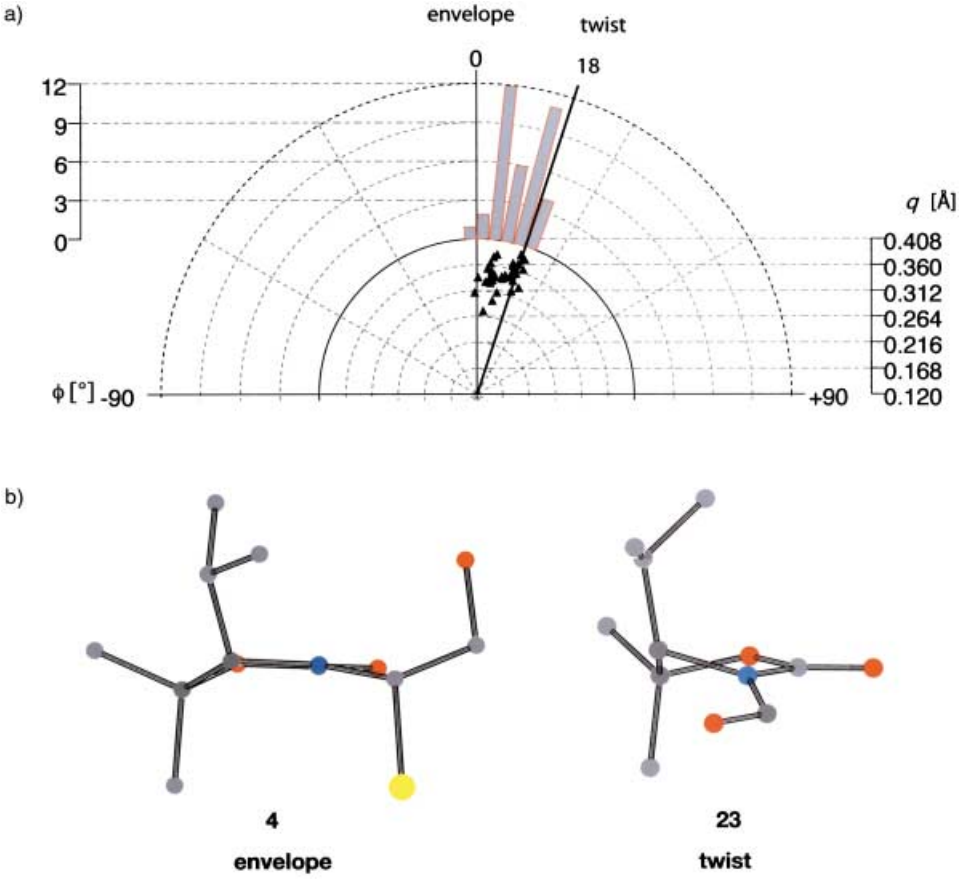

Fig. 6. *Ring puckering of oxazolidinone fragments and examples of ideal envelope and twist forms. a*) Polar scattergram of *Cremer-Pople* ring puckering coordinates [36] of the 37 oxazolidinone fragments (*Table 2*). The inner half-circle shows the phase ϕ *vs.* the amplitude q, envelope $\phi = 0°$, twist $\phi = 18°$. The outer part of the circle shows a histogram of the phase distribution. *b*) On the left, a typical envelope conformation (**4**); on the right, a twist conformation (**23**).

The crystal structures of compounds **24** and **26**–**31** were determined in the course of the Ph.D. Thesis of *T. Hintermann* [9] and *M. Brenner* (ETH-Dissertation No. 14409, 2001). The compounds **11**–**13** and **17** were investigated in the course of the Master Thesis work (Diplomarbeit) of *K. Schärer*, ETH-Zürich, 2000. Financial support of our group by *Novartis Pharma AG*, Basel, is gratefully acknowledged.

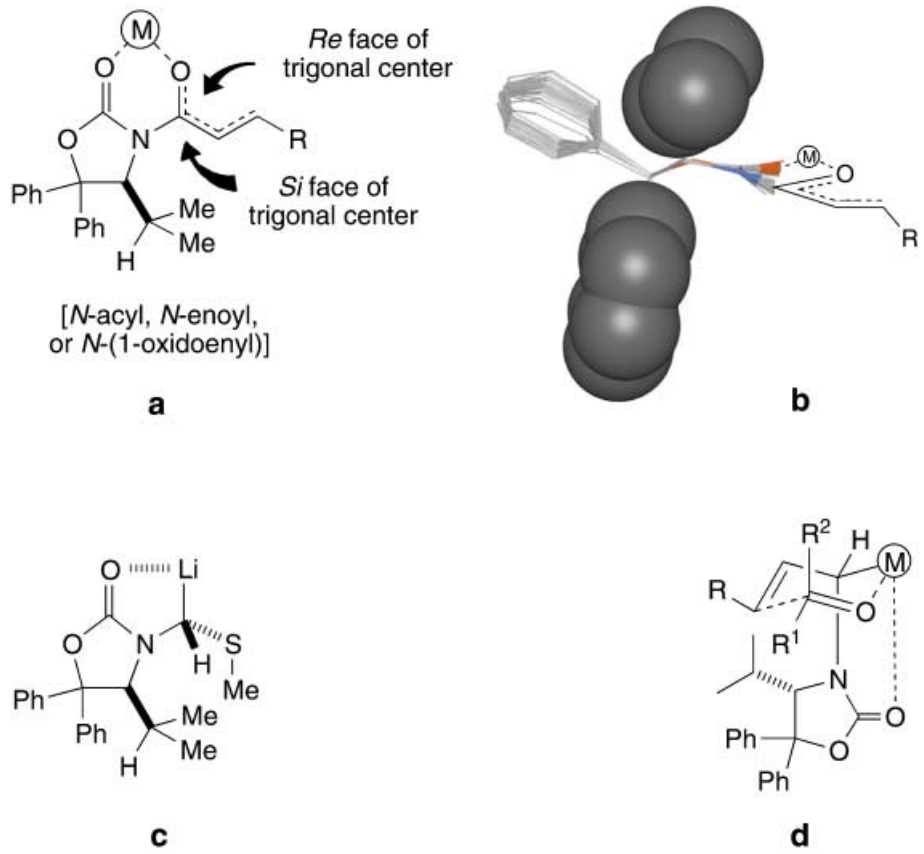

Fig. 7. *Structures, facial selectivities of derivatives of* **A**, *and stereochemical course of reactions.* In **a** and **b**, the face differentiation of metal-chelated derivatives is illustrated. The structure of the Li compound **c** has been derived from NMR measurements [14], and, in **d**, a model compatible with the observed outcome of additions of metallated *N*-allyl-**A** to carbonyl compounds is pictured [16].

Experimental Part

The reflections were collected on an *Enraf-Nonius CAD-4* diffractometer. If not indicated otherwise, the following procedure was used in X-ray crystal-structure determinations: the structures were determined by direct methods with SHELXS-96 [37], SIR92, or SIR97 [38]. In the case of compounds **A**, **2**, **12**, and **20**–**22**, parts of the structures were determined by direct methods with SIR97, and the remaining non-H-atoms were found from a difference *Fourier* map. The non-H-atoms were refined anisotropically with SHELXL-97 [37]. The H-atoms were calculated at idealized positions and included in the structure-factor calculations with fixed isotropic displacement parameters in SHELXL-97.

The crystallographic data of all new structures presented in *Table 1* have been deposited with the *Cambridge Crystallographic Data Centre* (*CCDC*). Copies of the data can be obtained free of charge on application to the *CCDC*, 12 Union Road, Cambridge, CB21EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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