Asymmetric Catalysis

Deutsche Ausgabe: DOI: 10.1002/ange.201504589
Internationale Ausgabe: DOI: 10.1002/anie.201504589

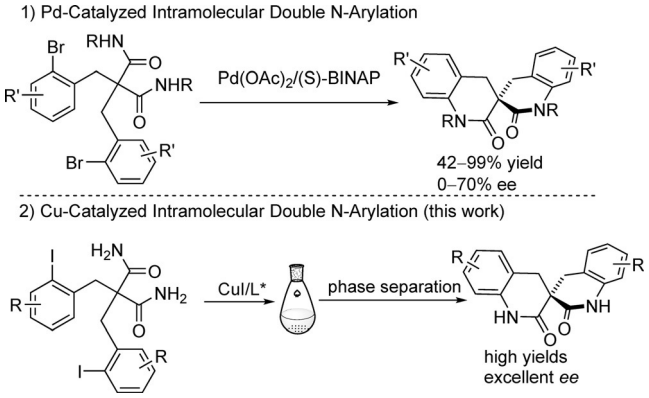
An Enantioselective Synthesis of Spirobilactams through Copper-Catalyzed Intramolecular Double N-Arylation and Phase Separation

*Jianguang Liu, Yingying Tian, Jialing Shi, Shasha Zhang, and Qian Cai**

Abstract: *Spirobicyclic structures are versatile building blocks for functional chiral molecules. An enantioselective synthesis of chiral spirobilactams via a copper-catalyzed double N-arylation was developed. Amplification of solution ee by in situ precipitation of the racemate was observed with this method and enantioenriched spirobilactams were obtained with excellent ee values through simple solid–solution phase separation.*

The spirobicyclic framework is a key structural unit found in many natural products, pharmaceuticals, materials, and chiral ligands.[1,2] The preparation of optically active spirocyclic compounds has attracted much attention from the synthetic community owing to their unique structural features and synthetic challenges. With the development of asymmetric organometallic chemistry and organocatalysis, a variety of methods for the asymmetric synthesis of spirobicyclic compounds have been realized.[3,4] However, the development of novel methods for the practical and efficient synthesis of chiral spirocyclic compounds is still of great interest.

N-containing spirobicyclic compounds[5] such as spirobilactams and dibenzospriodiamines are versatile building blocks for functional chiral molecules, such as ionophores or potential chiral auxiliaries.[6] In our continuous efforts towards the development of enantioselective desymmetric aryl C–N coupling reactions for the synthesis of N-heterocycles,[7,8] the products obtained in these reactions were further utilized for the synthesis of a variety of N-spirobicyclic compounds through later-stage transformations.[7a,b] Even though these transformations are simple, multiple steps are necessary and we believed that such structures could be formed more efficiently through copper-catalyzed double N-arylation, as shown in Scheme 1. There is only one similar example for this kind of reaction, a Pd-catalyzed method reported by Sasai in 2009.[9] In their work, excellent yields but only low to moderate enantioselectivities were obtained in most cases. The low enantioselectivity may be a consequence of the strong background reactions of the 2,2-bis(2-halobenzyl)-*N*,*N*′-dimethylmalonamide substrates themselves.



Scheme 1. Highly enantioselective synthesis of spirobilactams.

Enantiocontrol may also be a problem in copper-catalyzed double N-arylation with 2,2-bis(2-halobenzyl)malonamides, as observed in our previous enantioselective desymmetric N-arylation of maloamides for the synthesis of tetrahydroquinolines.[7d] It remains a challenge to improve the enantioselectivity of such reactions simply by modifying the chiral ligands.

The physical and chemical properties of racemic compounds may be very different from those of enantiomers. These differences have been exploited in the isolation of an enantioenriched isomer from scalemic compositions,[10] either through controlled crystallization, distillation, or sublimation. A variety of examples for enantioenrichment through phase separation have been reported by Morowitz,[11] Blackmond,[12,13] Bleslow,[14] Feringa,[15] Cooks[16] and other groups,[17,18] and such processes are well known in prebiotic chemistry for understanding the origin of homochirality.[19] Crystallization represents an ideal separation technology in terms of simplicity and cost effectiveness and is a practical and efficient method for enantioenhancement from scalemic compositions. Many compounds, such as amino acids, sugars, and tartaric acids, have been reported to be less soluble as racemates than as the pure enantiomers.[10] The amplification of solution *ee* may thus be realized through crystallization or precipitation of racemates from their enantiomeric counterparts.

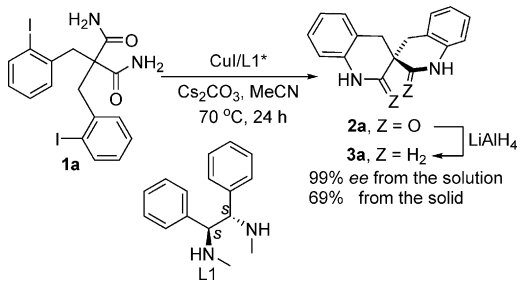
In this work, we observed an amplification of solution *ee* through in situ precipitation of the racemates. Highly enantioenriched spirobilactams were produced with good yields and excellent *ee* values through the combination of a copper-catalyzed reaction and simple in situ crystallization of the products.

L1 was initially chosen as the ligand to explore the model reaction of 2,2-bis(2-iodobenzyl)malonamide (**1a**). The reac-

[*] J. Liu, Y. Tian, S. Zhang, Prof. Dr. Q. Cai
Guangzhou Institutes of Biomedicine and Health
Chinese Academy of Sciences, No.190 Kaiyuan Avenue
Guangzhou Science Park, Guangzhou, 510530 (China)
E-mail: cai_qian@gibh.ac.cn
J. Shi
College of Chemistry and Chemical Engineering
Hunan Normal University
No. 36 Lushan Road, Changsha, 410081 (China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201504589.

tion was performed in MeCN at 70 °C for 24 h with Cs_2CO_3 as the base (Scheme 2). A higher concentration of **1a** benefits the reaction efficiency and leads to the starting material being



Scheme 2. Copper-catalyzed double N-arylation for the formation of spirobilactams.

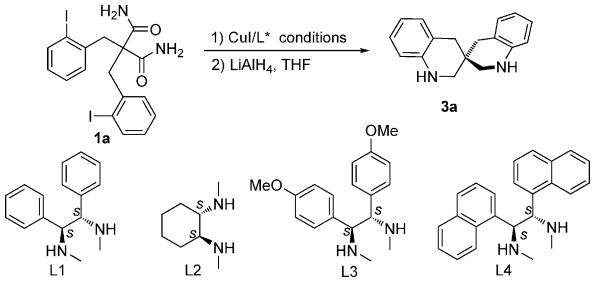
completely transformed into the spirobicyclic product **2a**, while a small amount of monocyclization byproduct was detected at a relatively lower concentration. After the reaction was complete, some precipitates were produced. After filtering off the solid, the double N-arylation product **2a** from both the solid and the solution was isolated through regular workup and the *ee* values were measured by HPLC by reducing the lactam into its corresponding benzospirodiamine **3a** in order to minimize measurement errors as a result of the poor solubility of **2a**. We were surprised to find that 99% *ee* was obtained for **2a** from the solution (13% yield) but only 69% *ee* for **2a** from the solid (86% yield).

Obviously, an amplification of solution ee existed in the model reaction as a result of the crystallization or precipitation of the racemate from the solution. To take advantage of this phenomenon, a highly enantioselective synthetic method for the formation of spirobilactams was developed.

First, for better evaluation of the efficiency of enantiocontrol by chiral ligands, we directly reduced **2a** into its spirodiamine **3a** after the double N-arylation was complete. Compound **3a** is soluble in organic solvents and determination of the *ee* value by HPLC is straightforward. With L1 as the ligand, other solvents like dioxane, toluene, and DMF were first screened and gave inferior results (Table 1, entries 2–4). Furthermore, bases and several 1,2-diamine-derived ligands were explored, with L4 giving slightly better enantioselectivity at 70 °C with Cs_2CO_3 as the base (Table 1, entry 9). Lower reaction temperature (55 °C) improved the enantioselectivity (Table 1, entry 10). However, at this temperature, the starting material was not completely transformed into the double N-arylation product, and monocyclized byproduct was detected.

With the best chiral ligand and optimized reaction conditions in hand (Table 1, entry 9), we then designed a practical process for the highly enantioselective formation of spirobilactams from **1a** through double N-arylation. Since most of the enantiopure product was also precipitated together with the racemate during the reaction, we added more solvent into the mixture, stirring for 1 hour to bring most of the desired solid product into solution at a relatively small cost in terms of *ee* values after the reaction was

Table 1: Screening Reaction Conditions.[a]



Entry	L*	Solvent	Base	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	L1	MeCN	Cs_2CO_3	70	93	73
2	L1	dioxane	Cs_2CO_3	70	82	63
3	L1	toluene	Cs_2CO_3	70	45	72
4	L1	DMF	Cs_2CO_3	70	67	73
5	L1	MeCN	K_2CO_3	70	60	70
6	L1	MeCN	K_3PO_4	70	85	72
7	L2	MeCN	Cs_2CO_3	70	89	68
8	L3	MeCN	Cs_2CO_3	70	94	70
9	L4	MeCN	Cs_2CO_3	70	96	77
10	L4	MeCN	Cs_2CO_3	55	82	82

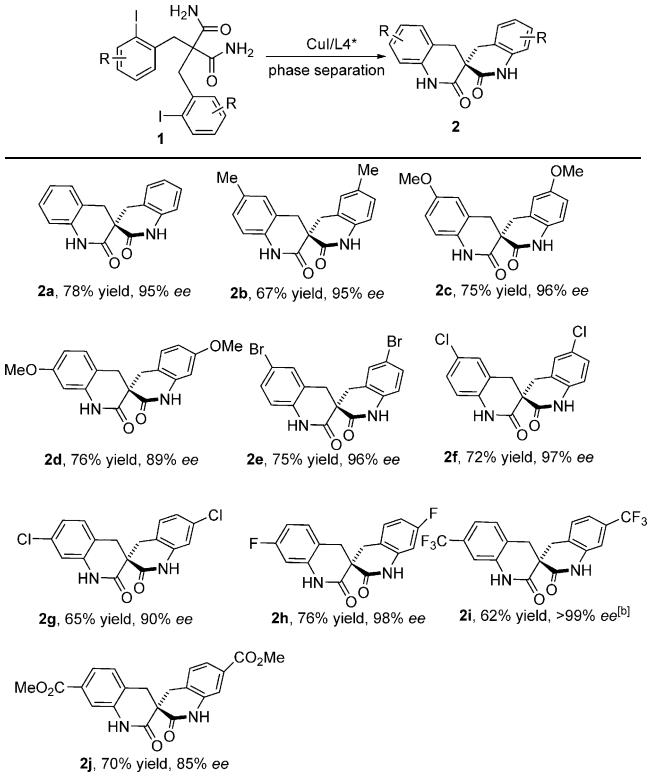
[a] Reagents and conditions: **1a** (0.20 mmol, 1.0 equiv), CuI (0.04 mmol, 20 mol%), ligand (0.05 mmol, 25 mol%), base, (0.5 mmol, 2.5 equiv), solvent (2 mL), stated temperature, 24 h. DMF = *N*,*N*-dimethylformamide. [b] Isolated yields. [c] Determined by HPLC analysis from reduced product **3a**.

complete. The precipitate was removed from the solution. Compound **2a** was obtained in 78% yield and with 95% *ee* from the filtrate through a regular workup process.

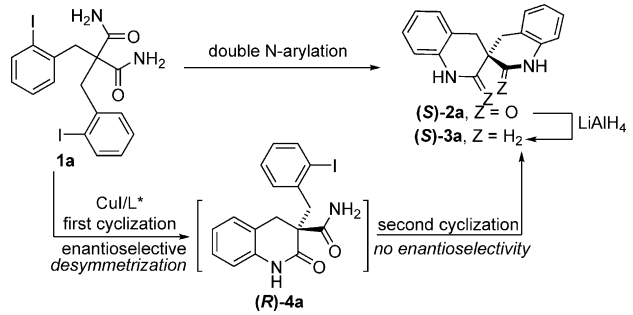
This approach provides a simple and efficient method for the enantioselective synthesis of chiral spirobilactams. We then explored the substrate scope with a variety of substrates (Table 2). All of the reactions proceeded very well and afforded the desired double N-arylation products in high yields and with excellent enantioselectivity. Substituents such as alkyl, methoxyl, halogen, and ester groups on the aryl ring were well tolerated. An exception is compound **2i**, which has a trifluoromethyl group on the aryl ring. In this case, the solid obtained from the precipitation of the reaction showed higher *ee* than from the solution. Therefore, after the reaction was complete and the solid–solution equilibrium was established, the mixture was directly filtered and the solid was purified through a regular workup process to afford **2h** in 62% yield and with 99% *ee*.

As previously reported[9] and observed in our experiments, such double N-arylation proceeds through a two-step process (Scheme 3). The enantioselectivity is established in the first desymmetric cyclization and no obvious kinetic resolution is observed in the second cyclization, as confirmed by a control experiment (see the Supporting Information). The cyclization/reduction of racemic monocyclic compound **4a** afforded the coupling product and the recovered starting material without enantioselectivity. The absolute configuration of compound **2a** obtained in the reaction was assigned as *S* by comparing its reduction product benzospirodiamine **3a** with our reported data.[7b] The absolute configurations of other products and monocyclized intermediates were assigned by analogy to that of compound **2a**.

Table 2: Substrate scope.[a]



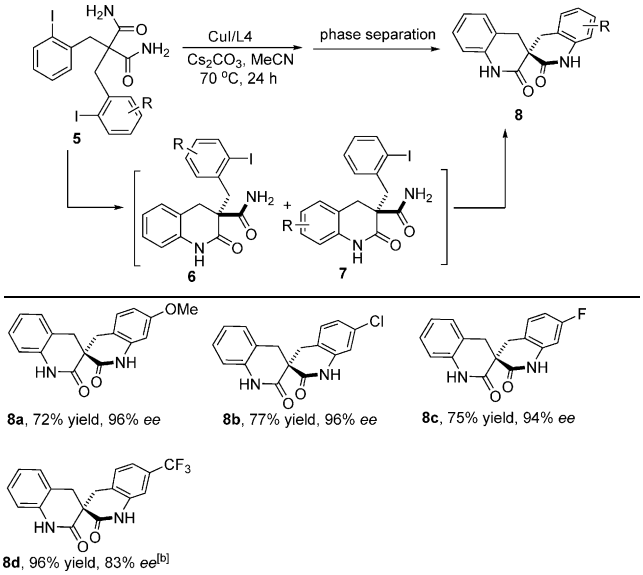
[a] Reagents and conditions: **1** (0.2 mmol, 1.0 equiv), CuI (0.04 mmol, 20 mol%), L4 (0.05 mmol, 25 mol%), Cs_2CO_3, (0.5 mmol, 2.5 equiv), MeCN (2 mL), 70°C, 24 h. Yields of isolated product are given. The *ee* values were determined by HPLC analysis after reduction. [b] Data obtained for the solid after filtration.



Scheme 3. The reaction process and assignment of absolute configuration.

Based on this understanding of the reaction process, we envisioned that the enantioselective synthesis of C1-symmetric spirobilactams should be feasible with this method. As shown in Table 3, although the first cyclization afforded a mixture of two monocyclization products, both of them furnished the same spirobilactams in the subqequent cyclization. The desired spirobilactam products were obtained in good yields and with excellent enantioselectivity through the combination of this copper-catalyzed method and phase separation. Different substituents on the aryl ring were well tolerated. Note that compound **8d**, which shows good

Table 3: Enantioselective synthesis of C1-symmetric spirobilactams.[a]



[a] Reagents and reaction conditions: **1** (0.2 mmol, 1.0 equiv), CuI (0.04 mmol, 20 mol%), L4 (0.05 mmol, 25 mol%), Cs_2CO_3, (0.5 mmol, 2.5 equiv), MeCN (2 mL), 70°C, 24 h. Yields of isolated product are given. The *ee* values were determined by HPLC analysis after reduction. [b] Without phase separation and the *ee* value was measured directly with **8d** through HPLC.

solubility in this system, provided no obvious amplification of solution *ee*.

In summary, we have developed a highly efficient and enantioselective synthesis of spirobilactams through copper-catalyzed double N-arylation and manipulation of the phase behavior. The precipitation of racemates greatly amplifies the solution *ee* and makes this process simple and practical. A wide range of substrates worked well with this method, affording the desired products in high yields and with excellent enantioselectivity. Further exploration and application of this method in organic synthesis is in progress in our laboratory.

Acknowledgements

The authors are grateful to National Natural Science Foundation (Grant 21272234) for financial support. We also thank Prof. Fayang Qiu from Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences for helpful discussions.

Keywords: asymmetric catalysis · copper · N-arylation · phase separation · spirobilactams

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 10917–10920
Angew. Chem. **2015**, *127*, 11067–11070

[1] a) V. I. Minkin, *Chem. Rev.* **2004**, *104*, 2751–2776; b) J. E. Aho, P. M. Pihko, T. K. Rissa, *Chem. Rev.* **2005**, *105*, 4406–4440; c) C. V. Galliford, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2007**, *46*,

8748; *Angew. Chem.* **2007**, *119*, 8902; d) B. M. Trost, M. K. Brannan, *Synthesis* **2009**, 3003 – 3025.

[2] a) K. Ding, Z. Han, Z. Wang, *Chem. Asian J.* **2009**, *4*, 32 – 41; b) J.-H. Xie, Q.-L. Zhou, *Acc. Chem. Res.* **2008**, *41*, 581 – 593; c) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2011**, *111*, PR284 – 437.

[3] a) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945 – 2963; b) R. Rios, *Chem. Soc. Rev.* **2012**, *41*, 1060 – 1074; c) A. K. Franz, N. V. Hanhan, N. R. Ball-Jones, *ACS Catal.* **2013**, *3*, 540 – 553.

[4] Selected examples for the enantioselective synthesis of spirocyclic compounds: a) A. Ashimori, L. E. Overman, *J. Org. Chem.* **1992**, *57*, 4571 – 4572; b) K. Tamao, K. Nakamura, H. Ishii, S. Yamaguchi, M. Shiro, *J. Am. Chem. Soc.* **1996**, *118*, 12469 – 12470; c) T. Takahashi, H. Tsutsui, M. Tamura, S. Kitagaki, M. Nakajima, S. Hashimoto, *Chem. Commun.* **2001**, 1604 – 1605; d) M. Hatano, K. Mikami, *J. Am. Chem. Soc.* **2003**, *125*, 4704 – 4705; e) K. Tsuchikama, Y. Kuwata, T. Shibata, *J. Am. Chem. Soc.* **2006**, *128*, 13686 – 13687; f) A. Wada, K. Noguchi, M. Hirano, K. Tanaka, *Org. Lett.* **2007**, *9*, 1295 – 1298; g) D. Hojo, K. Noguchi, M. Hirano, K. Tanaka, *Angew. Chem. Int. Ed.* **2008**, *47*, 5820 – 5822; *Angew. Chem.* **2008**, *120*, 5904 – 5906; h) X. N. Wang, Y. Y. Zhang, S. Ye, *Adv. Synth. Catal.* **2010**, *352*, 1892 – 1895; i) B. M. Trost, P. J. Morris, *Angew. Chem. Int. Ed.* **2011**, *50*, 6167 – 6170; *Angew. Chem.* **2011**, *123*, 6291 – 6294; j) B. Tan, N. R. Candeias, C. F. Barbas, *Nat. Chem.* **2011**, *3*, 473 – 477; k) X. M. Wang, Z. B. Han, Z. Wang, K. L. Ding, *Angew. Chem. Int. Ed.* **2012**, *51*, 936 – 940; *Angew. Chem.* **2012**, *124*, 960 – 964; l) N. V. Hanhan, N. R. Ball-Jones, N. T. Tran, A. K. Franz, *Angew. Chem. Int. Ed.* **2012**, *51*, 989 – 992; *Angew. Chem.* **2012**, *124*, 1013 – 1016; m) P. Chauhan, S. Mahajan, C. C. J. Loh, G. Raabe, D. Enders, *Org. Lett.* **2014**, *16*, 2954 – 2957; n) C. Guo, M. Schedler, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2014**, *53*, 10232 – 10236; *Angew. Chem.* **2014**, *126*, 10397 – 10401; o) S. Afewerki, G. Ma, I. Ibrahem, L. Liu, J. Sun, A. Córdova, *ACS Catal.* **2015**, *5*, 1266 – 1272; p) L. Yang, H. Zheng, L. Luo, J. Nan, J. Liu, Y. Wang, X. Luan, *J. Am. Chem. Soc.* **2015**, *137*, 4876 – 4879; q) J. Zheng, S.-B. Wang, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2015**, *137*, 4880 – 4883.

[5] For a recent review of spirocyclic N-heterocyclces, see: E. M. Carreira, T. C. Fessard, *Chem. Rev.* **2014**, *114*, 8257 – 8322.

[6] Early synthesis of racemic spirobilatams and spirodiamines and their applications: a) H.-J. Choi, Y. J. Park, M. G. Kim, Y. S. Park, *J. Heterocycl. Chem.* **2000**, *37*, 1305 – 1308; b) H.-J. Choi, Y. S. Park, M. G. Kim, Y. J. Park, N. S. Yoon, T. W. Bell, *Tetrahedron* **2006**, *62*, 8696 – 8701.

[7] a) F. Zhou, J. Guo, J. Liu, K. Ding, S. Yu, Q. Cai, *J. Am. Chem. Soc.* **2012**, *134*, 14326 – 14329; b) F. Zhou, G.-J. Cheng, W. Yang, Y. Long, S. Zhang, Y.-D. Wu, X. Zhang, Q. Cai, *Angew. Chem. Int. Ed.* **2014**, *53*, 9555 – 9559; *Angew. Chem.* **2014**, *126*, 9709 – 9713; c) J. Liu, J. Yan, D. Qin, Q. Cai, *Synthesis* **2014**, 1917 – 1923; d) N. He, Y. Huo, J. Liu, Y. Huang, S. Zhang, Q. Cai, *Org. Lett.* **2015**, *17*, 374 – 377.

[8] Selected reviews: a) E. García-Urdiales, I. Alfonso, V. Gotor, *Chem. Rev.* **2005**, *105*, 313 – 354; b) M. C. Willis, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1765 – 1784; c) A. Studer, F. Schleth, *Synlett* **2005**, 3033 – 3041; d) T. Rovi in *New Frontiers in Asymmetric Catalysis* (Eds.: K. Mikami, M. Lautens), Wiley, Hoboken, **2007**, pp. 275 – 309; e) I. Atodiresei, I. Schiffers, C. Bolm, *Chem. Rev.* **2007**, *107*, 5683 – 5712; f) M. D. Díaz-de-Villegas, J. A. Gálvaz, P. Etayo, R. Badorrey, M. P. López-Ram-de-Víu, *Chem. Eur. J.* **2012**, *18*, 13920 – 13935.

[9] K. Takenaka, N. Itoh, H. Sasai, *Org. Lett.* **2009**, *11*, 1483 – 1486.

[10] a) I. Weissbuch, M. Lahav, *Chem. Rev.* **2011**, *111*, 3236 – 3267; b) D. G. Blackmond, M. Klussmann, *Chem. Commun.* **2007**, 3990 – 3996; c) D. P. Curran, *Angew. Chem. Int. Ed.* **1998**, *37*, 1174 – 1196; *Angew. Chem.* **1998**, *110*, 1230 – 1255.

[11] H. J. Morowitz, *J. Theor. Biol.* **1969**, *25*, 491 – 494.

[12] a) M. Klussmann, H. Iwamura, S. P. Mathew, D. H. Wells, Jr., U. Pandya, A. Armstrong, D. G. Blackmond, *Nature* **2006**, *441*, 621 – 623; b) M. Klussmann, A. J. P. White, A. Armstrong, D. G. Blackmond, *Angew. Chem. Int. Ed.* **2006**, *45*, 7985 – 7989; *Angew. Chem.* **2006**, *118*, 8153 – 8157.

[13] a) C. Viedma, J. E. Ortiz, T. de Torres, T. Izumi, D. G. Blackmond, *J. Am. Chem. Soc.* **2008**, *130*, 15274 – 15275; b) W. L. Noorduin, T. Izumi, A. Millemaggi, M. Leeman, H. Meekes, W. J. P. Van Enckevort, R. M. Kellogg, B. Kaptein, E. Vlieg, D. G. Blackmond, *J. Am. Chem. Soc.* **2008**, *130*, 1158 – 1159.

[14] a) R. Breslow, M. S. Levine, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 12979 – 12980; b) R. Breslow, Z.-L. Cheng, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 9144 – 9146.

[15] S. P. Fletcher, R. B. C. Jagt, B. L. Feringa, *Chem. Commun.* **2007**, 2578 – 2580.

[16] S. C. Nanita, R. G. Cooks, *Angew. Chem. Int. Ed.* **2006**, *45*, 554 – 569; *Angew. Chem.* **2006**, *118*, 568 – 583.

[17] Selected examples: a) J. R. Cronin, S. Pizzarello, *Science* **1997**, *275*, 951 – 955; b) J. Huang, L. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 1873 – 1878; c) T. Katagiri, C. Yoda, K. Furuhashi, K. Ueki, T. Kubota, *Chem. Lett.* **1996**, 115 – 116; d) W.-L. Tsai, K. Hermann, E. Hug, B. Rohde, A. S. Dreiding, *Helv. Chim. Acta* **1985**, *68*, 2238 – 2243; e) P. Diter, S. Taudien, O. Samuel, H. B. Kagan, *J. Org. Chem.* **1994**, *59*, 370 – 373; f) A. Bellec, J.-C. Guillemin, *J. Fluorine Chem.* **2010**, *131*, 545; g) V. A. Soloshonok, H. Ueki, M. Yasumoto, S. Mekala, J. S. Hirschi, D. A. Singleton, *J. Am. Chem. Soc.* **2007**, *129*, 12112 – 12113; h) A. V. Tarasevych, A. E. Sorochinsky, V. P. Kukhar, A. Chollet, R. Daniellou, J.-C. Guillemin, *J. Org. Chem.* **2013**, *78*, 10530 – 10533; i) A. V. Tarasevych, A. E. Sorochinsky, V. P. Kukhar, J.-C. Guillemin, *Chem. Commun.* **2015**, *51*, 7054 – 7057.

[18] A recent example for the preparation of stereoisomers through phase separation: Y. Zhao, F. Jiang, J. Hu, *J. Am. Chem. Soc.* **2015**, *137*, 5199 – 5203.

[19] a) M. Calvin, *Molecular Evoluation*, Oxford University Press, Oxford, **1969**; b) P. Cintas, *Angew. Chem. Int. Ed.* **2008**, *47*, 2918 – 2920; *Angew. Chem.* **2008**, *120*, 2960 – 2962; c) J. E. Hein, D. G. Blackmond, *Acc. Chem. Res.* **2012**, *45*, 2045 – 2054; d) The Origin of Biological Homochirality. D. G. Blackmond, *Cold Spring Harbor Perspect. Biol.* **2010**, *2*, a002147; e) D. G. Blackmond, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5732 – 5736.

Received: May 21, 2015
Published online: July 23, 2015

