Reversal of the Stereochemical Course of 1-Methyl-1*H*-indole Addition to Cinnamaldehyde with *cis*-5-Benzyl-(2-fluoromethyl)-2,3-dimethylimidazolidin-4-ones as Catalysts – a Puzzling 'Fluorine Effect'

Preliminary Communication

by **Uroš Grošelj***, **Črtomir Podlipnik**, **Jure Bezenšek**, **Jurij Svete**, and **Branko Stanovnik**

Department of Organic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva cesta 5, P.O. Box 537, 1000 Ljubljana, Slovenia (fax: +386 1 2419 220; e-mail: uros.groselj@fkkt.uni-lj.si)

and

Dieter Seebach

Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, Hönggerberg HCI, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich (fax: +41 44 632 1144; e-mail: seebach@org.chem.ethz.ch)

Dedicated to Professor *Teruaki Mukaiyama* on the occasion of the 40th anniversary of the *Mukaiyama* aldol reaction

Replacement of the *cis*-Me group by CH_2F in the imidazolidinone organocatalyst specified in the title (so-called *McMillan* generation-I catalyst) leads to reversal of the product configuration in the title reaction. The topicity reversal in the nucleophilic addition step must arise either from *cis*-addition with respect to the benzylic substituent of an (*E*)-iminium ion intermediate or from *trans*-addition to the corresponding (*Z*)-iminium ion. Mechanistic investigations have not provided evidence for either one of these two possibilities, so far.

In one of the two reports [1][2], initiating the explosive renaissance of enantioselective organocatalysis [3], the imidazolidinone (*S*)-**1** (Arl = Ph, $R^{cis} = R^{trans} = Me$), was employed to catalyze the *Diels–Alder* reaction of cyclopentadiene with cinnamaldehyde [2], *via* an iminium ion **2** as the reactive intermediate (*Scheme*). This imidazolidinone (also called *MacMillan* generation-I catalyst) and numerous other derivatives of this type have become 'workhorses' for enantioselective iminium ion activation of aldehydes, enals, and enones [4]. From the product structures, the following, generally applicable model of the stereochemical course of the reactions was deduced: the iminium ions (*S*)-**2** of (*E*)-configuration are preferentially approached by nucleophiles from the (*Si*)-diastereotopic face, *i.e.*, *anti* to the $ArlCH_2$ and R^{cis} substituents on the heterocycle (*Scheme*)[1]). The thermodynamic stabilities of the (*E*/*Z*)-iminium ions **2** and their conformations around the benzylic bonds in the gas phase, in solution, and in the crystalline state have, in the meantime, been determined

[1]) Note that this relative topicity specification *like* (*S*/*Si*) may be reversed for other iminium ions [5].

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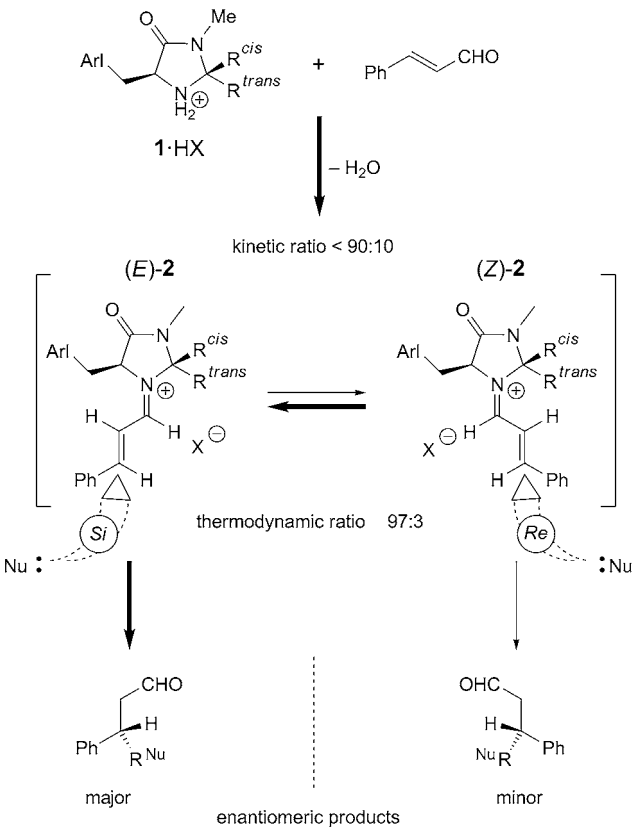
Scheme. *Experimentally and Computationally Identified Iminium Ion Intermediates (*E*)- and (*Z*)-***2*** of Imidazolidinone-Catalyzed Nucleophilic Additions to Cinnamaldehyde.* For specifications of Arl, R^{cis}, and R^{trans}, see *Table 1.*



computationally and experimentally (NMR spectroscopy and X-ray crystallography) [4][6][2]), leading to the following conclusions. *i*) The (*E*)-diastereoisomers **2** turned out to be thermodynamically more stable than the (*Z*)-forms[3]), which, in turn, may be kinetically favored [6e]. *ii*) Three major conformers of the iminium ions (*E*)-**2** around the exocyclic C(5)–CH_2Ph bond have been identified: (+)-*sc* (with the Ph group over the ring), (−)-sc (with the Ph group over the π-system), and (−)-*ac* (with an eclipsed $PhCH_2$ group) (*Fig. 1*). *iii*) With the observed small energy differences and rotational barriers between these conformers, equilibration takes place at ambient temperatures [6]. Thus, *cum grano salis*, the originally proposed mechanistic model [4] was confirmed.

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2) For nucleophilicity parameters of iminium ions (*E*)-**2** on the *Mayr* scale and for counterion effects, see [6h][7].

3) The (*E*)/(*Z*) ratios (in CD_3CN, (D_6)acetone, or (D_6)DMSO) of the 2,2-disubstituted salts **2** (R^{cis}, $R^{trans} \neq H$) is generally $\geq 97:3$ [6e].

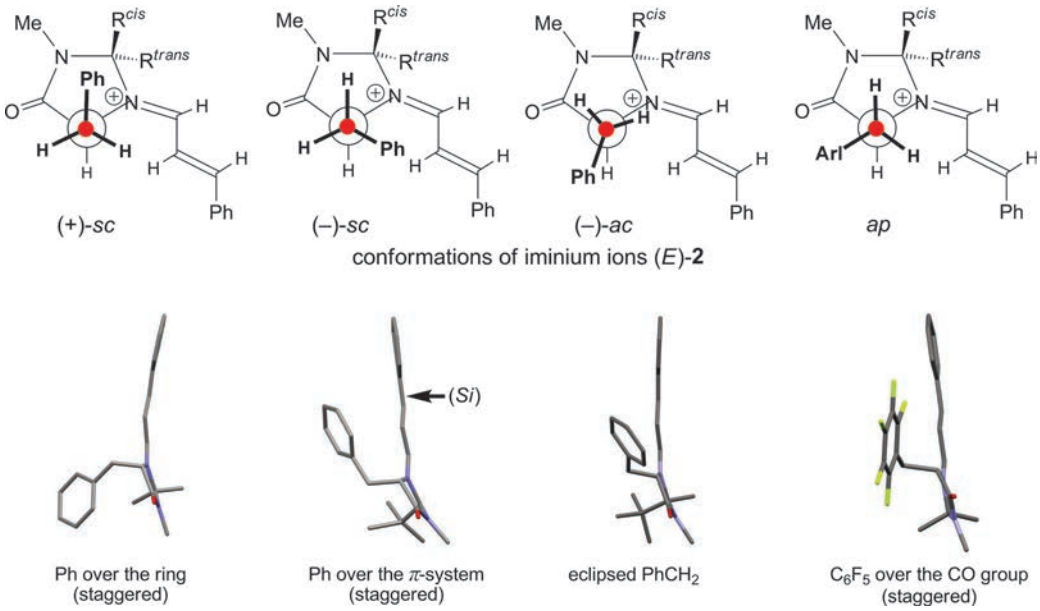

Fig. 1. *Four experimentally detected Arl–C–C–N conformers (*E*)-***2** (Arl = Ph or C_6F_5). The staggered *ap*-conformation is energetically unfavorable (DFT calculations [6a,d]) and has, so far, been detected only in an iminium salt with Arl = C_6F_5 [6h]. Views along the $PhCH_2$–C(5) bonds in the X-ray crystal structures (from left to right) of (*E*)-**2** with $R^{cis} = R^{trans}$ = Me [6b,e,f]; (*E*)-**2** with R^{cis} = ^{t}Bu, R^{trans} = H [6b,c]; (*E*)-**2** with R^{cis} = ^{t}Bu, R^{trans} = Me [6d]; and of (*E*)-**2** with $R^{cis} = R^{trans}$ = Me, Arl = C_6F_5 [6h].

Applying some previously prepared imidazolidinones[4])[5]) [6e] as catalysts, we have now discovered a type of derivative that leads to topicity reversal, as demonstrated for the addition of 1-methyl-1*H*-indole to cinnamaldehyde [9] to give 3-indolyl-3-phenylpropanal and, after reduction, the alcohol[6]) **3** (*Table 1*). While the 2,2-dimethyl and the *trans*-2-(fluoromethyl)-2-methyl derivatives, **1a** and **1b**, respectively, 'behaved normally' ((*S*)/(*R*) ratio up to 82 : 18), the *cis*-2-(fluoromethyl)-substituted catalysts **1c** gave the (*R*)-enantiomer preferentially ((*R*)/(*S*) ratio up to 93 : 7)!

This surprising result means that either the (*E*)-forms of the *cis*-iminium ions, (*E*)-**2c**, undergo nucleophilic attack from the (*Re*)-face, *syn* to the benzylic and the CH_2F group, or that the (*Z*)-**2c** diastereoisomers become the product-forming species (*cf. Scheme*). A conformational NMR analysis of the *cis*-iminium PF_6 salt, (*E*)-**2ca**, indicates that the conformation with the Ph group located over the π-system is present ((–)-*sc* in *Fig. 1*), and that the F-atom resides over the ring ((–)-*sc* in *Fig. 2,b*). DFT

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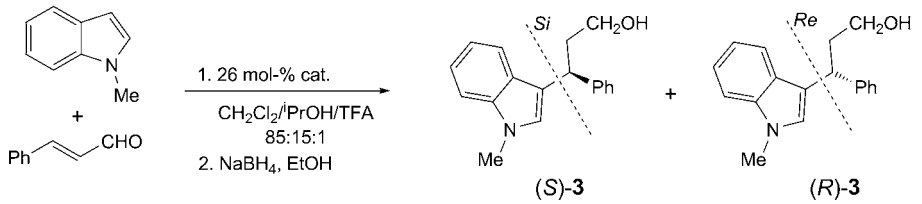
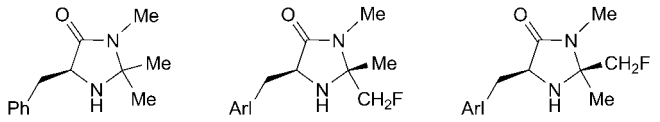
4) The imidazolidinones were prepared by known methods, either from the corresponding phenylalanines or from Boc-BMI [8]. An account with full experimental details, including those of the present communication, is in preparation.

5) For a conformational analysis (NMR, X-ray) of five (*E*)-**2**, with $R^{cis} = R^{trans}$ = Me, Arl = C_6F_5, $C_6H_2F_3$, OH–C_6H_4, $(MeO)_3C_6H_2$, 1-methyl-1*H*-indol-2-yl, see [6h].

6) Enantiomer-ratio (er) values reported for the *aldehyde* in several papers were actually determined at the *alcohol* stage, which is described only in corresponding *Supplementary Materials*, see [9][10].

Table 1. *Nucleophilic Addition of 1-Methyl-1*H*-indole to Cinnamaldehyde, Catalyzed by the Imidazolidinones* **1a**–**1c**, *to Give, after Reduction,* (S)-**3**/(R)-**3** *Mixtures.* If not stated otherwise, there was full conversion after the given reaction times. For comparison: **1**, Arl = Ph, R^{cis} = ^{t}Bu, R^{trans} = H, gives rise to an (*S*)/(*R*) ratio of 95 : 5 (– 55°, 45 h) [9].





Arl	Ph	4-MeO–C_6H_4	4-NO_2–C_6H_4	3,5-$(CF_3)_2$–C_6H_4
trans	**ba**	**bb**	**bc**	**bd**
cis	**ca**	**cb**	**cc**	**cd**

Catalyst		Temperature [°]	Time [h]	(*S*)-**3**/(*R*)-**3**[a])
1a		– 41[b])	48	72 : 28
1ba	*trans*	r.t.	2	76 : 24
		– 41	48	81 : 19
		– 61[b])	48	82 : 18
1bb	*trans*	– 41	48	79 : 21
1bc	*trans*	– 41	48	81 : 19
1bd	*trans*	– 41	48	70 : 30
1ca	*cis*	r.t.	2	47 : 53
		– 41	48	33 : 67
		– 61[b])	48	27 : 73
1cb	*cis*	– 41	48	29 : 71
1cc	*cis*	– 41	48	25 : 75
1cd	*cis*	r.t.	2	31 : 69
		– 41	48	11 : 89
		– 78[b])	72	7 : 93

[a]) Enantiomer ratio (er) determined by HPLC on *Chiralpak AD-H*, with hexane/^{i}PrOH 9 : 1. [b]) Partial conversion at this temperature.

Calculations of the (*E*)- and (*Z*)-3,5$(CF_3)_2$–C_6H_3 derivatives, **2cd**, confirm the higher stability of the (*E*)-form and the preference for the (–)-*sc*-conformation of the benzylic bond (*Fig. 2*, *c*). Thus, according to this *thermodynamic* NMR and DFT analysis presented in *Fig. 2*, the *cis*-CH_2F group appears to lead to a higher population of the iminium conformer with the Ph group over the π-system of (*E*)-**2c**, hindering (*Re*)-

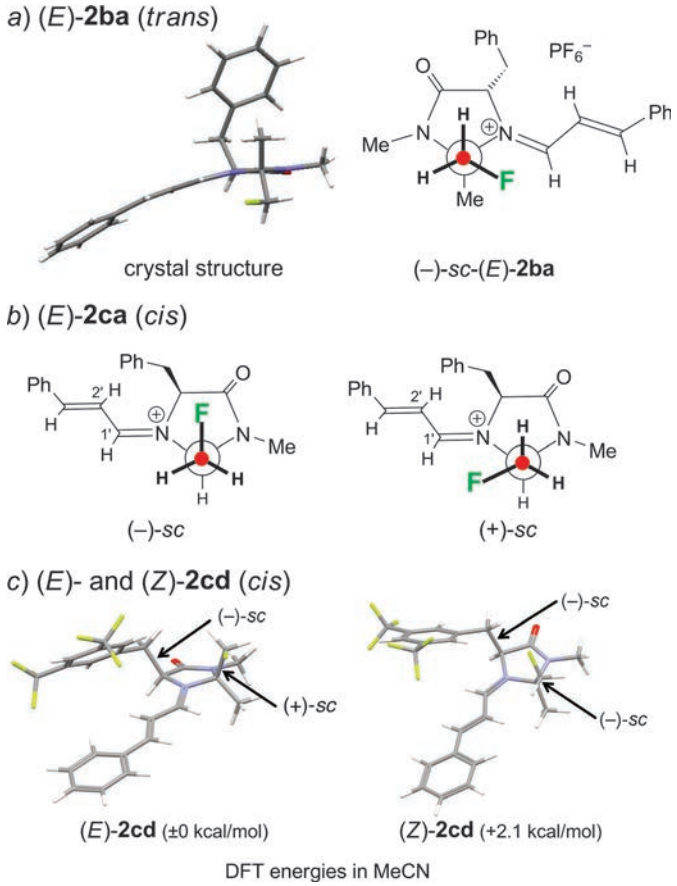


Fig. 2. *Conformational analysis of* trans- *and* cis-*CH_2F-substituted iminium ions* **2b** *and* **2c**. *a*) Crystal structure of *trans*-(*E*)-**2ba** [6e] with a *gauche* F–C–C–N^+ dihedral angle; as with the dimethyl derivative (*E*)-**2a** [6c,f,h], the NMR signal of the *cis*-Me group is shifted upfield. *b*) The two *sc*-conformations of *cis*-(*E*)-**2ca** with the stereoelectronically favored [11] *gauche* F–C–C–N^+ arrangement (*cf.* the powerful, so-called 'fluorine-iminium ion' *gauche* effect) [12]; in the ^{1}H-NMR spectrum of this PF_6 iminium salt, there is an upfield shift of H–C(2′) (7.2 *vs.* 7.9 ppm for the *trans*-isomer (*E*)-**2ba**); in the ^{13}C-NMR spectrum of (*E*)-**2ca**, there is a 3.6-Hz ^{19}F,^{13}C-through-space coupling of F with the benzylic C-atom; considering the shorter F–CH_2 distance in (–)-*sc*-(*E*)-**2ca**, we tentatively assign the structure with (–)-*sc*-conformation of the benzylic bond (see *Fig. 1*) and the (–)-*sc*-conformation of the CH_2F–C(2) bond to this compound. *c*) Most stable structures of (*E*)- and (*Z*)-**2cd** by DFT calculations (B3LYP [13a,b]/6-31 + + G* basis set [13c]/implemented in Jaguar [13d]).

attack, rather than favoring it. Turning to the second possibility, *i.e.*, preferential *kinetic* formation of the (*Z*)-isomer **2c** with slow (*E*/*Z*)-isomerization and trapping by the nucleophile from the *anti*-(*Re*)-face, we compared the initial (*E*)/(*Z*) ratios in the reactions of the dimethyl-, the *trans*-fluoromethyl-, and the *cis*-(fluoromethyl)imidazolidinonium PF_6 salts, **1a**–**1c**, respectively, with cinnamaldehyde by *in situ* NMR analysis. As is evident from the data in *Table 2*, there is no significant difference: the

Table 2. *Initial (*E*)/(*Z*) Ratios of Iminium Ions* **2** *Observed by NMR Analysis upon Mixing the Benzyl-trimethyl-* (*i.e.*, **1b**·HPF_6) *and the Benzyl-(fluoromethyl)-dimethyl-* (*i.e.*, **1b**·HPF_6 and **1c**·HPF_6) *Oxoimidazolidinium Salts with Cinnamaldehyde.* The (*E*)/(*Z*) ratios at equilibrium are 98 : 2 and 99 : 1, respectively.

	R^{cis}	R^{trans}	Time [min]	Conversion [%]	(*E*)/(*Z*)
1a	Me	Me	5	4	3.4 : 1[a])
			10	11	3.3 : 1 [6e]
			40	47	40 : 1 [6e]
1b	Me	CH_2F	3.5	2	2.0 : 1[a])
1c	CH_2F	Me	6	3	2.6 : 1[a])

[a]) With or without catalytic amount of Et_3N added.

(*E*)/(*Z*) ratios are between 2 : 1 and 3.4 : 1. Admittedly, the conditions of this experiment are different from those of the catalytic reaction, but there is no evidence for the *cis*-fluoromethyl analog to behave differently with respect to kinetic (*E*)/(*Z*) ratios, compared with the *trans*-fluoromethyl and the dimethyl derivative.

Thus, the structural analysis of the (*E*)-salts **2a**–**2c** has provided no evidence, as to why introduction of an F-atom in the *cis*-methyl group of the so-called *MacMillan* generation-I catalyst should lead to topicity reversal, most pronounced with the most sterically demanding benzylic group (in **1cd**). Although we have not presented evidence, we still *believe* that the observed reversal of the stereochemical course is due to kinetic trapping of the (*Z*)-iminium ion intermediate by 1-methyl-1*H*-indole in the catalytic reaction. If so, we are unable to offer a rationale how the F-atom could cause the required strong preference for (*Z*)-**2c** formation and slow (*Z*/*E*)-isomerization under these conditions; we are faced with yet another situation of *flustration*[7]).

To disclose whether we have discovered a *general*, simple way of topicity reversal in organocatalysis with imidazolidinones, other substitution patterns in 2-position of the 5-benzyl-3-methylimidazolidinone system and other reactions, typically catalyzed by this heterocycle, must be investigated; the results may shed light on the observed, puzzling 'fluorine effect', which we think is interesting enough to be reported herein without explanation.

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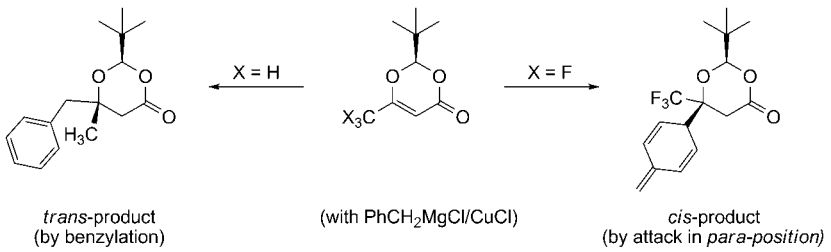
[7]) *Flustrates:* Name given to fluoro derivatives with non-rationalized, totally different behavior compared to non-fluorinated analogs, see Sect. 2.2 in [14]. A stunning example is published in [15]:



REFERENCES

[1] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.
[2] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.
[3] a) G. Bredig, P. S. Fiske, *Biochem. Z.* **1012**, *46*, 7; b) W. Langenbeck, 'Die organischen Katalysatoren und ihre Beziehung zu den Fermenten', Julius Springer, Berlin, 1935; c) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492; *Angew. Chem., Int. Ed.* **1971**, *10*, 496; d) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615.
[4] G. Lelais, D. W. C. MacMillan, 'Iminium Catalysis in Enantioselective Organocatalysis: Reactions and Experimental Procedures', Ed. P. I. Dalko, Wiley-VCH, Weinheim, 2007, pp. 95.
[5] D. Seebach, V. Prelog, *Angew. Chem.* **1982**, *94*, 696; *Angew. Chem., Int. Ed.* **1982**, *21*, 654.
[6] a) R. Gordillo, J. Carter, K. N. Houk, *Adv. Synth. Catal.* **2004**, *346*, 1175; b) D. Seebach, U. Grošelj, D. M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta* **2008**, *91*, 1999; c) U. Grošelj, W. B. Schweizer, M.-O. Ebert, D. Seebach, *Helv. Chim. Acta* **2009**, *21*, 1; d) D. Seebach, U. Grošelj, W. B. Schweizer, S. Grimme, C. Mück-Lichtenfeld, *Helv. Chim. Acta* **2010**, *93*, 90; e) D. Seebach, R. Gilmour, U. Grošelj, G. Deniau, C. Sparr, M.-O. Ebert, A. K. Beck, L. B. McCusker, D. Šišak, T. Uchimaru, *Helv. Chim. Acta* **2010**, *93*, 603; f) J. B. Brazier, G. Evans, T. J. K. Gibbs, S. J. Coles, M. B. Hursthouse, J. A. Platts, N. C. O. Tomkinson, *Org. Lett.* **2009**, *11*, 133; g) P. H.-Y. Cheong, C. Y. Legault, J. M. Um, N. Çelebi- Ölçüm, K. N. Houk, *Chem. Rev.* **2011**, *111*, 5042; h) M. C. Holland, S. Paul, W. B. Schweizer, K. Bergander, C. Mück-Lichtenfeld, S. Lakhdar, H. Mayr, R. Gilmour, *Angew. Chem.* **2013**, *125*, 8125; *Angew. Chem., Int. Ed.* **2013**, *52*, 7967.
[7] S. Lakhdar, J. Ammer, H. Mayr, *Angew. Chem.* **2011**, *123*, 10127; *Angew. Chem., Int. Ed.* **2011**, *50*, 9953; S. Lakhdar, H. Mayr, *Chem. Commun.* **2011**, *47*, 1866.
[8] D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem.* **1996**, *108*, 2880; *Angew. Chem., Int. Ed.* **1996**, *35*, 2708.
[9] J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172.
[10] B. F. Bonini, E. Capitó, M. Comes-Franchini, M. Fochi, A. Ricci, B. Zwanenburg, *Tetrahedron: Asymmetry* **2006**, *17*, 3135; X. Liang, S. Li, W. Su, *Tetrahedron Lett.* **2012**, *53*, 289.
[11] A. J. Kirby, 'Stereoelectronic Effects', Oxford University Press, Oxford, 1996.
[12] a) C. Sparr, W. B. Schweizer, H. M. Senn, R. Gilmour, *Angew. Chem.* **2009**, *121*, 3111; *Angew. Chem., Int. Ed.* **2009**, *48*, 3065; b) C. Sparr, R. Gilmour, *Angew. Chem.* **2010**, *122*, 6670; *Angew. Chem., Int. Ed.* **2010**, *49*, 6520; c) L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem.* **2011**, *123*, 12062; *Angew. Chem., Int. Ed.* **2011**, *50*, 11860; d) E.-M. Tanzer, L. E. Zimmer, W. B. Schweizer, R. Gilmour, *Chem. – Eur. J.* **2012**, *18*, 11342; e) C. Sparr, 'Fluorine Conformational Effects in Enantioselective Organocatalytic Reaction Design', Dissertation ETH No. 19894, Zürich, 2011.
[13] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; c) D. Feller, E. R. Davidson, '*Basis Sets for Ab Initio Molecular Orbital Calculations and Intermolecular Interactions*', in 'Reviews in Computational Chemistry', Eds. K. B. Lipkowitz, D. B. Boyd, VCH, New York, 1990, pp. 1; d) Suite 2012, Jaguar, version 7.9, Schrödinger, LLC, New York, 2012.
[14] D. Seebach, *Angew. Chem.* **1990**, *102*, 1363; *Angew. Chem., Int. Ed.* **1990**, *29*, 1320.
[15] M. Gautschi, D. Seebach, *Angew. Chem.* **1992**, *104*, 1061; *Angew. Chem., Int. Ed.* **1992**, *31*, 1083.

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