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The lactone concept—a novel approach to the metal-assisted atroposelective construction of axially chiral biaryl systems☆

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Dedicated to Dr. Waldemar Adam on the occasion of his 65th birthday.

Abstract

The atroposelective synthesis of axially chiral biaryls via configurationally unstable, lactone-bridged biaryls is reviewed. These key molecules are easily accessible by regioselective intramolecular cross-coupling of ester-linked, even sterically hindered aromatic portions and can be cleaved highly atropo-enantio- or -diastereoselectively by three principal options, either (a) by using a wide range of chiral metalated nucleophiles (usually with external asymmetric induction), (b) after Lewis acid activation of the lactone C=O function using uncharged chiral or achiral nucleophiles, or (c) with internal asymmetric induction, using the stereoelement of planar chirality originating from η^6-coordination (typically involving Cr or Ru complexes). The resulting ring-opened configurationally stable biaryls are obtained in mostly excellent chemical and optical yields. By the choice of the respective enantiomer of the nucleophile, the method allows the atropo-divergent synthesis of both atropisomers from the same immediate biaryl precursor and, if required, a recycling of the undesired minor atropisomer is possible, too. Such advantages are otherwise well-known for the stereoselective preparation of centrochiral compounds.

Keywords: Biaryls; Stereoselective synthesis; Atropisomers; Axial chirality; Ring opening; Dynamic kinetic resolution

1. Introduction

The presence of an axially chiral biaryl axis is the structurally dominating feature of a steadily growing number of chiral auxiliaries and natural products. As an example, binaphthyl-derived systems like BINAP (**1**) [1] (Fig. 1) provide a rigid framework for numerous chiral transition metal complexes, which are highly stereo-differentiating catalysts successfully applied in almost any area of asymmetric synthesis [2]. Axially chiral biaryls from nature, among them the famous antibiotic vancomycin (**2**) [3], show a broad structural variety and frequently offer attractive pharmacological profiles [4].

Despite the increasing importance of axial chirality, only few methods (for three selected examples, see Fig. 2) exist that permit an efficient regio- and stereoselective construction of biaryl compounds under mild conditions [5–8]. Most of them, however, suffer from low chemical and/or optical yields in the cross coupling of more sophisticated and sterically hindered aryl moieties. Also, there is often no possibility for the optional, 'atropo-divergent' preparation of both rotational isomers from the same precursor, in particular if the chiral auxiliary is attached to one or two of the coupling partners. The recently published enantioselective coupling protocols [9] using chirally modified Pd-catalysts are restricted to only few substrates and are not (or not yet) generally applicable.

☆ Novel Concepts in Directed Biaryl Synthesis, part 101. For part 100, see Ref. [75].

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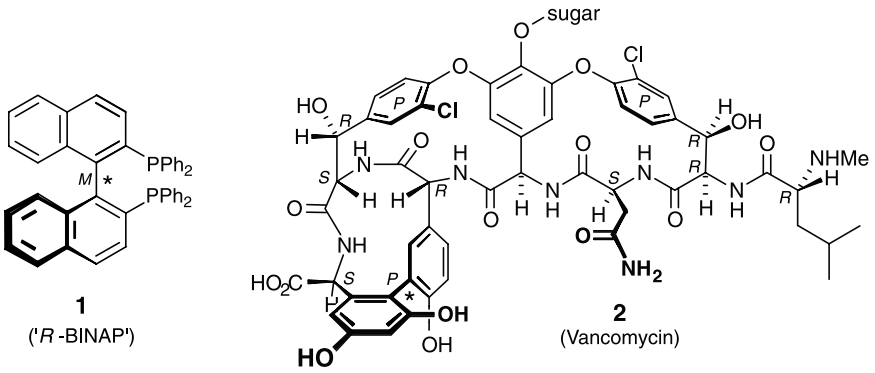


Fig. 1. Structures of the synthetic auxiliary BINAP (**1**) and the naturally occurring antibiotic vancomycin (**2**).

The obvious need for efficient procedures that permit the atroposelective construction of axially chiral biaryls, led us to face this challenging problem and to focus on the development of a method that fulfills the following demands: it should provide high chemical and optical yields and should be broadly applicable, i.a. to the regioselective cross coupling even of sterically severely hindered biaryl fragments; it should tolerate virtually any substitution pattern in the starting materials and should be compatible with usual functional groups. Furthermore, it should include the principle of atropodivergence, i.e. the directed preparation of both atropisomers from the same immediate precursor, and should provide the option for a recycling of undesired stereoisomeric by-products possibly likewise formed. With the '*lactone concept*' presented in this paper, we have tried to meet all these requirements [10–12]. Selected examples of applications of the strategy in the atroposelective synthesis of axially chiral biaryl auxiliaries and concrete naturally occurring target molecules will be reviewed in the following article [13].

2. The basic principle of the 'lactone concept'

A major problem of most of the known techniques for the stereoselective biaryl coupling results from the fact that they have to perform two difficult tasks simultaneously: The C–C-bond formation to create the axis and the introduction of the chiral information. Our idea was to solve these two problems consecutively, i.e. to achieve a non-stereoselective, but chemically highly efficient (since intramolecular) coupling reaction leading to a stereochemically not yet fixed biaryl, which would subsequently be converted into the axially chiral target molecule of any configuration. The possibility to reverse this process would permit the re-use of undesired atropisomers. To reach such a stereochemically undefined intermediate, the two aryl moieties had to be forced to lie 'in plane', or—at least—to adopt a slightly distorted and thus chiral arrangement, yet with a low isomerization barrier (see below), which can be achieved by connecting them by a short bridge. Thus, in contrast to many known methods (cp. Fig. 2), our strategy [10] does not use the bridge as a chiral auxiliary in the coupling step, but—besides bringing the coupling partners close together—rather as a tool that prevents the formation of a configurationally stable axis. This concept was realized as outlined in Scheme 1, with benzonaphthopyranones of type **11** [14] as the key intermediates.

In esters of type **10**, easily synthesized from simple aromatic compounds like **8** and **9**, the two biarylic portions are prefixed at a short distance to each other—

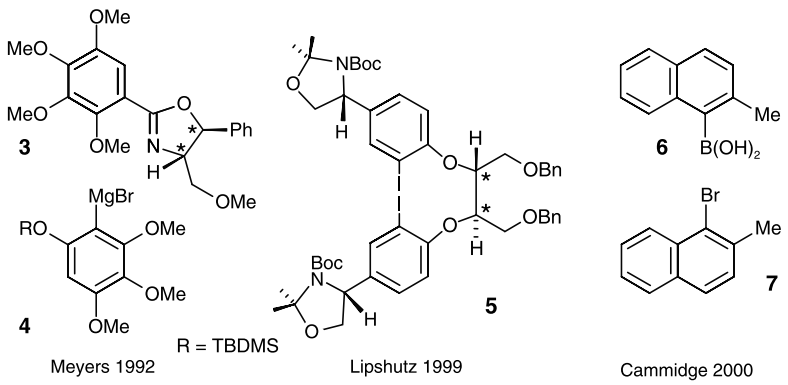


Fig. 2. A brief selection of methods for the stereoselective construction of axially chiral biaryls [6,7,9].

an ideal precondition for the following intramolecular biaryl coupling step (**10**→**11**), which proceeds with a reliable regioselectivity with respect to the bromine and the *ortho*-positions of the phenolic part. Using $Pd(OAc)_2$ or, even better, the more temperature-stable palladacycle **13** [15] as catalyst, the desired lactones **11** are obtained in good to excellent yields (Fig. 3) [16,17]. In this way, a set of useful, structurally diverse biaryl lactones **11a**–**f** has been prepared, equipped with steric hindrance at the biaryl axis which ranges from low (**11a**: R = H) to very high (**11f**: R = ^{t}Bu). Subsequent cleavage of the lactone function can be performed stereoselectively, leading to the now axially chiral target biaryls **12**. These possess a hydroxy group and a C_1-unit next to the axis—a useful structural array found in many naturally occurring axially chiral biaryls [4,10,13], which is, if required, also open for further transformations.

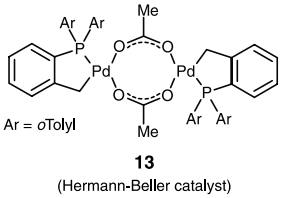
3. Structure and dynamics of the biaryl lactones

Among the two key steps of the procedure, the C–C-bond formation through intramolecular biaryl coupling and the ring cleavage reaction, the latter was found to be the stereochemically decisive one, since it is usually this step that establishes the ultimate configuration at the axis. The simplest explanation for this atropo-divergence in the ring opening reaction would be that the lactones are flat and thus achiral, and that the chiral ring cleavage reagent, with transient pyramidalization of the lactone carbonyl function, opens the ring with a defined 'twisting' at the previously planar-substituted axis. This, however, cannot be the case, because quantum chemical calculations [18,19] as well as experimental investigations like X-ray structure analyses [17,20,21] and NMR [23] clearly show that all of the lactones of type **11** are helically distorted—severely for R = ^{t}Bu and also for R = Me, but even for R = H (Fig. 4).

The optional preparation of either the *M*- or the *P*-configured ring opening product from the same lactone can thus only be brought into line with their configurational instability. Again in agreement with quantum chemical calculations [18,22], the halflife of this process was determined experimentally by racemization of enantiomerically enriched samples or by DNMR experiments on derivatives equipped with ethyl or isopropyl groups as stereochemical probes (Scheme 2) [23]. For small substituents R *ortho* to the axis like H or OMe, and even for R = Me, the interconversion occurs very rapidly at room temperature ($t_{1/2} < 1$ s). The process slows down with increasing size of R (e.g. R = Et: $t_{1/2}$ = ca. 1 min, ^{i}Pr: $t_{1/2}$ = ca. 30 min) and is eventually (almost) frozen for R = ^{t}Bu ($t_{1/2} > 2$ day). From these findings, the ring opening of **11** must follow the principle of a dynamic kinetic resolution, by which the enantiomer that gets consumed more rapidly, is constantly provided from the less reactive one, by the fast equilibrium (*M*)-**11**⇌(*P*)-**11**, while the configurationally stable lactone **11f** (R = ^{t}Bu) is an excellent substrate for 'normal' (i.e. non-dynamic) kinetic resolutions (see Section 7.2).

Yields of the Pd^{II}-catalyzed biaryl couplings of **10**:

11 / R	Pd^{II} $Pd(OAc)_2/PPh_3$ (10/20 mol-%)	**13** (1 mol-%)
a H	80	91
b OMe	77	90
c Me	75	87
d Et	71	83
e *i* Pr	72	82
f *t* Bu	44	81



13
(Hermann-Beller catalyst)

Fig. 3. Yields of the Pd^{II}-catalyzed coupling **10**→**11** and structure of the binary Pd-catalyst **13** [15].

4. Different options for the metal-assisted ring opening of the lactones

For the cleavage of the configurationally unstable biaryl lactones (**9**), with external or internal asymmetric induction, three fundamentally different strategies have been elaborated (Fig. 5).

4.1. Method I

Using chiral anionic nucleophiles like metalated amines, alcohols, hydride transfer reagents etc. for the cleavage of the lactone bridge of **11**; this method provides the most direct approach to axially chiral biaryls (see Section 5).

4.2. Method II

By Lewis acid activation of the lactone function of **11**, allowing to perform the ring opening even with un-

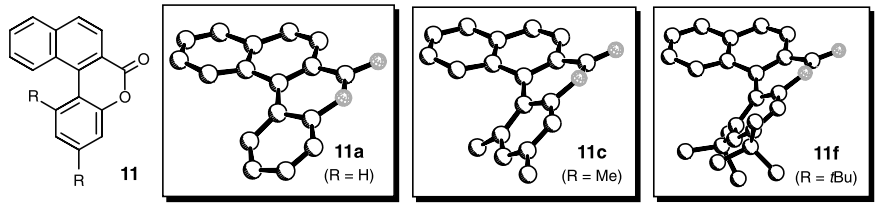
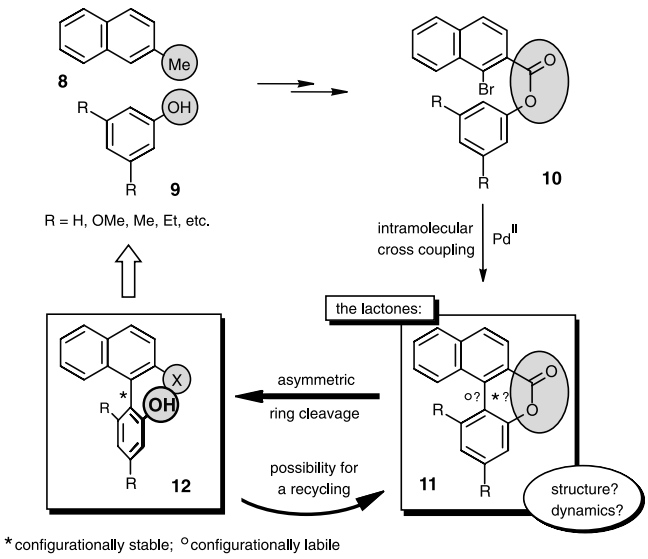
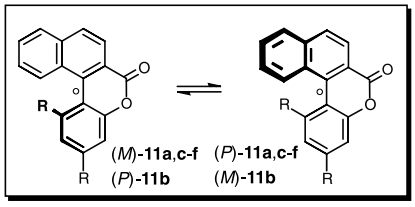


Fig. 4. Crystal structures (X-ray) of the helically distorted biaryl lactones **11**.



Scheme 1. The basic strategy of the lactone concept.



lactone 11	R	$t_{1/2}$ (rt)
a	H	<< 1 ms
b	OMe	*ca.* 1 ms
c	Me	*ca.* 1 s
d	Et	*ca.* 1 min
e	*i* Pr	*ca.* 30 min
f	*t* Bu	> 2 d

Scheme 2. Dynamic behavior of the biaryl lactones **9** (note that for stereochemically identical lactones **11a,c–f**, the CIP descriptors at the biaryl axis are opposite to those of **11b** [24]).

charged nucleophiles; in this case, the stereochemical information can be provided either by using a chiral Lewis acid or a chiral nucleophile; both options have been evaluated and are discussed in Section 9.

4.3. Method III

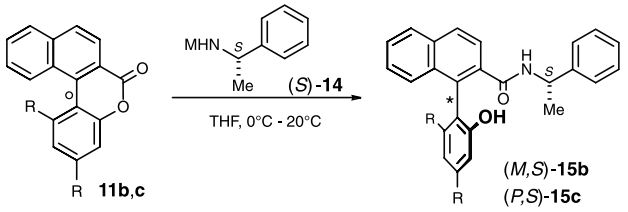
By η^6-coordination of a transition metal fragment to one of the aromatic rings of the biaryl **11**, leading to an activated species whose lactone bridge can be cleaved with simple achiral nucleophiles, with internal asymmetric induction through the stereoelement of planar chirality and, possibly, by additional stereocenters (see Section 10).

All three methods are idealized borderline cases, which in reality will act more or less cooperatively. For example, a bifunctional catalyst or a Lewis acidic transition metal as the counter ion will not only activate the nucleophile, but also coordinate to the carbonyl group and, thus, enhance the electrophilicity of the lactone function (combination of methods I and II; for specific examples see Sections 5.2 and 5.5).

5. Atroposelective ring opening reactions with metalated nucleophiles (Method I)

5.1. Lactone cleavage with chiral *N*-nucleophiles

First experiments were performed with the lactones **11b** and **11c** as the standard substrates, using the cheap and simple (*S*)-phenylethylamine [(*S*)-**14** (M = H)] as the *N*-nucleophile (Scheme 3) [25]. While no reaction occurred with the free amine, ring cleavage with the alkali metal activated derivatives (*S*)-**14** (M = Li, Na, K) proceeded smoothly, leading to the biaryl amides **15** in good yields of 70–99%. In these reactions, a strong dependence of the asymmetric induction from the counter ion became evident: Whereas with Li^+ a low stereo-differentiation (dr < 60:40) was observed, Na^+ and, in particular, K^+ delivered excellent diastereomeric ratios of up to 95:5. The degree of steric hindrance at the



(*M,S*)-**15b** (R = OMe):

M	dr	yield [%]
Li	51:49	93
Na	89:11	98
K	91: 9	70

(*P,S*)-**15c** (R = Me):

M	dr	yield [%]
Li	59:41	95
Na	92: 8[a]	99
K	95: 5	85

[a] Crystallization from petroleum ether / diethyl ether: dr 99.5:0.5 (yield 68%).

Scheme 3. Atropo-diastereoselective amidolyses of **11b,c** with the metalated (*S*)-1-phenylethylamides (*S*)-**14**.

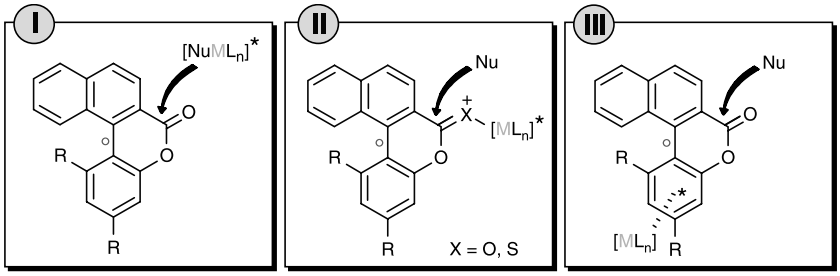


Fig. 5. Three principal options for the metal-assisted ring opening of the biaryl lactones **11**.

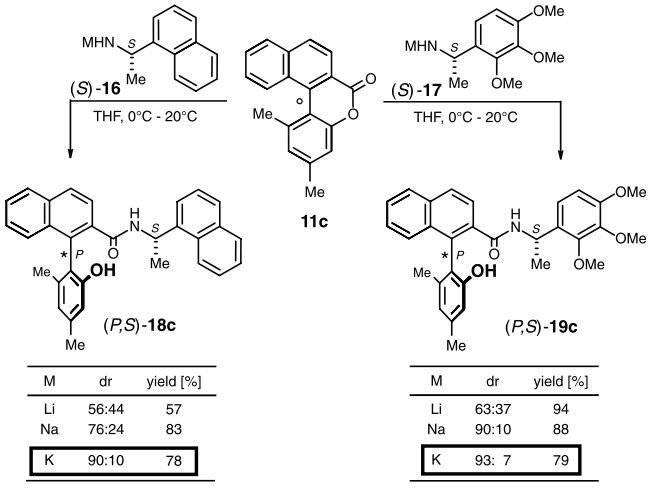
biaryl axis [**11b** (R = OMe) versus **11c** (R = Me)] had no major effect on the asymmetric induction. Diastereomerically pure biaryl amides, e.g. (*P*,*S*)-**15c**, were obtained by chromatographic separation or, more conveniently for larger-scale preparations, by crystallization from the crude product mixtures [25].

For the ring opening of the biaryl lactone **11c** with other enantiopure *N*-nucleophiles like the sterically more demanding and also commercially available (*S*)-1-naphthylethylamine [(*S*)-**16**] or the 2,3,4-trimethoxy derivative (*S*)-**17** [26] of (*S*)-1-phenylethylamine (Scheme 4) [25], the activating alkali metal had a similar influence on the asymmetric induction as observed with (*S*)-**14** (vide supra), thus delivering the best diastereomeric ratios with the potassium amides K–(*S*)–**16** [→ (*P*,*S*)-**18c**: dr 90:10] and K–(*S*)–**17** [→(*P*,*S*)-**19c**: dr 93:7]. With these more differentiated *N*-nucleophiles, improved stereoselectivities were not obtained, though.

5.2. Ring opening with chiral alcoholates

The ring cleavage of **11** with chiral *O*-nucleophiles leads to configurationally stable esters, which are versatile precursors for the construction of functionalized axially chiral biaryls since they offer manifold possibilities for further transformations. Moderate to good asymmetric inductions were achieved in the alcoholysis of **11b**, **c**, using the alkali menthoxides (*R*)-**20** (Scheme 5, left table) [27]. In this case, the dependence of the diastereomeric ratio on the counter ion was opposite to that observed for the *N*-nucleophiles (cf. Section 5.1), the highest dr of 14:86 being obtained with the more covalently *N*-bonded Li^+ as the activating metal ion.

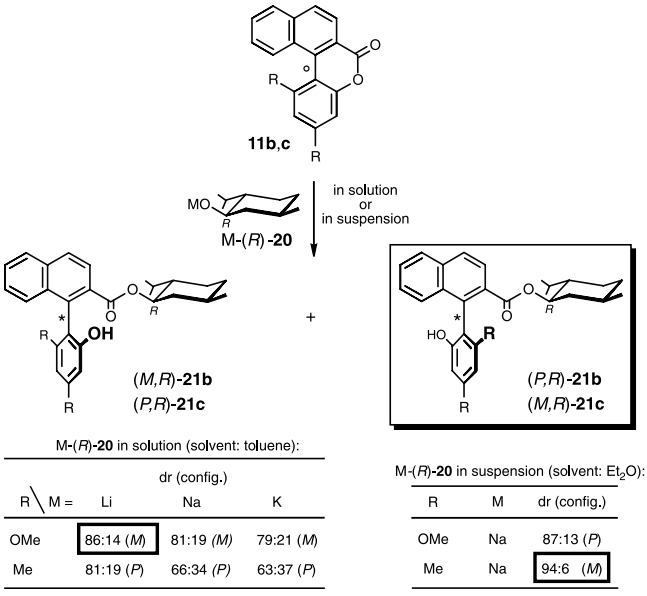
An unexpected result was achieved if sodium menthoxide [Na–(*R*)–**20**] was not used in solution, but in suspension as formed by deprotonation of (*R*)-menthol



M	dr	yield [%]
Li	56:44	57
Na	76:24	83
K	90:10	78

M	dr	yield [%]
Li	63:37	94
Na	90:10	88
K	93: 7	79

Scheme 4. Amidolyses of **11c** with the arylethylamides (*S*)-**16** and (*S*)-**17**.



M-(*R*)-**20** in solution (solvent: toluene):

R \ M =	Li	Na	K
	dr (config.)		
OMe	86:14 (*M*)	81:19 (*M*)	79:21 (*M*)
Me	81:19 (*P*)	66:34 (*P*)	63:37 (*P*)

M-(*R*)-**20** in suspension (solvent: Et_2O):

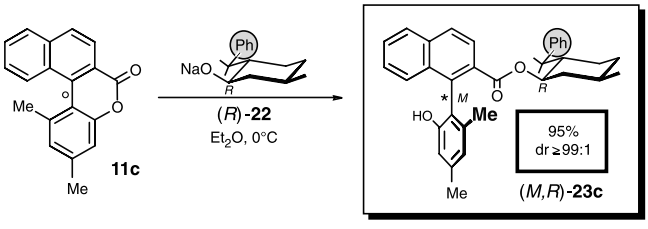
R	M	dr (config.)
OMe	Na	87:13 (*P*)
Me	Na	94:6 (*M*)

Scheme 5. Alcoholysis of **11** with metalated (*R*)-menthoxides as the O-nucleophiles.

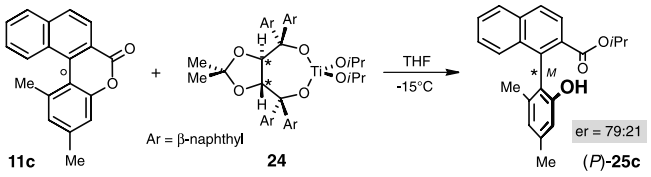
in ether (Scheme 5, right table) [27]: Not only did the ring opening in this case proceed with a higher degree of stereo-differentiation, reaching, dr's of up to 94:6, but it also provided an *inverse* asymmetric induction to give (*P*,*R*)-**21b** [and (*M*,*R*)-**21c**] as the major diastereomers! This is one of the rare cases in which both stereoisomers can be prepared from a single precursor and with the same reagent (even with the same enantiomer)—just by slightly changing the reaction conditions (here: solution vs. suspension).

The best stereocontrol with *O*-nucleophiles was achieved with sodium (*R*)-8-phenylmenthoxide [Na–(*R*)–**22**], in which, compared with sodium (*R*)-menthoxide [Na–(*R*)–**20**], the isopropyl substituent is replaced by the more bulky dimethylphenyl group (Scheme 6). Alcoholysis of **11** with Na–(*R*)–**22** gave exclusively the biaryl ester (*M*,*R*)-**23c** in 95% yield, the other atropodiastereomer not being detectable [27].

A first successful approach to a directly enantioselective variant of the method was achieved with Seebach's (^{i}PrO)$_2$Ti-TADDOLate (**24**) [28], which serves both as a chiral Lewis acid and as the *O*-nucleophile (Scheme 7). Treatment of **11c** with **24** delivered the ester (*P*)-**25c** [29], albeit as yet with a moderate er of 79:21 [30].



Scheme 6. Ring opening of **11c** with sodium (*R*)-8-phenylmenthoxide [(*R*)-**22**].



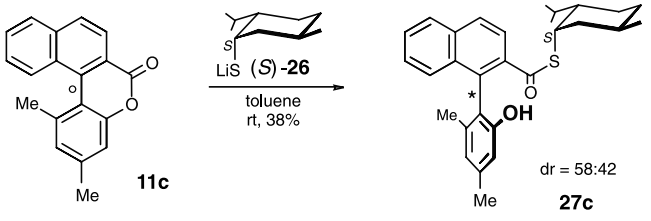
Scheme 7. Atropo-enantioselective alcoholysis of **11c** with the (^{i}PrO)$_2$Ti-TADDOLate **24**.

5.3. Less efficient: the use of chiral *S*-nucleophiles

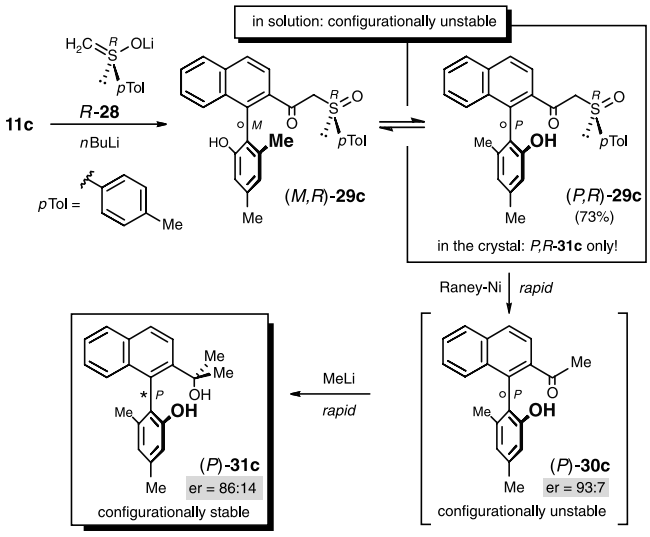
Different from the highly stereo-differentiating *N*- and *O*-nucleophiles (vide supra), chiral lithiated thiols like (*S*)-**26** (Scheme 8) have so far cleaved the lactone bridge of **11c** with disappointingly low asymmetric inductions (dr < 60:40) [31]. The resulting thioesters (here **27c)** are configurationally stable under neutral conditions, but easily cyclize back to the lactone **11c** under basic conditions. Thus, it is not clear whether the unsatisfying diastereoselectivities obtained are due to an insufficient stereocontrol in the ring opening step or whether they are the result of a subsequent loss of stereochemical homogeneity through equilibration via **11**, e.g. (*M*)-**27c**⇌**11**⇌(*P*)-**27c** (for a detailed discussion on such 'stereochemical leakages', see Section 8).

5.4. Ring cleavage with extension of the carbon framework: by reaction with *C*-nucleophiles

The ring opening of the lactones **11** with chiral *C*-nucleophiles should be particularly attractive, in combining the introduction of the stereogenic information at the biaryl axis with an extension of the C-skeleton. Practically, however, a severe problem, arises from the configurational instability of the products [11,12]. As an example, treatment of **11c** with the chiral lithiated sulfoxide (*R*)-**28** (Scheme 9) delivered the diastereomeric β-keto sulfoxides (*M*,*R*)-**29c** and (*P*,*R*)-**29c** as a 1:1 mixture, as a consequence of the interconversion of the two atropisomers at room temperature ($t_{1/2}$ = 1.5 h) [12]. In this particular case, the problem was overcome by converting essentially the entire material of **29c** into (*P*,*R*)-**29c** by fractional crystallization [23,32]. Rapid reductive desulfurization of now stereochemically homogeneous (*P*,*R*)-**29c** led to the likewise configurationally unstable ketone (*P*)-**30c** ($t_{1/2}$ = 7 h at 25 °C [23]), the subsequent alkylation of which gave the now configurationally stable alcohol (*P*)-**31c**, still with an er of 86:14 [12].



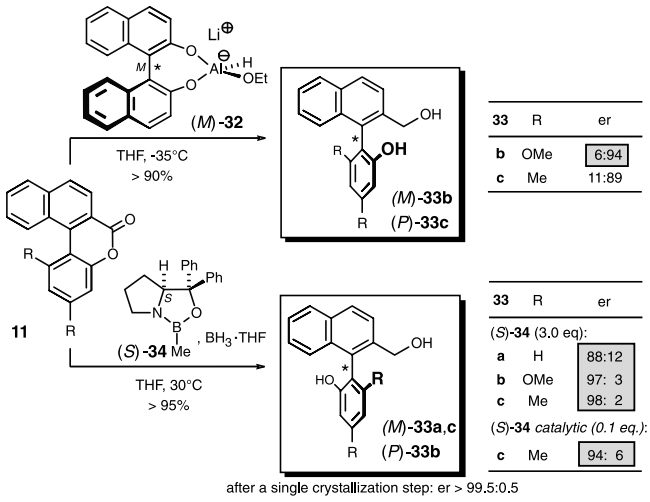
Scheme 8. Cleavage of **11c** with lithiated (*S*)-**26** as a chiral *S*-nucleophile.



Scheme 9. Preparation of the non-racemic alcohol (*P*)-**31c** by ring opening of **11c** with the lithiated sulfoxide (*R*)-**28**, 'stereo-focusing' by crystallization, followed by rapid desulfonylation and *C*-methylation.

5.5. Atropo-enantioselective lactone reductions

The atropo-enantioselective cleavage of lactones **11** with chiral hydride transfer reagents proved to be particularly successful (Scheme 10). Treatment of **11** with Noyori's BINAL-H [(*M*)-**32**] [33] gave the alcohols **33** with an er of up to 94:6 and in >90% yield [34]; reduction of **11** with borane-THF in the presence of Corey's CBS-reagent (*S*)-**34** [35] delivered **33** in even higher chemical (>95%) and optical yields (er of up to 98.5:1.5) [36,37] Since the substrates for these atropselective reductive ring cleavage reactions are lactones,

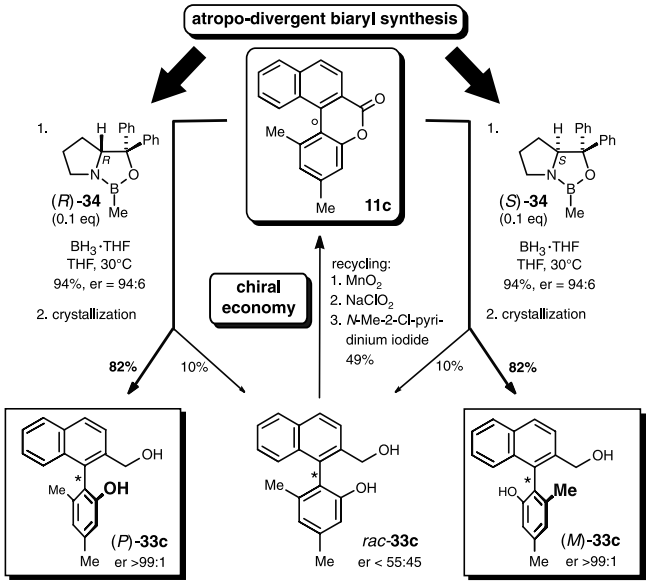


Scheme 10. Reduction of **11** with BINAL-H [(*M*)-**32**] and with the CBS-reagent (*S*)-**34**.

with diminished carbonyl reactivities as compared with ketones (for which the CBS-system has originally been developed), usually three equivalents of (*S*)-**34** are used. Still, with only slightly smaller asymmetric inductions also reductions of **11c** with borane–THF in the presence of 10 mol% (*S*)-**34** are possible, leading to (*M*)-**33c** with an er of 94:6—a truly catalytic atropo-enantioselective biaryl synthesis [37]. In each case, the biaryl alcohol was obtained in enantiopure form by a single crystallization step.

6. Atropo-divergence and chiral economy—two characteristic advantages of the lactone methodology

For an efficient stereoselective transformation, two crucial requirements have to be fulfilled: (1) it must allow an optional preparation of any of the two atropisomers from the same immediate precursor, and (2) it has to permit a recycling of an undesired stereoisomer possibly formed as a side product, in particular for the use of the method for 'precious' substrates resulting from multi-step syntheses. These two fundamental demands, which are well known from the field of centrochiral compounds, can, however, not (yet) be fulfilled [5–9] in the synthesis of axially chiral biaryls by other methods [38]. The basic principle of the lactone concept, however, the dynamic kinetic resolution of configurationally unstable lactone precursors, is suited to meet these demands perfectly. This is demonstrated in Scheme 11, exemplarily for the catalytic enantioselective reduction of the lactone **11c** with the CBS-catalyst **34** [37] (see also Section 5.5): Since both



Scheme 11. Additional advantages of the lactone strategy: atropo-divergent biaryl synthesis and chiral economy, as exemplified for the catalytic enantioselective reduction of **11c** with (*S*)-**34** and (*R*)-**34**.

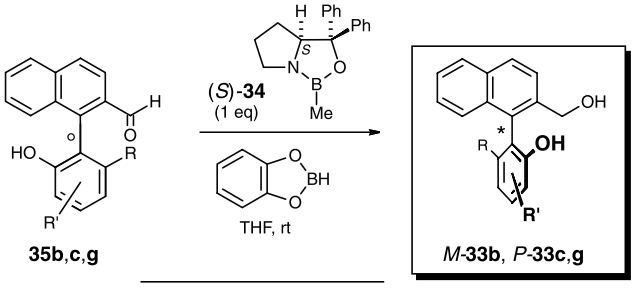
enantiomers of **34** are commercially available, both atropo-enantiomers of **33c** can be prepared from **11c** atropo-divergently just by using (*R*)-**34** [leading to (*P*)-**33c**] or, optionally, (*S*)-**34** [leading to (*M*)-**33c**]. The small amount of nearly racemic alcohol *rac*-**33c** as recovered from the mother liquor after crystallization, can be re-used by re-oxidation and recyclization back to the lactone **11c** and renewed ring cleavage, following the principle of chiral economy [39]. These two advantages are quite generally applicable to all the biaryls resulting from the ring opening reactions of **11** and related lactones (see Section 5).

7. Expansion of the lactone concept to other substrates

7.1. Configurationally unstable biaryl hydroxy aldehydes

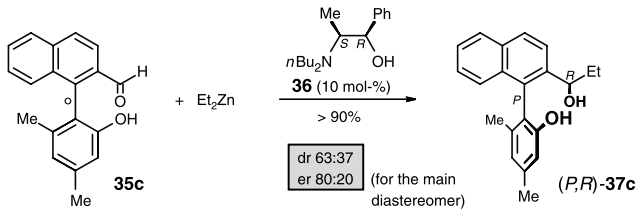
The strategy elaborated is not restricted to biaryl lactones as the substrates, but can be extended to other configurationally unstable biaryls. Such a remarkable case is the enantioselective reduction of biaryl hydroxy aldehydes of type **35** (Scheme 12), which are, although not being bridged biaryls as such, configurationally unstable too, since they can atropisomerize via their bridged lactol tautomers (for an explicit discussion of this mechanism, see Section 9) [40–42].

The CBS-reduction of **35** in the presence of a stoichiometric amount of (*S*)-**34** and with catecholborane as the achiral reductant showed a strong dependence of the enantiomeric ratio on steric hindrance at the axis [43]: While the less hindered derivative **35g** (R = H) was obtained with a high er of 92:8, the stereoselectivity was less significant with more bulky groups (R = OMe, Me) next to the axis (Scheme 12). Nevertheless, at least for sterically less hindered biaryl hydroxy aldehydes, CBS-reduction of **35** is a valuable complement to the lactone method, which, by contrast, delivered the best optical yields for sterically more hindered derivatives (optimum



35, 33	R	R'	er
g	H	3-*i*Pr	92:8
b	OMe	4-OMe	61:39
c	Me	4-Me	51:49

Scheme 12. CBS-reduction of the biaryl hydroxy aldehydes **35**.



Scheme 13. Catalytic enantioselective addition of Et_2Zn to **35c**.

for R = Me, see Section 5.5); for an application to natural product synthesis, see Ref. [44].

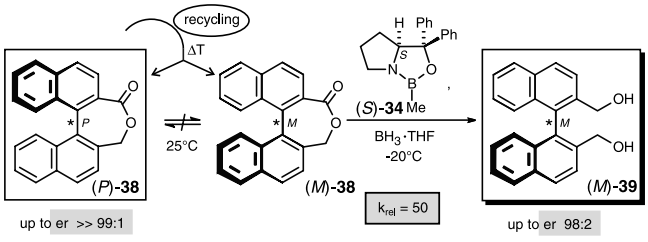
With the hydroxy aldehyde **35c**, we also succeeded in performing the first catalytic atropo-enantioselective addition of a *C*-nucleophile to a configurationally unstable biaryl (Scheme 13) [11]. Treatment of **35c** with diethylzinc in the presence of 10 mol% (−)-DBNE (**36**) [45] gave the secondary alcohol (*P*,*R*)-**37c**, albeit with a moderate asymmetric induction (dr = 63:37, er = 80:20) [46]. This reaction proceeded with double stereo-differentiation, simultaneously establishing the configuration at the axis and at the stereocenter.

These initial investigations already reveal that the hydroxy aldehydes are versatile precursors for the atroposelective construction of axially chiral biaryls, making a further evaluation of the potential of this class of precursors a rewarding task.

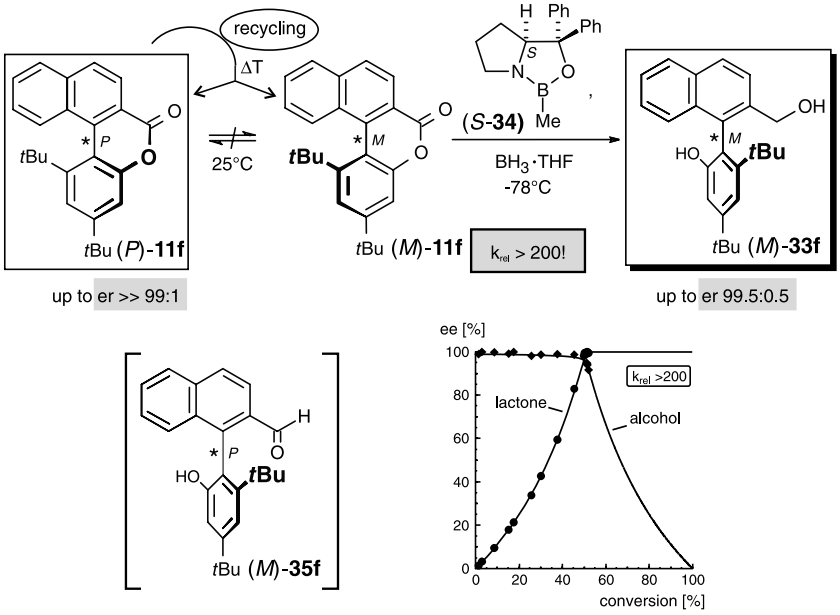
7.2. Non-dynamic kinetic resolution of configurationally stable lactones

In contrast to the rapidly atropisomerizing biaryls discussed in the preceding chapters, the lactone **11f**, equipped with a voluminous *tert*-butyl group next to the axis is configurationally nearly stable at room temperature ($t_{1/2} > 2$ day, see Section 3) [21,23]. Thus, **11f** is clearly not suited for a dynamic kinetic resolution, but might be a useful substrate for a normal, i.e. non-dynamic kinetic resolution (Scheme 14). This was confirmed by its CBS-reduction, which proceeded highly atroposelectively, with a relative rate constant $k_{rel} > 200$ [47,48]! Depending on the degree of conversion, either the alcohol (*M*)-**33f** or the lactone (*P*)-**11f** [49] can be obtained in almost enantiopure form (er > 99.5:0.5). Furthermore, if high quantities of (*M*)-**33f** are wanted, the unreacted lactone **11f**, enriched with the 'wrong' enantiomer (*P*)-**11f**, can be re-used by thermal racemization, and can then be re-submitted to the enantiomer-differentiating reduction. At low conversions, small portions of the now configurationally stable hydroxy aldehyde (*M*)-**35f**, the intermediate of the reduction **11f** → **33f**, can be isolated with high enantiopurity (er > 98:2), too.

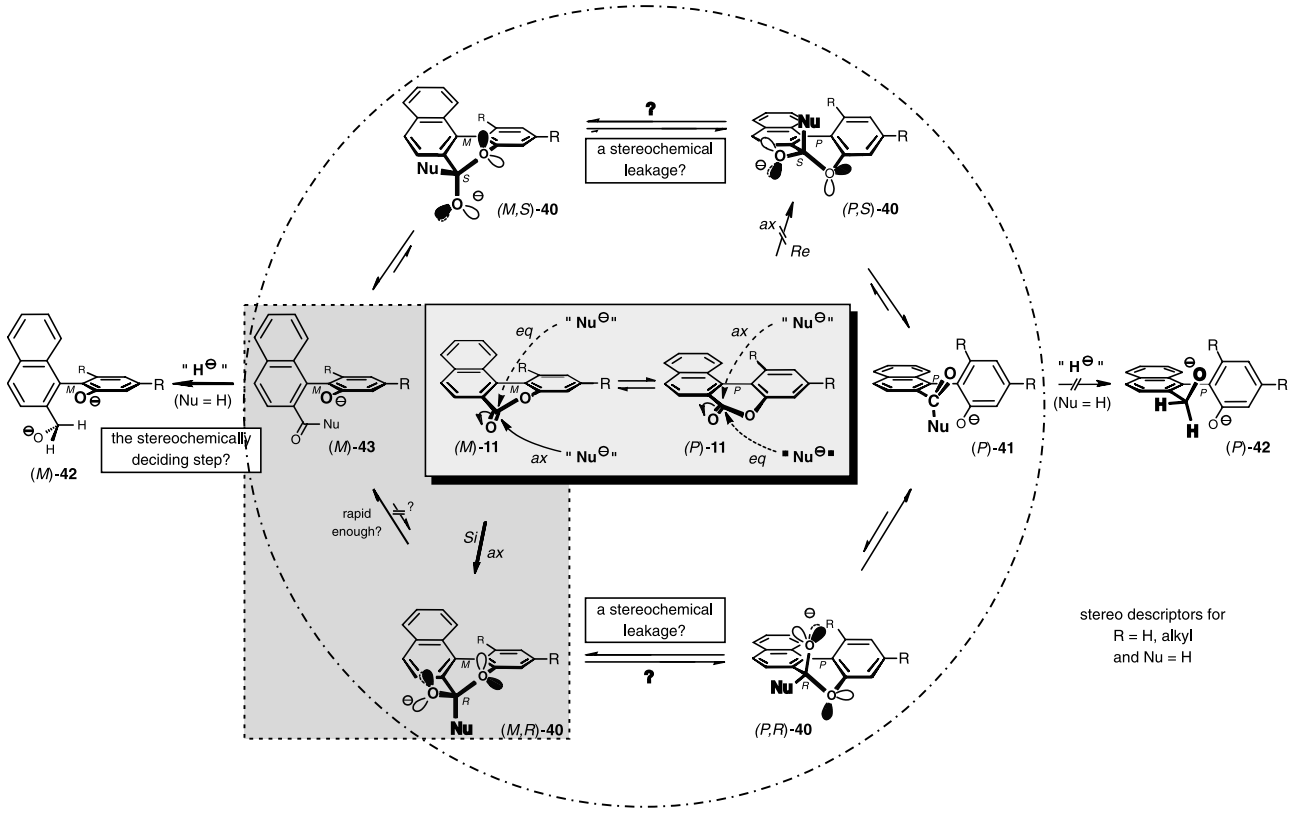
Likewise successful was the kinetic resolution of the again, configurationally stable seven-membered ring lactone **38** [50,51] (Scheme 15). In this case, a k_{rel} of 50 was found [52].



Scheme 15. Kinetic resolution of the configurationally stable seven-membered lactone **40**.



Scheme 14. Kinetic resolution of the configurationally stable lactone **11f**.



Scheme 16. The proposed mechanistic course of the lactone cleavage; for reason of simplicity, metalated species drawn in a purely anionic form.

8. The stereochemical course of the ring opening reaction

An intriguing question is where the high asymmetric inductions obtained by the lactone method come from, i.e. what the stereochemical principle is. The fast equilibrium between the two lactone enantiomers (*M*)-**11**⇌(*P*)-**11** (see Section 3) forms the basis for the ring cleavage reaction to proceed according to the principle of a dynamic kinetic resolution (Scheme 16). In principle, each helimer of **11**, (*M*)-**11** and (*P*)-**11**, can be attacked in an equatorial or axial fashion, but quantum chemical calculations indicate the latter mode of approach to be preferred leading to (*M*,*R*)-**40** and (*P*,*S*)-**40**, respectively, [22,53]. A chiral nucleophile that can differentiate between the atropo-enantiomers (*M*)-**11** and (*P*)-**11** will thus ideally give only one of the four possible intermediates, e.g. only (*M*,*R*)-**40**, which, if it opens immediately, will deliver the target biaryl (*M*)-**41**, exclusively. By this way, given the rapid interconversion (*M*)-**11**⇌(*P*)-**11**, the entire racemic starting material can be converted into a single, stereochemically uniform product.

This reaction pathway, however, bears the inherent risk of 'stereochemical leakage' [40,42] at the level of intermediates **40**, viz if (*M*,*R*)-**40** has a sufficient life time or if it gets steadily rebuilt via an equilibrium with the product (*M*)-**41**. As a bridged biaryl, (*M*,*R*)-**40** might, similar to the lactones **11**, helimerize to give its atropo-diastereomer (*P*,*R*)-**40**! If both (*M*,*R*)-**40** and (*P*,*R*)-**40** open with equal rates, any stereochemical information initially achieved will be lost and **41** will be formed as a racemic mixture. Furthermore, if the product initially formed, e.g. (*M*)-**41**, cyclizes back, both to (*M*,*R*)-**40** and (*M*,*S*)-**40**, again a complete loss of the stereochemical input might result via the whole 'outer circle' (*M*)-**41**⇌(*M*,*R*)-**40**⇌(*P*,*R*)-**40**⇌(*P*)-**41**⇌(*P*,*S*)-**40**⇌(*M*,*S*)-**40**⇌(*M*)-**41**. So, the decisive question is: Under which conditions or with which type of nucleophile does which pathway prevail?

In the ring cleavage of **11** with metalated *O*- and *N*-nucleophiles, the intermediates **40** are the (likewise deprotonated and metalated) ortho-esters, which indeed will rapidly (and largely irreversibly) burst open, due to the electron push of the exocyclic heteroatoms. This process may be further accelerated by the presence of bulky substituents *ortho* to the axis as an additional driving force. Thus, in the case of *O*- and *N*-nucleophiles, an intermediate of type **40**, once formed in the attack on lactone **11**, should spontaneously open, without any significant isomerization at the biaryl axis, so that in this case a direct pathway, e.g. (*M*)-**11**→(*M*,*R*)-**40**→(*M*)-**41**, is pursued without major risk of stereochemical leakage. Once achieved, high levels of asymmetric induction resulting from the initial attack on the lactone **11** will be transmitted to the product. Due to the comparably low chemical reactivity of the resulting ester

and (in particular) of the amide function, the product will not cyclize back and will thus be configurationally stable.

This direct, simple pathway may, however, no longer apply if the lactones **11** are cleaved with *C*- or *H*-nucleophiles. That is, the initially resulting, far more reactive intermediate ketone or aldehyde phenolates **41** (Nu = H or alkyl) can easily atropisomerize 'chemically', via the lactolates **40** [40,41,53,54] and, thus, may 'fall' into the stereochemical leakage. The consequence is that any asymmetric information introduced in the primary attack on **11** gets lost, which is indeed observed in the ring cleavage of **11c** with the chiral *C*-nucleophile (*R*)-**28** (cf. Section 5.4). This configurational instability of the hydroxy aldehydes **35** can in turn be utilized by their atropo-enantioselective reduction with dynamic kinetic resolution (cf. Section 7.1).

In contrast to the chiral *C*-nucleophiles, reductive cleavage reactions on the lactones **11** deliver excellent levels of asymmetric induction. Initial attack on **11** probably occurs highly stereoselectively as proven at least for the (non-dynamic) kinetic resolution of lactone **11f**, and as also seen from the configurationally stable hydroxy aldehyde **35f** obtained in high optical yield (see Section 7.2). For the subsequent steps, however, two completely different mechanistic explanations are imaginable, depending on the degree of steric hinderance *ortho* to the axis:

8.1. Route a

The lactolate stereoselectively formed, e.g. (*M*,*R*)-**40** (Nu = H), immediately bursts open to give the aldehyde phenolate (*M*)-**41**, which is trapped at once by a *rapid* second hydride shift. Thus, the asymmetric information introduced in the first attack on the lactone **11** is fully conserved in the resulting configurationally stable diolate (*M*)-**42**, without isomerization at the level of the intermediate species (*M*,*R*)-**40** and (*M*)-**41**, thus circumventing stereochemical leakage.

8.2. Route b

As the other extreme, there is a rapid equilibrium between all the isomeric species **40** and **41** (Nu = H) of the 'outer circle' of Scheme 16, leading to the loss of any stereochemical information possibly attained in the initial step. Consequently, it must be the second hydride transfer step, **41** → **42**, that is stereochemically decisive in this case, i.e. a dynamic kinetic resolution at the level of the intermediate aldehydes **41**: Ideally, only one of the two enantiomers (*M*)-**41** and (*P*)-**41** gets reduced, delivering the stereochemically highly enriched diolate experimentally found, e.g. (*M*)-**42**. The existence of this route **b** is substantiated by the successful enantioselective CBS-reduction of the (racemic!) hydroxy aldehydes **35**. These protonated analogs of **41** (Nu = H), however, gave high asymmetric inductions only for the less sterically hindered derivative **35a** (R = H) (cf. Section 7.1), thus indicating that for sterically more hindered lactones **11** (e.g. with R = OMe, Me) it is the *initial* attack on **11** that establishes the ultimate configuration at the biaryl axis (Section 8.1).

9. Ring opening of biaryl lactones activated by Lewis acids (method II)

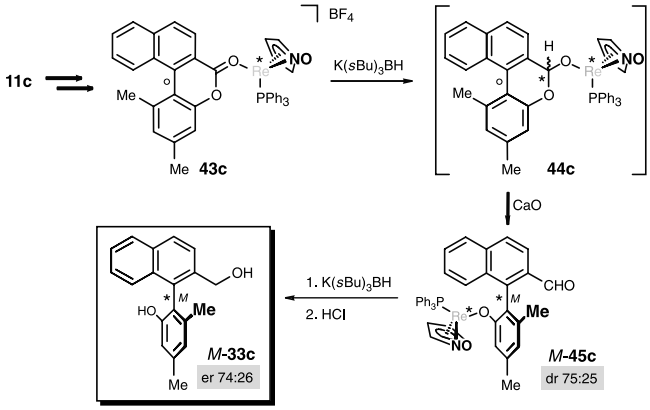
9.1. Lactones modified by a chiral rhenium complex fragment

An alternative approach that does not have to rely on an activation of the nucleophile is the activation of the lactones **11** themselves, by coordination of a Lewis-acidic transition metal, which in addition can serve as the chiral auxiliary for the ring opening step.

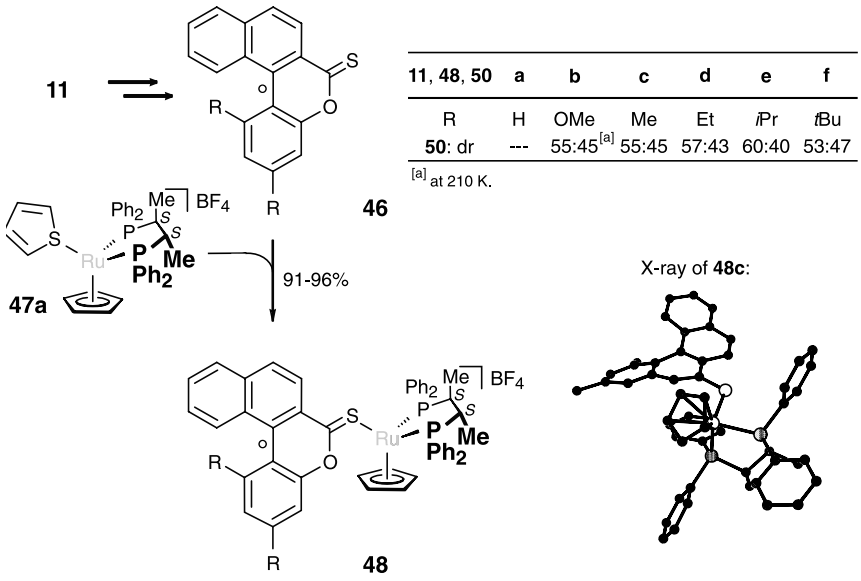
First experiments in this direction were performed with lactone **11c**, complexed with the chiral rhenium fragment Re*Cp(NO)(PPh_3) [55] (Scheme 17) [56]. Reduction of **43c** with the achiral hydride K-Selectride ($KsBu_3BH$) delivered the lactolate **44c**, which was ring-opened with CaO to give the aldehyde **45c**, yet in a moderate diastereomeric ratio of 75:25. In contrast to the configurationally unstable free hydroxy aldehydes (**35**) (see Sections 7.1 and 7.2), this metal-'protected' derivative was sufficiently configurationally stable such that the reduced and decomplexed alcohol (*M*)-**33c** could be obtained without considerable loss of atropisomeric purity.

9.2. Atropo-diastereoselctive ring opening of chiral thionolactone–ruthenium complexes

Better results were obtained with the respective ruthenium thionolactones of type **46** (Scheme 18) [57],



Scheme 17. Atroposelective reduction of the rhenium-complexed biaryl lactone **43c**.



11, 48, 50	a	b	c	d	e	f
R	H	OMe	Me	Et	*i*Pr	*t*Bu
50: dr	---	55:45[a]	55:45	57:43	60:40	53:47

[a] at 210 K.

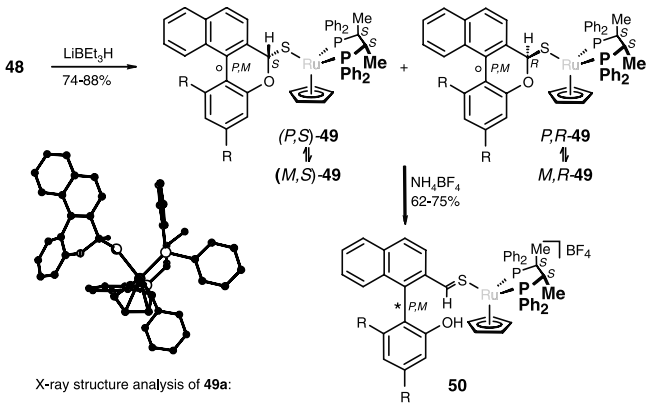
Scheme 18. Synthesis and atropo-diastereomeric equilibrium ratios of the biaryl-thionolactone complexes **50**, and, exemplarily for **50c**, crystal structure (hydrogen atoms and the BF_4^- anion omitted for reason of clarity).

activated and chirally modified by the coordinatively unsaturated complex fragment {CpRu[(*S*,*S*)-CHIRAPHOS)]}$^+$ [(*S*,*S*)-CHIRAPHOS = (2*S*,3*S*)-bis(diphenylphosphino)butane)] [58,59]. The key compounds **48a**–**f** were synthesized in excellent yields from the highly reactive thiophene complex **47a** [60] and the thionolactones **46a**–**f** (Scheme 18), which in turn had been obtained from the corresponding 'standard' lactones **11** by treatment with Lawesson's reagent.

As in the corresponding oxolactones **11**, the biaryl axis is configurationally unstable in the ruthenium complexes **48a**–**f**, and again, the diastereomerization rate (*M*)-**48**⇌(*P*)-**48** depends strongly on the size of the substituent R next to the axis (see also Section 3) [57]. The borderline cases are marked by **48a** (R = H), which, even at 210 K, exists as a mixture of rapidly equilibrating atropo-diastereomers, and **48c**–**f** (R = Me, Et, ^{i}Pr, ^{t}Bu), whose ^{31}P-NMR spectra up to 380 K exhibit two separate sets of signals for the two rotational diastereomers. Biaryl (**48b**) (R = OMe) shows two sets of signals at 210 K in a 55:45 ratio, which coalesce at 263 K ($\Delta G^{\neq} = 11$ kcal mol^{-1}). ^{1}H-NMR spectra of **48c** and **48d**, if recorded immediately after dissolution at 253 K, gave distinctly higher diastereomeric ratios, which, however, decreased within a short time indicating that the atropo-diastereomerization process has a halflife in the range of a few minutes at this temperature. Nevertheless, the influence of the stereogenic centers at the metal on the atropisomeric ratio in the thermodynamic equilibrium was relatively small.

An X-ray structure determination of complex **48c** shows that the biarylic thionolactone ligand preferentially adopts the *P*-configuration in the solid state (vide supra, Scheme 18) [57]. The thiolactone carbonyl atom of **48c** is perfectly shielded from the *si*-side by one of the phenyl groups of the (*S*,*S*)-CHIRAPHOS ligand. It is thus tempting to hope that nucleophiles will add from the *re*-side with high diastereoselectivities, provided that the structure in solution resembles that in the solid state. An important clue to that comes from the observation of two fairly different ^3J(P,C) couplings of the C=S group for the two diastereomeric forms of **48b**–**f**, indicating that the two dihedral angles C–S–Ru–P remain unequal in solution, too. Furthermore, the *M*-diastereomer must have a similar structure with a near-coplanar arrangement of C, S, Ru, and P. This can be deduced unequivocally from the fact that in the room temperature NMR spectra of **48a** and **48b** the ^{13}C signal of the thionolactone group still appears as a doublet of doublets with two unequal couplings. If the inversion of the biaryl axis was accompanied by a rotation of the Ru–S bond such as to expose the *si*-side for nucleophilic attack, then the two couplings ^3J(P,C) of the diastereomers should become equal and make the signal at $\delta =$ 200 appear as a triplet. The conclusion then is that for both diastereomers of the thionolactone complexes **48a**–**f**, *re*-addition should be strongly favored over a *si*-attack.

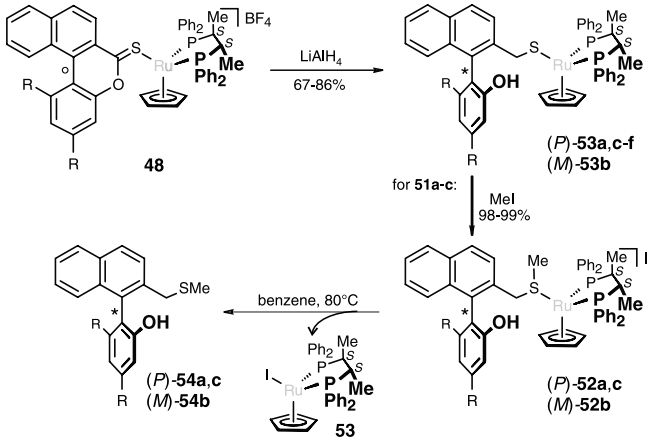
The stereochemical outcome of the reduction of **48a**–**f** with lithium triethylborohydride to give the thiolactolate complexes **49a**–**f** (Scheme 19) was found in perfect agreement with these assumptions. At room temperature, compounds **49a**–**f** are present as mixtures of two (**49a**, **b**) or four (**49c**–**f**) diastereomers. The ^{31}P-NMR spectrum of **49b** consists of two broad signals, which upon cooling to 270 K decoalesce into two AX spin systems due to a slowed atropisomerization at the biaryl axis. The X-ray structure determination of the major



48, 49, 50	a	b	c	d	e	f
R	H	OMe	Me	Et	*i*Pr	*t*Bu
(*S*)-**51**:(*R*)-**51**	93: 7	93: 7[a]	>90:10	>90:10	>90:10	>90:10
(*P,S*)-**51**:(*M,S*)-**51**	---	30:70[b]	58:42	59:41	61:39	50:50
(*P*)-**52**:(*M*)-**52**	53:47	46:54[b]	56:44	56:44	62:38	50:50

[a] at 220 K. - [b] The seemingly reversed asymmetric induction is only due to the CIP-formalism (OMe > OH > Alkyl)

Scheme 19. Hydride addition to biaryl-thionolactone complexes **48**, proton-induced ring opening of **49** to give **50**, and the crystal structure of (*P*)-**49a**; hydrogen atoms (except for the acetalic one) omitted.



48, 51, 52, 54	a	b	c	d	e	f
R	H	OMe	Me	Et	*i*Pr	*t*Bu
(*P*)-**53**:*M*-**53**	76: 24	54:46[a]	88:12	67: 33	67:33	53:47
(*P*)-**56**:*M*-**56**	75:25	54:46[b]	88:12	---	---	---

[a] at 220 K. - [b] The seemingly reversed asymmetric induction is only due to the CIP-formalism (OMe > OH > Alkyl).

Scheme 20. Twofold hydride addition to the biaryl-thionolactone complexes **48** and stepwise decomplexation of the Ru-thiolates **51** to give the enantiomerically enriched biaryl compounds **54**.

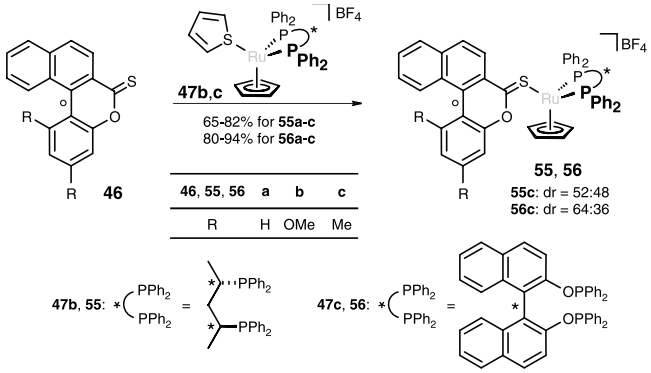
diastereomer of **49a** shows the expected *S*-configuration at the newly formed acetalic stereocenter at C70, while the biaryl axis has a fixed *P*-configuration in the crystal. While the diastereoselectivity of the hydride addition to **48** exceeded 80%, the atropisomeric ratio [(*M*)-**49**:(*P*)-**49**], which is thermodynamically controlled, was disappointingly low, apparently due to only faint energetic differences between the two diastereomers. It is thus not surprising that the proton-induced ring opening gives the thioaldehyde complexes **50a**–**f** in very low diastereoselectivities.

The acid-induced ring opening **49** → **50** can be reversed [57]: Addition of sodium carbonate to deep purple solutions of **50c**,**d** led to a color change back to yellow, with quantitative formation of **49c**,**d**. Overall, this step constitutes a stereochemical leakage as discussed in Section 9. Nevertheless, if the thioaldehyde intermediate **50** could be reductively trapped by a second hydride addition *before* an isomerization at the biaryl axis occurs, then it might be possible, despite this stereochemical leakage, to preserve the possibly high asymmetric induction attained in the initial attack on the thionolactone **50**. Indeed, treatment of **48a**–**f** with lithium aluminum hydride in THF gave, as expected, the configurationally stable thiolate complexes **51a**–**f** in good yields and in some cases quite good diastereoselectivities (Scheme 20). Exemplarily for **51a**–**c**, the chiral ruthenium fragment was removed by alkylation with methyl iodide giving the thioether complexes **52a**–**c**. By heating in benzene, these were cleaved to the enantiomerically enriched free thioethers **54a**–**c** and the iodo complex **53**, which can thus be re-used (see Scheme 18). The decomplexation sequence occurs with full retention of configuration at the biaryl axis.

For further experiments with other chelating phosphine ligands as chiral auxiliaries [61], the thionolactone complexes **55a**–**c** (enantiomerically pure) and **56a**–**c** (racemic) were synthesized (Scheme 21).

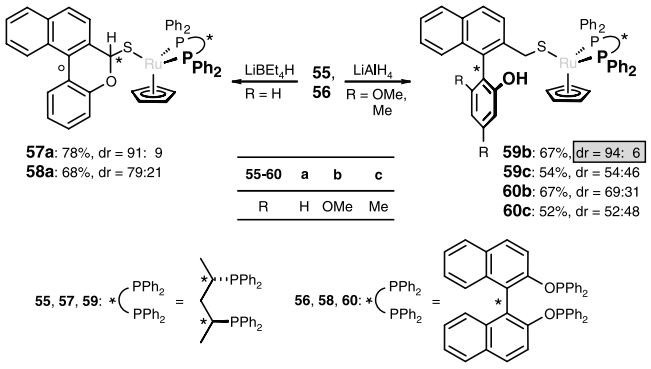
Ruthenium complexes **55a** and **56a** were reacted with lithium triethylborohydride to give **57a** and **58a** (Scheme 22). Chirality transfer from (2*S*,4*S*)-bis(diphenylphosphino)pentane (dr = 91:9) was comparable to that of (*S*,*S*)-CHIRAPHOS (dr = 93:7, see Scheme 19), whereas the binaphthol-derived bis(phosphinite) ligand gave a somewhat inferior result (dr = 79:21).

As expected, full reduction of **55b**,**c** and **56b**,**c** with $LiAlH_4$ in THF yielded the thiolate complexes **59b**,**c** and



46, 55, 56	a	b	c
R	H	OMe	Me

Scheme 21. Synthesis of the chiral biaryl–thionolactone complexes **55** and **56**.

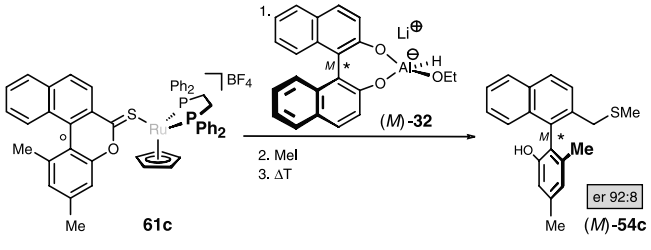


Scheme 22. Single and double hydride addition to biaryl–thionolactone complexes **57** and **58**.

60b,**c**. In the case of **61b**,**c**, the stereoselectivity was still insufficient. However, **59b** was formed in an excellent diastereomeric ratio of 94:6. This is particularly encouraging since the ring opening of the analogous methoxy-substituted thionolactone complex **48b** according to Scheme 20 was achieved with only very low stereocontrol, which again emphasizes the importance of the proper choice of chiral auxiliary.

9.3. Atropo-enantioselective ring cleavage of 'achiral' thionolactone–ruthenium complexes with chiral H-nucleophiles

As an alternative to the sequence described above, also an achiral ruthenium fragment in combination with a chiral hydride source can be used. This has been most successfully exemplified in the atropo-enantioselective reduction of the dppe-complex **61c** [60] with (*M*)-BINAL-H [(*M*)-**32**] (Scheme 23). After decomplexation, the thioether (*M*)-**54c** was obtained in almost quantitive yield and with an excellent enantiomeric ratio of 92:8 [62], showing that further investigations along this approach are highly rewarding for the future.



Scheme 23. Enantioselective reductive cleavage of the 'achiral' (more exactly: helical, but rapidly enantiomerizing) ruthenium complex **61c** with (*M*)-BINAL-H [(*M*)-**32**].

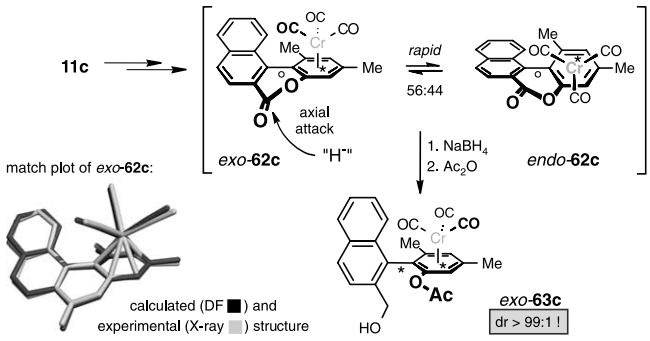
10. Ring opening of η⁶-complexed planar–chiral biaryl lactones (Method III) (Section 4.3)

10.1. Substrates for highly diastereoselective ring cleavage reactions: η⁶-Cr complexes

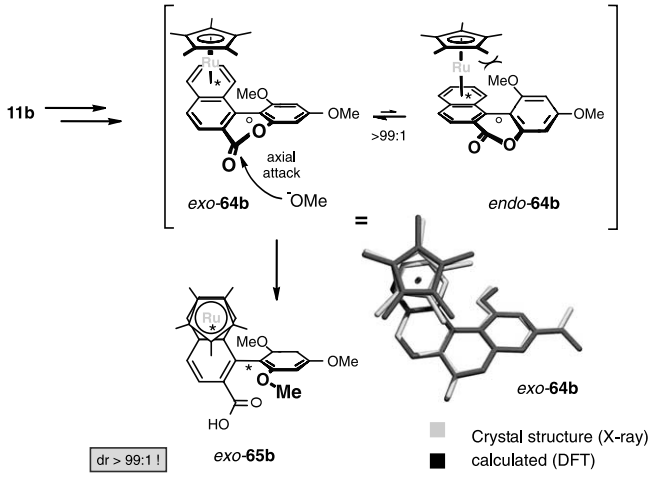
A third option to activate the lactones **11** is given by the η⁶-coordination of a transition metal fragment, which adds an additional element of planar chirality to the system. As an example, coordination of a tricarbonyl chromium unit to the phenolic part of **11c** delivered the (here still racemic) η⁶-complex **62c** (Scheme 24) [63]. The complexation site of the chromium fragment and the dynamic behavior of **62c** has been rationalized by density functional (DF) methods [64]. The calculated structural data of *exo*-**62c** are in good agreement with those from its X-ray analysis. Like the 'free' lactone **11c**, its complex **62c** is configurationally unstable and exists as a 56:44-mixture of the two (again racemic) atropo-diastereomeric forms *exo*-**62c**⇌*endo*-**62c** in solution. Out of this equilibrium, ring cleavage of **62c** with sodium borohydride proceeds highly stereoselectively, yielding the biaryl alcohol *exo*-**63c** exclusively. Its formation is in agreement with an axial attack of the hydride transfer reagent *anti* to the large $Cr(CO)_3$ fragment.

*10.2. Even more efficient and with a different regioselectivity: complexation with RuCp**

η⁶-Complexation of **11b** with Cp*–ruthenium, however, led to **64b**, with the sterically more demanding metal fragment now located on the distal naphthalene (Scheme 25) [65], i.e. on the sterically better accessible, yet less electron-rich ring as compared with the phenolic part (which, in turn, had been the site of coordination in the case of the less bulky $Cr(CO)_3$ fragment; vide supra). By contrast to the $Cr(CO)_3$ complex **62c**, in which the two atropisomers *exo*-**62c**⇌*endo*-**62c** are nearly equally [(56:44), see above] populated, the corresponding equilibrium in the RuCp* complex **64b** is entirely pushed towards the sterically less constrained atropo-diastereo-



Scheme 24. Atropo-diastereoselective reduction of the (still racemic) η⁶-complexed lactone **62c** with $NaBH_4$.



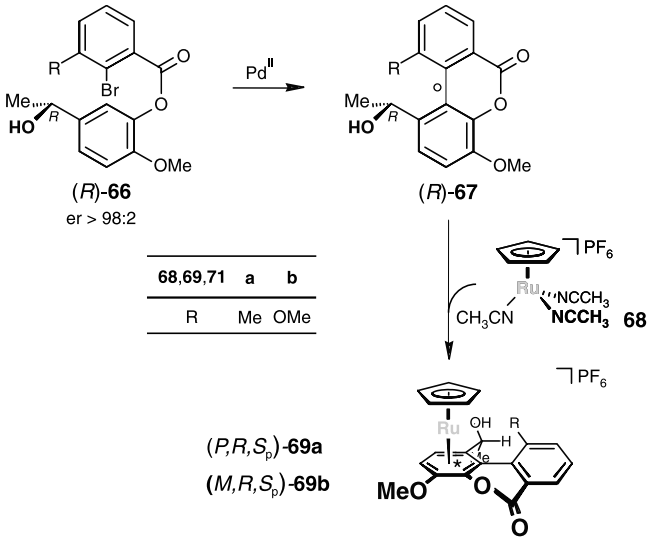
Scheme 25. Ring opening of the racemic Cp*–ruthenium-complexed lactone *exo*-**64b** with NaOMe.

mer *exo*-**64b**. [66] In agreement with this array and with an axial attack of the nucleophile *anti* to the RuCp* fragment, ring cleavage of *exo*-**64b** (racemic) even with NaOMe as a small and simple *O*-nucleophile thus gave the biaryl ester *exo*-**65b**, exclusively. As previously for the $Cr(CO)_3$ complexes (see above), all the experimental observations matched with the results of DF-calculations, here using the Fukui function [65].

10.3. Enantiopure RuCp complexes with stereocontrol for planar and axial chirality

The excellent diastereoselectivities achieved in the ring cleavage reactions of the η^6-complexed and thus planar–chiral (albeit still racemic) biaryl lactones **62c** and **64b** encouraged us to extend this strategy to the use of enantiomerically pure material and to develop methods for the stereoselective coordination of a transition metal fragment. Based on earlier investigations [69], the plan was to use a chiral benzylic alcohol of known absolute configuration, which should facilitate the regioselective coordination of the metal to that arene ring and, at the same time, allow a differentiation between the two (now diastereotopic) arene faces. This concept was realized as shown in Scheme 26 [70].

Intramolecular Pd-catalyzed coupling of (*R*)-**66a** (er > 98:2), as prepared from the corresponding ketone by CBS-reduction [35], delivered the biaryl lactone (*R*)-**67a** in 69% yield. Despite the (expected) presence of (*R*)-**67a** as an atropo-diastereomeric mixture, its treatment with $[CpRu(CH_3CN)_3]PF_6$ (**68**) in refluxing dichloroethane gave the desired centro-, axial- and planar–chiral Cp–ruthenium complex **69a** as a single regio- and stereoisomer in 51% yield. The absolute axial and planar configuration of **69a** was determined by X-ray crystallography. With the configuration of the secondary benzylic alcohol known to be *R*, the elucidation of

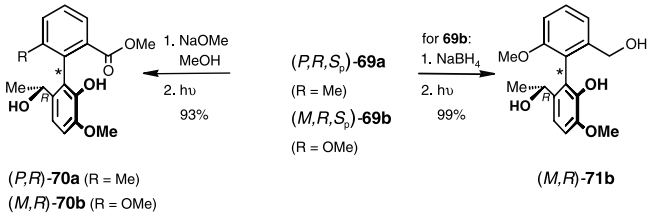


Scheme 26. Highly diastereoselective synthesis of the enantiopure Cp–ruthenium complexed biaryl lactones (*P*,*R*,S_p)-**69a** and (*M*,*R*,S_p)-**69b** (note that the change in the stereochemical denotation from **69a** to **69b** is only due to the formalism of the CIP-denotation [24]).

the relative stereo array established *P*-configuration at the biaryl axis and S_p-configuration for the planar–chiral stereo-element, so that the full stereostructure is *P*,*R*,S_p [70]. Surprisingly, the (*M*,*R*,S_p)-atropo-diastereomer of **69a** was not observed in solution, indicating a strong energetic differentiation between the two isomers. This fact is supported by *ab initio* calculations (B3LYP hybrid density function theory), which predict (*P*,*R*,S_p)-**69a** to be thermodynamically more stable by 2.1 kcal mol^{-1}.

The methoxy substituted analog (*M*,*R*,S_p)-**69b**, which was prepared in a similar way, was likewise obtained as a single regio- and diastereomer. In both cases, the Cp–ruthenium fragment was directed to the electron-rich hydroxymethyl and methoxy substituted arene ring, possibly assisted by an attractive interaction with the benzylic oxygen, permitting both the remarkable regio- and stereoselectivity, to give (*P*,*R*,S_p)-**69a** and (*M*,*R*,S_p)-**69b** (same stereoarray; opposite axial descriptors only for formal reasons) with the ruthenium fragment attached to one face of the arene.

Cleavage of the lactone bridge of **69** with achiral nucleophiles proceeded with complete stereocontrol (Scheme 27) [70]. Treatment of the ruthenium complexes (*P*,*R*,S_p)-**69a** and (*M*,*R*,S_p)-**69b** with sodium methano-



Scheme 27. Atroposelective ring cleavage and demetalation of **69**.

late in methanol followed by photo-oxidative demetalation using an Hg lamp gave the enantiopure, *ortho*-tetrasubstituted biaryl esters (*P*,*R*)-**70a** and (*M*,*R*)-**70b** in 93% yield, while reductive cleavage of (*M*,*R*,S_p)-**69b** succeeded with sodium borohydride (or also with lithium aluminium hydride) and subsequent demetalation delivered the chiral biaryl triol (*M*,*R*)-**71b** in 99% yield, again as a single diastereomer.

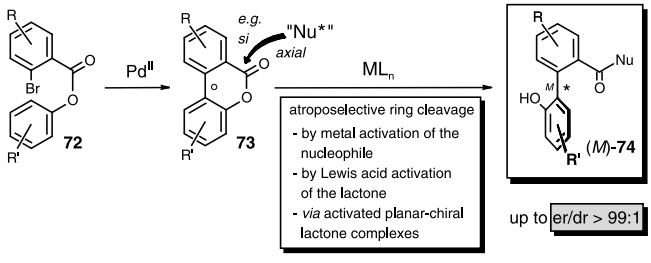
These results impressively prove the potential of planar–chirally modified biaryl lactone η^6-transition metal complexes in the atropo-stereoselective synthesis of axially chiral biaryls within the lactone concept.

11. Concluding remarks

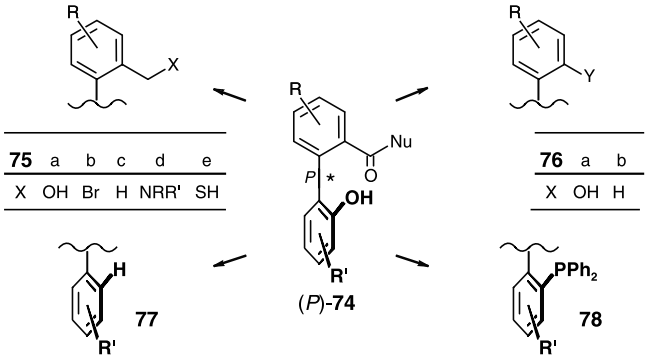
The lactone methodology constitutes an efficient novel tool [37] for the stereoselective preparation of axially chiral biaryls (Scheme 28). The key step is the dynamic kinetic resolution of the configurationally unstable lactones of type **73**, which are easily accessible by intramolecular coupling of appropriately substituted bromoesters (**72**), leading to the ring-opened and, thus, configurationally stable axially chiral biaryls (**74**) in high chemical and optical yields.

The lactone method thus does fulfill the demands mentioned in Section 1 to a very high degree. It permits the regioselective cross coupling of **72** in mostly excellent chemical yields, even for derivatives with severe steric hindrance, and the mild coupling and ring cleavage conditions are compatible with a variety of common functional groups. The method provides atropo-divergent access to any of the two atropisomers, (*M*)-**74** or, optionally, its (*P*)-isomer from the same immediate precursor **73**, and, last but not least, the recycling of an undesired minor atropisomer, formed to any extent is possible by its re-cyclization back to the lactone.

The scope of the lactone method is further extended by the fact that it gives rise to biaryls not only with the typical immediate substitution pattern: a C_1 unit and an oxygen function next to the axis, but also to a series of biaryls bearing different substituents. The previous carbonyl carbon atom of the lactones (**73**) may be transformed into a variety of functionalities. The obtained ring-opened products (**74**) (in Scheme 29



Scheme 28. The basic strategy of the lactone concept.



Scheme 29. Further enlargement of the spectrum of axially chiral biaryl molecules, by subsequent modification of the *ortho*-C_1- and the oxygen-substituents originally present after the atroposelective ring cleavage.

exemplarily for the *P*-isomer) can be converted, e.g. via **75a**, into the bromides **75b**, which can be further reduced down to the methyl group as in **75c**, or can readily undergo substitution reactions with several nucleophiles (for selected examples see **75d** and **e** [71]). Furthermore the hydroxymethylene group of **75a**, as also obtained directly from **73** by using *H*-nucleophiles for the ring cleavage, can be converted into a phenolic OH group like in **76a**, by oxidation to the corresponding aldehyde, followed by Baeyer–Villiger rearrangement and, via the respective *O*-triflate, [72] into numerous other groups, exemplarily shown for the reduction to **76b** (Scheme 29). The same applies to the phenolic OH group of the 'lower' ring of **74**, which has been transformed into phosphanes like **78** [73] or can be reductively eliminated as in **77** [74].

Of even greater importance, however, is the fact that the lactone method does not only work for the model systems described here, but has also proven its applicability in the synthesis of a broad series of (even highly functionalized) natural products and useful chiral auxiliaries. This is reviewed in the following article [13].

Acknowledgements

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