Reaction Design

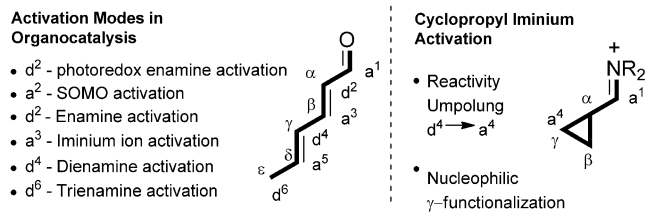
DOI: 10.1002/anie.201103360

# Cyclopropyl Iminium Activation: Reactivity Umpolung in Enantioselective Organocatalytic Reaction Design**

*Christof Sparr* and Ryan Gilmour**

*Dedicated to Professor Dieter Seebach*

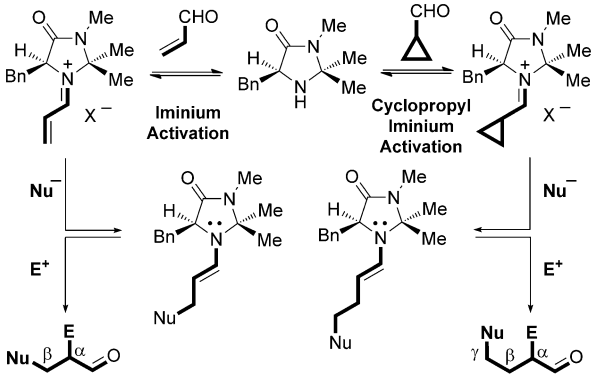
The intrinsic donor–acceptor reactivity pattern of conjugated, unsaturated carbonyl compounds predictably alternates along the carbon chain (Scheme 1). Consequently, electrophiles are




***Scheme 1.*** Organocatalytic cyclopropyl iminium activation (a = acceptor, d = donor).

predisposed to react at the $\alpha$ ($d^2$) and $\gamma$ ($d^4$) donor positions, whereas nucleophiles add to the $\beta$ ($a^3$) and $\delta$ ($a^5$) acceptor positions. Direct inversion of this inherent selectivity is known as reactivity umpolung,[1] and often provides a platform for the development of novel transformations. While various activation modes that allow for $\alpha$ ($a^2/d^2$), $\beta$ ($a^3$), $\gamma$ ($d^4$), and $\varepsilon$ ($d^6$) functionalization have been reported through secondary amine organocatalysis,[2] umpolung strategies remain elusive outwith the confines of SOMO activation[2b] and processes mediated by N-heterocyclic carbenes (NHCs).[3,4] Because pyrrolidine- and imidazolidinone-based organocatalysts require carbonyl substrates to generate the transient intermediates that are central for catalysis, the substrate scope is limited to aldehydes and ketones with varying degrees of unsaturation. With a view to extending the substrate scope of secondary-amine-catalyzed processes, and providing an entry point into the design of homologous variants of addition reactions to α,β-unsaturated iminium ions, we began exploring the reactivity of cyclopropane carbaldehydes.

Cyclopropane behaviour has striking parallels with that of olefins.[5] In addition to their ability to interact with adjacent π systems, cyclopropanes function as effective donors when activated by adjacent low-lying empty orbitals: this can be rationalized by considering the Walsh orbitals.[6,7] Striking manifestations of the electron-donating aptitude of cyclopropanes include: 1) the unusual thermodynamic stability of the cyclopropylcarbinyl cation,[8] and 2) the bond-length asymmetry of cyclopropanecarbonitirile ($\Delta d_{(distal-vicinal)} = 0.033$ Å) as a consequence of hyperconjugation.[9,10] Of particular pertinence to this study is the latter observation. It was envisaged that the well described conjugation between a cyclopropane moiety and polar multiple bonds might form the basis of an activation strategy involving cyclopropyl iminium salts. Indeed, Wang and co-workers have described that the nucleophilic addition of benzenethiols to cyclopropanecarbaldehydes can be catalyzed by proline.[11] The similarities in bonding between this species and that of conventional α,β-unsaturated iminium ions, together with the expected interaction of the cyclopropyl moiety with the conjugated iminium functionality, motivated us to investigate the reactivity of cyclopropane carbaldehydes[12] upon unification with secondary amines (Scheme 2). Formally, nucleophilic addition to the transient cyclopropyl iminium species would constitute a formal umpolung of the γ-position of a dienamine;[2c] $d^4 \rightarrow a^4$ (Scheme 1). Moreover, by intercepting the transient enamine with an electrophile, this strategy would give an unprecedented method for the organocatalytic formation of 1,3-difunctionalized products in a single operation (Scheme 2). Herein, we report the first secondary-




***Scheme 2.*** A comparison of classical iminium activation and cyclopropyl iminium activation. Bn = benzyl, E = electrophile, Nu = nucleophile.

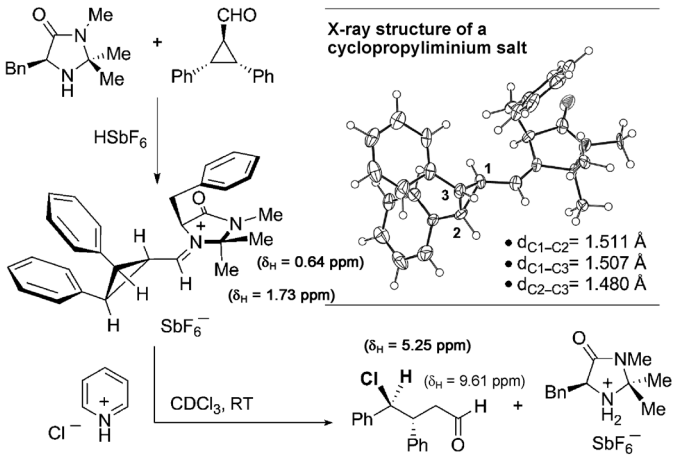
[*] C. Sparr, Prof. Dr. R. Gilmour
ETH Zürich, Laboratory for Organic Chemistry
Wolfgang-Pauli-Strasse 10, 8093 Zürich (Switzerland)
E-mail: christof.sparr@org.chem.ethz.ch
ryan.gilmour@org.chem.ethz.ch
Homepage: http://www.gilmour.ethz.ch

[**] We acknowledge generous financial support from the Alfred Werner Foundation (assistant professorship to R.G.), the Roche Research Foundation, Novartis AG (doctoral fellowships to C.S.), and the ETH Zurich. We thank Dr. W. B. Schweizer for X-ray crystal structure analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103360.

amine-catalyzed enantioselective activation/desymmetrization[13] of *meso*-cyclopropanecarbaldehyde compounds and demonstrate the synthetic value of this concept in the catalytic, asymmetric synthesis of 1,3-dichlorides.

Consistent with previous organocatalyst design approaches reported by our research group,[14] the catalytic process was deconstructed to first investigate the transient cyclopropyl iminium intermediate that was central to our working hypothesis. To that end, the cyclopropane carbaldehyde derived from *cis*-stilbene and diazoethylacetate was prepared and condensed with MacMillan's first-generation catalyst in the presence of hexafluoroantimonic acid. Pleasingly, the product cyclopropyl iminium salt could be generated and single crystals suitable for X-ray analysis were obtained (Scheme 3). Inspection of the solid-state structure




***Scheme 3.*** OTREP structure and reactivity of a preformed cyclopropyl iminium salt. Couterion omitted for clarity and thermal ellipsoids drawn at 50% probability.

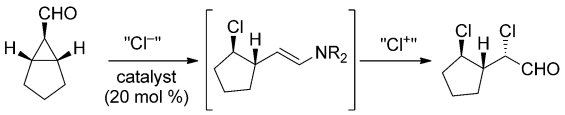
revealed a 0.03 Å bond-length asymmetry between the distal and vicinal bonds of the cyclopropane ($d_{C2-C3} = 1.480$ Å versus $d_{C1-C2} = 1.511$ Å and $d_{C1-C3} = 1.507$ Å; the mean bond length in cyclopropanes is 1.509(2) Å).[10f] It is also evident from this analysis that the iminium functionality bisects the average plane of the cyclopropane ring, and that the benzyl group of the imidazolidinone is positioned over the catalyst core such that the system benefits from a stabilizing CH–π interaction.[15] The $^1$H NMR studies confirmed that the dominant solution-phase conformer also has the benzyl group positioned in proximity to the methyl group of the catalyst core by virtue of the significant up-field shift of the *syn*-methyl group ($\delta_H = 0.64$ ppm versus $\delta_H = 1.73$ ppm for Me′).[14c]

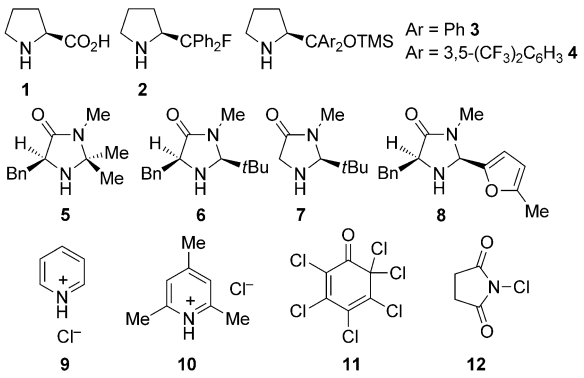
Collectively, these features contribute to a highly preorganized transient intermediate for reaction development, where the symmetry of the starting material is broken. Consequently, it was envisaged that nucleophilic addition to the cyclopropane moiety would proceed in an enantioselective fashion. To probe this hypothesis, we elected to study the reaction of the iminium salt with pyridinium hydrochloride[16] by $^1$H NMR spectroscopy. To our delight, after only 10 minutes the starting material was completely consumed and the expected chlorinated product was clearly identifiable ($\delta_{CHCl} = 5.25$ ppm). Having observed that chloride readily adds to activated cyclopropyl iminium species, we conceived that this reactivity could form an entry point for the development of a catalytic process. Initially, we elected to study the organocatalytic monochlorination of cyclopropanecarbaldehydes using pyridinium hydrochloride to furnish enantioenriched γ-chloroaldehydes. However, it was observed that the product was susceptible to racemization under the reaction conditions prompting a re-evaluation of the strategy. To circumvent this racemization pathway, we anticipated that the intermediate enamine that is formed after the initial addition could function as a second activated species that could be intercepted by an electrophile giving rise to an unusual $a^4 \rightarrow d^2$ reactivity sequence. Cognizant of the fact that this enamine reacts readily with electrophilic chlorine sources,[17] we envisaged that this strategy would provide an unprecedented method for the enantioselective synthesis of 1,3-dichlorides; a formal addition of $Cl_2$ across a cyclopropane bond.[18] Initially, we investigated the chlorination of the cyclopropane carbaldehyde[19] derived from cyclopentene (Table 1); the chlorination products of this material can be readily analyzed by GC on a chiral stationary phase. To facilitate analysis by $^1$H NMR spectroscopy, $CDCl_3$ was chosen as a screening solvent. Initially, the commonly used reagents **9** and **11** were selected as the $Cl^-$ and $Cl^+$ sources, respectively. Catalyst screening using a variety of secondary amine organocatalysts (**1**–**8**) quickly revealed that the first-generation MacMillan catalyst **5** furnished the expected 1,3-dichloride with the highest levels of diastereo- and enantiocontrol (Table 1, entry 5; e.r. 84:16, d.r. 91:9). It is important to note that no reaction is observed in the absence of a secondary amine catalyst. Having identified imidazolidinone **5** as the catalyst of choice for this transformation, we examined the effect of counterions on the stereoselectivity. The hydrochloride, trichloroacetate and trifluoroacetate salts of catalyst **5** (Table 1, entries 9, 10 and 11 respectively) were prepared and screened under analogous conditions. Notably higher levels of both diastereo- and enatioselectivity were observed with the HCl and TFA salts (Table 1, entries 9 and 11, respectively; up to e.r. 86:14, d.r. 91:9). For the remainder of the optimization process, the **5**·TFA was employed as the catalyst of choice. Interestingly, the selectivity of the reaction showed a clear solvent dependence (Table 1, entries 11–17) with the highest enantioselectivities being observed in $CDCl_3$. Finally, the chlorine sources were explored using combinations of **9** with *N*-chlorosuccinimide **12**, and **10** with perchlorinated quinone **11**. As is evident from Table 1, entry 18, using *N*-chlorosuccinimide **12** had a detrimental effect on the enantiomeric ratio. However, a substantial improvement was observed when pyridine hydrochloride **9** was replaced by the bulkier *sym*-collidine hydrochloride **10** (Table 1, entries 19 and 11, respectively; e.r. 91:9 versus 86:14).

Having developed an optimized set of conditions for the organocatalytic dichlorination of *meso*-cyclopropylcarbaldehydes, our attention was turned to investigating the scope and limitations of the method. In all cases the product dichlorides

***Table 1:*** Optimization of the organocatalytic desymmetrization of *meso*-cyclopropane carbaldehydes.[a]

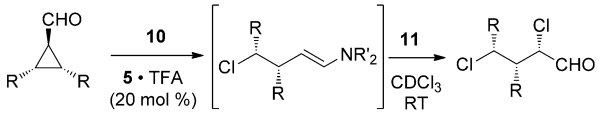


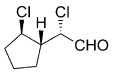
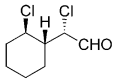
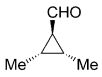
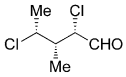
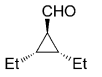
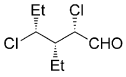
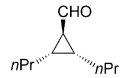
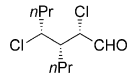
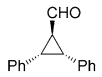
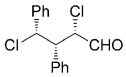




| Entry | Cat. | Solvent | "Cl⁻" | "Cl⁺" | e.r.[b] | d.r.[b] |
|---|---|---|---|---|---|---|
| 1 | **1** | $CDCl_3$ | **9** | **11** | 53:47 | 78:22 |
| 2 | **2** | $CDCl_3$ | **9** | **11** | 63:37 | 79:21 |
| 3 | **3** | $CDCl_3$ | **9** | **11** | 52:48 | 82:18 |
| 4 | **4** | $CDCl_3$ | **9** | **11** | 62:38 | 75:25 |
| 5 | **5** | $CDCl_3$ | **9** | **11** | 84:16 | 91:9 |
| 6 | **6** | $CDCl_3$ | **9** | **11** | 66:34 | 71:29 |
| 7 | **7** | $CDCl_3$ | **9** | **11** | 40:60 | 83:17 |
| 8 | **8** | $CDCl_3$ | **9** | **11** | 35:65 | 80: 20 |
| 9 | **5·HCl** | $CDCl_3$ | **9** | **11** | 85:15 | 91: 9 |
| 10 | **5·TCA** | $CDCl_3$ | **9** | **11** | 75:25 | 78:22 |
| 11 | **5·TFA** | $CDCl_3$ | **9** | **11** | 86:14 | 91:9 |
| 12 | **5·TFA** | $CH_2Cl_2$ | **9** | **11** | 80:20 | 94:6 |
| 13 | **5·TFA** | acetone | **9** | **11** | 64:36 | 85:15 |
| 14 | **5·TFA** | MeCN | **9** | **11** | 80:20 | 93:7 |
| 15 | **5·TFA** | toluene | **9** | **11** | 83:17 | 95:5 |
| 16 | **5·TFA** | THF | **9** | **11** | 81:19 | 97:3 |
| 17 | **5·TFA** | EtOAc | **9** | **11** | 80:20 | 95:5 |
| 18 | **5·TFA** | $CDCl_3$ | **9** | **12** | 75:25 | 81:19 |
| 19 | **5·TFA** | $CDCl_3$ | **10** | **11** | 91:9 | 94:6 |

[a] Reactions performed at room temperature with 2.00 equivalents of "$Cl^-$" and 1.05 equivalents of "$Cl^+$". TCA = trichloroacetic acid, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMS = trimethylsilyl. [b] GC measurements performed on a Supelco β-DEX 120 column (120 °C isotherm).

***Table 2:*** Enantioselective synthesis of 1,3-dichlorides.[a]




| Entry | Substrate | Product[b] | Yield [%][c] | e.r. | d.r. |
|---|---|---|---|---|---|
| 1 |  |  | 70 | 91:9[d] | 94:6[d] |
| 2 |  |  | 68[e] | 86:14[d] | 92:8[d] |
| 3 |  |  | 70[e] | 89:11[f] | 86:14[g] |
| 4 |  |  | 72 | 86:14[d,h] | 95:5[d,h] |
| 5 |  |  | 68 | 91:9[d] | 93:7[d] |
| 6 |  |  | 67[e] | 96:4[f] | >95:<5[g] |

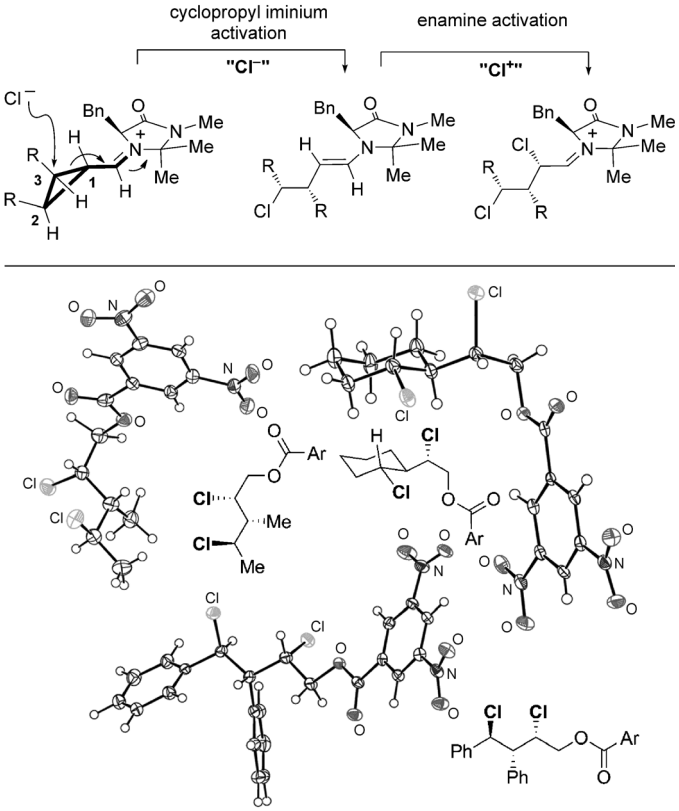
[a] Reactions performed with 100 μmol of aldehyde at room temperature with 2.00 equivalents of **10**, 1.05 equivalents of **11** and a concentration of 100 mmol $L^{-1}$ for 57–82 h. [b] Absolute and relative configuration assigned by X-ray crystallographic analysis and analogy. [c] Yield of isolated product over three steps (dichlorination, reduction using $NaBH_4$, and subsequent conversion into the 3,5-dinitrobenzoate). [d] GC measurements performed on a Supelco β-DEX 120 column (120 °C isotherm). [e] X-ray crystal structure was determined. [f] HPLC measurements performed on a Reprosil Chiral-OM column. [g] Determined by $^1$H NMR spectroscopy. [h] This experiment was repeated with a *exo*/*endo* (1:1) mixture of the *meso*-aldehyde substrate resulting in e.r. 70:30 and d.r. 64:36.

were reduced and converted into the dinitrobenzoate esters to 1) generate crystalline derivatives to determine the relative and absolute configuration of the product dichlorides by X-ray analysis, and to 2) allow for analysis by HPLC, thus providing an additional method to determine the enantioselectivities of each transformation. All yields in Table 2 refer to this three-step sequence. Initially, we elected to study bicyclic substrates (Table 2, entries 1 and 2). Reaction of the bicyclo-[3.1.0] system (Table 2, entry 1) furnished the desired 1,3-dichloride in excellent yield and with impressive levels of enantio- and diastereocontrol (91:9 and 94:6, respectively). Similarly, the bicyclo-[4.1.0] system (Table 2, entry 2) was smoothly converted into the desired product with comparable levels of chiral induction (e.r. 86:14 and d.r. 92:8, respectively). We then turned our attention to acyclic substrates starting with the simplest dimethyl-substituted *meso*-cyclopropanecarbaldehyde (Table 2, entry 3). Despite the relatively low steric demand of the substituents, efficient discrimination of the two carbon centers led to the optically enriched, linear 1,3-dichloride (e.r. 89:11). The corresponding ethyl and *n*-propyl substrates were also effortlessly converted into the expected dichloride compounds (Table 2, entries 4 and 5). To gain an additional insight into the substrate requirements, the reaction involving isomerically pure *exo*-*meso*-carbaldehyde (Table 2, entry 4) was compared to that of a 1:1 mixture of *exo*- and *endo*-*meso*-substrates. Comparable results would indicate that a pre-*endo* to *exo* isomerization is operational[20] similar to that observed for *E*/*Z* mixtures of α,β-unsaturated aldehydes.[21] Reactions involving an isomeric substrate mixture consistently gave lower levels of enantio- and diasteroselectivity (e.r. 70:30 and d.r. 64:36 versus e.r. 84:16 and d.r. 95:5). These results suggest that under the reactions condition reported here preisomerization is slower than chloride addition, and that high isomeric purity is essential to ensure high levels of chiral induction. Finally, the cyclopropane derived from *cis*-stilbene was processed to the 1,3-dichloride to test the tolerance of aromatic substrates. This

proved to be the case leading to the highest levels of enantio- and diasterocontrol observed to date (e.r. 96:4, d.r. $>95:<5$).

With a view to establishing a stereoinduction model, the relative and absolute configuration of the product 1,3-dichloride compounds was assigned by single-crystal X-ray analysis of the dinitrobenzoate derivatives (Scheme 4, see the Supporting Information).[22] Intriguingly, these analyses suggest that the addition of the initial chloride to the cyclopropane occurs at C3 with concomitant cleavage of the C1–C3 bond (Scheme 3). The origin of this counterintuitive regioselectivity is currently under investigation in our laboratory and will be reported in due course.




***Scheme 4.*** Regioselectivity of addition to cyclopropyl iminium ions and OTREP structures of 1,3-dichloride compounds. Thermal ellipsoids drawn at 50% probability. Ar = 3,5-$NO_2C_6H_3$.

In summary, we report an unprecedented enantioselective strategy for the synthesis of 1,3-dichlorides by a formal umpolung of the γ position of conventional dienamines using the cyclopropane trick; $d^4 \rightarrow a^4$. Not only does activation of the substrates by union with a secondary amine facilitate ring opening, it generates a second reactive enamine that can be intercepted by an electrophilic chlorinating reagent. This constitutes a formal addition of $Cl_2$ across the C1–C2 bond of cyclopropylcarbaldehyde compounds. Efforts to extent the synthetic utility of cyclopropyl iminium activation and understand the interactions that are responsible for orchestrating chiral induction[14c] are ongoing.

Received: May 16, 2011
Revised: June 30, 2011
Published online: July 22, 2011

**Keywords:** activation modes · cyclopropanes · dichlorination · organocatalysis · umpolung

[1] D. Seebach, *Angew. Chem.* **1979**, *91*, 259 – 278; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239 – 336.

[2] a) For selected reviews see the Organocatalysis Editions of *Acc. Chem. Res.* **2004**, *37*, 487 – 631 and *Chem. Rev.* **2007**, *107*, 5413 – 5883; A. Berkessel, H. Gröger in *Asymmetric Organocatalysis—From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**; M. J. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discovery Today* **2007**, *12*, 8 – 27; D. W. C. MacMillan, *Nature* **2008**, *455*, 304 – 308; C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44 – 50; *Angew. Chem. Int. Ed.* **2008**, *47*, 42 – 47; B. List, *Angew. Chem.* **2010**, *122*, 1774 – 1779; *Angew. Chem. Int. Ed.* **2010**, *49*, 1730 – 1734; b) for the seminal report of SOMO activation, see: T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582 – 585; c) for selected examples of dienamine catalysis, see: S.-H. Chen, B.-C. Hong, C.-F. Su, S. Sarshar, *Tetrahedron Lett.* **2005**, *46*, 8899 – 8903; B. J. Bench, C. Liu, C. R. Evett, C. M. H. Watanabe, *J. Org. Chem.* **2006**, *71*, 9458 – 9463; S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973 – 12980; B.-C. Hong, M.-F. Wu, H.-C. Tseng, J.-J. Liao, *Org. Lett.* **2006**, *8*, 2217 – 2220; K. Liu, A. Chougnet, W. D. Woggon, *Angew. Chem.* **2008**, *120*, 5911 – 5913; *Angew. Chem. Int. Ed.* **2008**, *47*, 5827 – 5829; G. Benivenni, P. Galzerano, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642 – 20647; J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmann, M. Christmann, *Org. Lett.* **2011**, *13*, 70 – 73; d) for an example of 1,6-conjugate addition of aldehydes to dienic sulfones, see: J. J. Murphy, A. Quintard, P. McArdle, A. Alexakis, J. C. Stephens, *Angew. Chem.* **2011**, *123*, 5201 – 5204; *Angew. Chem. Int. Ed.* **2011**, *50*, 5095 – 5098; e) for the use of trienamines in asymmetric organocatalysis see Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053 – 5061.

[3] a) T. Ukai, R. Tanaka, T. Dokawa, *J. Pharm. Soc. Jpn.* **1943**, *63*, 296 – 300; b) R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719 – 3726; c) for selected reviews, see: D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534 – 541; N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046 – 3058; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988 – 3000; D. Enders, O. Niemeier, A. Henseller, *Chem. Rev.* **2007**, *107*, 5606 – 5655.

[4] For an alternative catalytic asymmetric strategy for the functionalization of carbonyl compounds at the γ position based on nucleophilic phosphine catalysis, see: a) S. W. Smith, G. C. Fu, *J. Am. Chem. Soc.* **2009**, *131*, 14231 – 14233; b) R. Sinisi, J. Sun, G. C. Fu, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20652 – 20654.

[5] A. De Meijere, *Angew. Chem.* **1979**, *91*, 867 – 884; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809 – 826.

[6] a) A. D. Walsh, *Nature* **1947**, *159*, 165; b) R. Robinson, *Nature* **1947**, *159*, 400 – 401; c) C. A. McDowell, *Nature* **1947**, *159*, 508 – 509; d) A. D. Walsh, *Nature* **1947**, *159*, 712 – 713; e) R. Robinson, *Nature* **1947**, *160*, 162; f) J. W. Linnet, *Nature* **1947**, *160*, 162 – 163; g) A. D. Walsh, *Trans. Faraday Soc.* **1949**, *45*, 179 – 190.

[7] For an excellent discussion, see: E. V. Ansly, D. A. Dougherty in *Modern Physical Organic Chemistry*, (Ed.: J. Murdzek), University Science Books, **2006**, pp. 850 – 853.

[8] C. U. Pittman, Jr, G. A. Olah, *J. Am. Chem. Soc.* **1965**, *87*, 5123 – 5132.
[9] C. Th. Kiers, J. S. A. M. De Boer, D. Heijdenrijk, C. H. Stam, H. Schenk, *Recl. Trav. Chim. Pays-Bas.* **1985**, *104*, 7 – 9.
[10] a) E. Ciganek, *J. Am. Chem. Soc.* **1965**, *87*, 1149 – 1150; b) R. Hoffmann, *Tetrahedron Lett.* **1970**, *11*, 2907 – 2909; c) H. Günther, *Tetrahedron Lett.* **1970**, *11*, 5173 – 5176; d) R. Pearson, Jr., A. Choplin, V. Laurie, J. Schwartz, *J. Phys. Chem.* **1975**, *79*, 2949 – 2951; e) R. Pearson, Jr., A. Choplin, V. W. Laurie, *J. Phys. Chem.* **1975**, *62*, 4859 – 4861; f) also see: F. H. Allen, *Acta Crystallogr.* **1980**, *36*, 81 – 96.
[11] L. Li, Z. Li, Q. Wang, *Synlett* **2009**, 1830 – 1834.
[12] S. Danishefsky, *Acc. Chem. Res.* **1979**, *12*, 66 – 72.
[13] For the desymmetrization of spiro-activated *meso*-cyclopropanes using chiral amines by nucleophilic substitution, see: P. Müller, D. Riegert, *Tetrahedron* **2005**, *61*, 4373 – 4379.
[14] a) C. Sparr, W. B. Schweizer, H. M. Senn, R. Gilmour, *Angew. Chem.* **2009**, *121*, 3111 – 3114; *Angew. Chem. Int. Ed.* **2009**, *48*, 3065 – 3068; b) C. Sparr, E.-M. Tanzer, J. Bachmann, R. Gilmour, *Synthesis* **2010**, 1394 – 1397; c) C. Sparr, R. Gilmour, *Angew. Chem.* **2010**, *122*, 6670 – 6673; *Angew. Chem. Int. Ed.* **2010**, *49*, 6520 – 6523.
[15] C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558 – 569.
[16] a) L. Pellacani, P. A. Tardella, M. A. Loreto, *J. Org. Chem.* **1976**, *41*, 1282; b) E. Giacomini, M. A. Loreto, L. Pellacani, M. A. Tardella, *J. Org. Chem.* **1980**, *45*, 519.
[17] For seminal reports, see: a) M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108 – 4109; b) N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 4790 – 4791.
[18] To the best of our knowledge, no catalytic asymmetric method for 1,3-dichlorination has been reported. For a examples of enantioselective 1,2-dichlorination, see: a) S. Juliá, A. Ginebreda, *Tetrahedron Lett.* **1979**, *20*, 2171 – 2174; b) W. Adam, C. Mock-Knoblauch, C. R. Saha-Möller, M. Herderich, *J. Am. Chem. Soc.* **2000**, *122*, 9685 – 9691; c) S. A. Snyder, Z.-Y. Tang, R. Gupta, *J. Am. Chem. Soc.* **2009**, *131*, 5744 – 5745; d) S. A. Snyder, D. S. Treitler, A. P. Brucks, *J. Am. Chem. Soc.* **2010**, *132*, 14303 – 14314; K. C. Nicolaou, N. L. Simmons, Y. Ying, P. M. Heretsch, J. S. Chen, *J. Am. Chem. Soc.* **2011**, *133*, 8134 – 8137.
[19] For examples of chlorination of electrophilic cyclopropane derivatives using chlorosilanes, see: R. K. Dieter, S. Pounds, *J. Org. Chem.* **1982**, *47*, 3174 – 3177.
[20] M. K. Huber, R. Martin, M. Rey, A. S. Dreiding, *Helv. Chim. Acta* **1977**, *60*, 1781.
[21] S. G. Oullet, A. Walji, D. W. C. MacMillan, *Acc. Chem. Res.* **2007**, *40*, 1327 – 1339.
[22] CCDC 824640, 824639, 824638, and 824637 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/datarequest/cif.