University of Groningen

Enantioselective Symmetry Breaking Directed by the Order of Process Steps

Noorduyn, Wim L.; Meekes, Hugo; Enckevort, Willem J.P. van; Kaptein, Bernard; Kellogg, Richard M.; Vlieg, Elias

Published in:
Angewandte Chemie International Edition

DOI:
[10.1002/anie.200907231](https://doi.org/10.1002/anie.200907231)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Noorduyn, W. L., Meekes, H., Enckevort, W. J. P. V., Kaptein, B., Kellogg, R. M., & Vlieg, E. (2010). Enantioselective Symmetry Breaking Directed by the Order of Process Steps. *Angewandte Chemie International Edition*, 49(14), 2539-2541. <https://doi.org/10.1002/anie.200907231>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Supporting Information

© Wiley-VCH 2010

69451 Weinheim, Germany

Enantioselective Symmetry Breaking Directed by the Order of Process Steps**

*Wim L. Noorduin, Hugo Meekes, Willem J. P. van Enckevort, Bernard Kaptein, Richard M. Kellogg, and Elias Vlieg**

anie_200907231_sm_miscellaneous_information.pdf

Supporting Information

Unbiased reverse experiments

In a standard reaction vial (10 mL) 8.0 g glass beads and 6.25 g MeCN were added together with 0.15 g 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction vial was placed on a thermostated ultrasonic cleaning bath. After 5 minutes of ultrasonic induced mixing, the reaction vial was removed from the cleaning bath and 0.40 g (*RS*)-**1** was added. A saturated solution was created by frequently manually shaking the flask for 2 hours. Then, the reaction mixture was placed back in the ultrasonic cleaning bath and the solid phase was deracemized under grinding conditions. The enantiomeric excess (*ee*) in the solid phase was followed by taking ca. 0.2 mL slurry samples that were filtered on a P4 glass filter and washed with ca. 0.1 mL MeOH. Subsequently, the solid was completely dissolved in isopropanol and the *ee* was determined using a chiral HPLC (Chiralpak AD-H (250x4.6 mm ID), eluent n-hexane/2-propanol 80/20 v/v%, flow 1mL/min, detection $\lambda=254$ nm. Retention times (*R*)-**1** 7.9 min, (*S*)-**1** 8.5 min).

Biased nucleation deracemization experiments

To a standard reaction vial containing a magnetic stirring bar were added 0.01 g (*S*)-Phenyl glycine ((*S*)-**2**) 6.0 g MeCN, 0.3 g (*RS*)-**1** and 0.1 g DBU. The mixture was heated until a clear solution was obtained and gradually cooled down to room temperature under stirring conditions (300 rpm) overnight. The resulting precipitate was filtered and analyzed using the above described HPLC method. A similar experimental procedure was followed for (*R*)-phenyl glycine ((*R*)-**2**).

Biased dissolution directed deracemization experiments

First of all, two solutions need to be prepared (A and B).

A: In a standard reaction vial 0.3 g (*RS*)-**1** is partially dissolved in 6.0 g MeCN and shaken using the thermostated ultrasonic cleaning bath for 1h to establish a saturated solution.

B: In a standard reaction vial is placed ca. 0.0002 g (*S*)-Phenyl glycine with 5.7 g MeCN and mixed for 10 min using the thermostated ultrasonic cleaning bath. Subsequently, the solution was filtered over a 0.2 μm Whatman filter. To this solution was added 0.2 g DBU and 0.35 g (*RS*)-**1**. A saturated solution was created by frequently manually swirling the flask very gently for 2 hours. After this, the clear solution was gently removed using a pipette, leaving the crystals at the bottom of the reaction flask. To the flask were added 8.0 g glass beads and 5.5 g of the solution in flask A. This mixture was placed in the ultrasonic cleaning bath for 10 min. Then 0.2 g DBU was added to the mixture to initiate the solution phase deracemization reaction and the solid phase was deracemized under grinding conditions. The solid phase *ee* was determined using the method described above (Figure SI 1).

A similar procedure was followed for testing the (*R*)-phenyl glycine as an enantioselective dissolution additive.

Figure SI 1. The evolution of the *ee* in the solid phase during the deracemization of **1** after dissolution in the presence of enantiopure phenyl glycine **2**. Positive *ee* values are used for the (*S*)-**1**. Closed symbols are for the dissolution in the presence of (*S*)-**2**, open symbols for (*R*)-**2**.