CHEMISTRY
A EUROPEAN JOURNAL

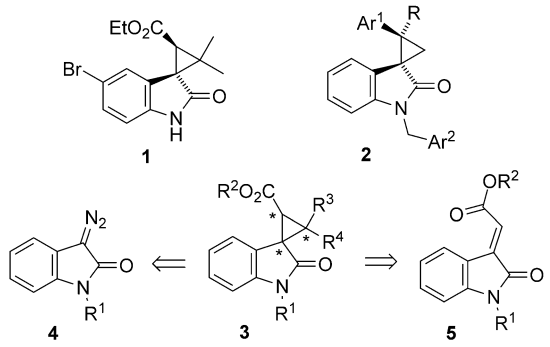
COMMUNICATION

DOI: 10.1002/chem.201203099

Highly Enantio- and Diastereoselective Generation of Two Quaternary Centers in Spirocyclopropanation of Oxindole Derivatives.

Artur Noole,[a, b] Natalia S. Sucman,[c] Mikhail A. Kabeshov,[a] Tõnis Kanger,[b] Fliur Z. Macaev,[c] and Andrei V. Malkov*[a]

Biologically active spirocyclopropane derivatives of indoles emerged recently as potent drug candidates. Thus, spirooxindole **1** exhibited nanomolar activity as an HIV-1 nonnucleoside reverse transcriptase inhibitor on both wild-type and drug-resistant mutant viruses,[1,2] whereas compounds of type **2** showed promising antitumor activity[3,4] and were also effective for treatment of obesity and diabetes (Scheme 1).[5] The stereochemistry of these compounds plays a crucial role in their biological activity.



Scheme 1. Biologically active spirocyclopropane derivatives of indoles.

In the past, the main strategies for the construction of spirocylopropyl oxindole motif **3** relied either on transition-metal-catalyzed cylopropanation using diazo oxindoles **4** with a suitable alkene partner[1,6–9] or addition of a carbenoid species to unsaturated oxindoles **5**.[1–3,10] Both strategies produced various degrees of diastereoselectivity, but so far were confined to racemic series. More recently, a few examples of successful asymmetric cyclopropanation of the parent oxindoles were reported.[4,11]

Organocatalytic approaches to spiro-annulation of oxindoles **5** offer a high degree of stereo- and enantiocontrol and have become extremely popular for the construction of five- and six-membered spiro-rings.[12–18] However, examples of a direct spirocyclopropanation of indole derivatives remain scarce.[19] The major challenge in the synthesis of **3** is to ensure a stringent control in the formation of the three contiguous stereocenters, which, in theory, can give rise up to eight stereoisomers (four diastereomeric pairs of enantiomers). In a recent report,[20] spirooxindoles **3**, featuring one quaternary center, were obtained in excellent diastereo- and enantioselectivities by a cascade cyclopropanation of **5** with bromonitromethane catalyzed by chiral thioureas. However, for the next member of the homologue series, 1-bromonitroethane, in which two adjacent quaternary centers are created, the diastereocontrol dropped dramatically. Furthermore, it has been recently revealed[11] that in the case of spirooxindoles **3**, in which $R^3 = NO_2$ and $R^4 = H$, the diastereomeric composition can be significantly enriched in favor of the more thermodynamically stable isomer by a base-catalyzed equilibration. Naturally, this option is not available for **3** with R^3, $R^4 \neq H$, which leaves the issue of diastereoselectivity in the asymmetric organocatalytic cyclopropanation wide open.

Herein, we focused on developing a formal [2+1] cycloaddition method for the highly enantio- and diastereoselective construction of spirocyclopropane oxindoles **3** featuring two quaternary centers using chiral catalysts **6–9** (Figure 1).

In recent years, α-halo-β-dicarbonyl compounds acquired a successful track record in asymmetric organocatalytic and metal-catalyzed cyclopropanations of α,β-unsaturated compounds including aldehydes,[21,22] the related conjugated ketones and esters,[23,24] and nitroalkenes.[25] The key feature of α-halocarbonyl compounds is the dual nucleophilic/electrophilic reactivity of the α-carbon, which is a prerequisite for the cascade cyclopropanation.

In a background racemic run, oxindole **5a** was treated with ethyl α-chloroacetoacetate **10** in the presence of K_2CO_3 in CH_2Cl_2 at room temperture to afford an equimolar mixture of all four possible diastereoisomers after 24 h (Table 1, entry 1). It is worth noting that the same reaction with un-

[a] A. Noole, Dr. M. A. Kabeshov, Prof. Dr. A. V. Malkov
Department of Chemistry
Loughborough University
Loughborough LE11 3TU (UK)
Fax: (+44) 1509-223925
E-mail: a.malkov@lboro.ac.uk

[b] A. Noole, Prof. Dr. T. Kanger
Department of Chemistry
Tallinn University of Technology
Akadeemia tee 15, Tallinn 12618 (Estonia)

[c] N. S. Sucman, Prof. Dr. F. Z. Macaev
Institute of Chemistry
Academiei str. 3, Chisinau 2028 (Moldova)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201203099.

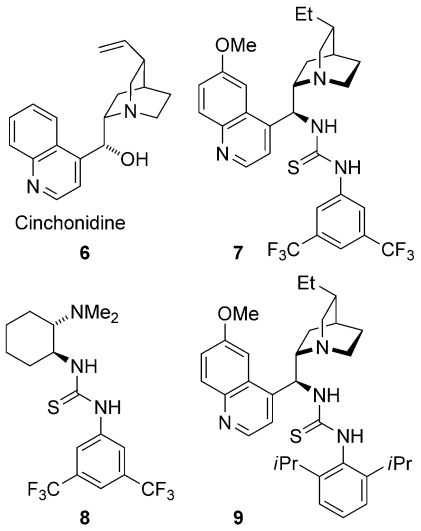
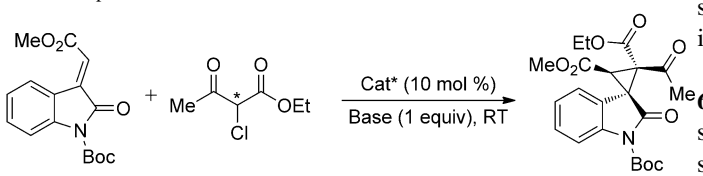


Figure 1. Chiral catalysts.

Table 1. Optimization of the reaction conditions.[a]



5a 10 11a

Entry	Cat.	Base	Solvent	Yield [%][b]	d.r. [%][b]	*ee* [%][c]
1	–	K_2CO_3	CH_2Cl_2	86	25:25:25:25	n.a.
2	**6**[d]	–	CH_2Cl_2	72	71:24:5	96:55:12
3	**7**	$NaHCO_3$	CH_2Cl_2	48	77:23	93:95
4	**7**	$NaHCO_3$	toluene	n.d.[e]	n.d.	n.d.
5	**7**	$NaHCO_3$	$CHCl_3$	97	78:22	94:96
6	**7**	$NaHCO_3$	THF	54	63:37	97:99
7	**7**	$NaHCO_3$	MeCN	87	9:31:52:8	n.d.
8	**7**	Na_2CO_3	$CHCl_3$	87	74:26	89:94
9	**7**	CsF	$CHCl_3$	76	77:23	93:95
10	**8**	$NaHCO_3$	$CHCl_3$	48	75:25	−93:−86
11	**9**	$NaHCO_3$	$CHCl_3$	82	93:7	91:94
12	**9**	$NaHCO_3$	$CHCl_3$	97[f]	91:9	91:82
13	**9**	$NaHCO_3$	$CHCl_3$	93[g]	90:10	87:83

[a] Unless stated otherwise, the reactions were carried out on a 0.15 mmol scale as a 0.15 M solution at RT for 24 h with 1 equiv of **5a**, 2 equiv of **10**, 1 equiv of base and 10 mol% catalyst loading. [b] Yield of isolated product. [c] Determined by chiral HPLC analyses after deprotection of *t*Boc. [d] 1 Equiv of catalyst was used. [e] Complex mixture of all possible diastereoisomers. [f] 0.3 M Solution. [g] 4 Equiv of **10** used.

protected oxindole **5** was complete in just 1 h and gave a similar outcome, but we opted for *tert*-butoxycarbonyl (Boc) protection, which may benefit stereodifferentiation in the presence of a chiral controller.

For the enantioselective version, we first tested cinchonidine **6**[26] (Figure 1) as a chiral base (1 equiv, CH_2Cl_2, RT). The reaction produced a 3:1 mixture of two main diastereoisomers and a minor quantity of a third diastereoisomer, which could be readily separated by flash chromatography (entry 2). Importantly, the major product showed 96% *ee*. However, attempted reduction of the catalyst loading to a more practical 10 mol% level had a detrimental effect on the reaction rate and selectivity. Therefore, we next turned to bifunctional thiourea catalysts **7**[27–29] and **8**,[30] which proved successful in the asymmetric spirocyclopropanation of **5** with bromonitromethane.[20]

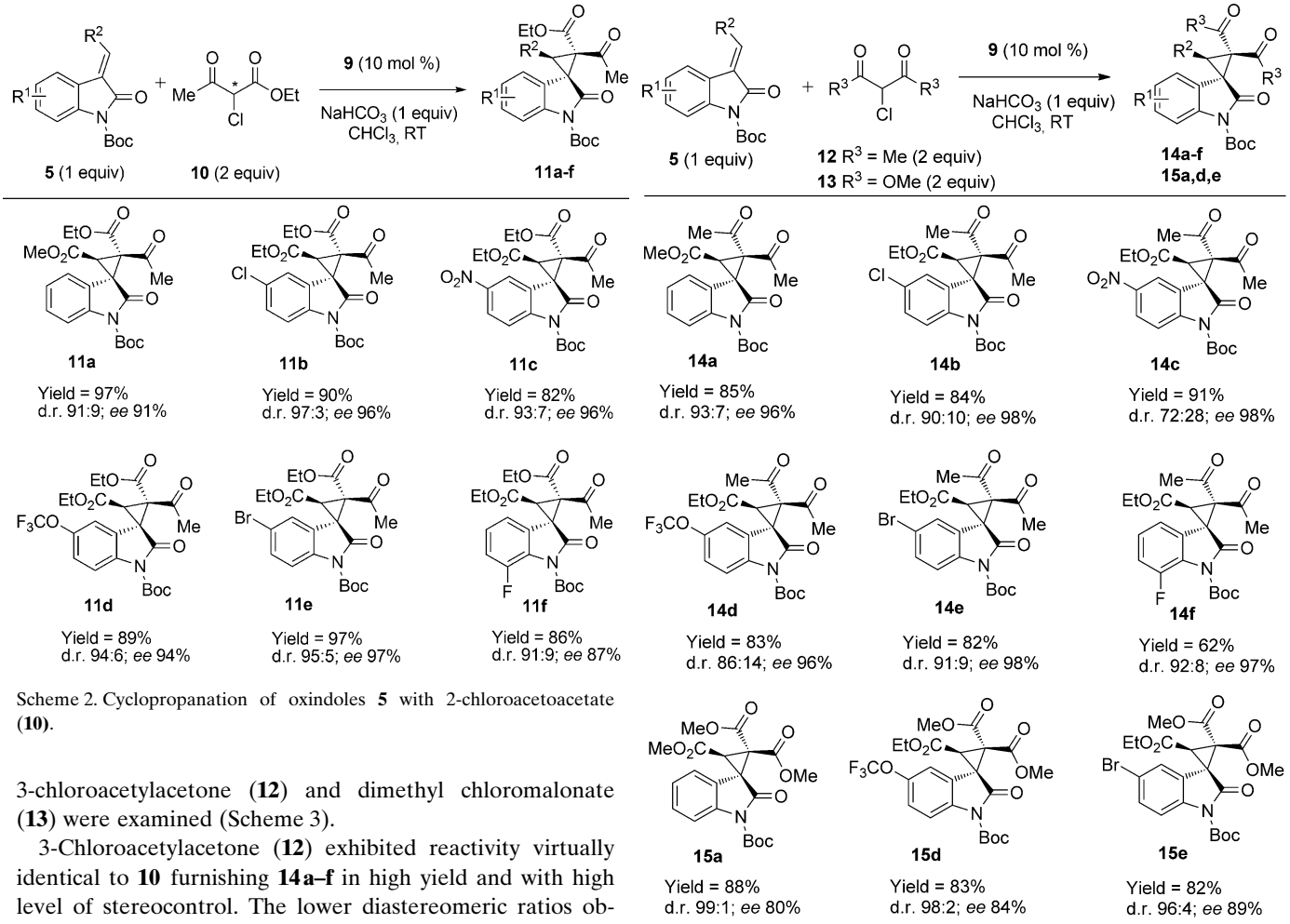
Quinine-derived thiourea **7** (10 mol%, CH_2Cl_2, RT, 24 h) combined with $NaHCO_3$ (1 equiv) afforded a 3:1 mixture of the same two diastereoisomers, as with **6**, in high enantioselectivity, but a low overall yield (entry 3). To optimize the reaction efficiency, various solvents and bases were examined. In toluene (entry 4) and MeCN (entry 7), diastereoselectivity dropped significantly to give mixtures of all possible isomers. The highest enantioselectivity was attained in THF, though the yield and diastereoselectivity were poor (entry 6). Chloroform emerged as a clear winner, showing the best overall performance (entry 5). Other inorganic bases, such as Na_2CO_3 and CsF (entries 8 and 9), proved slightly inferior to $NaHCO_3$. Catalyst **8** mirrored the results shown by **7** delivering the same 3:1 mixture of diastereoisomers of the opposite enantiomeric series (entry 10).

It appears that the commonly used commercial catalysts **6–8** under a variety of experimental conditions exhibited a similar reactivity pattern favoring formation of two diastereoisomers in a 3:1 ratio at best. Notably, the components of this mixture cannot be easily separated by chromatography, thus reducing the practical value of the method. Clearly, improvement in the catalyst design was required to overcome this problem.

A set of experiments revealed that diastereoselectivity was influenced by the substituents on the aromatic group of the thiourea catalyst, in particular by those restricting rotation about the C–N bond. A major improvement was achieved with catalyst **9** with bulky *i*Pr groups occupying the *ortho* positions; the diastereoselectivity soared to 13:1 while maintaining a good yield and a respectable enantioselectivity (entry 11). Effectively, only one of eight possible stereoisomers was produced! The yield was further improved by doubling the concentration of the reactants (entry 12), though using an excess of ethyl α-chloroacetoacetate **10** alone proved detrimental (entry 13).

The reaction scope was investigated following the optimized protocol: chloroform as a solvent (0.3 M solution), **5** (1 equiv), **10** (2 equiv), $NaHCO_3$ (1 equiv), and **9** (10 mol%) at room temperature. Under these conditions, the reactions were complete within 24 h (Scheme 2). The substitution pattern in the aromatic ring of the starting oxindoles **5a–f** did not affect the efficacy of the process: the spirocyclopropanes **11a–f** were uniformly obtained in high yields and high enantio- or diastereoselectivities.

The reaction is likely to proceed by Michael addition of the enolate of **10** to the unsaturated amide fragment in **5** to generate two new stereogenic centers followed by cyclization to create the final spiro-stereocenter. To shed more light on the stereoselectivity in each step, symmetrical



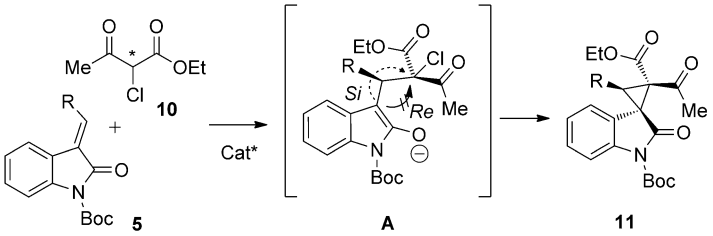
Scheme 2. Cyclopropanation of oxindoles **5** with 2-chloroacetoacetate (**10**).

Scheme 3. Cyclopropanation of oxindoles **5** with 3-chloroacetylacetone (**12**; 24 h) and dimethylchloromalonate (**13**; 48 h).

3-chloroacetylacetone (**12**) and dimethyl chloromalonate (**13**) were examined (Scheme 3).

3-Chloroacetylacetone (**12**) exhibited reactivity virtually identical to **10** furnishing **14a–f** in high yield and with high level of stereocontrol. The lower diastereomeric ratios observed in the case of **14c** and **d** resulted from the reversed diastereoselectivity in the racemic series, in which the minor isomers were formed predominantly. Chloromalonate **13** proved the least reactive of the three halodicarbonyl reagents. Under identical conditions, the reaction required 48 h to reach completion. The reduced reactivity appears to have a beneficial effect on the diastereoselectivity: the respective spirooxindoles **15a**, **d**, and **e** were formed as virtually single diastereoisomers, though in slightly lower enantioselectivity.

Dissecting the cyclopropanation cascade into two separate steps provides a useful insight into the role of the new catalyst **9** in attaining efficient stereodifferentiation. NOE NMR experiments revealed that the two diastereoisomers of **14a** differ by configuration of their single tertiary center in the cyclopropane ring, which is created in the first Michael addition step (for establishment of the relative configuration of diastereoisomers, see Supporting Information). Taking into account that catalyst **7** afforded **14a** in only a 3:1 diastereomeric ratio (**5a** + **12**, yield 58%, 43 h), the new catalyst **9** appears to have significantly enhanced enantioselectivity of the Michael addition. Similarity in the enantio- and diastereoselective outcome exhibited by chiral **10** and achiral **12** also indicates that Michael addition of **10** to **5** proceeds with remarkable diastereocontrol, since the configuration of stereogenic centers thus formed are not "adjusted" in the later stages of the reaction. The spirocenter is created in the second cyclization step, which in the case of **11** occurs through intermediate **A** (Scheme 4). In this step, both catalysts **7** and **9** proved equally competent ensuring *Si* facial selectivity for the major diastereoisomer (the opposite enantiomer was formed in the case of **8**). It can be speculated that in the C–C bond-forming event, the catalyst brings the two reactants together: the thiourea motif binds to the oxin-



Scheme 4. Facial selectivity in the spirocyclopropanation step (only nucleophilic attack from the *Si* face takes place).

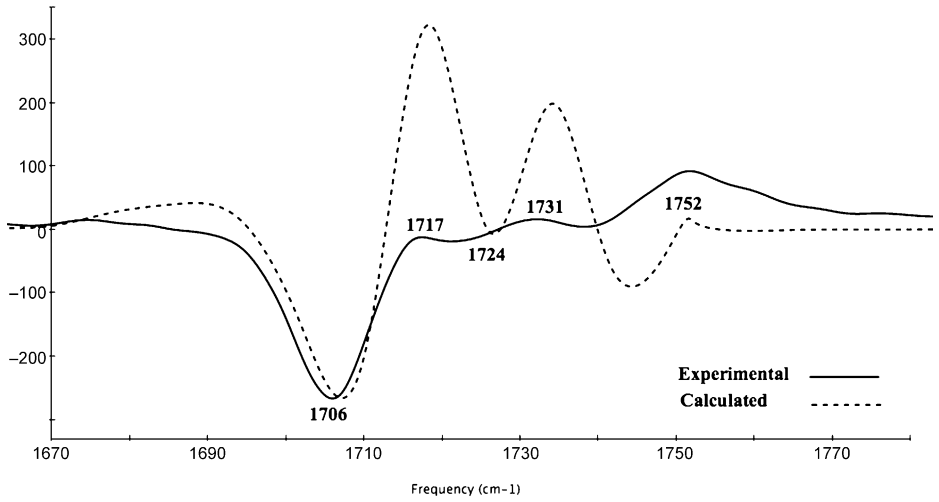


Figure 2. VCD analysis of **14a′**.

dole-Boc fragment by hydrogen-bonding, whereas the quinuclidine part binds the β-dicarbonyl nucleophile. However, a detailed computational analysis is required to build a more accurate mechanistic picture.

The absolute configuration of the spirooxindoles was determined by vibrational circular dichroism (VCD) of unprotected oxindole **14a′**. The carbonyl region of the compound produced the strongest VCD signal and was therefore chosen for the direct comparison with calculated spectra (for details see the Supporting Information). The calculated and experimental spectra provided an excellent match (Figure 2); other compounds in a series were assigned analogously.

In conclusion, we have developed an efficient enantio- and diastereoselective spirocyclopropanation of alkylidene oxindoles generating two quaternary centers. The structure of the quinine-derived thiourea catalyst **9** was optimized to provide high stereoselectivity in both cascade steps. With the new catalysts, cyclopropanation of alkylidene oxindoles with ethyl 2-chloroacetoacetate remarkably produced only one out of eight possible stereoisomers. Mechanistic and computational analysis to determine the mechanism of stereodifferentiation is in progress.

Experimental Section

General procedure for spirocyclopropanation (Schemes 2 and 3): Alkylidene oxindoles **5a–f** (0.15 mmol), sodium hydrogen carbonate (13 mg, 0.15 mmol), thiourea **9** (8.2 mg, 10 mol%, 0.015 mmol) and substrates **10**, **12** or **13** (0.3 mmol) were dissolved in chloroform (0.5 mL) and stirred at RT until TLC showed full conversion. The reaction mixture was directly purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate as eluent. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy and enantiomeric excess by chiral HPLC analysis.

Acknowledgements

We thank RSC for the International Joint Project grant JP090309 and TUT for travel fellowship to AN. We acknowledge COST-ORCA action (CM0905) for creating networking and exchange opportunities.

Keywords: asymmetric catalysis · cascade reactions · cyclization · organocatalysis · spiro compounds

[1] T. Jiang, K. L. Kuhen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T. Y.-H. Wu, Y. He, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105–2108.
[2] Y. He, T. Jiang, K. L. Kuhen, Y.-H. Ellis, B. Wu, T. Y.-H. Wu, B. Bursulaya, IRM LLC, Scripps Research Institute, Oxindoles with Anti-HIV Activity, **2004**, U. S. Patent WO 2004/037247 A1.
[3] P. B. Sampson, Y. Liu, S.-W. Li, B. T. Forrest, H. W. Pauls, L. G. Edwards, M. Feher, N. K. B. Patel, R. Laufer, G. Pan, University Health Network (Ontario, Canada), Kinase Inhibitors and Method of Treating Cancer with Same, **2010**, U. S. Patent WO2010/115279 A1.
[4] H. W. Pauls, S.-W. Li, P. B. Sampson, B. T. Forrest, University Health Network (Ontario, Canada), Plk-4 Inhibitors and Methods of Treating Cancer with Same, **2012**, U. S. Patent WO2012/048411 A1.
[5] L. Chen, L. Feng, Y. He, M. Huang, H. Yun, Hoffmann-La Roche AG, *Spiro Indol—Cyclopropane Indolinones Useful as AMPK Modulators* **2011**, U. S. Patent WO2011/70039 A1.
[6] C. Meyers, E. M. Carreira, *Angew. Chem.* **2003**, *115*, 718–720; *Angew. Chem. Int. Ed.* **2003**, *42*, 694–696.
[7] S. Chen, J. Ma, J. Wang, *Tetrahedron Lett.* **2008**, *49*, 6781–6783.
[8] S. Muthusamy, D. Azhagan, B. Gnanaprakasam, E. Suresh, *Tetrahedron Lett.* **2010**, *51*, 5662–5665.
[9] G. Kumari, Nutan, M. Modi, S. K. Gupta, R. K. Singh, *Eur. J. Med. Chem.* **2011**, *46*, 1181–1188.
[10] P. Ivashkin, S. Couve-Bonnaire, P. Jubault, X. Pannecoucke, *Org. Lett.* **2012**, *14*, 2270–2273.
[11] X. Dou, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 8315–8319.
[12] W. Sun, G. Zhu, C. Wu, L. Hong, R. Wang, *Chem. Eur. J.* **2012**, *18*, 6737–6741.
[13] K. Albertshofer, B. Tan, C. F. Barbas III, *Org. Lett.* **2012**, *14*, 1834–1837.
[14] B. Tan, N. R. Candeias, C. F. Barbas III, *Nat. Chem.* **2011**, *3*, 473–477.
[15] W.-B. Chen, Z.-J. Wu, Q.-L. Pei, L.-F. Cun, X.-M. Zhang, W.-C. Yuan, *Org. Lett.* **2010**, *12*, 3132–3135.
[16] K. Jiang, Z.-J. Jia, X. Yin, L. Wu, Y.-C. Chen, *Org. Lett.* **2010**, *12*, 2766–2769.
[17] G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336–7339; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200–7203.
[18] S.-W. Duan, Y. Li, Y.-Y. Liu, Y.-Q. Zou, D.-Q. Shi, W.-J. Xiao, *Chem. Commun.* **2012**, *48*, 5160–5162.
[19] For the most recent example, see A. Noole, I. Järving, F. Werner, M. Lopp, A. Malkov, T. Kanger, *Org. Lett.* **2012**, *14*, 4922–4925.
[20] F. Pesciaioli, P. Righi, A. Mazzanti, G. Bartoli, G. Bencivenni, *Chem. Eur. J.* **2011**, *17*, 2842–2845.
[21] R. Rios, H. Sundén, J. Vesely, G.-L. Zhao, P. Dziedzic, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1028–1032.

[22] I. Ibrahem, G.-L. Zhao, R. Rios, J. Vesely, H. Sundén, P. Dziedzic, A. Córdova, *Chem. Eur. J.* **2008**, *14*, 7867–7879.
[23] C. D. Papageorgiou, M. A. Cubillo de Dios, S. V. Ley, M. J. Gaunt, *Angew. Chem.* **2004**, *116*, 4741–4744; *Angew. Chem. Int. Ed.* **2004**, *43*, 4641–4644.
[24] C. C. C. Johansson, N. Bremeyer, S. V. Ley, D. R. Owen, S. C. Smith, M. J. Gaunt, *Angew. Chem.* **2006**, 118, 6170–6175; *Angew. Chem. Int. Ed.* **2006**, *45*, 6024–6028.
[25] H. J. Lee, S. M. Kim, D. Y. Kim, *Tetrahedron Lett.* **2012**, *53*, 3437–3439.
[26] T. Marcelli, H. Hiemstra, *Synthesis* **2010**, 1229–1279.
[27] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969.
[28] J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483.
[29] S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525–6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370.
[30] T. Inokuma, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2006**, *128*, 9413–9419.

Received: August 31, 2012
Published online: October 30, 2012

