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# Atropo-enantioselective reduction of configurationally unstable biaryl lactones with BINAL-H[1]

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**Abstract**

The atropo-enantioselective reduction of configurationally unstable biaryl lactones with BINAL-H yields axially chiral biaryl alcohols in high enantiomeric ratios of up to 94:6 (er >99.5:0.5 after one crystallization step). Within this two-step reduction process the stereochemically deciding step is the first attack on the lactones and not the reduction of the likewise configurationally unstable biaryl lactol/hydroxy aldehyde intermediates, as evident from the non-stereoselective reduction of the latter under the same conditions. 

## 1. Introduction

Given the increasing importance of axially chiral biaryls both for biologically active natural products and useful reagents for asymmetric synthesis, the availability of efficient and reliable methods for the regio- and stereocontrolled biaryl coupling is an urgent demand.[2] A versatile novel solution to this problem is offered by the 'biaryl lactone concept' (Scheme 1).[3,4] Configurationally unstable model biaryl lactones like **2**, which are easily built up by $Pd^{II}$-catalyzed intramolecular coupling of the esters **1**,[5] can be ring-opened to axially chiral biaryls by reduction (e.g. to **4-A**),[6–8] alcoholysis,[3,4,9,10] or aminolysis[3,4,9] in good to excellent optical and chemical yields. This useful principle has been applied successfully to the synthesis of numerous biaryl natural products[11,12] and chiral auxiliaries.[13]

The key step in this process is the dynamic kinetic resolution of the helically distorted and thus chiral, but rapidly interconverting lactones **2-A**⇌**2-B**.†[3] Particularly high enantiomeric ratios (er) of up to 98.5:1.5 have been obtained in the CBS-reduction of **2** with borane activated by Corey's[14] oxazaborolidine **3**, giving the diols **4-A** in high enantiomeric purities.[6,8] In an early screening for *H*-nucleophiles for the asymmetric ring cleavage of the lactones **2**, Noyori's BINAL-H[15] initially seemed

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† In order to avoid different *M*/*P*-descriptors for stereochemically analogous biaryls that just differ by the residue R, a substituent-invariant **A**/**B**-denotion (**A**=*P* for R=Me and **A**=*M* for R=OMe and *vice versa* for **B**) is used in this paper instead.

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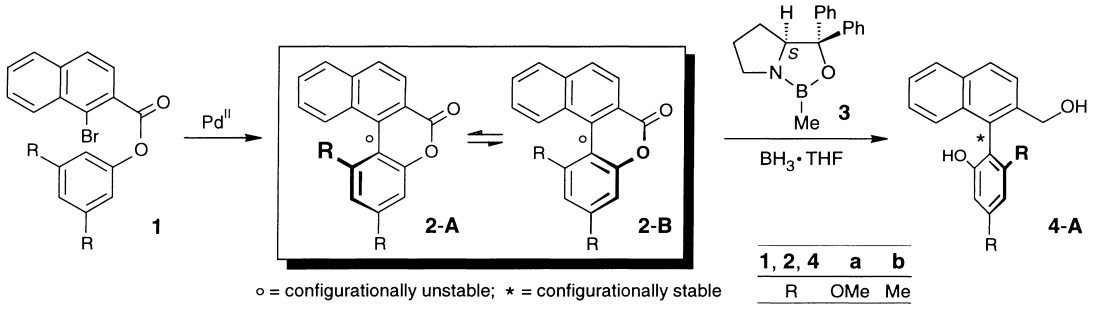


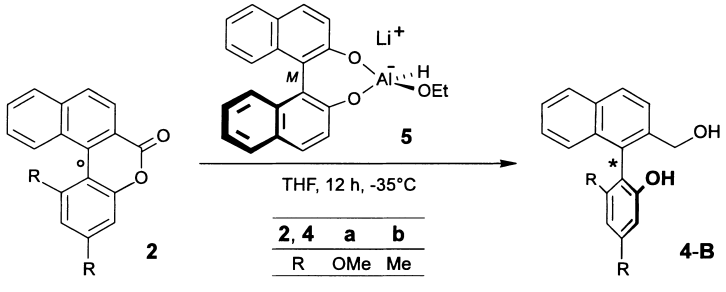

Scheme 1. Synthesis and atropo-selective ring opening of the configurationally unstable lactones **2**

to be inferior to other reagents.[7] Nonetheless, in view of the excellent results with other nucleophiles meanwhile achieved[3,12,13] and the sometimes low isolated yields in the application of the CBS-reduction to alkaloid syntheses,[12] we have looked at the BINAL-H reductions more closely. We now report on the efficient atropo-enantioselective BINAL-H reduction of **2** and on new mechanistic aspects of the introduction of the stereochemical information within this intriguing ring opening process.

## 2. Results and discussion

### *2.1. Atropo-enantioselective BINAL-H reduction of the biaryl lactones **2***

The stereoselective reductions of **2a** and **2b** with BINAL-H (**5**) were performed in THF giving the alcohols **4a-B** and **4b-B** respectively, as the main enantiomers (Scheme 2 and Table 1). This nicely complements the tendency of the L-proline derived oxazaborolidines **3** to deliver **4-A**[6,8] — which now can likewise be attained by reduction of **2** with *ent*-**5**. For the dimethyl lactone **2b**, the good **B**:**A** ratio of 86:14, as achieved at 20°C (entry 1), was further improved by lowering the reaction temperature to −35°C (er 89:11, entry 2). The best asymmetric induction (er 94:6) was attained with the dimethoxy compound **2a** (entry 3). For both alcohols **4a** and **4b**, the isolated chemical yields (91% and 94%, respectively) were high.




Scheme 2. Atropo-enantioselective reductions of the lactones **2** with BINAL-H (**5**)

The enantiomerically enriched alcohols **4-B** can be easily transformed into virtually enantiopure material (er >99.5:0.5), by fractionated crystallization[6,8] from petroleum ether:diethyl ether. Thus, within the lactone concept, the BINAL-H reductions of **2** open a worthy new access to axially chiral biaryl alcohols **4**. Additionally, either by changing the chiral reductant [oxazaborolidine **3**/$BH_3$[6,8] vs BINAL-H (**5**)], or by varying its configuration (e.g. **5** vs *ent*-**5**), both enantiomers of **4** are easily accessible from the same lactone precursor **2** — an efficient atropo-enantiodivergent reaction principle. The application

Table 1
Stereocontrolled ring cleavage of **2** with BINAL-H (**5**)

| entry | lactone | temp. [°C] | conversion[a] | yield [%][b] | **4-B**:**4-A**[c] |
|---|---|---|---|---|---|
| 1 | **2b** | 20 | quantitative | ---[d] | 86:14 |
| 2 | **2b** | -35 | quantitative | 94 | 89:11 |
| | | | | 70 | > 99.5:0.5[e] |
| 3 | **2a** | -35 | quantitative | 91 | 94:6 |
| | | | | 77 | > 99.5:0.5[e] |

[a]Estimated by tlc.

[b]Isolated yield.

[c]Determined by HPLC analysis (Chiralcel OD-H).

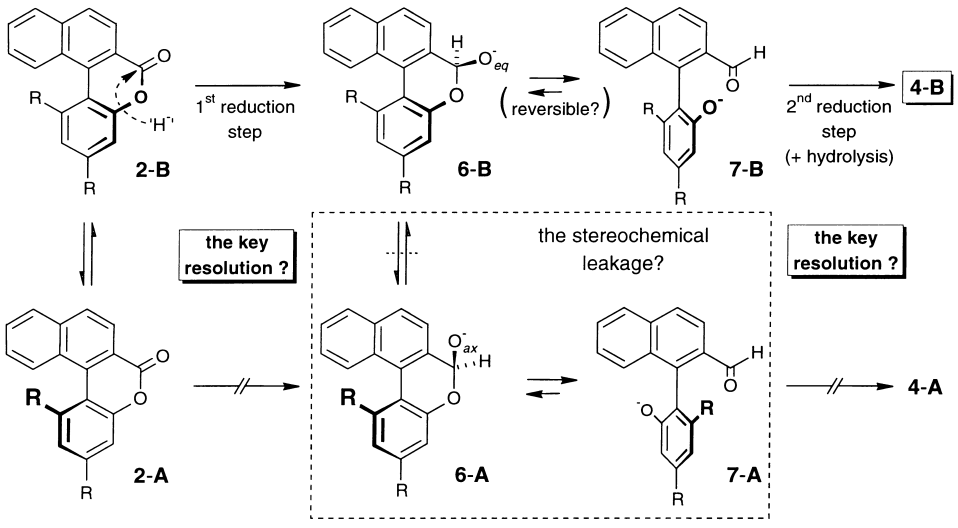
[d]Not determined.

[e]After crystallization from petroleum ether / diethyl ether.

of this stereocontrolled BINAL-H reduction to the atropisomer-selective synthesis of axially chiral biaryl natural products is currently under investigation.

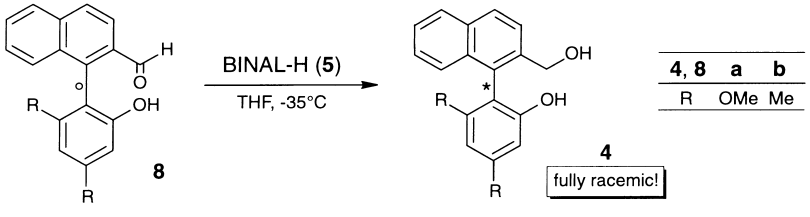
### *2.2. On the stereochemically deciding step of the BINAL-H reduction*

The atropo-enantioselective reduction of lactones **2** involves two reductive steps. As for other stereocontrolled ring cleavage reactions, in particular with *O*- and *N*-nucleophiles,[3,4,9,10] and as suggested by quantum chemical calculations,[16,17] it is assumed that — in the sense of a dynamic kinetic resolution — the chiral hydride transfer reagent attacks **2-B** exclusively, i.e. only one of the two interconverting helimeric forms **2-A**⇌**2-B** (for a simplified reaction course, see Scheme 3). This presumably[16,17] axial attack should give rise to the initial formation of the lactolate **6-B** only. If **6-B** bursts open immediately, it should specifically give **7-B**, whose further reduction (and hydrolysis) would lead to **4-B**, with full conservation of the chirality information at the axis. There is, however, the risk of a significant loss of that stereoinformation (the 'stereochemical leakage'[3,4,8]) by the experimentally[8,18,19] and quantumchemically[17,20] known configurational instability of lactols of type **6-B**[8] (and related compounds[18,19]): like the lactones **2** themselves,[3–5] the lactols are bridged biaryls with low atropoisomerization barriers. If interconversion **6-B**⇌**6-A** occurs faster than ring cleavage and further reduction to **4-B**, then the high asymmetric inductions actually attained must result from a preferential reduction of **7-B** over **7-A**, again in the sense of a dynamic kinetic resolution, but at the level of the second reduction step.




Scheme 3. Two possible stereochemical courses of the atropo-enantioselective reduction of **2**; metallated intermediates formulated as anionic, for reasons of clarity

For differentiating between these two stereochemical courses, the configurationally unstable racemic hydroxy aldehydes **8a** and **8b**[18] (i.e. the 'non-anionic' analogs of **7**) were reduced with BINAL-H (**5**) (Scheme 4) under the same conditions as the lactones **2** (cf. Scheme 2). It is feasible that through initial deprotonation of **8** by **5**,[‡] intermediate species originate that are similar (if not identical) to the postulated intermediates **6-A/B**⇌**7-A/B** of the lactone reduction (cf. Scheme 3). In addition, even if the reduction process should be more rapid than the deprotonation, the hydroxy aldehydes (**8**) themselves should display closely related (also still non-deprotonated) model substrates for **7**. In both cases, for **8a** and **8b**, the reduction led to the fully racemic alcohols **4-A**/**4-B**, clearly showing that racemic **8a** and **8b** do not constitute substrates for a dynamic kinetic resolution. This provides strong evidence that the asymmetric induction in the atropo-selective BINAL-H reduction of biaryl lactones **2** is achieved in the first, not in the second reduction step, without a significant loss of stereochemical information at the level of the intermediates **6** and **7**.




Scheme 4. Reduction of the configurationally unstable hydroxy aldehydes **8** with BINAL-H (**5**)

Configurationally unstable biaryl lactones of type **2** can thus be reduced highly atropo-enantioselectively to give the virtually enantiopure axially chiral biaryl alcohols **4**, further assisted by a simple crystallization step. Apparently the stereochemically deciding step is the first hydride transfer, which, out of the equilibrium of rapidly interconverting helimeric lactone enantiomers **2-A**⇌**2-B**, reduces only **2-B**, in the sense of a dynamic kinetic resolution, and allows conservation of

[‡] This deprotonation would also explain the low conversion (11%) obtained in the reduction of **8b** with only 1.0 equiv. of **5**.

this stereochemical information into the target molecule, despite the configurational instability of the lactolate and hydroxy aldehyde intermediates.

## 3. Experimental section

HPLC analyses were carried out with a combination of a Waters M 510 pump, a Chiralcel OD-H column (Daicel Chem. Ind. Ltd., 4.6×250 mm), and an ERC-7215 UV-detector. $LiAlH_4$ and *M*-BINOL were purchased from Aldrich; THF was freshly distilled from potassium. All reactions were performed in dry glassware under an argon atmosphere using the Schlenk tube technique.

### *3.1. General procedure for the BINAL-H reductions and enantiomer analysis of the alcohols **4***

A solution of 4.4 equiv. of *M*-BINOL in THF (5 ml/mmol *M*-BINOL) was slowly added to 4.0 equiv. of $LiAlH_4$ (1.0 M in THF) at room temp. After 30 min of stirring, 4.4 equiv. of ethanol were added and stirring was continued for additional 30 min. If a large quantity of material precipitated, the suspension had to be discarded and the preparation was started from the beginning.[15] The freshly prepared BINAL-H solution was cooled to −35°C and 1.0 equiv. of the biaryl compound were added. After 12 h the reaction mixture was carefully hydrolyzed with water (20 ml/mmol biaryl), slightly acidified with 2 N HCl, and extracted with diethyl ether (3×20 ml/mmol biaryl). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Chromatographic purification gave the crude alcohols **4**, the spectroscopic data of which were identical to those of material previously obtained.[8,21] The enantiomer analysis of the biaryl alcohols **4a** and **4b** was done by HPLC on a chiral phase (Chiralcel OD-H, UV-detection at 280 nm, flow rate 1.0 ml/min): **4a** (eluent *n*-hexane:2-propanol, 92:8): $t_R$=20 min (**4a**-**A**), $t_R$=23 min (**4a**-**B**); **4b** (eluent *n*-hexane:2-propanol, 95:5): $t_R$=16 min (**4b**-**A**), $t_R$=22 min (**4b**-**B**). The absolute configurations were assigned according to the literature.[8]

### *3.2. Preparative ring opening of **2a***

According to the general procedure, 123 mg (400 μmol) of **2a** were reduced. Purification of the crude product by column chromatography on silica gel (petroleum ether:diethyl ether, 1:1) gave the alcohol **4a**-**B** (113 mg, 364 μmol, 91%, er 94:6). Crystallization of **4a**-**B** from petroleum ether:diethyl ether resulted in virtually enantiopure (er >99.5:0.5) colorless crystals of **4a**-**B** (95.6 mg, 308 μmol, 77%).

### *3.3. Preparative ring opening of **2b***

According to the general procedure, **2b** (110 mg, 400 μmol) was reduced and the crude product purified by column chromatography on silica gel (petroleum ether:diethyl ether, 2:1). The alcohol **4b**-**B** (105 mg, 377 μmol, 94%, er 89:11) was obtained as a colorless oil. Crystallization of **4b**-**B** from petroleum ether:diethyl ether gave virtually enantiopure (er >99.5:0.5) colorless crystals of **4b**-**B** (77.9 mg, 280 μmol, 70%).

### 3.4. Reduction of the hydroxy aldehydes **8**

The hydroxy aldehydes **8a** and **8b** (50 μmol each) were reduced according to the general procedure until conversions were quantitative. The resulting alcohols **4** were purified by TLC on silica gel (petroleum ether:diethyl ether. 2:1). In both cases no enantiomeric excesses were detected by HPLC.

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## References

1. Part 77 in the series *Novel Concepts in Directed Biaryl Synthesis*; for part 76 see Bringmann, G.; Pabst, T.; Rycroft, D. S.; Connolly, J. D. *Tetrahedron Lett*. **1999**, *40*, 483–486.
2. (a) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303. (b) Bringmann, G.; Walter, R.; Weirich, R. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th edn; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds; Thieme Verlag: Stuttgart, 1995; E21a, pp. 567–687. (c) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem*. **1990**, *102*, 1006–1019; *Angew. Chem., Int. Ed. Engl*. **1990**, *29*, 977–991.
3. (a) Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, in press. (b) Bringmann, G.; Tasler, S. In *Current Trends in Organic Synthesis*; Scolastico, C.; Nicotra, F., Eds; Plenum Publishing Cooperation: New York, 1999, in press.
4. (a) Bringmann, G. *S. Afr. J. Chem*. **1994**, *47*, 83–102. (b) Bringmann, G.; Göbel, L.; Schupp, O. *GIT Fachz. Lab*. **1993**, 189–200.
5. Bringmann, G.; Hartung, T.; Göbel, L.; Schupp, O.; Ewers, C. L. J.; Schöner, B.; Zagst, R.; Peters, K.; von Schnering, H. G.; Burschka, C. *Liebigs Ann. Chem*. **1992**, 225–232.
6. Bringmann, G.; Hartung, T. *Angew. Chem*. **1992**, *104*, 782–783; *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 761–762.
7. Bringmann, G.; Hartung, T. *Synthesis* **1992**, 433–435.
8. Bringmann, G.; Hartung, T. *Tetrahedron* **1993**, *49*, 7891–7902.
9. Bringmann, G.; Walter, R.; Ewers, C. L. J. *Synlett* **1991**, 581–583.
10. Seebach, D.; Jaeschke, G.; Gottwald, K.; Matsuda, K.; Formisano, R.; Chaplin, D. A.; Breuning, M.; Bringmann, G. *Tetrahedron* **1997**, *53*, 7539–7556.
11. (a) Bringmann, G.; Reuscher, H. *Angew. Chem*. **1989**, *101*, 1725–1726; *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 1672–1673. (b) Bringmann, G.; Holenz, J.; Weirich, R.; Rübenacker, M.; Funke, C.; Boyd, M. R.; Gulakowski, R. J.; François, G. *Tetrahedron* **1998**, *54*, 497–512. (c) Bringmann, G.; Pabst, T.; Busemann, S.; Peters, K.; Peters, E.-M. *Tetrahedron* **1998**, *54*, 1425–1438.
12. (a) Bringmann, G. Ochse, M. *Synlett* **1998**, 1294–1296. (b) Bringmann, G.; Saeb, W.; Rübenacker, M. *Tetrahedron* **1999**, *55*, 423–432.
13. Bringmann, G.; Breuning, M. *Tetrahedron: Asymmetry* **1998**, *9*, 667–679.
14. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc*. **1987**, *109*, 5551–5553. (b) Corey, E. J.; Helal, C. J. *Angew. Chem*. **1998**, *110*, 2092–2118; *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1986–2012.
15. (a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc*. **1984**, *106*, 6709–6716. (b) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc*. **1979**, *101*, 3129–3131.
16. Bringmann, G.; Vitt, D. *J. Org. Chem*. **1995**, *60*, 7674–7681.
17. Bringmann, G.; Güssregen, S.; Vitt, D.; Stowasser, R. *J. Mol. Model*. **1998**, *4*, 165–175.
18. Bringmann, G.; Breuning, M.; Endress, H.; Vitt, D.; Peters, K.; Peters, E.-M. *Tetrahedron* **1998**, *54*, 10677–10690.
19. (a) Bringmann, G.; Hartung, T. *Liebigs Ann. Chem*. **1994**, 313–316. (b) Bringmann, G.; Schöner, B.; Peters, K.; Peters, E.-M.; von Schnering, H. G. *Liebigs Ann. Chem*. **1995**, 439–444.
20. Bringmann, G.; Vitt, D.; Kraus, J.; Breuning, M. *Tetrahedron* **1998**, *54*, 10691–10698.
21. Bringmann, G.; Hartung, T.; Göbel, L.; Schupp, O.; Peters, K.; von Schnering, H. G. *Liebigs Ann. Chem*. **1992**, 769–775.