Asymmetric Synthesis

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A Catalytic Asymmetric Chlorocyclization of Unsaturated Amides**

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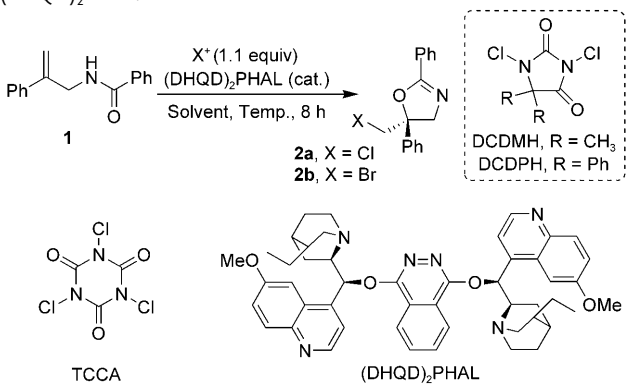
Stereodefined carbon–halogen bonds are ubiquitous in nature with several natural products exhibiting this motif.[1] While the biogenetic origins of this unique chiral functionality has been a subject of several investigations in the past,[2] attempts by organic chemists to forge the carbon–halogen bond stereoselectively have largely been unsuccessful. This problem has come into focus only recently. Several elegant reports of asymmetric halogenations of alkenes and alkynes followed by an intramolecular attack of a pendant nucleophile have appeared in the literature in the last decade. Kang et al. reported a cobalt–salen catalyzed iodoetherification reaction.[3a] An asymmetric fluorocyclization of allyl silanes mediated by a cinchona alkaloid dimer was reported by Gouverneur and co-workers.[3b] Tang and co-workers disclosed an asymmetric bromolactonization of enynes catalyzed by a cinchona alkaloid derived urea; other bromolactonizations have also appeared following the disclosure of their report.[3c–e] More recently, Veitch and Jacobsen reported an asymmetric iodolactonization reaction mediated by chiral thiourea catalysts.[3f] Polyene cyclizations induced by chiral halonium ions have also been realized as reported by the research groups of Ishihara and Snyder.[4a–c] However, given the fledgling nature of this research area, one may find it easy to highlight the many drawbacks and limitations even in the present state of the art—for example, the relatively large catalyst loadings (superstoichiometric quantities in some cases) to achieve meaningful levels of enantioselectivity or the lack of a robust catalytic system that can catalyze a number of diverse reactions rather than one specific reaction. Moreover, efficient asymmetric chlorocyclizations have remained underdeveloped. This situation is attributable, at least in part, to the highly reactive nature of chloronium ions, which are known to exist in equilibrium with the corresponding carbocation rather than exclusively as cyclic chloronium ions,[5a–c] thus making the development of chlorocyclizations a formidable challenge.

Our research group has recently reported the catalytic asymmetric chlorolactonization of alkenoic acids.[7] Herein, we disclose the efficient halocyclization of unsaturated amides to furnish chiral heterocycles. Furthermore, these heterocycles have been transformed into useful chiral building blocks such as amino alcohols.

Chiral heterocycles such as oxazolines and dihydrooxazines are commonly encountered motifs in natural products,[8a] molecules of pharmaceutical interest,[8b] and in several chiral ligands.[8c] Their syntheses, however, usually employ stoichiometric quantities of chiral amino alcohols. With only one precedented method to access these molecules in a catalytic asymmetric fashion,[6] we were intrigued by the possibility of one-step access to these versatile chiral heterocycles by a catalytic asymmetric halocyclization of easily accessed unsaturated amides.

We chose the conversion of benzamide **1** into oxazoline **2** as our initial test reaction. Among the several ligands screened for the test reaction, $(DHQD)_2PHAL$ emerged as the best candidate, thus affording the desired oxazoline **2** in 57% *ee* (Table 1, entry 1) with DCDMH as the terminal chlorine source.[9] Reactions with other chlorenium sources

Table 1: Halocyclization of unsaturated amides mediated by $(DHQD)_2PHAL$.[a,b]



Entry	X^+ source	Solvent, T [°C]	Cat. [mol%]	*ee* [%][c]
1	DCDMH	$CHCl_3$, −20	10	57
2	TCCA	$CHCl_3$, −20	10	18
3[d]	NCS	MeCN/CCl_4, RT	10	67
4	Chloramine T·3 H_2O	$CHCl_3$, −20	10	43[e]
5[d]	NBS	MeCN/CCl_4, −20	10	28
6[d]	DBDMH	MeCN/CCl_4, −20	10	5
7	DCDPH	$CHCl_3$, −40	10	63
8[d]	DCDPH	MeCN/CCl_4 −40	10	80
9	DCDPH	CF_3CH_2OH, −40	10	90
10	**DCDPH**	**CF_3CH_2OH, −30**	**2**	**90**

[a] All reactions were run on a 0.04 mmol scale. Complete conversion was observed for all reactions within 8 h. [b] See Supporting Information for the determination of absolute configuration. [c] Determined by HPLC on a chiral stationary phase. [d] Solvent ratio was 1:1. [e] Conversion was less than 20% as judged by NMR analysis of the crude product. DBDMH = *N*,*N*-dibromo-5,5-dimethylhydantoin, NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide.

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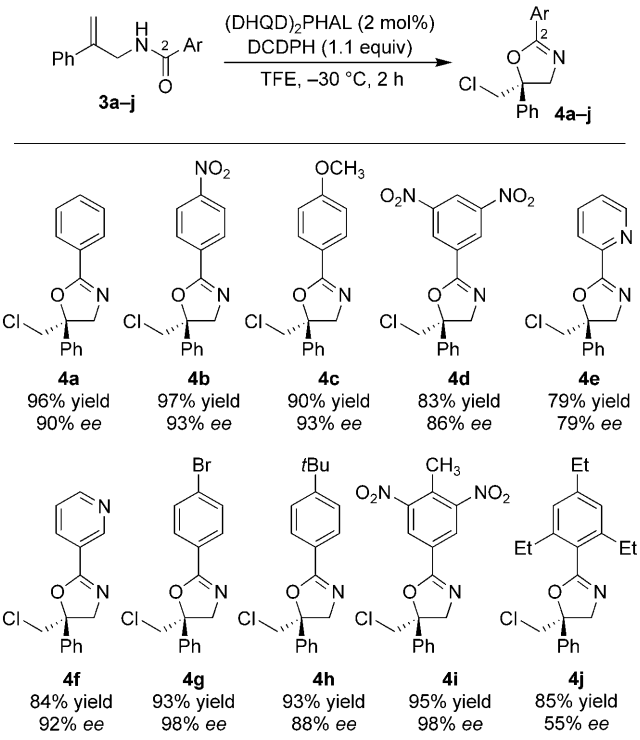
were marred with poor enantioselectivities and/or poor conversions. For example, TCCA gave the desired oxazoline with full conversion of the starting material into product albeit in only 18% *ee* (Table 1, entry 2). Employing NCS or Chloramine-T·3 H_2O resulted in very sluggish reactions (less than 20% conversion after 8 h). Running the reaction at elevated temperatures with NCS in a MeCN/CCl_4 solvent system gave the desired product in 67% *ee* (Table 1, entry 3), while Chloramine-T·3 H_2O gave the desired product in a modest 43% *ee* (Table 1, entry 4). Resorting to DCDPH[10] as the terminal chlorine source led to a more promising 63% *ee* (Table 1, entry 7) in $CHCl_3$ and 80% *ee* in a MeCN/CCl_4 solvent system. Analogous bromocyclizations were poorly selective. NBS returned the corresponding product in 28% *ee* (Table 1, entry 5), while the significantly more reactive DBDMH led to only 5% *ee* (Table 1, entry 6).

An exhaustive solvent-screening process revealed that trifluoroethanol (TFE) is the optimal solvent for the chlorocyclization, thus giving the desired product in 90% *ee* (Table 1, entry 9). The effect of catalyst loading, concentration, and temperature was then studied. It was observed that the stereoselectivity of this reaction was not diminished even at a catalyst loading of 2 mol% (90% *ee*; Table 1, entry 10). It also emerged that a concentration of 0.04 M and a temperature of −30 °C was optimal.

All further attempts at tweaking the reaction parameters to increase stereoselectivity (order of addition, slow addition, catalyst aging, etc.) were infructuous. Nonetheless, the aryl group at C2, which ultimately is revealed as the acid-labile functionality of the oxazoline product, could be viewed as a sacrificial entity (see Scheme 2). As such, optimization of the reaction through alteration of the aryl group at C2 could provide the opportunity for electronic and steric fine-tuning. The results of optimization studies for the aryl substituent at C2 are summarized in Scheme 1.

The precise nature of the substrate–catalyst interaction is still under investigation, however, we believe that *para* substituents on the C2 aryl ring provide a steric (rather than electronic) bias for better catalyst–substrate interaction. Substituents at the *para* position of the aryl ring at C2 increased the *ee* value regardless of their electron-donating/-withdrawing properties. For example, when the C2 substituent was an unsubstituted phenyl ring, the product **4a** was formed in 90% *ee*. However, the 4-$NO_2C_6H_4$ and the 4-$OMeC_6H_4$ substituted products, **4b** and **4c**, were both formed in a slightly enhanced 93% *ee*. Likewise, comparison of **4d** and **4i** is also indicative of the crucial role of the *para* substituent of the aryl ring. The 3,5-dinitrophenyl substituent (86% *ee*) is clearly inferior to the 3,5-dinitro-4-methylphenyl substituent (98% *ee*), thus indicating that the methyl group at the *para* position is essential for good stereoselectivity in the latter case. The 4-BrC_6H_4 substituted product **4g** was also formed with an excellent 98% *ee*. The significantly more bulky *t*Bu group gave the corresponding product **4h** with a lower *ee* value (88%). Heterocyclic rings such as 2-pyridyl (**4e**, 79% *ee*) and 3-pyridyl (**4f**, 92% *ee*) were also well tolerated as the C2 substituent in this reaction. The sterically demanding 2,4,6-triethylphenyl substituent significantly diminished the stereoselectivity of the reaction to give the product **4j** in only a 55% *ee*. It merits mention that the yields for all these reactions were excellent (79–97%) with no significant quantities of side products. The 4-BrC_6H_4 substituent was ultimately chosen as the optimal aryl group at C2 for further studies.[11]

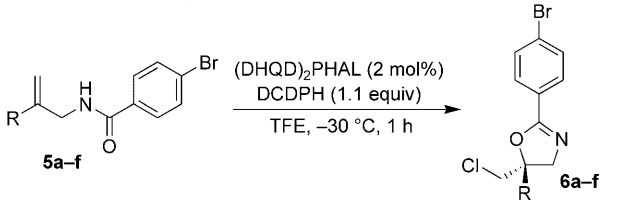


Scheme 1. Modulation of the substrate-catalyst interaction by variation of amide end functionality. Yields refer to the product isolated after column chromatography; the *ee* values were determined by HPLC analysis.

In order to probe the substrate scope for this reaction, a series of 1,1-disubstituted olefins were subjected to the optimized reaction conditions (Table 2). The strongly electron-withdrawing NO_2 group at the *meta* position significantly decreased the enantioselectivity of the reaction. The desired product **6b** was isolated in 75% yield and a modest 68% *ee* (Table 2, entry 2). Interestingly, switching the NO_2 group with the electron-donating OMe group at the *meta* position restored the stereoselectivity of the reaction to give the product **6c** in 93% *ee* (Table 2, entry 3). Halogenated aryl rings were well tolerated (**6d**–**6f**; Table 2, entries 4–6).

We were delighted to discover that the same reaction conditions could be extended to *trans*-disubstituted and trisubstituted olefin substrates, which yielded the corresponding dihydro-4-*H*-1,3-oxazines (Table 3). These reactions were inherently more stereoselective and required no steric or electronic fine-tuning of the C2 substituent. Almost all of the substituted phenyl rings evaluated as the C2 substituent gave 99% or better enantioselectivity when R^1 was a Ph ring (these results are not shown in Table 3; see the Supporting Information for a short list). Having already determined that the 4-BrC_6H_4 was the optimal amide end functionality for the 1,1-disubstituted olefin substrates, we retained the same functionality for these substrates as well. Electron-deficient

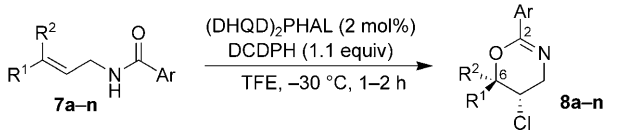
Table 2: Substrate scope: 1,1-disubstituted olefin substrates.[a,b]



Entry	R	Product	Yield [%][a]	*ee* [%][b]
1	C_6H_5	**6a**	93	98
2	3-$NO_2C_6H_4$	**6b**	75	68
3	3-$OMeC_6H_4$	**6c**	72	93
4	4-FC_6H_4	**6d**	65	87
5	4-BrC_6H_4	**6e**	89	84
6	4-ClC_6H_4	**6f**	94	87

[a] Yields of products isolated after column chromatography. [b] Determined by HPLC on a chiral stationary phase.

Table 3: Substrate scope: *trans*-disubstituted and trisubstituted olefin substrates.[a,b]



Entry	R^1	R^2	Ar	Prod.	Yield [%][a]	*ee* [%][b]
1	C_6H_5	H	4-BrC_6H_4	**8a**	91	99
2	C_6H_5	H	4-$OMeC_6H_4$	**8b**	93 (81)	>99 (>99)
3	4-FC_6H_4	H	4-BrC_6H_4	**8c**	99	95
4	4-BrC_6H_4	H	4-BrC_6H_4	**8d**	85	93
5	4-$CF_3C_6H_4$	H	4-BrC_6H_4	**8e**	94	95
6	4-$OMeC_6H_4$	H	4-BrC_6H_4	**8f**	84	20
7	4-MeC_6H_4	H	4-BrC_6H_4	**8g**	93	60[d]
8	2-MeC_6H_4	H	4-BrC_6H_4	**8h**	99	87
9	2-MeC_6H_4	H	4-$OMeC_6H_4$	**8i**	64	91
10	C_6H_5	C_6H_5	4-BrC_6H_4	**8j**	92	86
11	C_6H_5	Me	4-BrC_6H_4	**8k**	52[c]	91
12	Cy	H	4-BrC_6H_4	**8l**	77[c]	>99
13	*n*-C_5H_{11}	H	4-BrC_6H_4	**8m**	90 (77)[c]	>99 (>99)
14	CH_2Cy	H	4-BrC_6H_4	**8n**	80[c]	88

[a] Yields of product isolated after column chromatography. Yields and *ee* values in parentheses refer to reactions carried out on a 1 g scale. [b] Determined by HPLC on a chiral stationary phase. [c] Reaction was run in 1-nitropropane in the presence of 300 wt% M.S. (4 Å). [d] Substrate was added over a period of 2 h. Cy = cyclohexyl.

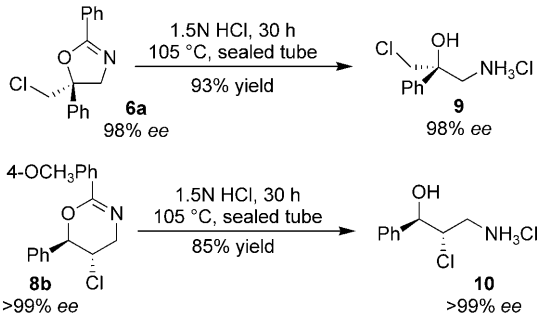
aryl rings as R^1 presented no problems and resulted in excellent stereoselectivities (products **8a**–**8e**; Table 3, entries 1–5). The absolute configuration of **8a** was verified by the X-ray crystal structure (see the Supporting Information) and was inferred by analogy with other substrates. Electron-rich R^1 substituents led to a significant erosion of the stereoselectivity. For example, the 4-$OMeC_6H_4$ substituted amide gave the corresponding product **8f** in only 20% *ee* and 84% yield (Table 3, entry 6).[12] The 4-MeC_6H_4 substituent also led to only moderate levels of stereoinduction, thus affording **8g** in 60% *ee* (Table 3, entry 7). The 2-MeC_6H_4 group was better tolerated and returned the corresponding product **8h** in excellent yield (99%) and good enantioselectivity (87% *ee*; Table 3, entry 8). Interestingly, the product **8i** with the 2-MeC_6H_4 as the C6 substituent but with the 4-$OMeC_6H_4$ as the C2 substituent was formed with a slightly enhanced *ee* value (91%; Table 3, entry 9). This result indicates that the amide end functionality is an invaluable handle for electronic and steric fine-tuning, thus allowing the systematic optimization of the enantioselectivity for a given substrate. Trisubstituted olefin substrates were also compatible with this chemistry (**8j** and **8k**; Table 3, entries 10 and 11).

Substrates with aliphatic olefin substituents gave poor yields of isolated product when TFE was employed as the solvent. Fortunately, the use of 1-nitropropane in the presence of molecular sieves (4 Å) alleviated this problem. The cyclohexyl-substituted product **8l** was isolated in 77% yield and near complete enantioselectivity (>99% *ee*; Table 3, entry 12). Likewise, the conformationally more flexible *n*-pentyl substituent was also well tolerated and returned the corresponding product **8m** in excellent yield (90%) and *ee* (>99%; Table 3, entry 13). It is important to note that no regioisomeric five-membered rings were detected under the optimized reaction conditions for the aliphatic substrates. Also, the absolute configuration of the products with aliphatic substituents was the same as that for products with aryl substituents (as verified by the X-ray crystal structure of **8l**[13]). In fact, the face selectivity for the formation of the choloronium ion intermediate with $(DHQD)_2PHAL$ is the same for all the amide substrates examined thus far. Substrates with *Z* olefins did not undergo halocyclization to the desired products presumably as a result of the stereoelectronic constraints that are well precedented in halolactonization reactions of similar substrates.[14]

We have also been able to demonstrate that this reaction can lend itself to preparative scale synthesis by synthesizing the dihydro-4-*H*-1,3-oxazines **8b** and **8m** on a gram scale (Table 3, entries 2 and 13). Both **8b** and **8m** were synthesized in excellent enantioselectivities (>99% *ee*) by employing just 1 mol% of the catalyst.

While the products shown in Scheme 1, Table 2, and Table 3 are of interest in their own right, they are adorned with several functional handles which can be manipulated and converted into useful synthetic building blocks. Compounds **6a** and **8b** were efficiently transformed into their corresponding 1,2- and 1,3- chiral amino alcohols **9** and **10**, respectively, by a simple acid hydrolysis of the cyclic imidate functionality (Scheme 2). These reactions proceed with complete stereochemical fidelity.

In summary, we have developed a highly stereoselective chlorocyclization of unsaturated amides to chiral heterocycles mediated by catalytic amounts (1–2 mol%) of the commercially available $(DHQD)_2PHAL$. The reaction is operationally simple with no need to resort to strictly anhydrous or inert reaction conditions. The reaction scope is fairly general with regards to the substitution pattern of the olefin. Both aliphatic and aromatic residues on the olefin are well tolerated. The mechanistic underpinnings of this transformation are currently under investigation.



Scheme 2. Transformation of dihydrooxazolines and dihydro-4*H*-1,3-oxazines into aminoalcohols.

Experimental Section

DCDPH (35 mg, 0.11 mmol, 1.1 equiv) was suspended in trifluoroethanol (2.2 mL) in a screw capped vial equiped with a stir bar. The resulting suspension was cooled to −30 °C with an immersion cooler. $(DHQD)_2PHAL$ (1.56 mg, 312 μL of a 5 mg mL^{-1} solution in TFE, 2 mol %) was then introduced into the reaction mixture. After stirring vigorously for 10 min, the substrate (0.10 mmol, 1.0 equiv) was added in a single portion. The vial was capped and the stirring was continued at −30 °C until the reaction was complete (as evident by TLC). The reaction was quenched by the addition of 10 % aq. Na_2SO_3 (3 mL) and diluted with CH_2Cl_2 (3 mL). The organics were seperated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in the presence of a small quantity of silica gel. Pure products were isolated by column chromatography on silica gel using EtOAc/hexanes (1:19) as the eluent.

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[1] G. W. Gribble, *Acc. Chem. Res.* **1998**, *31*, 141.
[2] a) L. C. Blasiak, C. L. Drennan, *Acc. Chem. Res.* **2009**, *42*, 147; b) C. S. Neumann, D. G. Fujimori, C. T. Walsh, *Chem. Biol.* **2008**, *15*, 99; c) C. Wagner, M. El Omari, G. M. König, *J. Nat. Prod.* **2009**, *72*, 540.
[3] a) S. H. Kang, S. B. Lee, C. M. Park, *J. Am. Chem. Soc.* **2003**, *125*, 15748; b) S. Wilkinson, O. Lozano, M. Schuler, M. Pacheco, R. Salmon, V. Gouverneur, *Angew. Chem.* **2009**, *121*, 7217; *Angew. Chem. Int. Ed.* **2009**, *48*, 7083; c) W. Zhang, S. Zheng, N. Liu, J. B. Werness, I. A. Guzei, W. Tang, *J. Am. Chem. Soc.* **2010**, *132*, 3664. For a brief review of recent developments in this field, see G. Chen, S. Ma, *Angew. Chem.* **2010**, *122*, 8484; *Angew. Chem. Int. Ed.* **2010**, *49*, 8306. During the course of preparation of this manuscript, two elegant reports of asymmetric bromolactonizations were reported: d) L. Zhou, C. K. Tan, X. Jiang, F. Chen, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2010**, *132*, 15474; e) K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura, H. Fujioka, *Angew. Chem.* **2010**, *122*, 9360; *Angew. Chem. Int. Ed.* **2010**, *49*, 9174; for an organocatalytic iodolactonizatin, see: f) G. E. Veitch, E. N. Jacobsen, *Angew. Chem.* **2010**, *122*, 7490; *Angew. Chem. Int. Ed.* **2010**, *49*, 7332.
[4] For polyene cyclizations induced by chiral halonium ions, see: a) A. Sakakura, A. Ukai, K. Ishihara, *Nature* **2007**, *445*, 900; b) S. Snyder, D. Treitler, *Angew. Chem.* **2009**, *121*, 8039; *Angew. Chem. Int. Ed.* **2009**, *48*, 7899; c) S. A. Snyder, D. S. Treitler, A. P. Brucks, *J. Am. Chem. Soc.* **2010**, *123*, 14303.
[5] a) G. A. Olah, J. M. Bollinger, J. Brinich, *J. Am. Chem. Soc.* **1968**, *90*, 2587; b) G. A. Olah, J. M. Bollinger, Y. K. Mo, J. M. Brinich, *J. Am. Chem. Soc.* **1972**, *94*, 1164; c) B. K. Ohta, R. E. Hough, J. W. Schubert, *Org. Lett.* **2007**, *9*, 2317.
[6] A solitary example of a catalytic asymmetric synthesis of dihydrooxazoles from olefins is known in literature: S. Minakata, M. Nishimura, T. Takahashi, Y. Oderaotoshi, M. Komatsu, *Tetrahedron Lett.* **2001**, *42*, 9019.
[7] D. C. Whitehead, R. Yousefi, A. Jaganathan, B. Borhan, *J. Am. Chem. Soc.* **2010**, *132*, 3298.
[8] a) B. S. Davidson, *Chem. Rev.* **1993**, *93*, 1771; b) S. Castellano, D. Kuck, M. Sala, E. Novellino, F. Lyko, G. Sbardella, *J. Med. Chem.* **2008**, *51*, 2321; c) For a review on metal-bisoxazoline catalysis, see A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1.
[9] See the Supporting Information for determination of the absolute configuration.
[10] We have previously reported an expedient synthesis of a variety of chlorinated hydantoins including DCDPH: D. C. Whitehead, R. J. Staples, B. Borhan, *Tetrahedron Lett.* **2009**, *50*, 656.
[11] Aliphatic C2 substituents gave only moderate levels of stereoinduction. For example, when the C2 substituent was a CH_3 group, the product was formed in only 54 % *ee*.
[12] The erosion in stereoselectivity is likely attributable to the nonselective background reaction: ca. 80 % conversion to product in the absence of the catalyst under otherwise identical conditions.
[13] CCDC 799027, 799028, 799029 and 799030 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[14] S. E. Denmark, M. T. Burk, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20655, and references therein.

