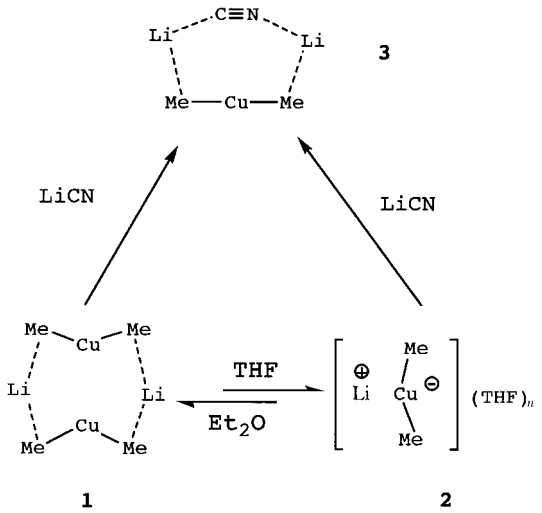
minor changes in the cyanide environment.[11, 12] The lack of a strong solvent dependence for the IR spectra of cyanocuprates is most likely due to the interaction of CN^-, Li^+, and $[CuMe_2]^-$ to give **3** (Scheme 1) regardless of solvent. The structure of **3** is supported by IR measurements and theoretical calculations.[11] The present data suggest that, in the absence of cyanide, dimethylcuprate is largely dimeric **1** in Et_2O and monomeric **2** in THF.



Scheme 1. Structural conversion of dimethylcuprates in THF and Et_2O as well as in the presence of cyanide.

In summary, XAS measurements have revealed solvent-dependent effects for the structures of dimethylcuprates derived from CuI. Dimeric $(CuMe_2Li)_2$ species are predominant in Et_2O and DMS, while a monomeric $[CuMe_2]^-$, or at most a weakly associated aggregate, appears to be the main species in THF. The structures of cyanocuprates are less susceptible to solvent, probably due to the association of the cyanide (or the $[Li_2CN]^+$ unit) with the $[CuMe_2]^-$ unit. This may account for the higher yield for cuprate reactions with CuCN as a precursor.

Experimental Section

Organocuprate samples (0.1M) were prepared under dry N_2 using Schlenk techniques.[11] CuCN (99%), CuBr (99.999%), and CuI (99.999%) were purchased from Aldrich. Halide-free MeLi (1.4M in Et_2O, Aldrich) was titrated with 2-butanol using 1,10-phenanthroline as an indicator. THF was freshly distilled from Na/benzophenone; Et_2O and DMS were freshly distilled from CaH_2. The solutions in DMS and THF contain 14% Et_2O from MeLi addition. Sample preparation and data collection and analysis were previously described.[6b] Solutions in THF and Et_2O were measured in the transmission mode, while solutions in DMS were measured in the fluorescence mode. Data for all samples were evaluated in an identical way.

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Ansa Macrolides as Molecular Workbenches: Stereocontrolled *syn* Additions to *E* olefins

Johann Mulzer,* Karin Schein, Jan W. Bats, Jürgen Buschmann, and Peter Luger

Stereocontrolled dihydroxylations and epoxidations of acyclic 1,2-disubstituted *E* olefins are in favorable cases carried out catalytically,[1] otherwise with substrate-induced diastereodifferentiation; this method, however, requires allylic or homoallylic hydroxy or amide groups.[2] In general an effective face discrimination is difficult because of the high conformative mobility of the substrate. We herein report a new approach to solving this problem. In this, the acyclic *E*

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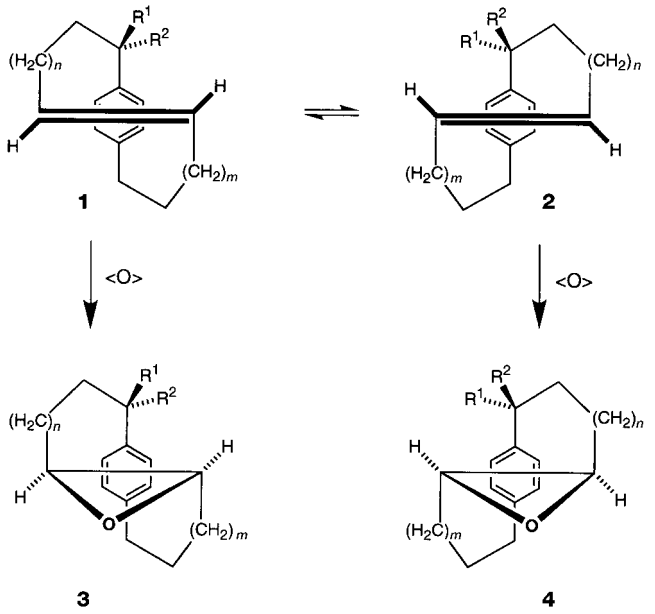
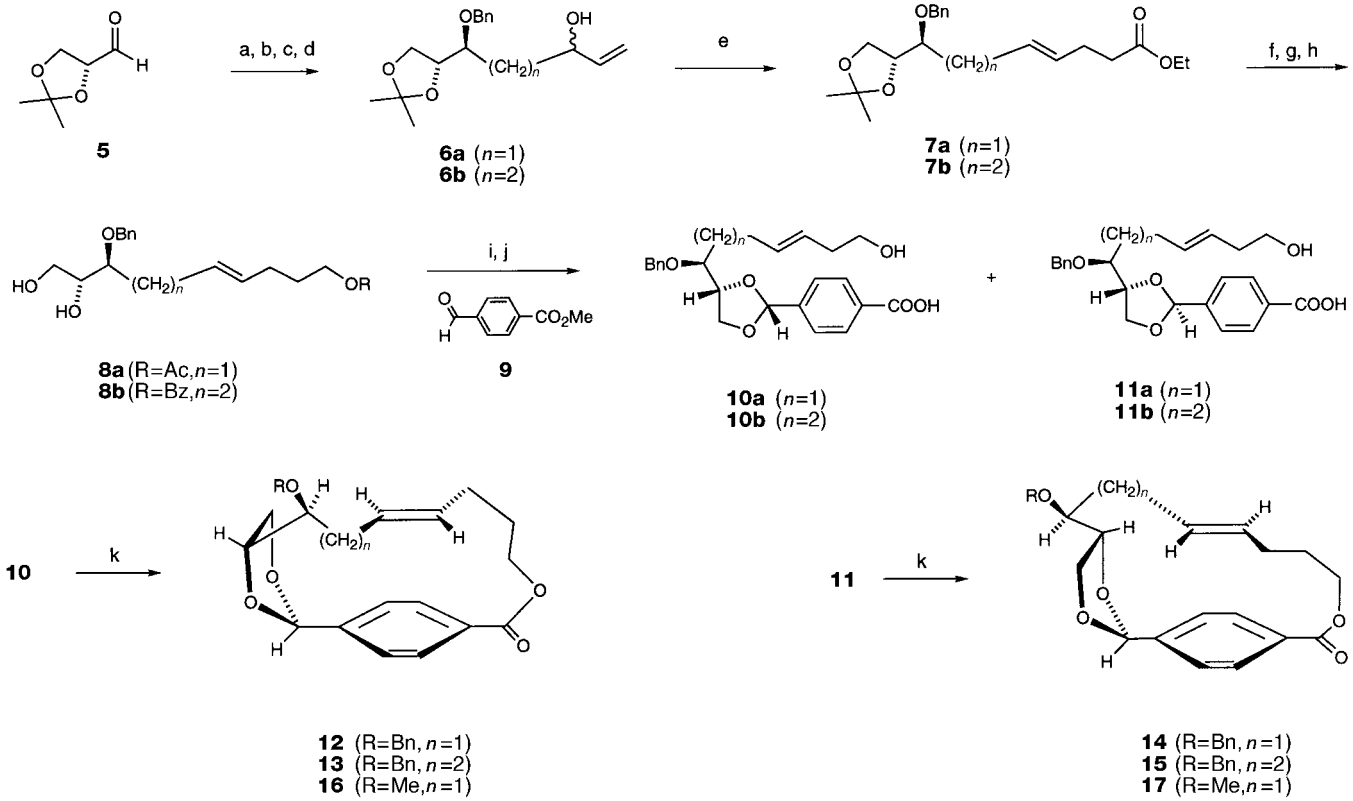
olefin is covalently attached to a benzene ring in the 1,4 positions through appropriate functional groups. This olefin is then sterically shielded from one side. A crucial problem is the conformational equilibrium which is to be expected[3] between the two helical forms **1** and **2**(Scheme 1): Even if the double bond is attacked only from "the front side", two diastereomers are obtained, for example **3** and **4**, after epoxidation. A stereochemically defined outcome of the reaction is only possible if one of the two conformers **1** and **2** predominates under the influence of the arene. The latter then works as a "molecular workbench", fixing the substrate in a rigid conformation.

To put this concept into effect,[4] we chose the easily accessible olefinic diols **8** as substrates, as they can be bonded to the arene **9** with the aid of the diol unit and (after deacylation) of the terminal hydroxy group, to form a cyclic ketal and an ester, respectively. With these functional groups a preferred conformational orientation is expected on closure to form the ansa macrolide ring, as five-membered ring ketals usually adopt an envelope conformation and the ester group should line up coplanar to the arene. The compounds **8** were synthesized stereoisomerically pure according to Scheme 2 from (*R*)-isopropylidene glyceraldehyde (**5**). The Claisen–Johnson rearrangement of **6** to **7** ensures the *E* configuration (>95%) of the alkene unit. The diastereomeric acetals obtained as a 1:1 mixture in the reaction of **8** with **9** were separated chromatographically and then transformed into the seco acids **10a,b** and **11a,b** on a gram scale. These were then macrolactonized in a 10^{-4} M solution according to Yamaguchi's method[5] in approximately 60% yield.



Scheme 1. Arenes as "molecular workbenches".

The macrolides **12**, **14**, and **15**, as well as the methoxy derivatives **16** and **17** prepared in an analogous fashion, are



Scheme 2. Synthesis of the ansa-macrolide alkenes **12**–**17**. a) Allyl- (for **6a**) or 3-butenylmagnesium bromide (for **6b**), THF, −30 °C; removal of the main isomer; b) NaH, BnCl, imidazole, DMF; c) O_3/PPh_3, CH_2Cl_2; d) vinylmagnesium bromide, THF, 0 °C; **6a** 25%, **6b** 31%; e) $CH_3C(OEt)_3$, cat. $EtCO_2H$, toluene, reflux; **7a** 79%, **7b** 79%; f) $LiAlH_4$, THF, 0 °C; g) *n* = 1: Ac_2O, CH_2Cl_2/NEt_3 (1/1); *n* = 2: BzCl, pyridine; h) 50% HOAc; **8a** 83%, **8b** 86%; i) **9**, cat. TsOH, molecular sieve 4 Å, separation by HPLC; j) LiOH, H_2O/MeOH/THF; **10a** 40%, **10b** 38%, **11a** 38%, **11b** 33%; k) 2,4,6-trichlorobenzoyl chloride, NEt_3, THF, 2 h, then DMAP, toluene, reflux, 20 h; **12** 62%, **13** 64%, **14** 60%, **15** 58%. Bn = benzyl, Bz = benzoyl, TsOH = *p*-toluenesulfonic acid, DMAP = 4-dimethylaminopyridine.

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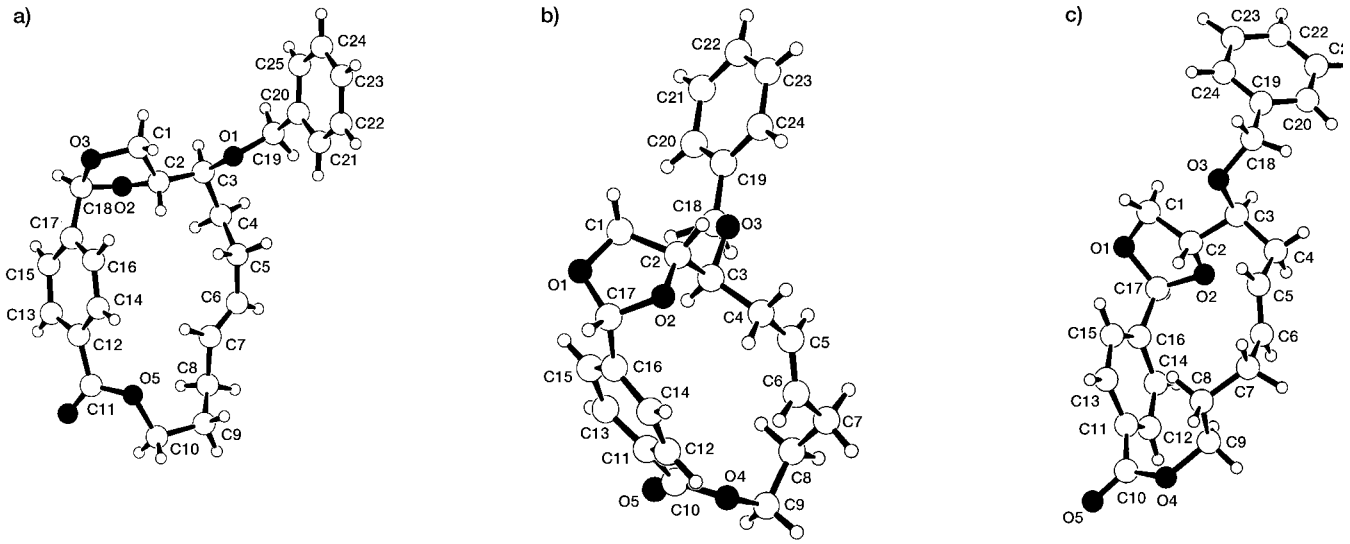
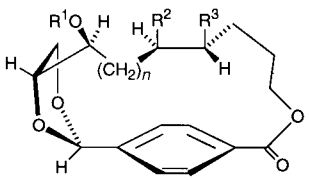


Figure 1. Structures of the ansa-macrolide olefins **15** (a), **12** (b), and **14** (c) in the crystal.[6]

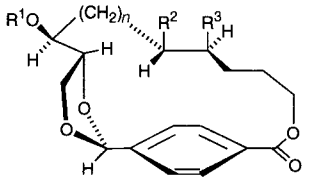
crystalline and were characterized by single-crystal X-ray diffraction (examples of the structures are given in Figure 1).[6] A common feature of all compounds is the antiperiplanar arrangement of the C–O(R) bond and the vicinal C–O bond of the ketal, which is probably due to electrostatic repulsion and acts as a conformational anchor. The benzene rings are deformed in all five macrolides, with bow and stern of the boat lifted above the ring plane by about 0.07 Å each, regardless of the remaining structure. The "pore size" of the macrocycle and therefore its conformational mobility decreases when going from $n=2$ to $n=1$ and from the *cis*- to the *trans*-ketal; accordingly, the effective shielding of the "inner face" increases. Remarkably, the helicity of the double bond moiety in **12** and **14** as well as in **16** and **17** is determined by the configuration of the acetal center: **14** and **17** have the same helicity as **1**, whereas **12** and **16** show the same helicity as **2**, and no definite assignment is possible for **15**.

For a conformational analysis of the compounds in solution, ^{1}H NMR measurements were conducted between -75 and 100 °C. They show that in the "large" lactones **13** and **15**, the arene rotates around the *para* axis. The coalescence temperatures of the signals for the *ortho* and *meta* protons are about 80 (**15**) and -10 °C (**13**). This effect does not occur in **12** and **14**. Nevertheless, the ansa chain should display rapid helical inversion in the sense of **1** $\rightleftharpoons$ **2** in all cases. Evidence for this inversion is obtained from preliminary studies on the molecular dynamics of **12**, **14**, **16**, and **17**, which, however, also show that the "helicamers" observed in the crystal dominate overall.

The stereoselectivities for epoxidations and dihydroxylations (Table 1) are fully in accordance with the expectations deduced from the structures: They are high for the "tight" macrolides **12**, **14**, **16**, and **17** and low for the "wide" macrolides **13** and **15**. The reagent preferentially attacks from the "outside", as expected. This can be gathered from the structures[6] of the diol derivatives **18a** and **20a** and of the epoxide **19c** in the crystal. Moreover, superimposition of the structures **16** and its epoxide **19c** shows that the conformation changes only slightly after the addition and that the arene can



18 (R^2=R^3=OH)
19 (R^2,R^3=-O-)



20 (R^2=R^3=OH)
21 (R^2,R^3=-O-)

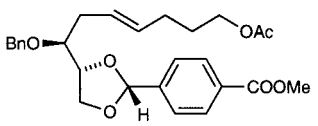
18, 19, 20, 21	R^1	*n*
a	Bn	1
b	Bn	2
c	Me	1

Table 1. Diastereoselectivities for the *syn* addition to the ansa-alkenes **12**–**17**.

Alkene	Diastereoselectivity	
	Epoxidation[a]	Dihydroxylation[b]
13	1.6:1 (**19b**)	1.5:1 (**18b**)
15	2.0:1 (**21b**)	2.1:1 (**20b**)
16	7.1:1 (**19c**)	> 20:1 (**18c**)
12	9.5:1 (**19a**)	> 20:1 (**18a**)
17	> 20:1 (**21c**)	> 12:1 (**20c**)
14	> 20:1 (**21a**)	> 20:1 (**20a**)

[a] *m*CPBA, CH_2Cl_2, 0.5 M NaH_2PO_4/Na_2HPO_4, 0 °C → RT, 3 h. [b] OsO_4, NMO, acetone, H_2O, 0 °C → RT, 12 h. Yields: 76–92%. *m*CPBA = *m*-chloroperbenzoic acid, NMO = *N*-methylmorpholine-*N*-oxide.

indeed function as a workbench. The tolerance of the ansa macrolide ring toward a poor fit is surprisingly low. Thus, one CH_2 unit is already sufficient(compounds **12**/**13** and **14**/**15**) to obtain a conformationally nondetermined structure instead of a determined structure. The fact that the dihydroxylation and the epoxidation of **22**, the acyclic analogue of **12**, show almost



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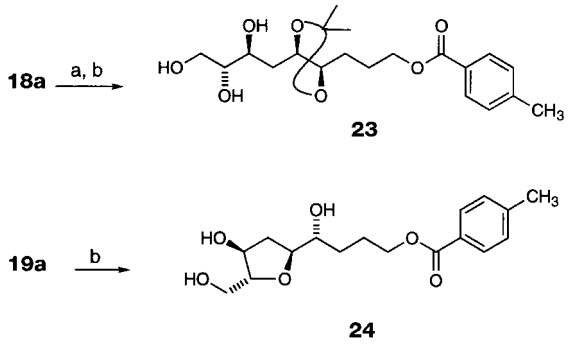
no selectivity clearly indicates that the stereogenic centers of the substrate are unsuitable for acyclic stereocontrol.

Can one dispose of the workbench after the job is done? As exemplified for the dihydroxylation product **18a,** the benzyl acetal can not be hydrolyzed under mild acid catalysis, but is easily cleaved hydrogenolytically (Scheme 3). Thus one



Scheme 3. Cleavage of the "workbench". a) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 94%; b) H_2/Pd/C, EtOAc; **23** 97%, **24** 97%. PPTS = pyridinium-*p*-toluene sulfonate.

obtains the partially protected hexol derivative **23**; the arene remains bonded to one of the primary hydroxy groups as the 4-methyl benzoate protecting group. Epoxides such as **19a** are transformed into tetrahydrofuran derivatives (e.g. **24**) by an S_N2 attack of the hydroxy group liberated after debenzylation. The arene **9** that is incorporated into the macrolide can therefore be understood as a polyfunctional protecting group that amplifies the influence of the substrate's stereogenic centers. As such it thus represents a new type of "stereoactive protective group".[7]

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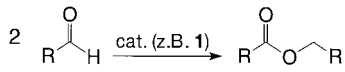
Homoleptic Lanthanide Amides as Homogeneous Catalysts for the Tishchenko Reaction**

Helga Berberich and Peter W. Roesky*

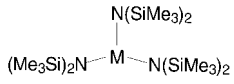
The Tishchenko reaction (or Claisen – Tishchenko reaction), that is, the dimerization of aldehydes to form the corresponding carboxylic ester [Eq. (1)], has been known for about a century.[1] Its industrial importance is mirrored in the



(1)

great number of patents. Thus the Tishchenko ester of 3-cyclohexenecarbaldehyde is the precursor for the formation of epoxy resin, which is durable against environmental influences.[2] Traditionally aluminum alkoxides[2a, 3] have been used as homogeneous catalysts for the catalytic variations of the Tishchenko reaction. More recently other catalysts such as boric acid[4] and a few transition metal complexes[5] are used. However, these alternative catalysts are either only reactive under extreme reaction conditions (e.g. boric acid), difficult to prepare (e.g. $[(C_5Me_5)_2LaCH(SiMe_3)_2]$),[5a] slow (e.g. $[(C_5H_5)_2ZrH_2]$),[5b] expensive (e.g. $[H_2Ru(PPh_3)_2]$),[5c] or give small yields (e.g. $K_2[Fe(CO)_4]$).[5d]

Herein we report that the homoleptic bis(trimethylsilyl) amides of Group 3 metals and lanthanides, $M[N(SiMe_3)_2]_3$[6] **1** (M = Sc, Y, Ln (lanthanide)), are highly active catalysts for the Tishchenko reaction. Compound **1** belongs to a class of materials that has been known for the last 25 years. Recently, in particular, it has proven to be a valuable starting material in lanthanide chemistry through the easy cleavage of the silylamide group.[7] Compound **1** can either be prepared from a simple one-step synthesis or it can be bought (M = Y). Therefore it is even more surprising to find that up till now there is no known use of **1** as a catalyst.



1

To compare the reaction rates of **1** with other catalysts the standard reaction of benzaldehyde to benyzl benzoate was

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