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The directed synthesis of axially chiral ligands, reagents, catalysts, and natural products through the 'lactone methodology'☆

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Dedicated to Professor Dr. Peter Welzel on the occasion of his 65th birthday

Abstract

Axially chiral biaryls have become increasingly important during the past years—as structurally, biosynthetically, and pharmacologically remarkable natural products, but also as useful tools in asymmetric synthesis: as chiral reagents, ligands, and catalysts. Nevertheless, only few generally applicable synthetic protocols for the atropo-enantio- or -diastereoselective construction of biaryl bonds have been developed. The 'lactone methodology' as described in detail in the preceeding article, provides directed, atropo-divergent access to any of the two respective atropisomers starting from the identical immediate precursor, a (usually) configurationally unstable, since lactone-bridged biaryl. In this article the efficiency of the 'lactone method' in the total synthesis of natural products and in the preparation of axially chiral ligands is demonstrated for selected examples.

Keywords: Biaryl axis; Asymmetric synthesis; Natural products; Biaryl ligands; Axial chirality; Enantioselective catalysis

1. Introduction

Among the few established methods for the atropo-selective construction of biaryl systems [1–3], the 'lactone concept' as developed in the authors' laboratories holds a unique position since it separates the biaryl bond formation step from the actual introduction of stereo-information. The fundamental concept has initially been elaborated on easily available model systems, shown in Scheme 1. A bromoarene carboxylic acid **1** and a phenol **2** are attached to each other by forming an ester **3**. This array permits the biaryl coupling to occur intramolecularly and in high yields, even against strong steric hindrance, leading to lactones of type **4**, which are, as a rule, configurationally *unstable*. These biaryl lactones are the key intermediates of this concept since they can be ring-opened with chiral nucleophiles according to the principle of a *dynamic* kinetic resolution to yield—now configurationally stable—biaryls **5** in excellent yields and atropisomeric ratios.

The quality, practicability, and thus usefulness of a new method, however, can only be shown in its application to the synthesis of even complex molecules with a great variety of additional functional groups, with different electronic and steric effects. Therefore, this article focuses on recent achievements in atroposelective syntheses of biarylic natural products and ligands for asymmetric catalysis by using the lactone methodology. In order for the reader to easily recognize the biaryl

☆ Novel Concepts in Directed Biaryl Synthesis, part 102. Part 101, see Ref. [2].

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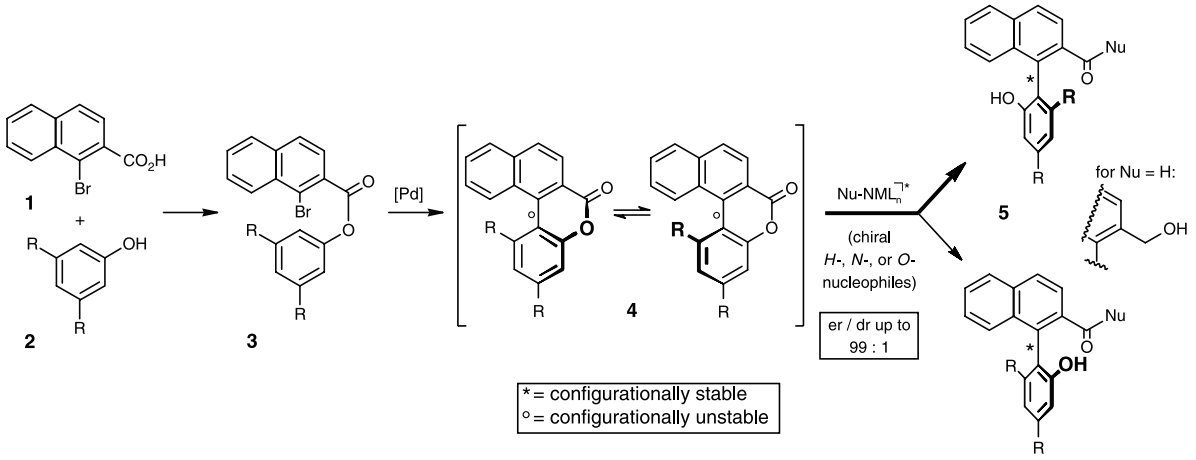


Scheme 1. The lactone concept.

lactone unit and the regularities in their ring openings, all synthetic intermediates have been drawn in a way that this structural feature is oriented like in the model lactones **4**.

2. Atroposelective synthesis of natural products

Over the past years, the outstanding efficiency of the lactone concept has already been proven in more than 25 applications of the method, just to count those in the field of natural product syntheses [3–5]. In the beginning, most of the target molecules prepared belonged to the group of naphthylisoquinoline alkaloids, an intriguing class of structurally, biosynthetically, and pharmacologically remarkable natural products, which constitute a major synthetic challenge i.a. because of their variety in coupling patterns [3,4]. More recent work has focused on the applicability of the lactone method to the preparation of natural products of a broader structural diversity, leading to good or even excellent results in the areas of sesquiterpenoid biphenyls like mastigophorene A [(*P*)-**6**] (Fig. 1), of bicoumarins [e.g. isokotanin A (**7**)], biarylic biscarbazoles like bismurrayaquinone-A (**8**), and cross-coupled phenylanthraquinones such as knipholone (**9**). Furthermore, the application of the lactone method has been extended to the total synthesis of natural products that are devoid of oxygen- or (at least 'free') C_1-substituents next to the biaryl axis—groups that previously seemed essential for constructing the ester bridge between the two aromatic portions (cf. Scheme 1)—like in dioncophylline C (**10**) [6] and korupensamine B [(*M*)-**11**].

In this paper, only the two decisive steps of this concept are dealt with in detail, viz the intramolecular biaryl coupling and the subsequent atropo-enantio- or -diastereoselective lactone opening. Further details of relevance to the other steps of these total syntheses (like e.g. the preparation of the aromatic molecular portions) can be taken from the original literature cited and from other summarizing articles [3–5].

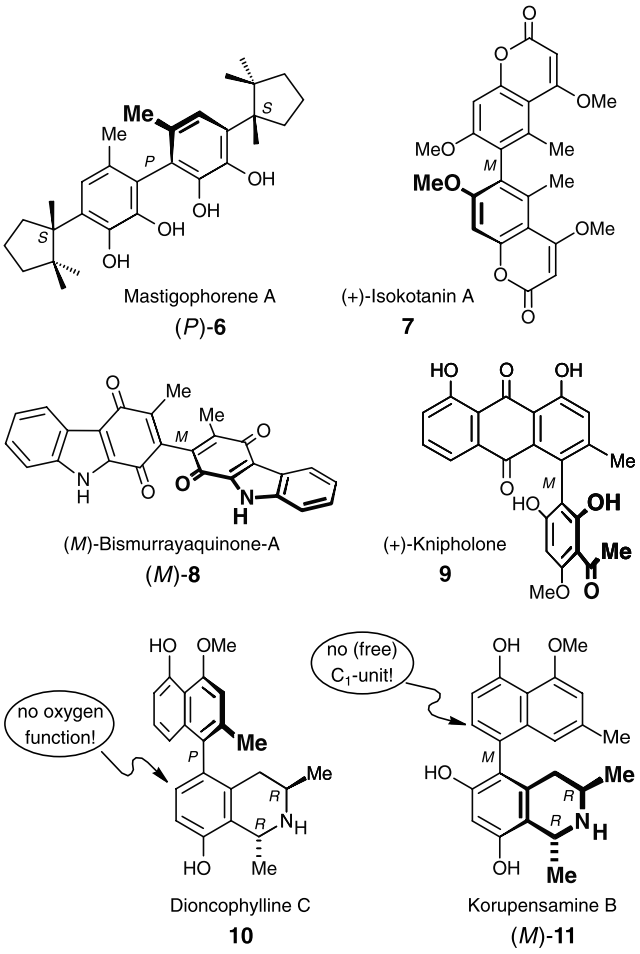
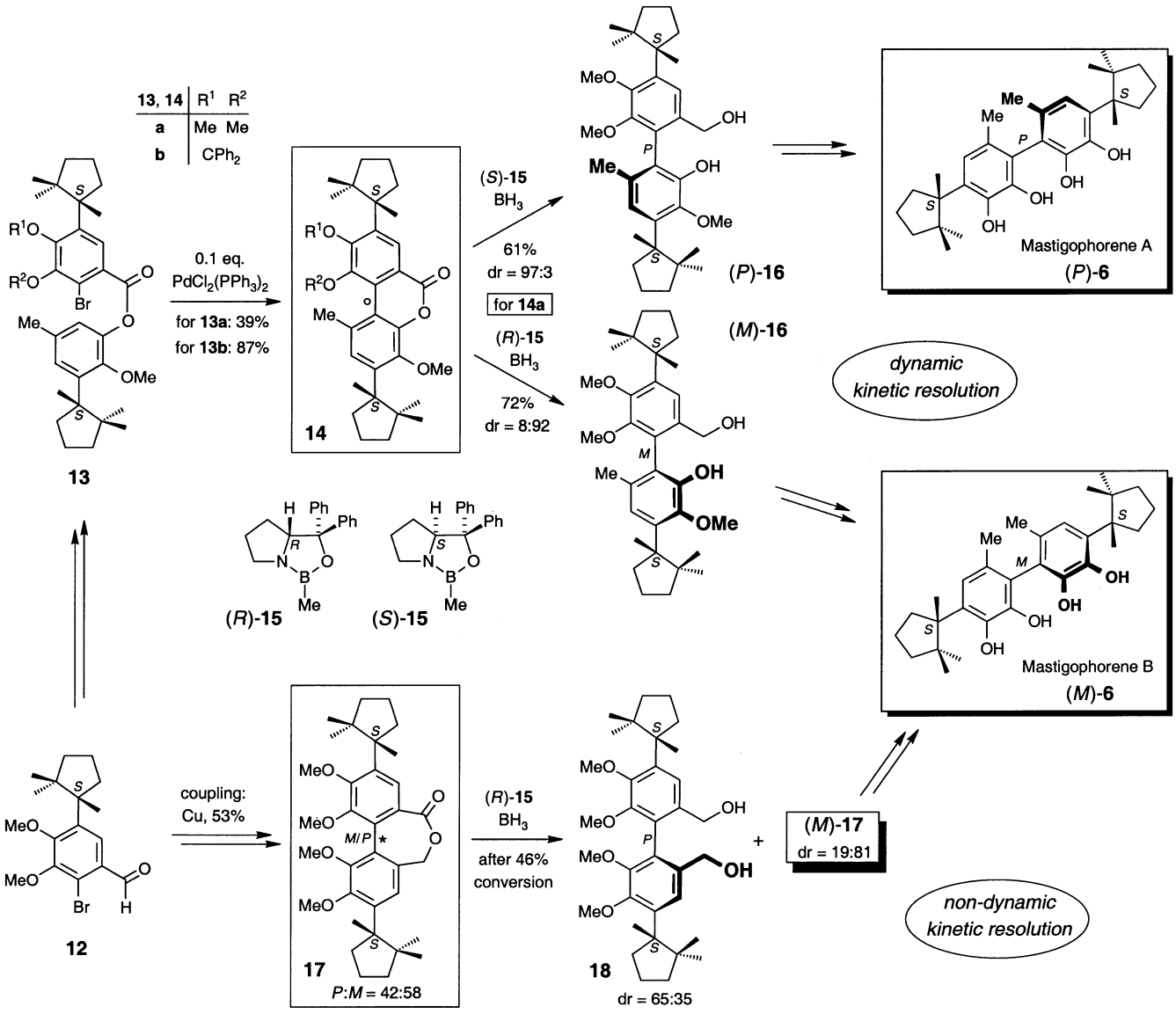


Fig. 1. Selected biarylic natural products prepared by the lactone method.



Scheme 2. Syntheses of the mastigophorenes **6** involving six- and seven-membered biaryl lactones.

2.1. Mastigophorenes A and B: atroposelective syntheses following two different strategies

The preparation of the nerve-growth stimulating [7] dimeric sesquiterpenes mastigophorenes A [(*P*)-**6**] and B [(*M*)-**6**] (Scheme 2) represents an instructive example to compare the advantages and disadvantages of two different variants of the lactone concept, one including a dynamic kinetic resolution of the configurationally unsuitable six-membered lactone **14** [8] similar to those of type **4** shown in Scheme 1, while the second one uses related, but configurationally *stable* seven-membered lactones **17**. These owe their stereochemical stability to an additional CH_2-unit in the bridge, thus necessitating to perform the ring cleavage reaction according to the principle of a 'normal', i.e. *non*-dynamic kinetic resolution.

To start with the synthesis via six-membered biaryl lactone **14**, a certain disadvantage of this strategy is that, even in the case of constitutionally symmetric target molecules like **6**, two different aromatic units are required for the construction of the coupling precursor **13**, viz a bromobenzoic acid and a phenol, thus in some cases leading to additional synthetic steps to achieve this divergence prior to the coupling step—and to ultimately return to a symmetric biaryl. This makes understandable that the lactone methodology via six-membered lactones is particularly useful for the synthesis of constitutionally *unsymmetric* target molecules. Even though the ester linkage in precursors like **13** generally permits high coupling yields due to its intramolecular fashion [2,3], the catalytic (0.1 equivalent) Pd-mediated 'redox-neutral' coupling of **13a** afforded lactone **14a** in only moderate 39% yield after 1.5 h, along with 41% of

recovered starting material **13a** [8]. Longer reaction times resulted in decomposition both of **13a** and the product. Apparently, in this case the electron-rich character of the benzoic acid moiety slows down the steps following the oxidative addition of Pd(0) to the aryl bromide in the catalytic cycle so that side reactions like the formation of palladacycles [8,9] through C–H activation in the adjacent methoxy group can compete with the biaryl bond formation, as evidenced by control experiments. Based on these considerations, a significant improvement of the coupling yield was achieved with an *O*-protective group devoid of such critical α-protons, so that, by using a diphenylmethylene acetal group as in **13b**, the respective lactone **14b** was obtained in an excellent 87% coupling yield. The atropo-diastereoselective ring cleavage of **14a** succeeded with borane activated by oxazaborolidine (*S*)-**15** to give the primary alcohol (*P*)-**16**—or by (*R*)-**15** to give (*M*)-**16**. Apparently, the long reaction time of 4 days at 0 °C was again a consequence of the electron-rich nature of the benzoic acid unit, decreasing the activity of the ester carbonyl towards a nucleophilic attack. The dynamic kinetic resolution permitted good yields (61 and 72%) and excellent to good atropisomeric ratios of 97:3 and 8:92, respectively. From (*P*)-**16** and (*M*)-**16**, the ultimate target molecules, mastigophorenes A and B were attained in a few further standard steps [8].

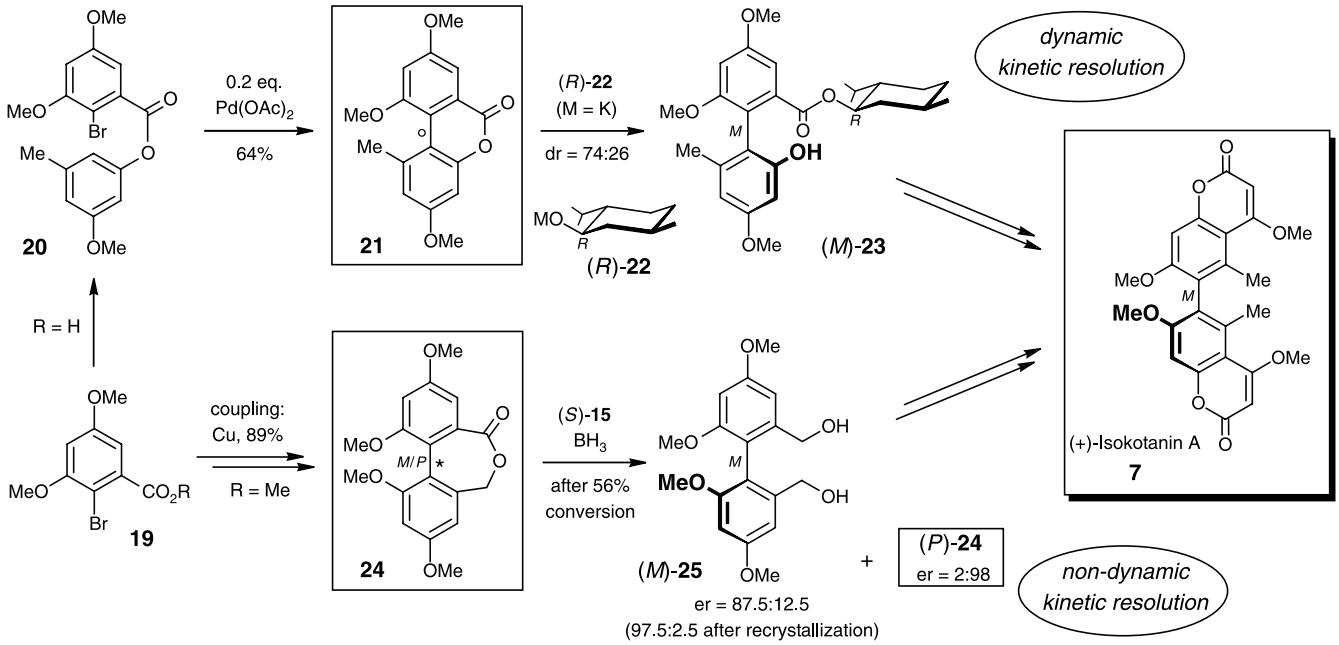
Within the variant of the method via seven-membered biaryl lactones, the biaryl bond is generally formed in an Ullmann-type coupling of identical aryl halides, thus permitting an easy construction of symmetric biaryls like the mastigophorenes from only one 'monomeric' unit. In the case of **6**, this was achieved by using copper bronze in DMF for aryl bromide **12** to give the corresponding biaryl, which was converted to the configurationally stable biaryl lactone **17** by a Cannizzaro reaction and intramolecular esterification (Scheme 2) [10]. This strategy, however, bears the disadvantage that—as a consequence of the configurational stability of the seven-membered lactone **17**—its kinetic resolution can only be a non-dynamic one. Thus, by principle ca. 50% of the starting material (viz the portion with the 'wrong' axial configuration) will be lost in the reductive ring cleavage step, here of **17** using e.g. (*R*)-oxazaborolidine-activated borane (*R*)-**15**·BH_3—unless the material with the undesired configuration is recycled by subsequent racemization through thermal equilibration, which can indeed be achieved. Since the relative rate constant (k_{rel}) for this reaction was only moderate even at −20 °C, it proved better to use the remaining unreacted lactone (*M*)-**17** than the corresponding ring opened product, here (*P*)-**18** [10]. After 46% conversion, the diastereomerically enriched unreacted lactone **17** (dr = 81:19) was reduced with $LiAlH_4$ to give (*M*)-**18**, which was further converted into mastigophorene B [(*M*)-**6**].

The two different strategies for the preparation of constitutionally symmetric biaryls like mastigophorenes A or B, either via configurationally unsuitable six-membered or configurationally suitable seven-membered lactones, permit the flexibility of deciding which of the alternatives is the individually better one for the particular target molecule.

2.2. Isokotanin A: again by dynamic and by non-dynamic kinetic resolution strategies

Based on the same two concepts, the biaryl portion of isokotanin A (**7**) was prepared both via six- and seven-membered biaryl lactones (Scheme 3) [11,12]. The 'redox-neutral' coupling of ester **20** with 0.2 equivalent $Pd(OAc)_2$ as the catalyst provided the configurationally unstable lactone **21** (here along with a minor regioisomer, with the coupling site between the two oxygen functions of the 'lower' ring). In this case, the atropisomer-selective ring cleavage reaction was achieved by using an *O*-nucleophile, e.g. with potassium (1*R*)-mentholate [K-(*R*)-**22**], resulting in a dr of 74:26 in favor of (*M*)-**23** [11]. It should be stated that this early work reflects the state of the methodology before we have started opening lactones with chiral *H*-nucleophiles such as the CBS-system [13,14]. It which would be rewarding to use this reagent combination now to render the ring cleavage of **21** certainly much more efficient and selective than previously.

In this particular case, again given the constitutionally symmetric structure of the ultimate target molecule, isokotanin A (**7**), an approach via seven-membered biaryl lactones like **24** appeared to be more efficient than via six-membered ones since here an additional advantage to that mentioned for the synthesis of the mastigophorenes occurred: not only did the preparation of the lactone **24** require just one aromatic substrate for the Ullmann coupling, viz bromo ester **19** (R = Me), but it also circumvented the regioselectivity problem arising in the Pd-mediated coupling of diaryl ester **20**. The reductive coupling of bromo ester **19** (R = Me) with copper bronze in DMF afforded the corresponding biaryl in 89% yield, which was transformed into the configurationally stable biaryl lactone **24** by standard steps [12]. The non-dynamic kinetic resolution of this intermediate, again achieved by using (*S*)-oxazaborolidine-activated borane (*S*)-**15**·BH_3 (here at −20 °C for 2 h), proceeded with $k_{rel} = 43$ at an analytical level and $k_{rel} = 27$ on a preparative scale. After 56% conversion, 46% of the ring opened diol (*M*)-**25** were obtained with an enantiomeric ratio of 87.5:12.5 (further enriched to 97.5:2.5 by a single crystallization step) in favor of the (*M*)-product, along with 43% of almost enantiomerically pure lactone (*P*)-**24**, which can be re-used after thermal racemization. Diol (*M*)-**25** was taken as the starting material for the completion of the synthesis of

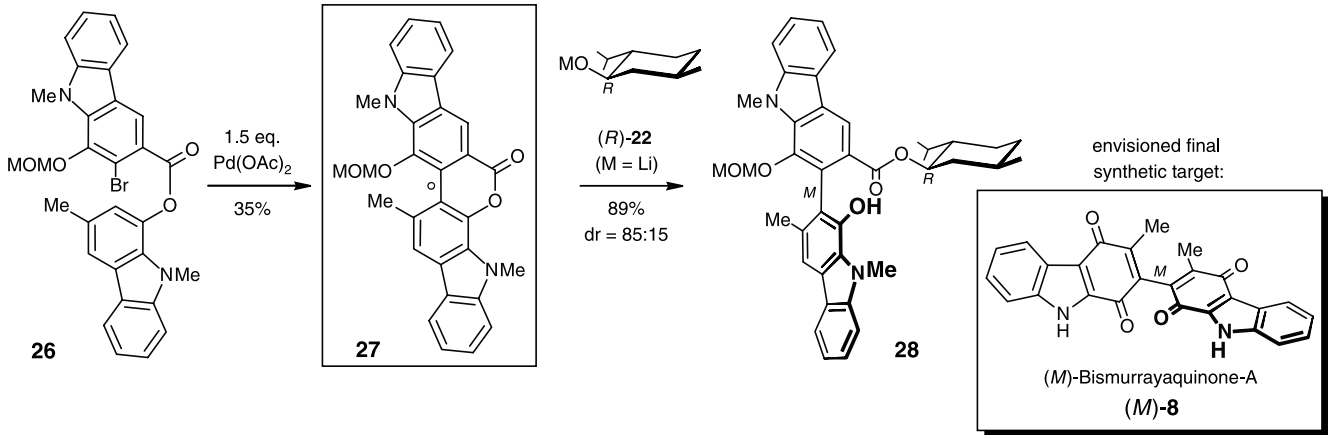


Scheme 3. Two atroposelective pathways to isokotanin A (**7**).

isokotanin A (**7**) according to a literature protocol [12,15].

2.3. Axially chiral biscarbazole alkaloids: first atroposelective construction of the biaryl axis

Completely different challenges occurred during the first atroposelective synthesis of a biscarbazolic skeleton *en route* to bismurraquinone-A (**8**), a representative of an intriguing class of (mostly) axially chiral compounds stereochemically neglected for a long time [16,17]. While the high electron density throughout the carbazole nuclei makes these substrates ideal for phenolic or non-phenolic oxidative coupling reactions [17–20], it renders reductive and redox-neutral approaches extremely difficult. For a first atroposelective approach to 2,2′-coupled biscarbazoles, however, *non*-oxidative coupling protocols had to be envisaged since a non-phenolic oxidative coupling led to unsymmetric *C*,*N*-bonded biscarbazoles [17,18], and the phenol oxidative variant was only successful with carbazoles possessing an intact, non-functionalized 3-methyl substituent [19,20], which—once the dimer had been formed—could not be transformed into a biaryl lactone (six- or seven-membered). Ullmann-type reductive couplings of appropriately substituted carbazole monomers yielded 2,2′-biaryls in yields of at most 28% [21]. Given the fact that furthermore 50% of the starting material would be 'wasted' during a non-dynamic kinetic resolution of seven-membered biaryl lactones (unless subsequently recycled by thermal racemization, which can indeed be done, see below), these coupling yields did not seem sufficiently good for further pursuing this concept. For the first realization of an atroposelective synthesis, hence via six-membered lactones, biscarbazole ester **26** (Scheme 4) was prepared [16]. A protection of the carbazolic nitrogens already at an early stage proved to be decisive, so that for a first exploratory development of this synthetic approach the small and robust methyl group was chosen, even though its cleavage at the end was expected to be difficult. Apparently due to the electronic nature of the carbazole nucleus, the intramolecular coupling of lactone precursor **26**, however, could not be achieved catalytically in this case. The best results were obtained with 1.5 equivalents $Pd(OAc)_2$: after 1.5 h, 35% of biscarbazole lactone **27** were isolated, along with up to 30% of the corresponding hydro-dehalogenated material. Longer reaction times only led to decomposition of product already formed. Despite the extremely electron rich nature of both of the carbazolic units as a consequence of the endocyclic nitrogen atoms, the oxidative addition of Pd(0) to the aryl bromide does not seem to be a major problem since all of the starting material was already consumed after 1.5 h—but only 65% of it were converted into the biaryl and hydro-dehalogenation products. Besides such a quenching of an aryl-Pd species by a proton, again an interaction with the adjacent OCH_2-portion of the MOM group, to form a pallada cycle as discussed above for the synthesis of mastigophorenes [8,9], could probably account for the loss of 35% of the starting material **26**. For the atropisomer-selective ring opening of **27**, the otherwise very effective oxazaborolidine/borane system [3–5] did not succeed in cleaving the lactone function to a substantial degree, apparently due to the endocyclic nitrogen, which turns



Scheme 4. First stereoselective synthesis of a biarylic biscarbazole.

the ester group into a phenylogous carbamate and thus diminishes the carbonyl reactivity. The problem was overcome by using the usually less efficiently atropoenantiomer differentiating [3]—but more reactive—*O*-nucleophile lithium (1*R*)-mentholate [Li-(1*R*)-**22**], leading to (*M*)-biscarbazole **28** in a good 89% yield and with a now most satisfying dr of 85:15.

Against the mentioned difficulties, which result from the electronic nature of these particular substrates, the lactone method proved to be capable of achieving the first stereoselective biscarbazole synthesis. The strategy is now planned to be applied to the preparation of bismurrayaquinone-A (**8**), by using appropriate *N*-protective groups that are eventually easy to remove.

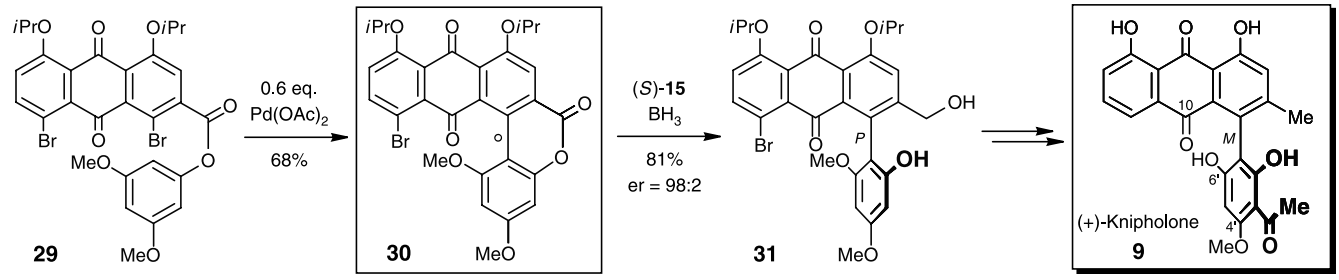
2.4. Preparation of knipholone

The first total synthesis of knipholone (**9**), an antimalarial [22], axially chiral phenylanthraquinone first isolated from the torch lily, *Kniphofia foliosa* [23], was immediately an atroposelective one, by application of the lactone concept [24]. Following this method, good to excellent yields were obtained for the decisive steps, the biaryl bond formation and the enantioselective lactone cleavage, despite strong steric hindrance (an anthraquinone-oxygen in the *peri*-position next to the coupling site) and functional groups previously not present (such as a quinone structure), again emphasizing the outstanding capabilities of the lactone methodology. Like in the synthesis of biscarbazoles (vide supra), an effective coupling of the bromo ester **29** required larger quantities of palladium, viz 0.6 equivalent $Pd(OAc)_2$, giving an isolated yield of 68% of lactone **30** after 4.5 h reaction time (Scheme 5) [24]. The atroposelective ring opening of this lactone with (*S*)-oxazaborolidine-activated borane, (*S*)-**15**·BH_3, at 0 °C left the anthraquinone carbonyl groups unaffected and afforded biaryl **31** in an excellent er of 98:2 and in 81% chemical yield [25]. The higher carbonyl reactivity of the bridging ester unit compared to that of the anthraquinone carbonyl functionalities (one of which is a vinylogous carbonate anyway), can be explained by an activation by ring strain in the biaryl lactone part, as also manifest in the distortion of the arylic portions. This reactivity allows a reduction to occur specifically at this group, despite the general inactivity of the oxazaborolidine/borane system towards (non-activated) esters [13]. Compound **31** was further converted into knipholone (**9**) and four likewise naturally occurring phenylanthraquinones, viz its 6′-*O*-methyl- and 4′-*O*-demethyl derivatives, bulbine knipholone (4′-*O*-demethyl-6′-*O*-methylknipholone), and knipholone anthrone, which is the 10-dihydrodeoxy analog of **9** (both not shown) [24,26].

2.5. Synthesis of korupensamines A and B, biarylic alkaloids without a free C_1-unit next to the axis

The korupensamines A [(*P*)-**11**] and B [(*M*)-**11**], two antimalarial [27] naphthylisoquinoline alkaloids and also halves of the quaterarylic anti-HIV active michellamines [28], constituted a special challenge for the lactone methodology: at first sight, the essential C_1-unit next to the biaryl axis is missing, therefore a prefixation of the two aromatic portions in the form of an ester bridge prior to the biaryl coupling seemed impossible. The simple solution of this task is that the required C_1-unit is indeed present in the molecule, just hidden in the distal naphthyl ring. Building up a *phenyl*isoquinoline equipped with such a C_1-substituent, instead, would permit an atroposelective biaryl formation, then to be followed by the anellation of the second aromatic ring of the naphthyl part [29].

The initial coupling of ester **32** under standard conditions, with 0.1 equivalent $Pd(OAc)_2$ and PPh_3, unexpectedly afforded only 26% of biaryl lactone **33** after 18 h (Scheme 6). To reach higher reaction temperatures, a Pd species was required that would not rapidly decompose above 120 °C. With 0.1 equiva-

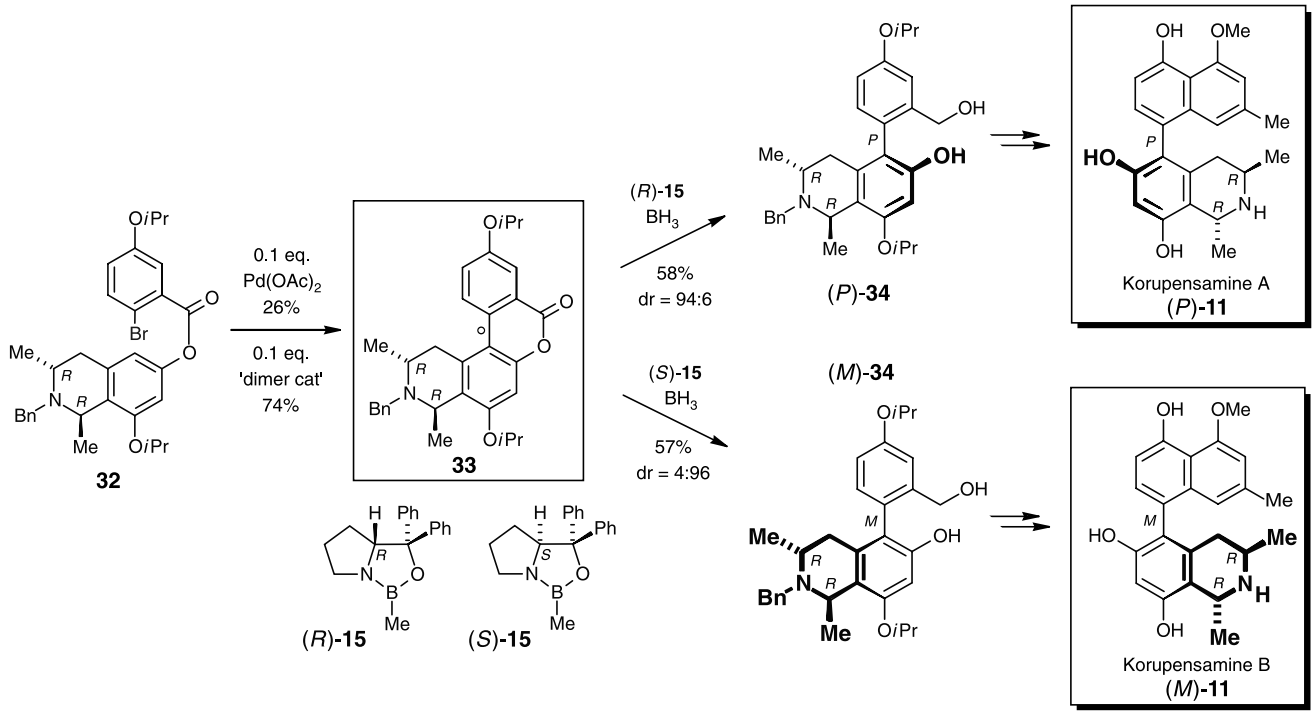


Scheme 5. The lactone concept in the total synthesis of knipholone (**9**).

lent of the binary Herrmann–Beller catalyst [30] ('dimer cat'), a palladium complex prepared from $Pd(OAc)_2$ and $P(o\text{-Tol})_3$, which, because of its higher temperature stability, permits couplings of even deactivated aryl halides, the coupling yield in **32** was improved to 74% after 22 h at 140 °C. Probably due to the lack of a fourth substituent next to the axis leading to a smaller degree of strain-induced carbonyl activation, the atropo-diastereoselective ring opening reactions of **33** with oxazaborolidine-activated borane succeeded in only moderate chemical yield to give the (*P*)-configured product (*P*)-**34** when using (*R*)-**15**, or, optionally, (*M*)-**34** by the use of (*S*)-**15**. These yields were, however, acceptable here, since excellent diastereomeric ratios of 94:6 and 4:96 *P*:*M* were obtained. Even with L-Selectride as an *achiral H*-nucleophile, a dr of 17:83 in favor of the (*M*)-isomer of **34** was obtained, now in addition giving higher chemical yields (83%). From the diastereomerically pure compounds (*P*)- and (*M*)-**34**, the respective target molecules, korupensamines A and B (**11**), were attained in a few standard steps, thus finalizing the first truly atropo-divergent synthesis of these bioactive naphthylisoquinoline alkaloids [29].

2.6. Natural biaryl synthesis by the lactone method—a conclusion

As can be seen from the total syntheses presented, the lactone methodology gives excellent results for both structurally and electronically extremely different target molecules, offering practicable solutions for almost any kind of difficulty arising in the course of its application. It shows a great functional group tolerance and, keeping in mind the two variants involving six- and seven-membered biaryl lactones, is very effective for the construction of constitutionally symmetric and unsymmetric substrates [31], most of which had never been synthesized before.



Scheme 6. First atropo-divergent synthesis of korupensamines A [(*P*)-**11**] and B [(*M*)-**11**].

3. Synthesis of useful C_1-symmetric chiral auxiliaries

The lactone concept has also been used as an efficient device for the preparation of chiral auxiliaries and ligands as useful tools for asymmetric synthesis. Since it is not possible to mention all aspects of our approaches and applications developed, the focus has been set on some selected highlights and on currently ongoing work.

3.1. Novel non-C_2 symmetric N,O-ligands for the asymmetric addition of diethylzinc to aldehydes

The enantioselective ligand-accelerated addition of organozinc reagents [34,35], like Et_2Zn, to aldehydes can efficiently be achieved by using chiral catalysts like β-aminothiols [36], oxazaborolidines [37], or titanium complexes [38–40], but the most common and widely used ligands are dialkylated amino alcohols [35,34] like (−)-DAIB (**35**) [41], (−)-DBNE (**36**) [42], and (*S*)-DPMPM (**37**) [43] (Fig. 2).

Axially chiral C_2-symmetric ligands, otherwise powerful tools in stereoselective syntheses [44], by contrast, have so far shown good asymmetric inductions in Et_2Zn additions to aldehydes only when being used in a polymer-bonded form [44–46], as titanum complexes [39,40,46], or as biscarboxamide derivatives [47]. Only little work has been reported, by contrast, on the use and rational design of biarylic amino alcohols as constitutionally unsymmetric (i.e. C_1-symmetric) axially chiral ligands [48,49]. We anticipated that axially chiral phenols like (*M*)-**40** with an amino group in the side chain should be promising candidates for this type of catalysis, and should be easily available in both enantiomeric forms by application of the lactone method (Scheme 7) [3,50]. Starting with the atropisomerically pure diol (*M*)-**38**, as obtained from biaryl lactone **4** (R = Me) [51], the benzyl-protected bromo compound (*M*)-**39** was prepared in 95% yield over two steps. The amino function was introduced by nucleophilic substitution, followed by *O*-deprotection with BCl_3 leading to the desired ligands of type (*M*)-**40**.

In initial studies, the chiral biaryl ligands **40** were tested in the enantioselective addition of Et_2Zn to benzaldehyde (**41a**) (Table 1). The best asymmetric induction was achieved in *n*-hexane at 20 °C with 20 mol% of the tertiary amine (*M*)-**40c** as the catalyst, while the secondary amine (*M*)-**40a** gave only moderate selectivities. The quantity of the catalyst (*M*)-**40c** can be reduced to 2 mol% without any loss of asymmetric induction, delivering the alcohol (*R*)-**42a** in 95% yield and with an excellent er of 99:1.

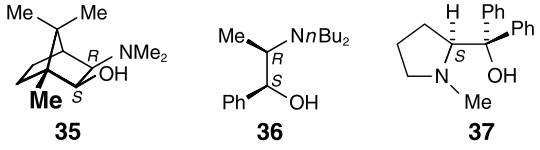


Fig. 2. Structures of the chiral amino alcohol ligands **35**, **36**, and **37**.

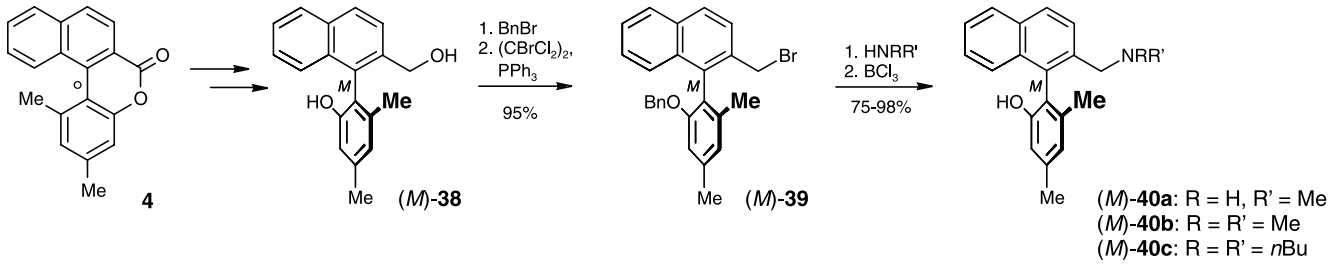
The broad synthetic potential of (*M*)-**40c** as a novel catalyst was proven in the addition of Et_2Zn to a series of different aldehydes **41** (Scheme 8). The respective alcohols **42** were obtained in high yields and enantiomeric ratios of up to 99:1, and even the often problematic [35] aliphatic aldehyde *n*-heptanal **41d** delivered a good er of 96:4. Non-linear effects following the principle of asymmetric amplification [52], however, were not found for this type of catalyst.

Interestingly, the naturally occurring naphthylisoquinoline alkaloid dioncophylline C (**10**) [53], a particular amino alcohol likewise prepared by the lactone concept [6], gave moderate but significant enantioselectivities (er up to 65:35) in the asymmetric Et_2Zn addition to **41a** (see Scheme 9) [54], a promising first application of axially chiral natural product in asymmetric synthesis.

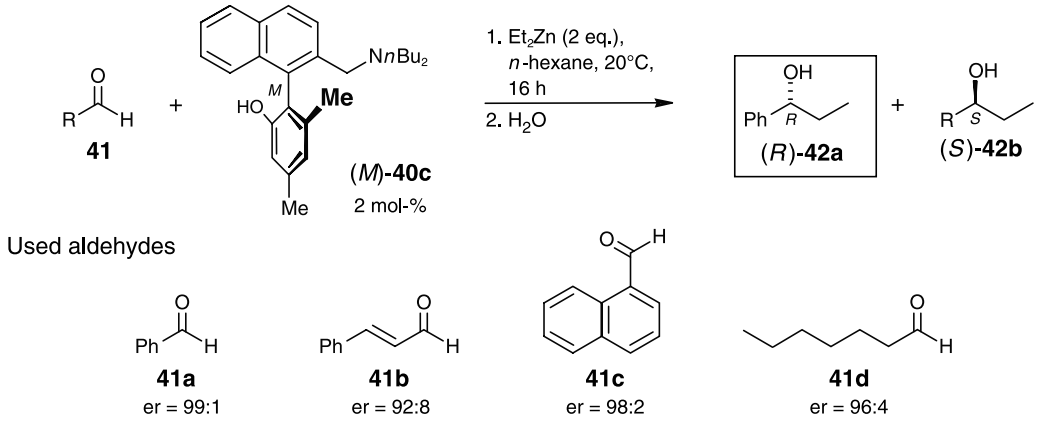
3.2. Likewise from biaryl lactones: synthesis of MOP ligands the for the enantioselective hydrosilylation of styrenes

Axially chiral biphosphanes like BINAP [55] are widely used chelating ligands in many areas of asymmetric synthesis, since they efficiently create a chiral environment around the metal [43,56]. However, in some metal-catalyzed reactions, like the palladium-mediated enantioselective hydrosilylations of olefins, which are most useful for the preparation of optically active alcohols [57], there is only one free coordination site accessible during some steps of the catalytic cycle. In these cases, *mo*nodentate *p*hosphine (= MOP) ligands with sterically hindered biaryl axes have been applied most successfully [57,58]. To this class of C_1-symmetric biaryls, the lactone concept provides convenient access, too: thus, the new phosphine (*P*)-**46** was synthesized from the configurationally unstable lactone **4** (R = Me), by its conversion into the phenol (*P*)-**43**. Treatment of (*P*)-**43** with triflic anhydride afforded (*P*)-**44**, which was transformed into the desired phosphine (*P*)-**46** by Pd-mediated phosphonylation and reductive *P*-deoxygenation (Scheme 10) [59]. Due to the good crystallization properties of the intermediate phosphine oxide (*P*)-**45**, confirmation of its anticipated structure succeeded by an X-ray diffraction analysis.

For an evaluation of the catalytic potential of (*P*)-**46**, the asymmetric hydrosilylation of styrenes **47a**–**d** was chosen. The reactions were carried out with $[PdCl(\pi\text{-}C_3H_5)]_2$ as the catalyst, yielding the silanes **48a**–**d** regioselectively and in high chemical yields. Oxidation of these products delivered the benzylic alcohols **49a**–**d**, with the *S*-configured product prevailing in all cases (Scheme 11 and Table 2). The enantiomeric ratios (up to 62:38) obtained at room temperature, however, were



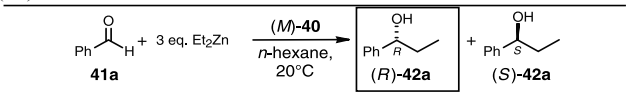
Scheme 7. Synthesis of novel N,O-ligands of type (M)-**40**.



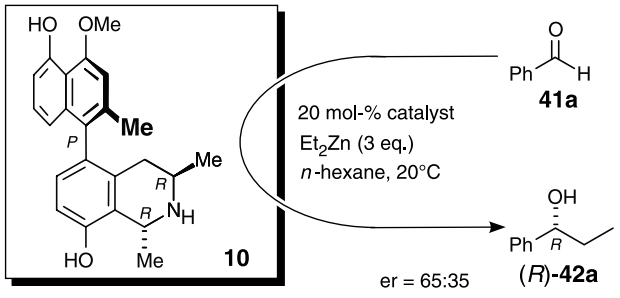
Scheme 8. Applications of (M)-**40c** as a chiral ligand in asymmetric catalysis.

only moderate. Lowering the temperature to 0 °C led to improved stereocontrol, delivering an er of up to 75:25 for **49c**.

Table 1
Enantioselective addition of Et_2Zn to benzaldehyde (**41a**) catalyzed by (M)-**40**



Ligand (mol-%)	Conversion [%]	(*R*)-**42**:(*S*)- **42**
(M)-**40a** (20)	50	86:14
(M)-**40b** (20)	100	98:2
(M)-**40c** (20)	100	99:1
(M)-**40c** (2)	100	99:1



Scheme 9. The use of dioncophylline C (**10**) as a catalyst for the asymmetric addition of $ZnEt_2$.

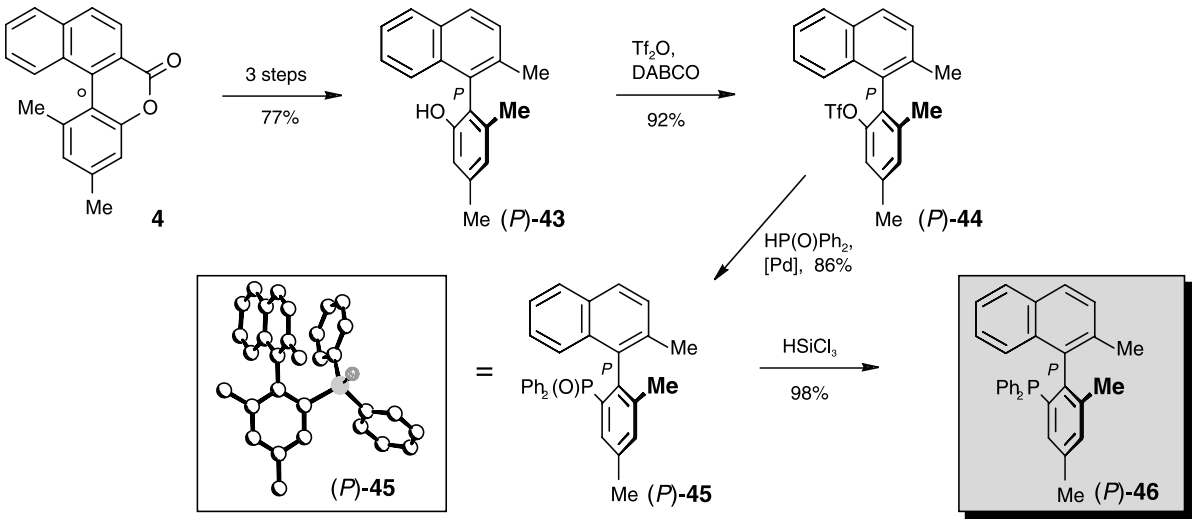
Encouraged by these first promising results, steric and electronic modifications of the ligand system were envisaged, e.g. by replacement of the naphthalene C_1-group by an ethoxymethylene function, as in (M)-**50**, and by the synthesis of the more electron rich and thus probably more strongly binding dimethoxy-substituted derivative (P)-**51** (Fig. 3).

In the hydrosilylation reactions, the use of the newly designed phosphines (M)-**51** and (P)-**52** lead to improved enantioselectivities of up to 90:10 (Table 3) [60].

Future work will focus on the fine-tuning of these ligands, hopefully providing versatile alternatives to existing MOP ligands (which deliver ee's of up to 99%) [57,58].

3.3. Preparation of a novel aryl-ferrocenyl ligand

Another important and rapidly growing class of ligands are the planar-chiral ferrocenes [61], which have been used for numerous applications in asymmetric syntheses [62], even on an industrial scale [63]. Not much has so far been reported, however, on the combination of a chiral ferrocene unit with an axially chiral biaryl moiety. Most ligands that do combine these two elements of chirality, have a biaryl moiety attached to a separate ferrocenyl portion simply via a carbon chain [64] and only a few 'true' ferrocenyl biaryls in which these parts are bonded directly to each other, have been described [65]. Ligands like **52** (Fig. 4, left), with a



Scheme 10. Synthesis of the MOP ligand (*P*)-**46**.

ferrocenyl cyclopentadiene being part of a biaryl substructure, should provide a conceptionally novel chiral environment, which might be utilized in several asymmetric processes. As a model, the aryl-ferrocenyl (R_p)-**53**, which should most likely be configurationally unstable at the axis, was chosen (Fig. 4, right) [66].

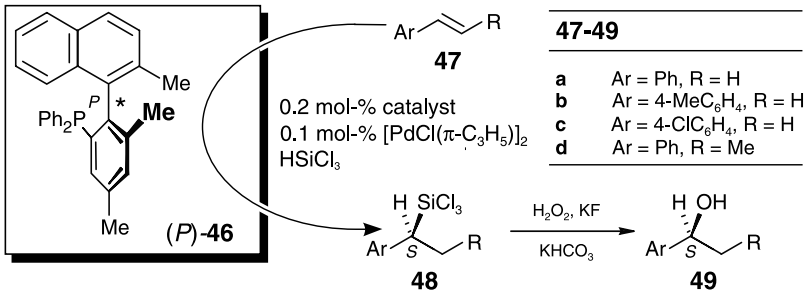
The chirality in the ferrocenyl part was introduced by the use of enantiomerically pure 2-iodoferrocene carboxylic acid [(S_p)-**54**], which is easily accessible in both enantiomeric forms [67]. For the biaryl coupling according to our lactone concept, the two molecular portions, (S_p)-**54** and 2-iodophenol (**55**), were connected via an ester bridge, as in (S_p)-**56**. In this case, the intramolecular *C*,*C*-bond formation did not succeed in the ususal Pd-catalyzed way, but was accomplished using a nickel-mediated reductive biaryl coupling procedure [68,69], leading to the desired lactone (R_p)-**57** as the main product, along with the hydro-dehalogenated ester **58** and the (likewise halogen-free) homo-coupling product **59** (Scheme 12) [70].

After the formation of the crucial *C*,*C*-bond, the target molecule (R_p)-**53** was easily attained by reductive ring cleavage with $LiAlH_4$ (Scheme 13).

Even though the biaryl axis in (R_p)-**53** indeed was found to be configurationally unstable, the accomplished synthesis of (R_p)-**53** is an important step towards the design of novel ferrocenyl-ligands; and even in (R_p)-**53**, the axis will probably adjust its (relative) configuration depending on the type of transition metal complex chosen for a catalytic system to form a stereochemically homogeneous complex, thus possibly representing a 'self-adapting' ligand, whose induced axial chirality might help to amplify the asymmetric induction achieved by the planar-chiral element of the ferrocenyl unit. This and the use of aryl-ferrocenyls like **52** in asymmetric synthesis, and the preparation of sterically more hindered analogs that are configurationally stable at the axis, are currently under investigation.

3.4. Axially chiral tripod ligands

The design of novel C_3-symmetric ligands for stereoselective catalytic conversions is a field of increasing importance in asymmetric synthesis, because reactions of their octahedral metal complexes will give rise to a decreased number of diastereomorphous transition states—in analogy to the use of C_2-symmetric ligands in tetrahedral or square-planar complexes [71]. In particular centrochiral trialkanolamines [72,73] are well suited for this purpose, because they form stable



Scheme 11. The asymmetric hydrosilylation of styrenes **47** catalyzed by (*P*)-**46**.

Table 2
The use of (*P*)-**46** in the asymmetric hydrosilylation of styrenes

Styrene	Temperature (°C)	Time (h)	Yield **48** (%)	Yield **58** (%)	Er (*S*:*R*)
47a	23	18	84	91	55:45
47b	23	18	99	96	58:42
47c	23	24	88	91	60:40
47d	23	48	93	92	62:38
47a	0	24	86	91	68:32
47b	0	24	99	94	64:36
47c	0	96	87	92	75:25
47d	0	144	88	91	65:35

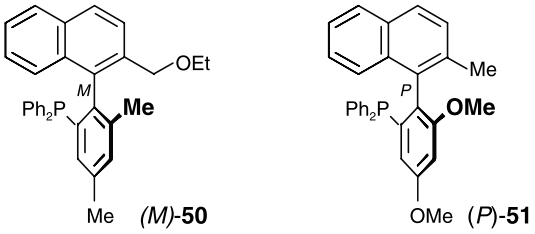


Fig. 3. The new MOP ligands (*M*)-**50** and (*P*)-**51**.

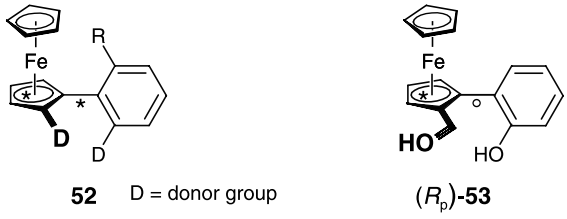


Fig. 4. The aryl-ferrocenyls **52** and (R_p)-**53**.

discrete complexes with oxophilic group-4 and -5 transition metals, the so-called metallatranes [74,75]. These have been successfully used in several asymmetric reactions [72], e.g. in stereoselective ring openings of *meso*-epoxides [76] and in Ti(IV)-catalyzed asymmetric sulfide oxidations [77]. However, nearly nothing has been reported about the combination of C_3-symmetry and axial chirality [78], i.e. about threefold axially chiral tripodal ligands.

Treatment of the enantiopure bromide (*M*)-**39** with liquid ammonia gave the primary amine (*M*)-**60**, which was further alkylated in situ with two additional equivalents of (*M*)-**39** to yield (*M*,*M*,*M*)-**61**. This stepwise procedure proved superior to a direct, one-step formation of (*M*,*M*,*M*)-**61** from (*M*)-**39** and NH_3. Deprotection with BCl_3 furnished the required tripodal ligand (*M*,*M*,*M*)-**62** in a nearly quantitative yield (Scheme 14) [79].

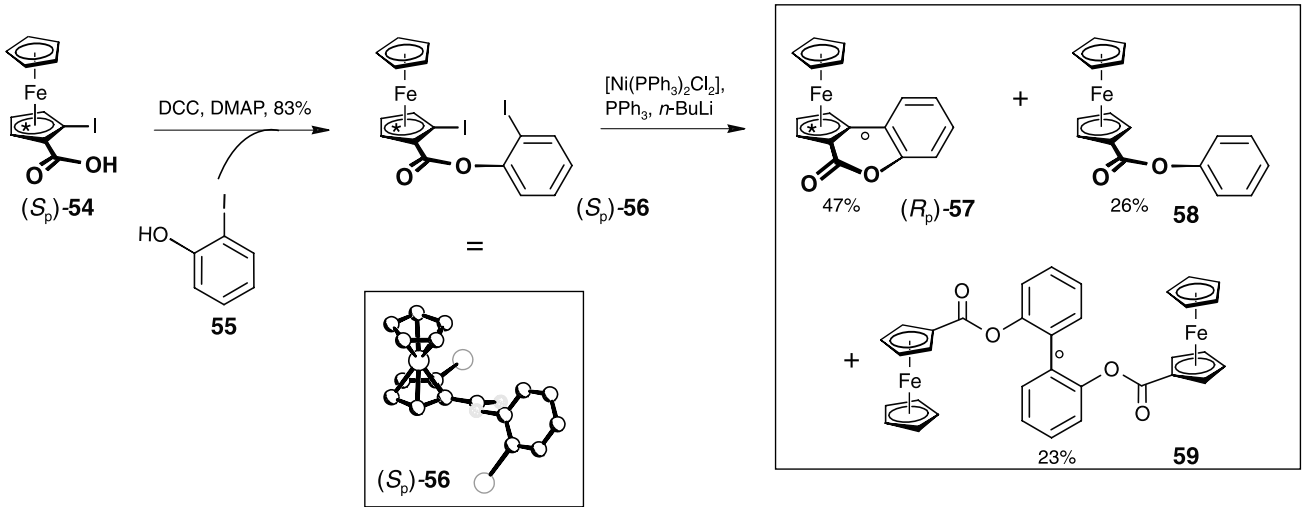
The biarylic portions of (*M*,*M*,*M*)-**62** form a cavity which is capable of incorporating oxophilic Lewis acidic elements. In first exploratory investigations, the integration of a phosphorous moiety and of a titanium fragment—leading to (*M*,*M*,*M*)-**63** and (*M*,*M*,*M*)-**64**, respectively—was accomplished (see Scheme 15).

More recent experiments have concentrated on the evaluation of the potential of (*M*,*M*,*M*)-**62** to mediate

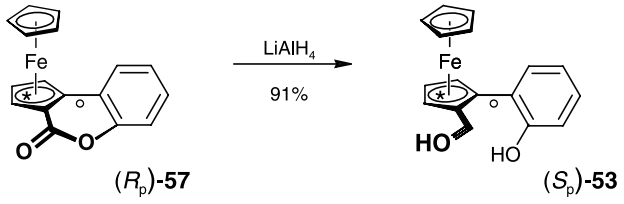
Table 3
The use of (*M*)-**50** and (*P*)-**51** in the asymmetric hydrosilylation of the styrenes **48**

Styrene	Ligand	Temperature (°C)	Time (h)	Yield **49** (%)	Yield **50** (%)	Er (*S*:*R*)
47a	(*M*)-50	23	18	82	95	62:38
47b	(*M*)-50	23	18	90	97	80:20
47c	(*M*)-50	23	18	72	98	68:32
47d	(*M*)-50	23	48	81	92	50:50
47a	(*M*)-50	0	18	98	78	68:32
47b	(*M*)-50	0	18	91	94	90:10
47c	(*M*)-50	0	18	91	95	77:23
47d	(*M*)-50	0	144	n.r. [a]		
47a	(*P*)-51	23	18	99	95	67:33
47b	(*P*)-51	23	18	94	95	64:36
47c	(*P*)-51	23	18	92	95	67:33
47d	(*P*)-51	23	48	87	91	74:26
47a	(*P*)-51	0	18	95	92	79:21
47b	(*P*)-51	0	18	89	95	71:29
47c	(*P*)-51	0	18	90	95	80:20
47d	(*P*)-51	0	144	84	92	79:21

[a] n.r., no reaction.



Scheme 12. Synthesis of the aryl-ferrocenyl lactone (R_p)-**57**.

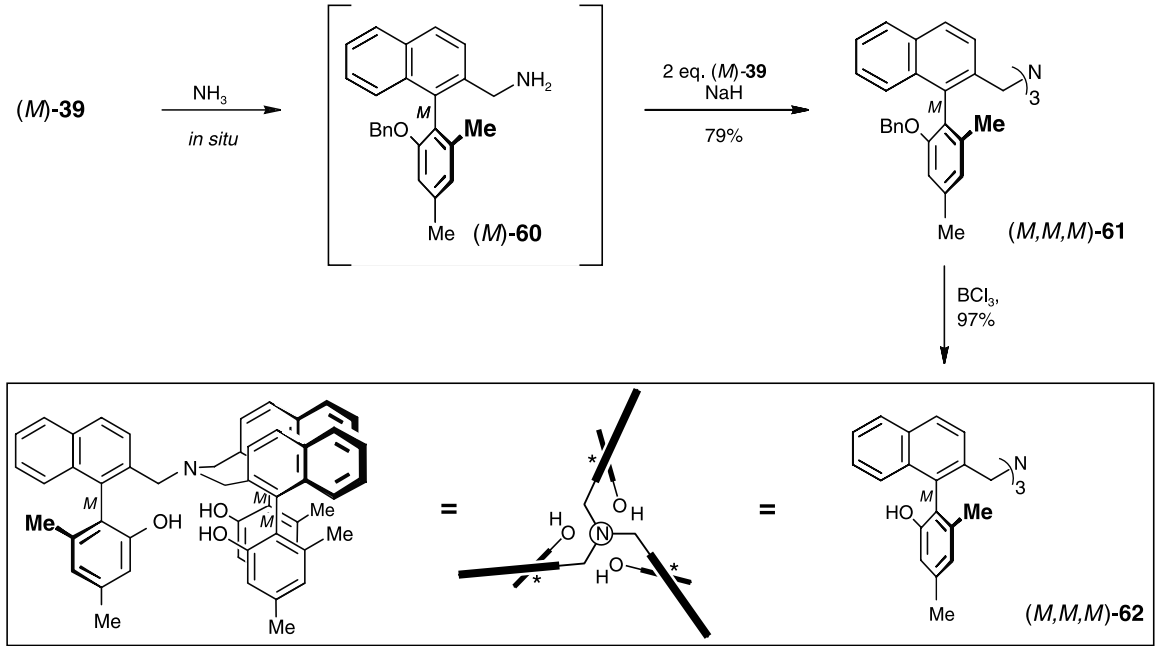


Scheme 13. Synthesis of (R_p)-**53** (axial configuration arbitrary).

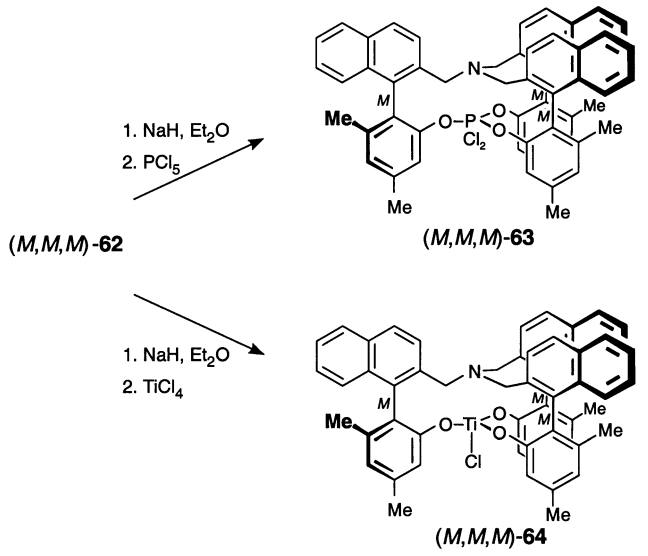
catalytic enantioselective Et_2Zn-additions to benzaldehyde (**41a**) (Scheme 16), which, however, showed only moderate activities with likewise moderate asymmetric inductions.

3.5. A further extension of the lactone method: first synthesis of a twofold lactone-bridged teraryl

Only few natural products are based on a teraryl system [80], i.e. with three aromatic systems linked via two biaryl axes, most of them occurring in fungi [83] or lichens [84]. Non-natural teraryls have been applied as liquid crystals [85], as building blocks for polymers [86], and as chiral crown ethers usable as chiral recognition hosts [87]. It thus seemed rewarding to extend our method to the synthesis of twofold lactone-bridged teraryls like **66**, which may be suitable precursors for the formation of C_2-symmetric teraryls. Of particular interest were stereochemical questions, since it was not



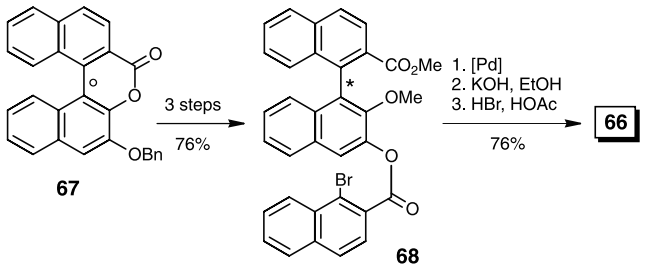
Scheme 14. Synthesis of (M,M,M)-**62**.



Scheme 15. Incorporation of a titanium and a phosphorous fragment into (*M*,*M*,*M*)-**62**.

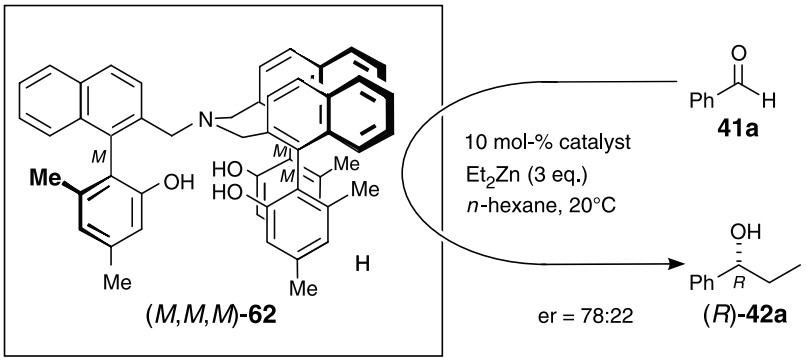
clear a priori whether **66** would exist as a racemic mixture of the C_2-symmetric forms (*P*,*P*)-**66** and (*M*,*M*)-**66** or in its *meso*-form (*M*,*P*)-**66** (see Scheme 17), or as a mixture of all three isomers.

The synthesis of **66** did, unfortunately, not succeed directly, by a rational twofold intramolecular Pd-catalyzed coupling of the diester **65** as scheduled in Scheme 17, so that **66** had to be built up by a stepwise procedure (see Scheme 18), by starting from the monolactone **67**, which was converted into the transiently ring-opened racemic diester **68**. The synthesis was accomplished by palladium-catalyzed intramolecular coupling, with subsequent ester (and lactone) saponification, methyl ether cleavage, and twofold ring closure to give the bislactone **66** [88].

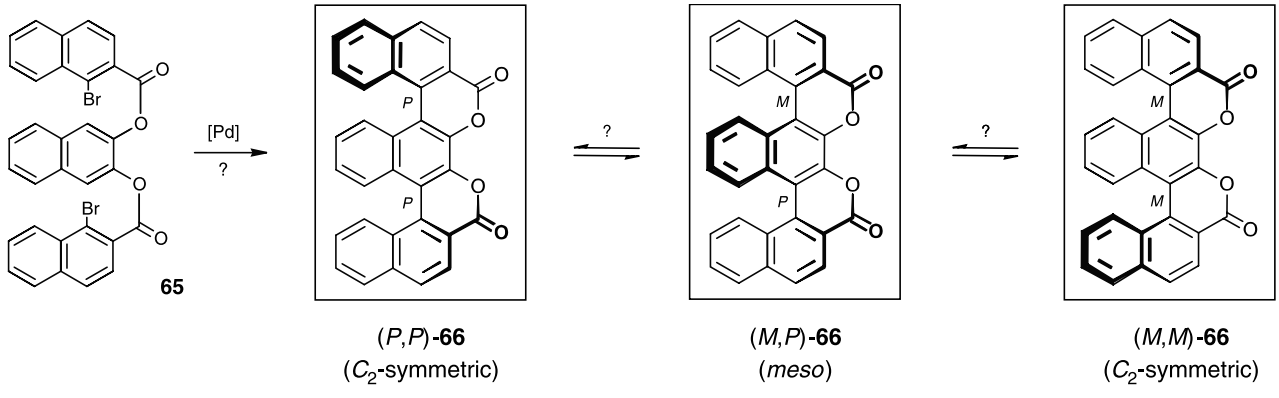


Scheme 18. Synthesis of the bislactone **66** successfully achieved by consecutive coupling steps.

Semiempirical (AM1, PM3) and ab initio calculations (DF) indicated that the *meso*-form of **66** should be strongly favored energetically and should hence be largely predominant as compared to (*P*,*P*)-**66** and (*M*,*M*)-**66**. In agreement with this, only one stereoisomeric species was observed in solution (NMR), and an



Scheme 16. The use of (*M*,*M*,*M*)-**62** in the asymmetric addition of Et_2Zn to benzaldehyde (**41a**).



Scheme 17. The novel ternaphthyl bislactone **66**: atropisomeric forms and scheduled rational synthesis.

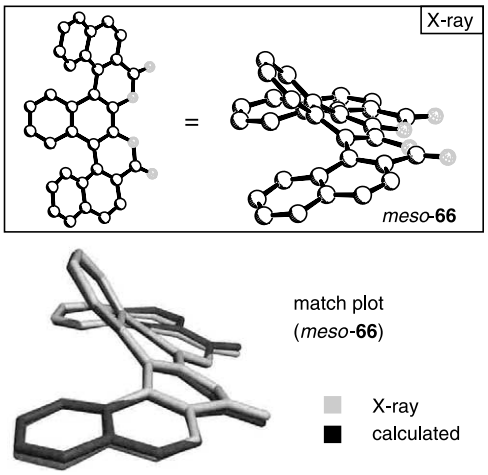
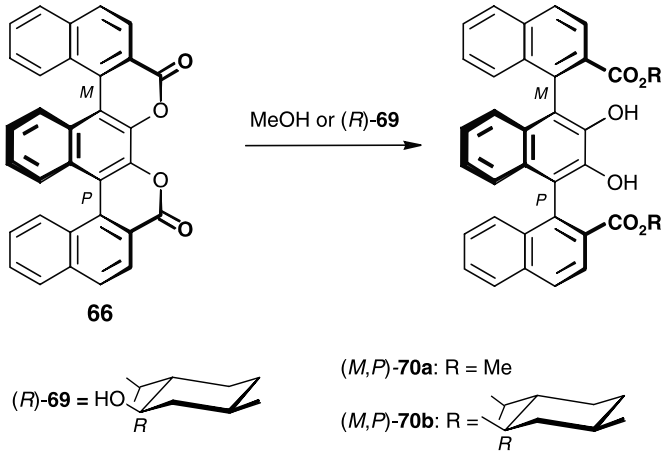


Fig. 5. Crystal and calculated structure of *meso*-**66**, hydrogen-atoms are omitted for reason of clarity.



Scheme 19. Preparation of **70**.

X-ray diffraction analysis revealed **66** to be *meso*—at least in the crystal. The experimental structural data are in good accordance with the results of the calculations, which is demonstrated impressively by the matchplot in Fig. 5.

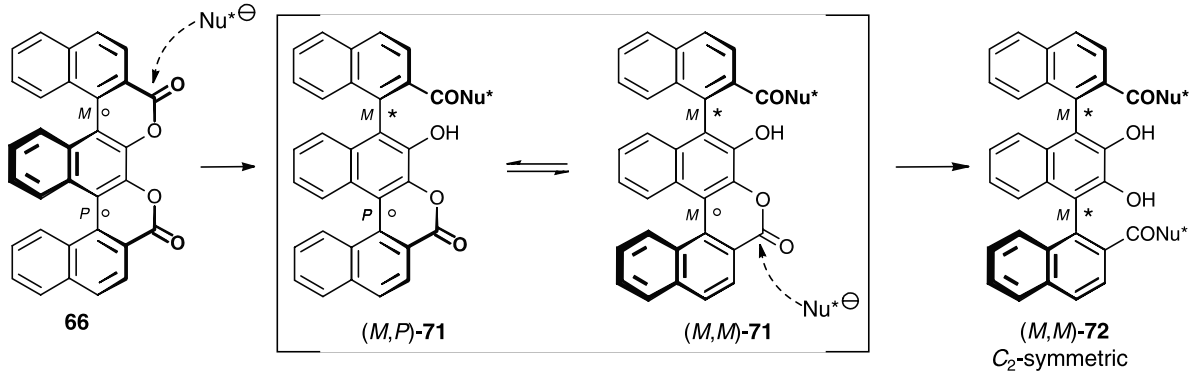
That the species in solution was indeed the *meso*-diastereomer, was further plausibilized by its rapid ring cleavage with methanol, to give the *meso*-configured dimethylester (*M*,*P*)-**70a** (structure proven by an X-ray diffraction analysis [89], not shown), exclusively (Scheme 18). Unfortunately, all attempts to open **66** in a homochiral way by using chiral *O*-nucleophiles like mentholate [(*R*)-**69**], aiming at the synthesis of a C_2-symmetric terarylic product like (*M*,*M*)-**70b** (cf. Scheme 19), failed. In all cases, only products with *meso*-like heterochiral axes like (*M*,*P*)-**70b** were attained.

To obtain C_2-symmetric teraryls by this approach, might still only be possible in the following way: after having opened one of the lactone bridges of **66** atroposelectively (e.g. only the *M*-configured one), the remaining (here now *P*-configured) lactone portion of the initial product (*M*,*P*)-**71** would have to equilibrate to (*M*,*M*)-**71** before its further cleavage (Scheme 20). The second nucleophilic attack is, however, apparently too fast to 'wait' for this equilibration step—or the configurationally stable first biaryl axis of **71** (the 'upper one') exerts an asymmetric induction in the 'wrong' (i.e. heterochiral) direction, so that ultimately not (*M*,*M*)-**71**, but, unfortunately, (*M*,*P*)-**71** is further cleaved (as shown in Scheme 20).

Further investigations to design, prepare, and atroposelectively cleave constitutionally more appropiate bislactones (and even higher homologs) that do lead to C_2-symmetric teraryls, are in progress.

3.6. Synthesis of axially chiral reagents using the lactone method—a summary

As shown by the presented syntheses, the lactone concept permits the design, preparation and fine-tuning of broad spectrum of useful auxiliaries, varying in electronic, steric demands, and symmetry. The method is particulary valuable for the preparation of constitutionally unsymmetric, but also C_2- and C_3-symmetric biaryl ligands, reagents, and catalysts, which are usually accessible in just a few synthetic steps, and with any



Scheme 20. Equilibration of **71** as a necessary precondition for a (not observed) selective ring opening to a C_2-symmetric teraryl, (*M*,*M*)-**72**.

desired axial configuration from the atropisomerically pure lactone ring cleavage products.

Acknowledgements

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