Asymmetric Catalysis

DOI: 10.1002/anie.201408020

Experimental and Computational Study of the Catalytic Asymmetric 4π-Electrocyclization of N-Heterocycles**

*Sadiya Raja, Masaki Nakajima, and Magnus Rueping**

Abstract: *The first asymmetric metal-catalyzed Nazarov cyclization of N-heterocycles has been developed. The use of a chiral catalyst allows the enantioselective electrocyclization of N-heterocycles under mild conditions and the corresponding products are obtained in good yields with excellent enantio- and diastereoselectivity. The reaction mechanism and the absolute configuration of the obtained products are explained by means of computational studies.*

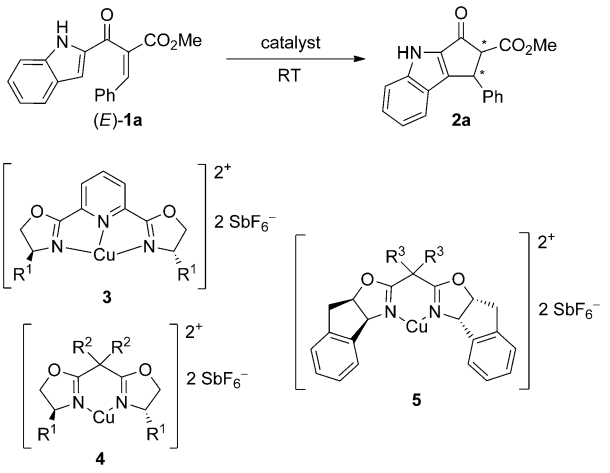
Chiral five-membered rings are not only important building blocks in organic synthesis, but also form the core structure of many natural products and biologically active compounds. A particularly versatile method for the construction of such five-membered rings is the Nazarov reaction, a 4π-electrocyclization of cross-conjugated dienones.[1] In general, the reaction can be carried out using Brønsted or Lewis acid catalysis; however, only few asymmetric versions have been developed.[2–5] With regard to the asymmetric versions, the Nazarov cyclization of aromatic and heteroaromatic substrates presents a major challenge.[4–7] To our knowledge, an asymmetric 4π-electrocyclization of N-heterocycles has not been described so far.

Many alkaloids with interesting biological properties contain a cyclopenta[*b*]indole structural motif.[8] Therefore, the development of a Nazarov cyclization of indole derivatives appeared to be of great importance, since it would also be the first example of an asymmetric reaction of this substrates class.

We began our study with the search for a suitable catalyst for the asymmetric electrocyclization of indole-β-keto ester **1a**. Several chiral Brønsted acids were tested and it was found that even the highly acidic *N*-triflylphosphoramides[9] were not able to catalyze the reaction, which demonstrates the poor reactivity of these substrates. Since metal complexes such as [Cu^{II}(box)] and [Cu^{II}(pybox)] complexes have served as strong Lewis acids in various enantioselective reactions, as well as in the Nazarov cyclization,[4b,d] we decided to investigate the Nazarov reaction of **1a** in the presence of Lewis acid catalysts (Table 1). Initial experiments showed already that the reaction can be catalyzed by chiral [Cu^{II}(pybox)] complexes **3**;[10,11] however, the product was formed in all cases with only a low to moderate enantioselectivity. Compared to the best [Cu^{II}(pybox)] complex **3a**, which afforded the product in 70% yield and an enantiomeric ratio of 75:25, the use of [Cu^{II}(box)] complex **4a** delivered the product with a higher yield of 82% and a selectivity of 76.5:23.5. Based on these results we have investigated different substituted box ligands in further experiments.

In the presence of complex **4a** in CH_2Cl_2, the reaction proceeded only with moderate yield and selectivity. An increase in the selectivity could be obtained when the reaction was carried out in $CHCl_3$, whereby a much longer reaction time was needed (Table 1, entries 1 and 2). With a 1:1 ratio of CH_2Cl_2 and $CHCl_3$, the reaction proceeded faster, but with a lower level of enantioselectivity (Table 1, entry 5). Catalysts

Table 1: Evaluation of Lewis acid catalysts and solvents for the enantioselective Nazarov cyclization.



Entry[a]	Cat.	R^1	R^2	R^3	Solvent	*t* [h]	e.r.[b]
1	**3a**	*i*Pr	–	–	CH_2Cl_2	12	25:75
2	**4a**	Ph	Bn	–	CH_2Cl_2	48	76.5:23.5
3	**4a**	Ph	Bn	–	$CHCl_3$	96	81:19
4	**4a**	Ph	Bn	–	$CH_2Cl_2/CHCl_3$ 10:1	24	74:26
5	**4a**	Ph	Bn	–	$CH_2Cl_2/CHCl_3$ 1:1	36	80:20
6	**4b**	Bn	Me	–	CH_2Cl_2	58	74.5:25.5
7	**4c**	Bn	Et	–	CH_2Cl_2	60	75:25
8	**4d**	Bn	Bn	–	CH_2Cl_2	36	57.5:42.5
9	**5a**	–	–	Et	CH_2Cl_2	2	84.5:15.5
10	**5a**	–	–	Et	$CHCl_3$	3	90:10
11	**5b**	–	–	Me	$CHCl_3$	3	89.5:10.5
12	**5c**	–	–	Bn	$CHCl_3$	2	95:5

[a] Reaction conditions: Substrate (*E*)-**1a**, 10 mol% catalyst **3**, **4**, or **5** in the solvent noted (0.05 M). [b] Enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase (Chiralcel AD-H).

[*] Dr. S. Raja, Dr. M. Nakajima, Prof. Dr. M. Rueping
Institut of Organic Chemistry, RWTH Aachen
Landoltweg 1, 52074 Aachen (Germany)
E-mail: magnus.rueping@rwth-aachen.de

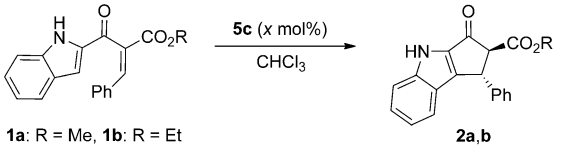
[**] We thank D. Fabry and I. Atodiresei for their support.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201408020.

4b–d were not particularly effective (Table 1, entries 6–8). A significant increase in the selectivity could be achieved when the sterically demanding catalyst **5a** was used. Interestingly, with **5a** as the catalyst the reaction proceeded fast in both CH_2Cl_2 and $CHCl_3$, with the best enantiomeric ratio being obtained in $CHCl_3$ (Table 1, entries 9 and 10). When the benzyl-substituted catalyst **5c** was employed, the product **2a** was isolated with an enantiomeric ratio of 95:5 (Table 1, entry 12). In addition, the reaction was completed within 2 h.

Next, we studied the Nazarov reaction in the presence of various amounts of the Cu complex **5c** at different temperatures (Table 2). The catalyst loading was reduced to 2 mol% without loss of enantioselectivity, albeit the reaction time had to be extended. Even at 0°C the product was obtained in the presence of 2 mol% **5c** with an excellent enantiomeric ratio (Table 2, entry 9). With methyl ester **1a** as the substrate, the best result was produced with a catalyst loading of 5 mol% at 10°C (Table 2, entry 5).

Under the optimized conditions, the scope of the asymmetric Nazarov reaction was then investigated (Table 3). In general, substrates bearing either aromatic residues with electron-withdrawing or electron-donating substituents or heteroaromatic residues were used to give products with good enantio- and diastereoselectivities (Table 3). The absolute

Table 2: Evaluation of the reaction parameters for the enantioselective Nazarov cyclization.[a]



Entry[a]	x mol% **5c**	**1a/b**	*T* [°C]	*t* [h]	e.r.[b]
1	10	**1a**	RT	2	95:5
2	5	**1a**	RT	5	95:5
3	2	**1a**	RT	10	94.5:5.5
4	10	**1a**	10	9	96:4
5	5	**1a**	10	13	96:4
6	2	**1a**	10	22	96:4
7	10	**1a**	0	15	96:4
8	5	**1a**	0	36	96:4
9	2	**1a**	0	48	96:4
10	5	**1a**	50	0.5	93:7
11	5	**1b**	RT	7	94:6

[a] Reaction conditions: Substrate (*E*)-**1** and catalyst **5c** in Chloroform (0.05 M). [b] Enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase (Chiralcel AD-H).

configuration of the products was determined as 2*S*,3*R* by X-ray structure analysis of **2j**.[12]

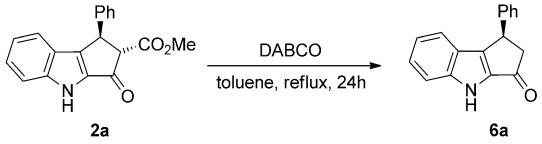
The products obtained in the Nazarov cyclization can be easily modified. For example, product **2a** can be quantitatively decarboxylated in the presence of 1,4-diazabicyclo-[2.2.2]octane (DABCO; Scheme 1).

Regarding the reaction mechanism, we propose that in the first step, the β-keto ester (*E*)-**1a** coordinates with the two carbonyl oxygen atoms to the [Cu^{II}(box)] complex, resulting in a six-membered chelate ring **7** which possesses a boat

Table 3: Scope of the Lewis acid catalyzed Nazarov cyclization.[a]

Entry[a]	R^1	R^2	**2**	Yield [%][b]	e.r.[c]	d.r.
1	Ph	H	**2a**	89	96:4	93:7
2	Ph	5-F	**2c**	87	95:5	97:3
3	4-MeC_6H_4	H	**2d**	89	97.5:2.5	95:5
4	3-MeC_6H_4	H	**2e**	86	95.5:4.5	>99:1
5	2,4-$Me_2C_6H_3$	H	**2f**	90	93.5:6.5	94:6
6	4-$MeOC_6H_4$	H	**2g**	77	93:7	94:6
7	2-$MeOC_6H_4$	H	**2h**	90	93.7	95:5
8	4-FC_6H_4	H	**2i**	85	96.5:3.5	95:5
9	4-ClC_6H_4	H	**2j**	80	97:3	94:6
10	4-BrC_6H_4	H	**2k**	78	96:4	97:3
11	4-$CF_3C_6H_4$	H	**2l**	87	99:1	>99:1
12	2-FC_6H_4	H	**2m**	84	92.5:7.5	93:7
13	2-ClC_6H_4	H	**2n**	81	92:8	94:6
14	2-$CF_3C_6H_4$	H	**2o**	89	92:8	95:5
15	1-naphthyl	H	**2p**	93	96:4	96:4
16	thienyl	H	**2q**	80	98:2	97:3
17	4-PhC_6H_4	H	**2r**	93	97:3	98:2
18	*i*Pr[d]	H	**2s**	64	80:20	>99:1

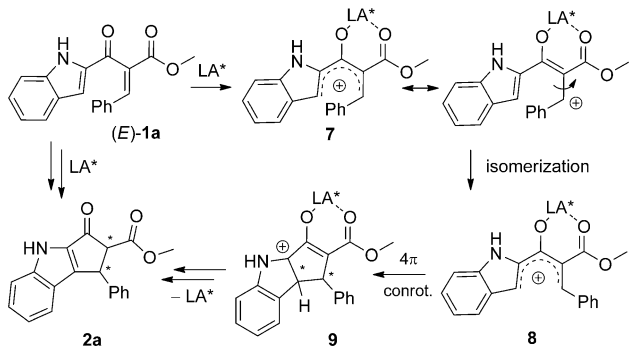
[a] Reaction conditions: Substrate (*E*)-**1** and 5 mol% **5c** in chloroform (0.05 M) at 10°C. [b] Yields after purification by column chromatography. [c] Enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase (Chiralcel AD-H and IA) and supercritical liquid chromatography (SFC). [c] Reaction at room temperature.



Scheme 1. Decarboxylation of **2a** with DABCO.

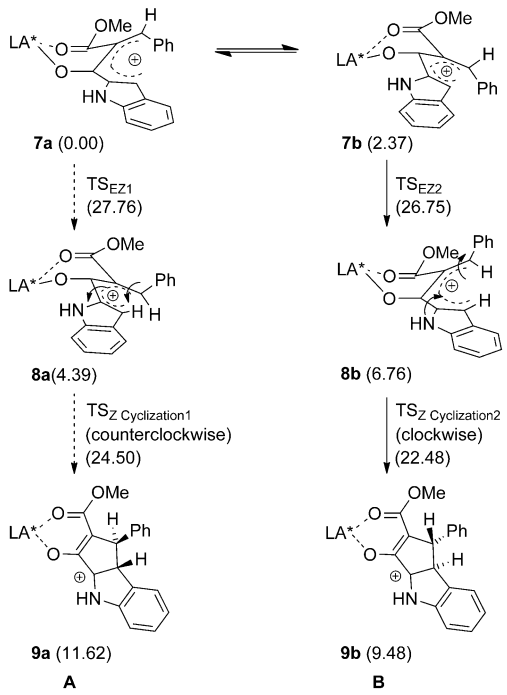
conformation.[13] Isomerization[14] and 4π conrotatory electrocyclization or direct cyclization affords after subsequent deprotonation/protonation the product **2a** (Scheme 2). In considering the catalytic cycle, a series of questions regarding the detailed reaction mechanism and the observed high asymmetric induction arose. In particular, the catalyst structure provided no clear explanation for the course of the reaction and the observed absolute configuration of the products.

Therefore, we decided to perform DFT calculations to verify our proposed mechanism and to determine the origin of the enantioselectivity. The geometry optimization and frequency calculations of the complexes and transition states were performed using the Gaussian 09 program package[15–17] at the UB3LYP/6-31G* level.[18,19] The thermal corrections were calculated at 298 K. Solvent effects were taken into account at the PCM/UB3LYP/6-31G*//UB3LYP/6-31G* level.[20] The corrections for dispersion interactions were calculated with the DFT-D3 program developed by Grimme.[21]



Scheme 2. Currently proposed reaction mechanism. LA* = chiral Lewis acid.

Due to the substrate structure, two diastereomeric complexes **7a** and **7b** are possible (Scheme 3, Figure 1SI). In these two diastereomeric complexes copper coordinates with the two carbonyl oxygen atoms of the substrate, leading to two six-membered ring chelates which possess a boat conformation with the copper and alkenyl group at the apices. According to our calculations, complexation through the carbonyl and NH groups is less probable as the resulting complex is higher in energy. Isomerization leads to intermediates **8a** and **8b** which finally undergo cyclization to give derivatives **9a** and **9b**.[22] In the case of **8a**, in which the CHCHPh residue is below the plane of the indole group, a counterclockwise conrotatory cyclization is favored.[23] In the case of **8b**, where the CHCHPh residue is above the plane of the indole group, a clockwise conrotatory cyclization is favored. Following the Curtin–Hammett principle, when **7a** and **7b** are in equilibrium, pathway B (Scheme 3 right) is favored as the transition state for the isomerization is lower in energy than that in pathway A.



Scheme 3. Illustration of the proposed reaction course. Values in brackets: relative energies in kcal mol^{-1}.

In summary, we have developed a catalytic asymmetric Nazarov cyclization of indole derivatives. This copper-catalyzed reaction gives the corresponding cyclopenta[*b*]indole products in good yields and with excellent selectivities under mild reaction conditions. The computer-aided studies on the asymmetric Nazarov reaction provide a better understanding of the reaction mechanism and explain the absolute configuration of the products. Given these results, further DFT calculations should lead to the development of suitable catalysts for such processes and an acceleration of the reaction optimization which demonstrates the advantage of the interplay between computational studies and experiment.

Received: August 6, 2014
Revised: November 5, 2014
Published online: December 22, 2014

Keywords: electrocyclization · indole alkaloids · Lewis acid catalysis · Nazarov reaction

[1] For reviews on the Nazarov cyclization, see: a) K. L. Habermas, S. E. Denmark, T. K. Jones, *Org. React.* **1994**, *45*, 1 – 158; b) S. E. Denmark in *Comprehensive Organic Synthesis*, *Vol. 5* (Eds.: B. M. Trost, I. Flemming), Pergamon, Oxford, **1991**, p. 51; c) A. J. Frontier, C. Collison, *Tetrahedron* **2005**, *61*, 7577; d) H. Pellissier, *Tetrahedron* **2005**, *61*, 6479; e) M. A. Tius, *Eur. J. Org. Chem.* **2005**, 2193; f) W. Nakanishi, F. G. West, *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 732; g) N. Shimada, C. Stewart, M. A. Tius, *Tetrahedron* **2011**, *67*, 5851; h) T. Vaidya, R. Eisenberg, A. J. Frontier, *ChemCatChem* **2011**, *3*, 1531.

[2] For asymmetric Brønsted acid catalyzed Nazarov cyclizations, see: a) M. Rueping, W. Ieawsuwan, A. P. Antonchick, B. J. Nachtsheim, *Angew. Chem. Int. Ed.* **2007**, *46*, 2097; *Angew. Chem.* **2007**, *119*, 2143; b) M. Rueping, W. Ieawsuwan, *Adv. Synth. Catal.* **2009**, *351*, 78; c) A. Jolit, P. M. Walleser, G. P. A. Yap, M. Tius, *Angew. Chem. Int. Ed.* **2014**, *53*, 6180; *Angew. Chem.* **2014**, *126*, 6294.

[3] For a catalyzed Nazarov cyclization with chiral diamines, see: a) A. K. Basak, N. Shimada, W. F. Bow, D. A. Vicic, M. A. Tius, *J. Am. Chem. Soc.* **2010**, *132*, 8266. With stoichiometric amounts of chiral diamines: b) W. F. Bow, A. K. Basak, A. Jolit, D. A. Vicic, M. A. Tius, *Org. Lett.* **2010**, *12*, 440. For an asymmetric aza-Nazarov cyclization, see: c) N. Shimada, B. O. Ashburn, A. K. Basak, W. F. Bow, D. A. Vicic, M. A. Tius, *Chem. Commun.* **2010**, *46*, 3774.

[4] Selected examples of the metal-catalyzed enantioselective Nazarov cyclization: a) G. Liang, S. N. Gradl, D. Trauner, *Org. Lett.* **2003**, *5*, 4931; b) V. K. Aggarwal, A. J. Belfield, *Org. Lett.* **2003**, *5*, 5075; c) G. Liang, D. Trauner, *J. Am. Chem. Soc.* **2004**, *126*, 9544; d) I. Walz, A. Togni, *Chem. Commun.* **2008**, 4315; e) P. Cao, C. Deng, Y.-Y. Zhou, X.-L. Sun, J.-C. Zheng, Z. Xie, Y. Tang, *Angew. Chem. Int. Ed.* **2010**, *49*, 4463; *Angew. Chem.* **2010**, *122*, 4565; f) J. Huang, D. Leboeuf, A. J. Frontier, *J. Am. Chem. Soc.* **2011**, *133*, 6307; g) N. Shimada, C. Stewart, W. F. Bow, A. Jolit, K. Wong, Z. Zhou, M. A. Tius, *Angew. Chem. Int. Ed.* **2012**, *51*, 5727; *Angew. Chem.* **2012**, *124*, 5825; h) G. E. Hutson, Y. E. Türkmen, V. H. Rawal, *J. Am. Chem. Soc.* **2013**, *135*, 4988.

[5] For a diastereoselective example: a) M. Janka, W. He, I. E. Haedicke, F. R. Fronczek, A. J. Frontier, R. Eisenberg, *J. Am. Chem. Soc.* **2006**, *128*, 5312; For experimental and theoretical

studies on diastereoselective tandem Nazarov cyclization/Wagner–Meerwein rearrangement, see: b) D. Lebœuf, J. Huang, V. Gandon, A. J. Frontier, *Angew. Chem. Int. Ed.* **2011**, *50*, 10981; *Angew. Chem.* **2011**, *123*, 11173; c) D. Lebœuf, V. Gandon, J. Ciesielski, A. J. Frontier, *J. Am. Chem. Soc.* **2012**, *134*, 6296; For theoretical investigations of the retro-Nazarov reaction, see: d) M. Harmata, P. R. Schreiner, D. R. Lee, P. L. Kirchhoefer, *J. Am. Chem. Soc.* **2004**, *126*, 10954.

[6] Nazarov cyclization of N-, O-, and S-heteroaromatic compounds: a) J. A. Malona, J. M. Colbourne, A. J. Frontier, *Org. Lett.* **2006**, *8*, 5661; b) C. Song, D. Knight, M. A. Whatton, *Org. Lett.* **2006**, *8*, 163; c) M. Kawatsura, Y. Higuchi, S. Hayase, M. Nanjo, T. Itoh, *Synlett* **2008**, 1009; d) P. Bachu, T. Akiyama, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3764; e) M. Fujiwara, M. Kawatsura, S. Hayase, M. Nanjo, T. Itoh, *Adv. Synth. Catal.* **2009**, *351*, 123; f) T. Vaidya, R. Cheng, P. N. Carlsen, A. J. Frontier, R. Eisenberg, *Org. Lett.* **2014**, *16*, 800.

[7] T. Vaidya, A. C. Atesin, I. R. Herrick, A. J. Frontier, R. Eisenberg, *Angew. Chem. Int. Ed.* **2010**, *49*, 3363; *Angew. Chem.* **2010**, *122*, 3435.

[8] J. Bergman, L. Venemalm, *Tetrahedron* **1990**, *46*, 6067.

[9] a) M. Rueping, B. J. Nachtsheim, R. M. Koenigs, W. Ieawsuwan, *Chem. Eur. J.* **2010**, *16*, 13116; b) M. Rueping, B. J. Nachtsheim, W. Ieawsuwan, I. Atodiresei, *Angew. Chem. Int. Ed.* **2011**, *50*, 6706; *Angew. Chem.* **2011**, *123*, 6838; c) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.* **2011**, *40*, 4539; d) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047.

[10] For recent reviews on the use of Box ligands in catalysis, see: a) R. Rasappan, D. Laventine, O. Reiser, *Coord. Chem. Rev.* **2008**, *252*, 702; b) G. C. Hargaden, P. J. Guiry, *Chem. Rev.* **2009**, *109*, 2505; c) L. M. Stanley, M. P. Sibi in *Privileged Chiral Ligands and Catalysts* (Ed.: Q.-L. Zhou), Wiley-VCH, Weinheim, **2011**, pp. 171–219.

[11] See the Supporting Information for details.

[12] S. Raja, M. Bolte, *Acta Crystallogr. Sect. E* **2011**, *67*, o2991.

[13] Based on X-ray crystal structure analysis, Evans reported that Cu-box forms complexes with alkylidene malonates which adopt a boat configuration: a) D. A. Evans, T. Rovis, M. C. Kozlowski, J. S. Tedrow, *J. Am. Chem. Soc.* **1999**, *121*, 1994; b) D. A. Evans, T. Rovis, M. C. Kozlowski, C. W. Downey, J. S. Tedrow, *J. Am. Chem. Soc.* **2000**, *122*, 9134.

[14] W. He, I. R. Herrick, T. A. Atesin, P. A. Caruana, C. A. Kellenberger, A. J. Frontier, *J. Am. Chem. Soc.* **2008**, *130*, 1003.

[15] Gaussian 09, Revision A.02, Gaussian, Inc., Wallingford CT, **2009**.

[16] The calculations were performed using the computing resources of the computing center of RWTH Aachen.

[17] The calculations were performed with the methyl-substituted catalyst **5b**.

[18] a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; b) B. Miehlich, A. Savin, H. Stoll, H. Preuss, *Chem. Phys. Lett.* **1989**, *157*, 200; c) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; d) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623.

[19] a) V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995; b) J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999.

[20] a) W. J. Hehre, R. Ditchfeld, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257; b) C. Hariharan, J. A. Pople, *Theor. Chim. Acta* **1973**, *28*, 213.

[21] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.

[22] A favorable direct cyclization is also possible. However, if the suggested mechanism is followed, cyclization of **7a** will not lead to the product actually obtained.

[23] In this case, a conrotatory clockwise cyclization is less likely due to the interactions between the two residues. See the Supporting Information for a graphical representation.

