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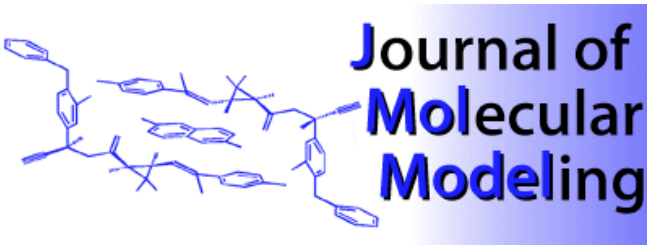

FULL PAPER

The Atropisomer-Selective Ring Cleavage of Helically Distorted, Configuratively Unstable Biaryl Lactones with a Chiral Metallated *N*-Nucleophile - the Complete PM3 Mechanistic Course and its Video Presentation

Part 67 of the series "Novel Concepts in Direct Biaryl Synthesis", for part 66 see ref. [1]

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Abstract The complete mechanistic sequence of the atropo-diastereoselective ring opening reaction of configuratively unstable lactone-bridged biaryls with the chiral 2*R*,5*R*-1-lithio-2,5-dimethylpyrrolidine was calculated using the semiempirical PM3 method. It was shown that the stereochemically deciding key step of the reaction sequence is the first attack of the chiral nucleophile to the carbon atom of the lactone moiety. The diastereoselectivity of this synthetically useful and mechanistically challenging biaryl synthesis was found to originate from a dynamic kinetic resolution of the axially chiral, but configuratively unstable lactone substrates. For a further understanding of the complex stereochemical process, the geometries resulting from IRC-calculations have been visualized and are presented as an Quicktime-movie.

Keywords Biaryls, Stereoselective synthesis, PM3, Lactones, Chiral *N*-nucleophiles, Dynamic kinetic resolution, Video visualization

Introduction

The directed, *i.e.* regio- and stereoselective construction of stereochemically hindered and thus chiral biaryl compounds is of increasing importance to organic synthesis, because of the growing number of known axially chiral bioactive natural products and useful biaryl auxiliaries for synthetic chemistry [1,2]. We have developed a novel procedure for the efficient stereocontrolled synthesis of axially chiral biaryls, in which, for the first time, the formation of the crucial *C,C*-

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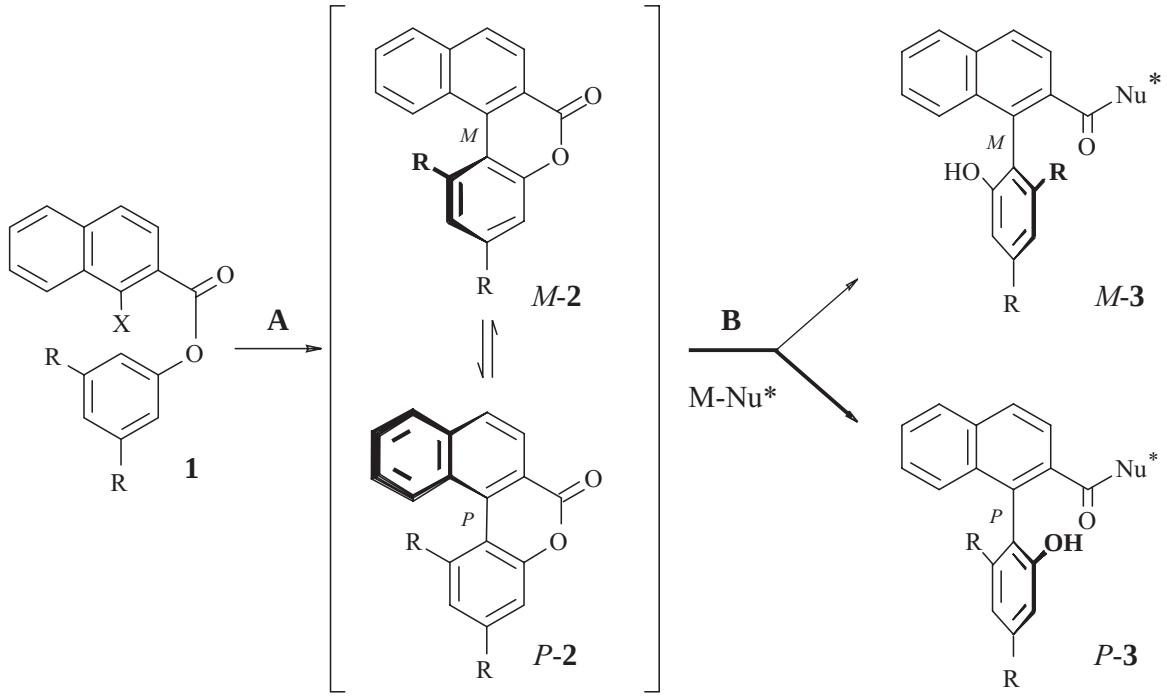


R	H	OMe†	Me	Et	iPr	tBu
1-3	**a**	**b**	**c**	**d**	**e**	**f**

† Note that for formal reasons, the C.I.P descriptors are opposite for **1b - 3b** (R = OMe)

Scheme 1 *The 'lactone method' for the stereoselective synthesis of axially chiral biaryl compounds by separation of the C,C-bond formation (**A**) and the asymmetric induction at the axis (**B**)*

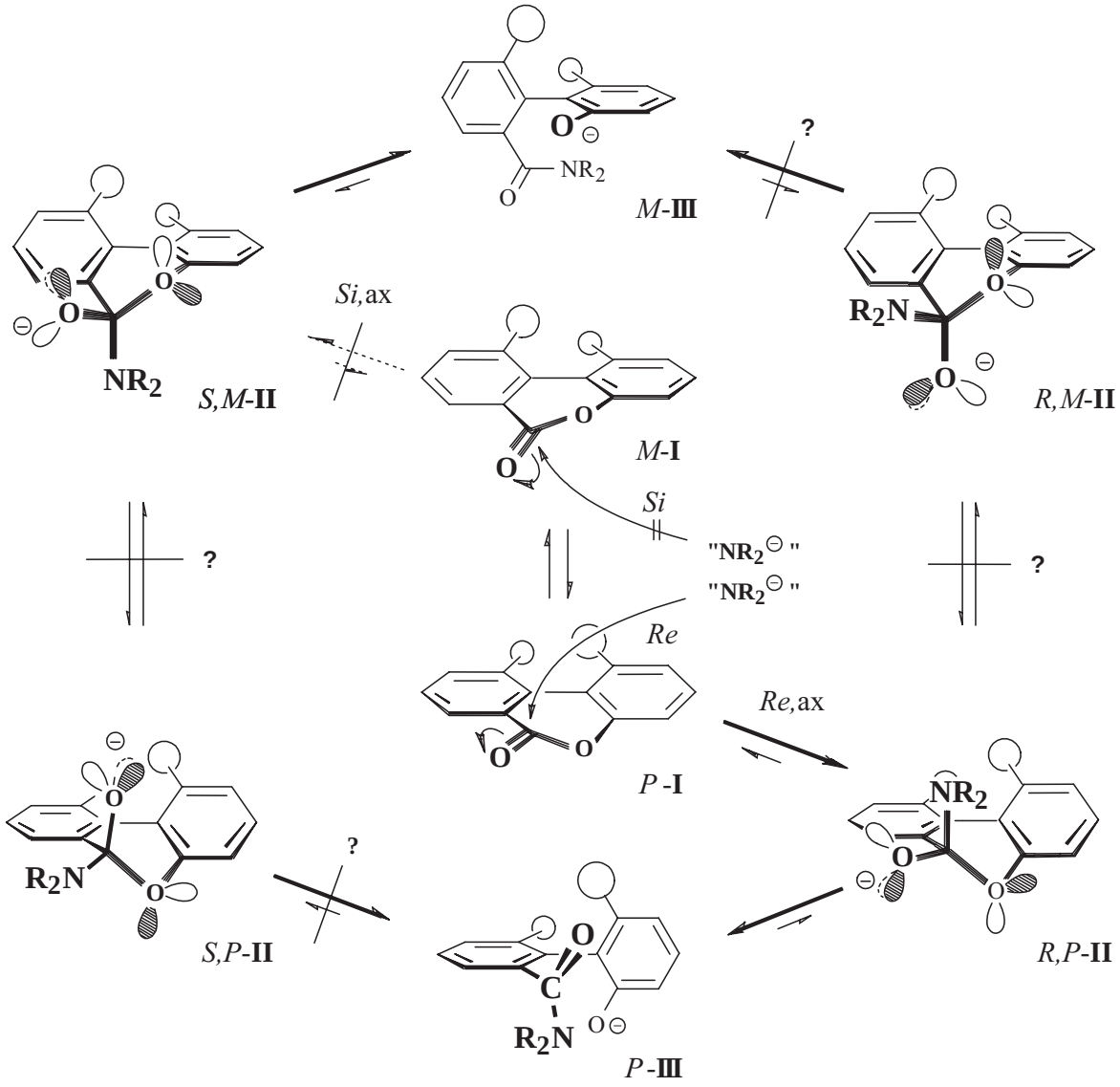
bond, *viz.* the biaryl axis, is separated from the introduction of the asymmetric induction at this axis (Scheme 1). According to this principle, the two coupling partners are first prefixed *via* an ester bridge as in compound **1** and are then coupled intramolecularly to give the stereochemically unstable lactones **2** (Step **A**). Using chiral nucleophiles, the lactone functionality can then be cleaved such that selectively only one of the - now configuratively stable - atropisomeric biaryl products **3** (here: *P*-**3**) is formed in high selectivity [3,4].

This preparatively and conceptually novel separation of the coupling step **A** from the introduction of stereochemical information at the axis, step **B**, thus allows a separate optimization of the two reaction steps. The mechanistically interesting step **B**, apparently an enantiomer-differentiating nucleophilic attack to the carbonyl group, can be attained *e.g.* with chiral metallated *H*-, *O*-, or *N*-nucleophiles [3-7], sometimes leading to very high asymmetric inductions.

For this unprecedented formal 'twisting' of a previously (nearly) flat biaryl axis, we have established a mechanistic working hypothesis, which is outlined in Scheme 2. Accordingly, lactone **I** (as a generalized form of **2**) occurs as a pair of helically twisted, non-planar and thus chiral atropoenantiomers, *P*-**I** and *M*-**I**. Depending on the steric demand of the *ortho*-substituents next to the axis, these helimeric lactones rapidly interconvert ('helimerize') *via* two convex/concave-twisted and thus likewise chiral enantiomeric transition states [8].

This substrate can be attacked either in its *M*- or its *P*-helical form, with the nucleophile coming either from the *Re*- or from the *Si*-side, thus in principle giving rise to four possible stereoisomeric forms of **II**, of which selectively one might originate, *e.g.* only *R*,*P*-**II** - through a selectively axial attack to *P*-**I** from the *Re*-side. The ring strain of these intermediates and the high electronic pressure of both the nitrogen- and the *exo*-oxygen functions on the benzylic carbon atom (or *vice versa* the stereodynamic stability of the reaction products) should lead to a rapid and irreversible 'burst open' of the central heterocycle and thus to a stereocontrolled formation of only one of the two atropisomeric forms of **III** (here *e.g.* only *P*-**III**).

Within this reaction cascade, the role of the intermediates **II** is, however, not yet known. Should they be long-living enough - as previously stated for the primary lactolate reaction products arising from an attack of an *H*-nucleophile [9-11] - then they might undergo an atropisomerization (here *e.g.* to give *R*,*M*-**II**), which, through the again possible ring cleavage (here now likewise giving *M*-**III**), would lead to the formation of both atropisomeric products *P*- and *M*-**III** and would thus give rise to a loss of the initially attained stereoselectivity, in the sense of a postulated [4,5] 'stere-

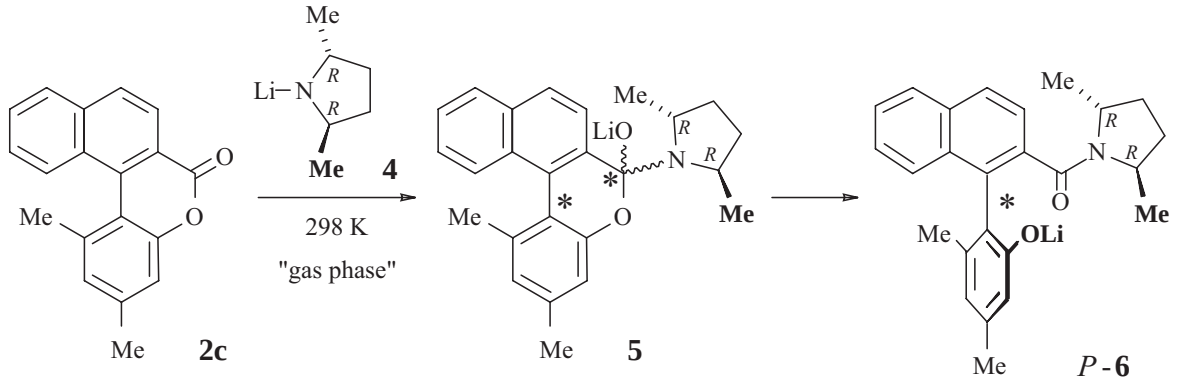


Scheme 2 *Mechanistic working hypothesis for the atropisomer-selective ring cleavage of configuratively labile biaryl lactones **I** to give configuratively stable acid amides **III**. For the CIP denotion, the generalized substituents (marked as o) have arbitrarily been attributed lower priority compared with the concrete ones*

ochemical leakage'. A cyclization reaction of the products **III** (here *e.g.* of *P*-**III**) back to the intermediates **II** (here *e.g.* also to *S,P*-**II**), helimerization at the biaryl axis, and subsequent cleavage to any of the two isomeric forms of **III** would likewise destroy the stereochemical purity once attained - provided sufficiently high reactivity of the carbonyl group of the ring cleavage product *P*-**III**.

For a more profound understanding of this stereochemically challenging and synthetically efficient type of reaction, we have already performed quantum chemical investigations on structures and dynamics of the lactone-bridged substrates **2** [8] and on their ring cleavage using oxazaborolidine-activated borane as an efficient *H*-nucleophile [9,11]. These investigations showed that semiempirical calculations give good results for the description of this class of molecules and reactions. This encouraged us to likewise calculate the complete mechanistic course of the reaction of the lactone **2c** (see Scheme 3) with 2*R*,5*R*-1-lithio-2,5-dimethylpyrrolidine (**4**) as a chiral *N*-nucleophile, using the semiempirical PM3 method.

Our particular interest was due to the identification of the rate- and selectivity-determining step of the reaction as well as the stereochemical behavior of the intermediates **5** (Scheme 3), corresponding to **II** in Scheme 2. The reaction course using *N*-nucleophiles is expected to be straightforward, since compound **6**, the formal reaction product, is an unreactive amide, which would make a reaction back to **5** – and thus a secondary isomerization – improbable. An argument for the



Scheme 3 *The investigated reaction of lactone* ***2c*** *with the chiral nucleophile* ***4***

use of a rigid C_2-symmetric *N*-nucleophile, existing in only one conformation, was that it does not increase the number of competing transition states during the course of the individual reaction steps by its conformational flexibility.

Numerous previous theoretical investigations on the structures of lithium amides [12-15] reveal a strong tendency of such lithium compounds to form oligomers and to coordinate to solvent molecules. The results suggest that the influence of the solvent – the reaction under investigation is carried out in dry THF – and additional nucleophile molecules may be of importance. Due to the complexity of the reaction, however it was required in the present work to treat the nucleophile as a monomer and to neglect any solvent effects. These considerations will be subject to future investigation.

Only little theoretical work has been done on the reactivity of lithium amides - and of *N*-nucleophiles in general. Loew *et al.* [16-18] calculated the reaction of ammonia and glycine with formic acid. These investigations revealed the existence of two distinct mechanistic possibilities for the attack of the amino group, which can take place either in two steps according to an addition/elimination mechanism, *via* a tetrahedral intermediate, or in one step by nucleophilic substitution and direct cleavage of the C-O-bond. The latter possibility was found to be energetically less favorable, espe-

Scheme 4 *The first step of the investigated reaction is an adduct* ***7*** *formation of the lactone* ***2c*** *with the nucleophile* ***4***

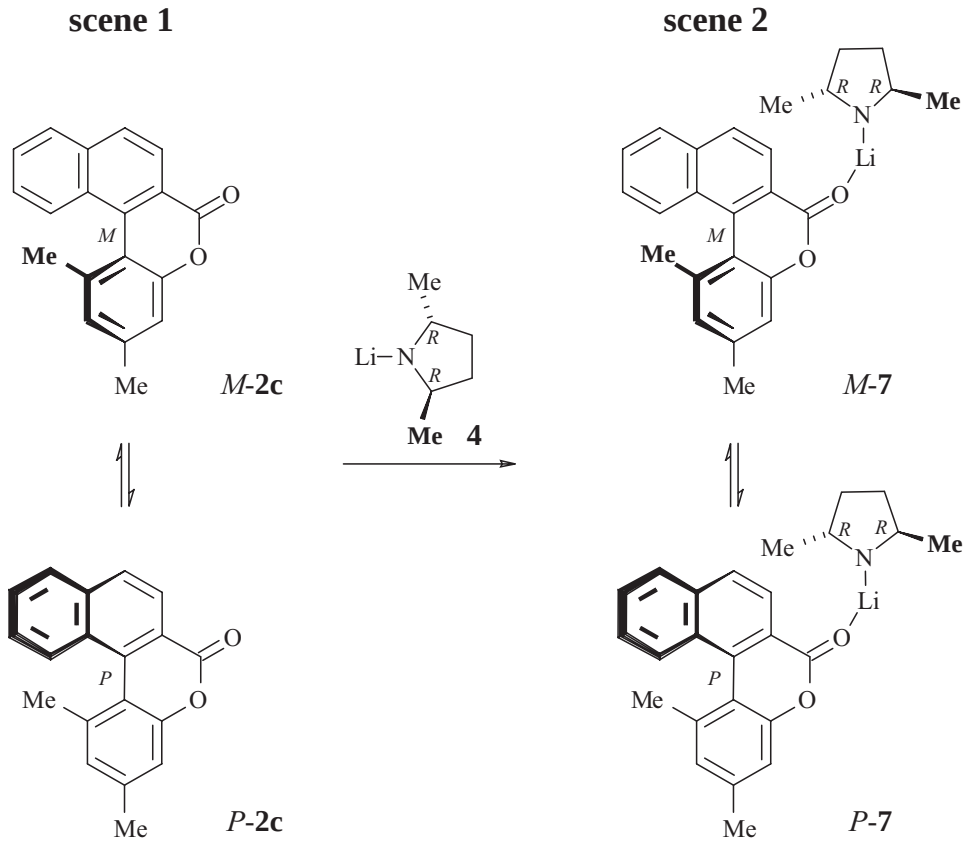


Table 1 *Relative heats of formation ΔH_f [kcal/mol] and relative energies of the involved intermediates [a]*

	adduct **7**[b]	
	M-**7**	P-**7**
ΔH_f^{rel}	-17,2	-17,1
ΔE	≡ 0	0,1
	intermediates **5** [b]	
	R,P-**5**	*R,M*-**5**
ΔH_f^{rel}	-10,9	-9,1
ΔE	0,4	2,2
N-substituent	axial	equatorial
	S,P-**5**	*S,M*-**5**
ΔH_f^{rel}	-8,0	-11,3
ΔE	3,3	° 0
N-substituent	equatorial	axial
	products **6** [b]	
	P-**6**	*M*-**6**
ΔH_f^{rel}	-38,8	-36,0
ΔE	≡ 0	2,7

*[a] all heats of formation are values relative to the sum of the heats of formation of the free lactone **2c** and the free nucleophile **4***
[b] only the conformers lowest in energy are presented

cially when homogeneous catalysis by a second nucleophile molecule was taken into account.

Corresponding results were found by test calculations using lithium amide as the nucleophile [19]. Therefore we assume an addition/elimination mechanism in this work [a].

Computational methods

The calculations were performed on Silicon Graphics INDIGO (R4000) and LinuX workstations. The conformational analyses were carried out with the RANDOMSEARCH method as part of the SYBYL program package [20], using the implemented Tripos force field [21]. Semiempirical PM3 calculations were performed using the molecular orbital package VAMP 5.0 [22]. Minima structures were optimized by the EF algorithm with a gradient norm specification of 0.01 mdyn/Å, whereas transition structures were optimized by the NS01A algorithm [23] and a gradient norm of 0.1 mdyn/Å using the corresponding keywords of the VAMP program package. Starting geometries to optimize the transition structures TS[**7** → **5**] were obtained from the corresponding conformations of **5** applying the GRID technique, by variation of the *C-N*- and the *C-O*$_{endo}$-bonds in steps of 0.1 Å. Starting geometries for the optimization of the transition structures TS[**5** → **6**] were obtained by slightly stretching the *C-O*$_{endo}$-bond. Every stationary point was validated by calculating its normal frequencies. In all cases, the correspondence of transition structures to their local minima was determined by IRC calculations. All heats of formation were calculated relative to the sum of the heats of formation of the free lactone **2c** and the free nucleophile **4** and are corrected by the zero point energy.

Results and discussion

For a better illustration, the energetically favored reaction course as resulting from the calculations, was visualized as MPEG1-movie (see Movie 1), using the IRC geometries as obtained by the PM3 method. The presentation thus corresponds to the series of geometries on the potential hypersurfaces of the heat of formation ΔH_f. In the following, the reaction course is discussed in detail, following the 'movie scenes'. The structures of the calculated intermediates and transition structures are available as PDB files.

Scene 1: Structure and dynamics of the lactone substrate 2c (Scheme 4, left part)

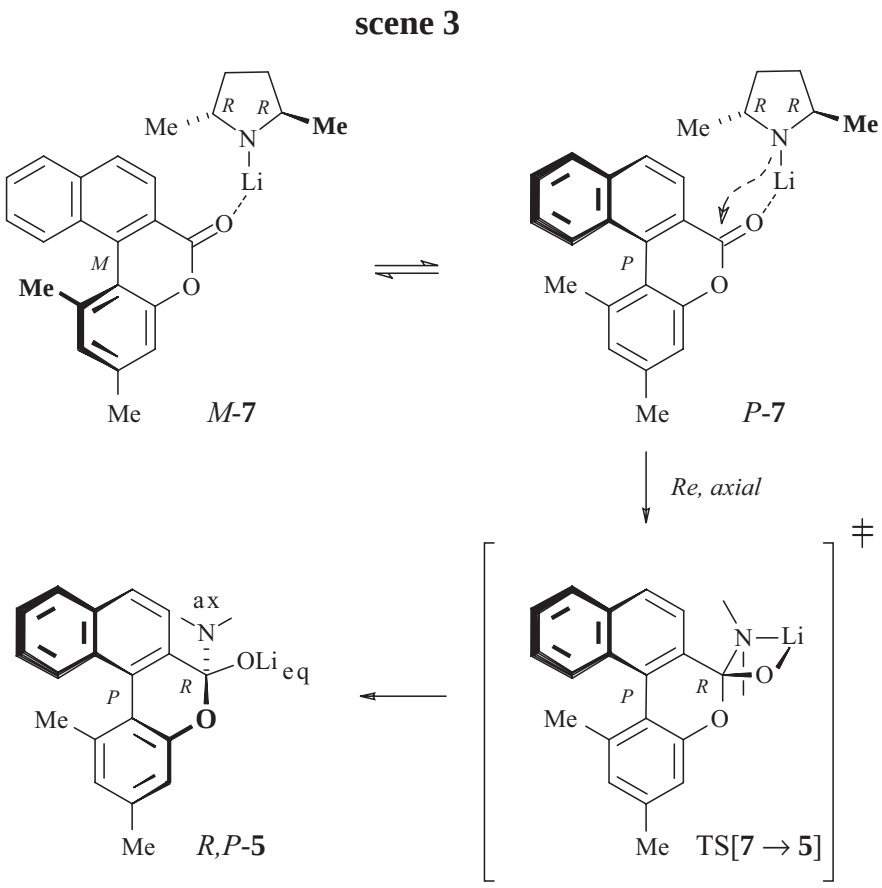
The isomerization process of the two atropisomeric lactone substrates, *P*-**2** and *M*-**2**, has already been intensively investigated using semiempirical and *ab initio* methods, in the past [8]. Accordingly, the activation barrier for the interconversion of *P*-**2c** and *M*-**2c** is 18.3 kcal/mol (PM3). This corresponds to a rapid enantiomerization of the compound *via* two enantiomorphous transition structures, TS[*M*-**2c** ⇋ *P*-**2c**]$_A$ and TS[*M*-**2c** ⇋ *P*-**2c**]$_B$, at room temperature.

Scene 2: Structure and dynamics of the nucleophile-lactone adduct M/P-7

The calculated reaction course begins with the adduct **7**, which is formed/originates from the lactone substrate **2c** and the nucleophile **4** (Scheme 4). In the gas phase the formation of this adduct, which was found at the endpoint of IRC calcula-

[a] Despite extensive attempts, we were not able for the authentic system to localize the transition state for the direct attack. The corresponding potential surface obtained using the GRID approach is very steep in the corresponding area. Therefor the transition state does either not exist at all, or it is of very high energy.

Scheme 5 *The second step of the investigated reaction is the intramolecular attack of the nucleophile on the lactone moiety*



tions starting from the corresponding transition states TS[**7** → **5**], occurs without significant barrier. Although similar adducts have already been reported in the literature [24], the existence of **7** is very likely to be related to the neglect of any solvent effects. Like the lactone substrate itself (Scheme 4, left part), also the adduct **7** undergoes a rapid atropisomerization (Scheme 4, right part).

As a consequence of the Lewis acid character [25,26] of the coordinating nucleophile, the activation barrier of the helimerization was found to be somewhat lower (14.8 kcal/mol, see Table 2) than for the enantiomerization of the free lactone substrate **2c** (18.3 kcal/mol, see above [8]). The two transition structures to be overcome for this now atropodiastereomerization *M*-**7** ⇋ *P*-**7** are consequently no longer enantio- but now diastereomorphous, yet with no major stereodifferentiation, the energetic difference between the two transition structures TS[*M*-**7** ⇋ P-7]$_A$ and TS[*M*-**7** ⇋ *P*-**7**]$_B$ being only 0.1 kcal/mol (see Table 2).

Scene 3: Stereoselective (atropisomer- and diastereofacial-differentiating) intramolecular attack of the nucleophile to the carbonyl group

The now following rate-determining step is the intramolecular attack of the amino function to the carbonyl C-atom of the adduct **7**, with formation of a new stereogenic center. There are four principal possibilities for this *C,N*-bond formation: The attack can occur out of the *M*- or the *P*-helical form, with the nitrogen atom coming from the *Re*- or from the *Si*-side, the stereocombinations *P,Re* and *M,Si* corresponding to an axial attack and the combinations *P,Si* and *M,Re* leading to an equatorial position of the nitrogen in the primary four-memberd adduct transition structures TS[**7** → **5**].

The calculations indicate that this step is rate- and thus selectivity-determining, consequently the overall stereoselectivity is predetermined at this early point. The calculations furthermore reveal that in principle an axial attack should be favored over an equatorial one, by 2-3 kcal/mol (Table 2). Moreover, an attack from the *Re*-side is by 1-3 kcal/mol more favorable than from the *Si*-side. The energetically most favorable reaction is thus the attack to the *P*-isomer from the *Re*-side and consequently leads to a preferential formation of the intermediate *R,P*-**5**, with *P*-configuration at the axis and *R*-configuration at the newly generated stereocenter. The relative heats of formation of the four transition structures TS[**7** → **5**] are mostly determined by the steric interactions between the pyrrolidine residue of the nucleophile and the benzonaphthopyran fragments. The lithium atom diminishes the energetic differentiation somewhat by stabilizing the equatorial transition states. The heats of formation are summarized in Table 2.

A central question was the stereochemical stability of the intermediate bridged biaryl **5** with respect to its axial con-

Table 2 *Relative heats of formation ΔH_f^{rel} [kcal/mol], relative energies ΔE [kcal/mol], imaginary frequencies ν_i [i×cm^{-1}] of all transition structures[a]*

	Transition structures TS[M-**7** ⇋ P-**7**]	
	TS[M-**7** ⇋ P-**7**]$_A$	TS[M-**7** ⇋ P-**7**]$_B$
ΔH_f^{rel}	-2.4	-2.5
ΔE	0.1	≡ 0
$\Delta H^{\ddagger}$	14.8 [b]	14.9 [b]
ν_i	75.0	74.4

	Transition structures TS[**7** → **5**]			
	P→R.P	*P→S.P*	*M→S.M*	*M→R.M*
Attack	*Re*	*Si*	*Si*	*Re*
	axial	*equatorial*	*axial*	*equatorial*
ΔH_f^{rel}	5.4	8.5	6.8	7.8
ΔE	≡ 0	3.1	1.4	2.4
$\Delta H^{\ddagger}$	22.5	25.6	24.9	23.9
ν_i	302.6	304.6	300.4	311.0

	Transition structures TS[M-**5** ⇋ P-**5**]			
	[R.M ⇋ R.P]$_A$	[R.M ⇋ R.P]$_B$	[S.M ⇋ S.P]$_A$	[S.M ⇋ S.P]$_B$
ΔH_f^{rel}	4.9	8.2	9.4	5.7
ΔE	≡ 0	3.3	4.5	0.8
$\Delta H^{\ddagger}$	14.0 [c]	17.3 [c]	20.7 [d]	17.0 [d]
ν_i	61.6	89.6	100.9	61.9

	Transition structures TS[**5** → **6**]			
	R.P→P	*S.M→M*	*S.P→P*	*R.M→M*
ΔH_f^{rel}	-9.3	-11.7	-4.3	-0.9
ΔE	2.4	º 0	7.4	10.8
$\Delta H^{\ddagger}$	1.6	-0.47	3.7	8.2
ν_i	296.2	130.5	250.6	251.8

*[a] all heats of formation are values relative to the sum of the heats of formation of the free lactone **2c** and the free nucleophile **4***

*[b] relative to M-**7***
*[c] relative to R,M-**5***
*[d] relative to S,M-**5***

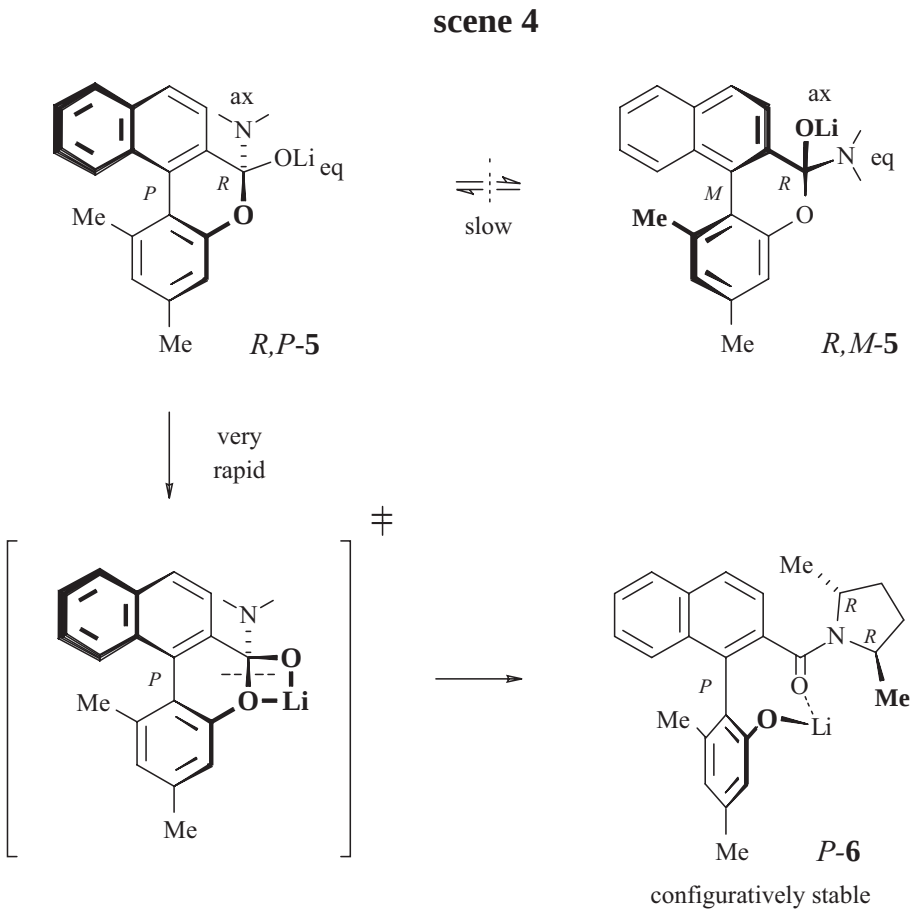
figuration (Scheme 5), *i.e.* the calculation of the atropisomerization barrier of this species and a comparison with the competing (desired) ring opening reaction (Table 2). If the activation enthalpy for this isomerization (or for the reaction back to the starting materials) was lower than for the ring cleavage to give the desired final product amide, this would possibly lead to a loss of the stereoselectivity attained in the first reaction step (the 'stereochemical leakage').

Scene 4: The cleavage of 5 - rapid enough to avoid a stereochemical loss by atropisomerization and thus to conserve the asymmetric induction

The ring cleavage of the central heterocycle, with destruction of the previously constructed transient stereocenter and simultaneous ultimate fixation of the stereoinformation at the biaryl axis, is the last step of the overall reaction (Scheme 6).

Investigations gave very low activation enthalpies for this important last reaction step for all of the four imaginable stereoisomeric forms of the intermediate **5**. Thus, the activa-

Scheme 6 *The last step of the reaction is the opening of the central pyranone ring under conservation of the stereochemical information at the axis.*



tion enthalpy for *S,M*-TS[**5** → **6**], taken into account the zero point vibrational energy, is -0.47 kcal/mol (Table 2). For stereoelectronic reasons, this ring cleavage is distinctly assisted by the lone electron pair on the nitrogen atom: if that electron pair cannot adopt the required antiperiplanar position as in *R,M*-TS[**5** → **6**], the activation enthalpy for the ring cleavage is increased up to 11.1 kcal/mol.

This spontaneous 'burst open' process of the stereochemically important central auxiliary bridge is distinctly more rapid than any other imaginable competing reaction. Thus, the activation enthalpy for the reaction back to *T*-**7** is 14.7 kcal/mol and for the isomerization at the axis of **5** (*i.e. R,P*-**5** ⇋ *R,M*-**5**) is by 14.2 kcal/mol higher than the activation barrier for the cleavage of the *C,O*$_{endo}$-bond. In contrast to the corresponding intermediate in the atropisomer-selective ring cleavage of lactones by chiral *H*-nucleophiles [9], a 'stereochemical leakage' by a possible atropisomerization of the intermediate **5** can thus be excluded for the reaction investigated here.

The geometry of the transition structures TS[**5** → **6**] distinctly depends on the coordination of the lithium cation, a two-fold coordination of lithium to the *exo*- and to the *endo*-oxygen atom being most favorable. The cleavage of the endocyclic *C,O*-bond is, in addition, accelerated by the fact that the lone electron pair on the nitrogen can be positioned antiperiplanar to the endocyclic *C,O*-bond, for the *R,P*-**5** isomer initially formed. The resulting $n \rightarrow \pi^*$ interaction thus leads to a destabilization on the *C,O*$_{endo}$-bond, already for the corresponding conformer of **5**.

Based on the activation enthalpies obtained, the expected stereoselectivity can be calculated using the Boltzmann statistic, with neglect of the activation entropy. Thus, a ratio of the two product atropisomers of

$$\frac{M-\mathbf{6}}{P-\mathbf{6}} = \frac{e^{-\Delta H\left(TS[M-\mathbf{7}\rightarrow R,M-\mathbf{5}]\right)/RT} + e^{-\Delta H\left(TS[M-\mathbf{7}\rightarrow S,M-\mathbf{5}]\right)/RT}}{e^{-\Delta H\left(TS[P-\mathbf{7}\rightarrow R,P-\mathbf{5}]\right)/RT} + e^{-\Delta H\left(TS[P-\mathbf{7}\rightarrow S,P-\mathbf{5}]\right)/RT}}$$

can be calculated, here leading to a predicted diastereoselectivity of 92% in favor of *P*-**6** at 273 K.

Summary

The stereochemically complex mechanistic course of the atropselective ring opening reaction of the axially prostereogenic biaryl lactone **2c** with the chiral *N*-nucleophile **4** was calculated using the semiempirical PM3 method. It was found that the overall reaction is a very exothermic and straightforward process. The relative stabilities of the transition structures TS[**7** → **5**] and thus the stereoselectivity of

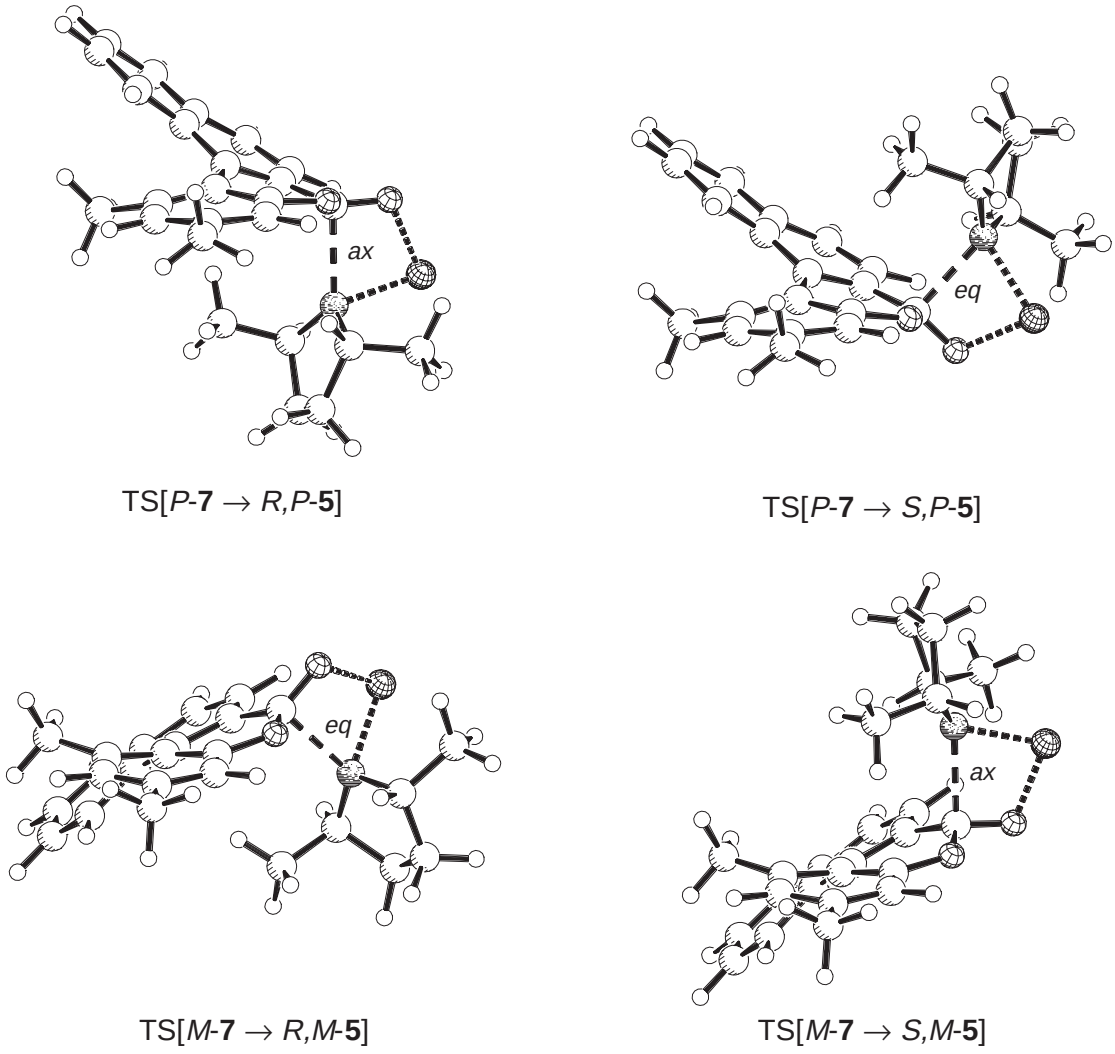


Figure 1 *Geometries (PM3) of the transition structures TS[7 → 5]*

the intramolecular attack were determined by steric interactions between the benzonaphthopyran ring system and the pyrrolidine residue on the one hand, and by the extent of the coordination of the lithium atom on the other. This step is followed by a fast and irreversible ring opening reaction of the intermediates **5** with very low activation energies. As a consequence of the fast ring opening reaction, the overall stereoselectivity is influenced by the first reaction step, exclusively. Despite the as yet required neglect of dimer or oligomer formation of lithiated species and of solvent effects, the calculations do give valuable insight in the mechanistic details and the nature of stereocontrol of this remarkable type of reaction.

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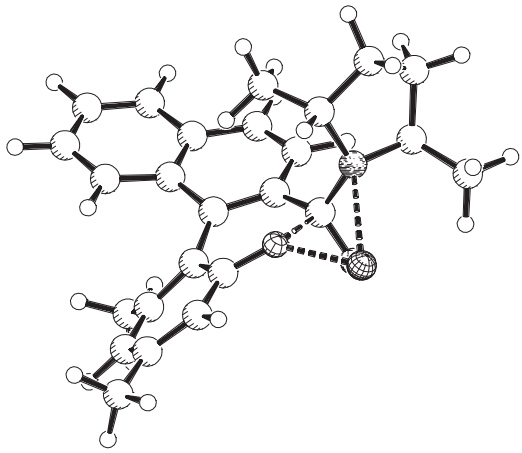
Supplementary material available statement For a better illustration, the energetically favored reaction course as resulting from the calculations, was visualized as MPEG1-movie (see Movie 1), using the IRC geometries as obtained by the PM3 method. The structures of the calculated intermediates and transition structures are available as PDB files as listed below.

Intermediates:

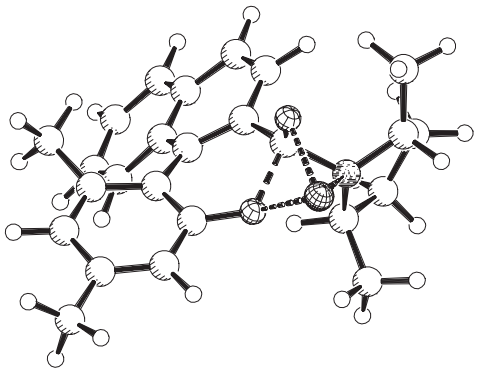
0165s01.pdb	M-7;	0165s02.pdb	P-7;
0165s03.pdb	R,P-5;	0165s04.pdb	S,P-5;
0165s05.pdb	R,M-5;	0165s06.pdb	S,M-5;
0165s07.pdb	P-6;	0165s08.pdb	M-6

Transition states:

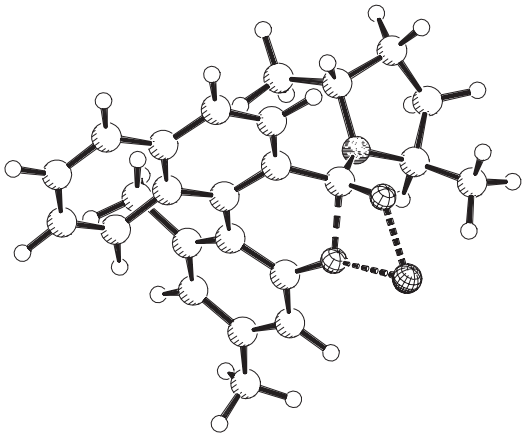
0165s09.pdb	R,M-5 → M-6;	0165s10.pdb	S,M-5 → M-6;
0165s11.pdb	R,P-5 → P-6;	0165s12.pdb	S,P-5 → P-6;



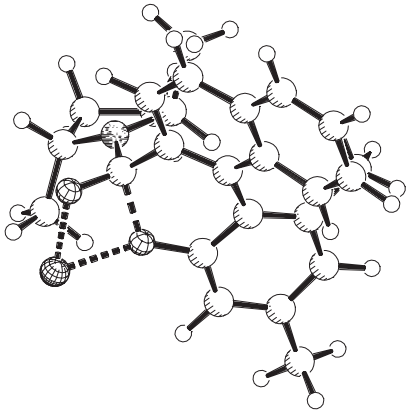
TS[*S,P*-**5** → *P*-**6**]



TS[*R,M*-**5** → *M*-**6**]



TS[*R,P*-**5** → *P*-**6**]



TS[*S,M*-**5** → *M*-**6**]

Figure 2 *Geometries (PM3) of the transition structures TS[**5** → **6**]*

0165s13.pdb M-7 → R,M-5; 0165s14.pdb P-7 → R,P-5;
0165s15.pdb M-7 → S,M-5; 0165s16.pdb P-7 → S,P-5;
0165s17.pdb R,P-5 ↔ R,M-5;
0165s18.pdb S,P-5 ↔ S,M-5; 0165s19.pdb P-7 ↔ M-7

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