

Iodine Monochloride–Amine Complexes: An Experimental and Computational Approach to New Chiral Electrophiles

Jürgen Haas, Stewart Bissmire, and Thomas Wirth*[a]

Abstract: Lactonizations are important steps in many synthetic sequences. Substrate-controlled reactions that use chiral auxiliaries or chiral alkenes have already been studied in depth. This study focuses on stereoselective reagent-controlled iodolactonizations, by application of a new method that uses complexes of iodine monochloride and

various donor molecules. (*R*)-1,2,3,4-Tetrahydro-1-naphthylamine and other amines with similar structures were found to be efficient in the iodocycliza-

Keywords: computer chemistry • electrophiles • iodine • iodolactonization • stereoselective synthesis

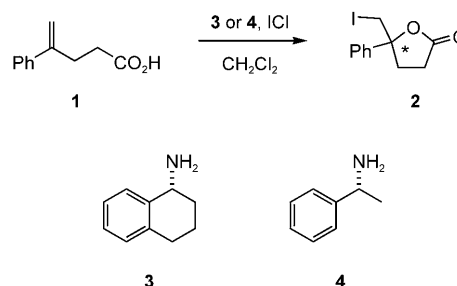
tion of 4-aryl-4-pentenoic acids. Calculations were performed on complexes of (*R*)-1,2,3,4-tetrahydro-1-naphthylamine with XCl (X=I, H) to identify possible reactive species in these iodocyclizations. Calculations were carried out at various levels of theory, including B3LYP/6-31+G (d,p) by using a modified SDD basis set for iodine.

Introduction

Reactions of double bonds with electrophilic reagents play an important role in many transformations in organic synthesis. Electrophile-promoted cyclizations of unsaturated substrates are an important transformation in heterocyclic chemistry, and much effort has been devoted to the control of such cyclizations and the development of enantioselective versions. Stereocontrol can be achieved by using *substrate*-controlled reactions, albeit with the disadvantage of having to remove the chiral auxiliary after the reaction. Most of the reactions described to date are limited to this variant. Enantiomerically pure electrophilic reagents can, however, generate new stereogenic centers under *reagent*-controlled conditions.

We have already investigated selenium^[1] and hypervalent iodine reagents^[2] for this purpose, and now report the use of chiral iodine electrophiles for *reagent*-controlled stereoselective iodocyclizations. Iodocyclizations have been studied extensively, and this transformation serves as an important key reaction in many syntheses.^[3] Iodine monochloride (ICl) is about 400 times more reactive than elemental iodine and,

therefore, we focused our attention on complexes of ICl and various donor molecules. Although it is known that oxygen-containing compounds like carbonyl compounds,^[4] ethers,^[5] and nitrogen-containing molecules^[6] can form 1:1 complexes with ICl, we found that complexes of enantiomerically pure primary amines are suitable reactive and selective electrophilic species for iodolactonizations. Recently, we reported preliminary results on stereoselective iodolactonizations of 4-phenyl-4-pentenoic acid **1** and other substrates by employing mixtures of enantiomerically pure amines with ICl as reagents^[7] (Scheme 1). (*R*)-1,2,3,4-Tetrahydro-1-naphthylamine **3** and other amines with similar structure, such as (*R*)-1-phenyl-1-ethylamine **4**, were found to be efficient amines for the iodolactonization, yielding lactones **2** with up to 45 % *ee*. Chiral halonium ion complexes with dihydroquinidine^[8] or 2-menthyl-pyridine^[9] have been reported for stereoselective iodo- and bromolactonizations, although only



Scheme 1. Reagent-controlled stereoselective iodolactonization.

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low enantiomeric ratios (up to 57:43) were obtained. Recently, the first example of a catalytic enantioselective iodocyclization of unsaturated alcohols was reported,^[10] and results with chiral phase-transfer catalysts in iodolactonizations were also described.^[11]

Results and Discussion

To understand the nature of the stereoselective induction in this iodolactonization, and to be able to further optimize the chiral reagent, we investigated and analyzed the amine–ICl mixtures in a number of ways. Elemental analysis of the yellow powder, which precipitated from mixing **3** and ICl in dichloromethane, indicated a 1:1 composition.^[12] Unfortunately, it was impossible to obtain further information from powder diffraction analysis. A titration of amine **4** with ICl was monitored by performing NMR spectroscopy, in which the resonance of the benzylic proton at 4.15 ppm showed a shift to a higher field, which reverted after the addition of more than one equivalent of ICl (Figure 1, left). This behavior indicates a more complex reaction than a simple 1:1 adduct formation. By contrast, the chemical shift of the methyl protons (1.42 ppm) does not show this behavior (Figure 1, right).

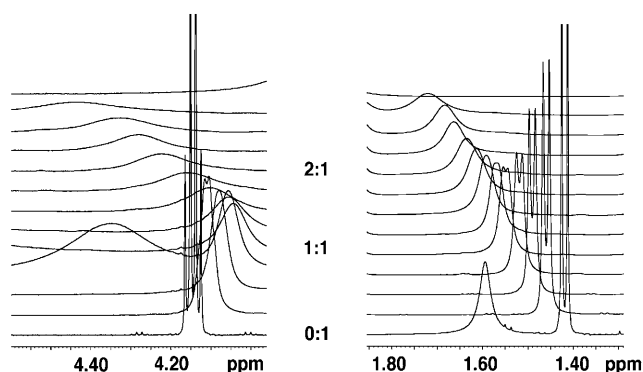


Figure 1. Titration of phenylethylamine **4** with ICl (ratio of **4**:ICl is indicated) monitored by conducting NMR spectroscopy (300 MHz, CDCl₃, RT).

A 1:1 mixture of amine **3** and ICl was then observed by performing UV/Vis spectroscopy over a period of time. The spectra displayed significant changes during the first 30 min after mixing, but thereafter, remained almost unchanged. Two isosbestic points at 237 and 262 nm indicate that at least two species are in equilibrium (Figure 2).^[13]

The stability and dynamics of the amine–ICl complexes under different conditions were investigated by conducting a series of crossover experiments with the unsaturated acid **1** as a substrate. Amine **3** yielded (*R*)-**2** with 45% *ee*, whereas amine **4** gave the opposite enantiomer, (*S*)-**2**, in 26% *ee*. One equivalent of **4** was added (at RT) to a preformed 1:1 complex of amine **3** and ICl, and the subsequent iodolactonization of **1**, performed at –78°C, generated (*R*)-**2** with

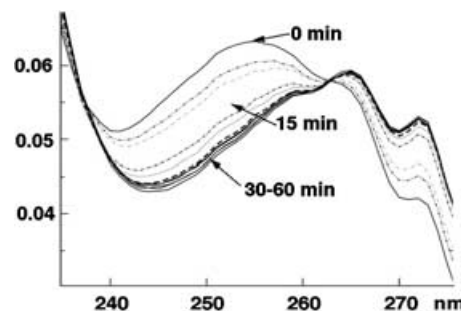


Figure 2. UV/Vis spectra of a 1:1 mixture of amine **3** and ICl (1×10^{-5} M in CH₂Cl₂ at RT).

7% *ee*. Reversing the order of the amines (first **4**, then **3**) resulted in (*R*)-**2** with 6% *ee*. These values are very close to the expected 10% *ee* for (*R*)-**2**, in which an equal participation of amines **3** and **4** in the reaction is assumed. However, the addition of **4** to a preformed complex of **3** and ICl at –78°C, instead of at room temperature, resulted in (*R*)-**2** with 10% *ee*, and reversing the order of the amines yielded 1% *ee* (*R*)-**2**.^[14] This shows that, even at –78°C, the exchange of the amine ligands on the iodine cation is rapid, although an equilibrium with equal contributions of both amines was not reached and slightly different results were obtained.

To gain further insight into the reaction between primary amine **3** and ICl, quantum chemical studies were performed by using the Gaussian 98 programme package.^[15] Molecules containing heavy elements pose a great problem in ab initio calculations, because these elements contain a large number of core electrons, which, although unimportant in a chemical sense, must be characterized by using a large number of basis functions to properly describe the valence orbitals. This difficulty can be overcome by the use of effective core potentials (ECP). These functions model the core electrons and prevent the valence electrons from collapsing into the core.^[16] The valence electrons are then treated explicitly, yielding results comparable in quality to all-electron calculations at a fraction of the computational cost. To design an ECP, a good quality all-electron wave function must be generated first. This is usually achieved by using a numerical Hartree–Fock or a relativistic Dirac–Hartree–Fock calculation. The valence orbitals are then replaced by pseudo orbitals, which are designed to behave correctly on the outer part, but lack the nodal structure in the core region that is observed in regular orbitals. Finally, the core electrons are replaced by a potential that is designed so that the solutions of the Schrödinger equation produce valence orbitals, matching the pseudo orbitals. These potentials effectively include relativistic effects, which effect mainly core electrons. In the SDD basis set used for iodine in our calculations, the 46 electron (krypton) core of iodine is described by using an ECP.^[17] The two s-electrons are described at a double zeta level, and the five p-electrons at a triple zeta level. To improve results in the following calculations, a set of d-orbitals optimized in the ICl–ethene complex was added. The expo-

ment of the d-type Gaussian function was varied in a series of single point MP2 calculations on ICl with simultaneous geometry optimization. A cubic fit to the data resulted in an optimum value for the exponent (see below). A further shell of sp diffuse functions was added for a better description of long-range effects important for complexations (e.g., polarizability). The exponent for these was estimated by extrapolating beyond the values for the 6–311+G diffuse functions in halogens up to bromine^[18] (Table 1).

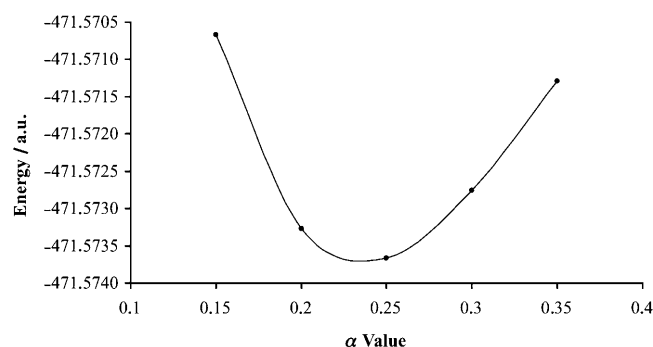
Table 1. Data for optimization of the exponent α .

Exponent α	I–C distance [Å]	Energy [a.u.]
0.15	2.386	–471.57067
0.2	2.371	–471.57327
0.25	2.365	–471.57367
0.3	2.364	–471.57276
0.35	2.368	–471.57129

A cubic fit of energy plotted against exponent leads to the function described in Equation (1):

$$f(x) = -1.09x^3 + 1.08779x^2 - 0.331693x - 471.542 \quad (1)$$

Differentiation shows that an exponent of $\alpha=0.237$ leads to a minimum in energy (Figure 3).

Figure 3. Plot of energy versus α with cubic fit.

For higher accuracy, all other elements were treated at a higher level of theory. The 6–31G basis set was used with polarized and diffuse functions for the same reasons as those mentioned above.

A set of preliminary calculations was conducted to compare the results obtained from calculations performed by using the modified basis set in B3LYP, B3PW91, and MP2 with experimental results. Experimental data were obtained from a study carried out by Legon on a series of interactions between iodine monochloride and simple Lewis bases.^[19] Comparison of results was restricted to interactions between ICl and nitrogen, and ICl and unsaturated carbon atoms, and both of these interactions are relevant to this study. Nitrogen–iodine interactions are important for the formation of the reactive species, in which both complexation and

transfer must be investigated. Interactions between iodine and double bonds are of interest in investigating the addition to the double bond in lactonization reactions. Results obtained by using the LANL2DZ basis set in combination with B3LYP are also included (Table 2).

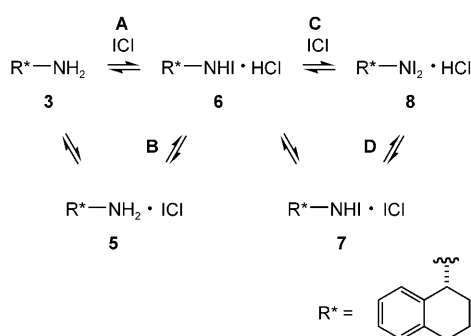
Table 2. Comparison of experimental and calculated X–ICl bond lengths [Å].

	Exptl	B3LYP/ SDD+pd	B3PW91/ SDD+pd	MP2/ SDD+pd	B3LYP/ LANL2DZ
N ₂ ·ICl	3.180	3.144	3.120	3.096	3.242
CO·ICl	3.011	2.820	2.712	3.063	2.918
C ₂ H ₂ ·ICl	3.115	3.098	3.011	3.217	3.163
C ₂ H ₄ ·ICl	3.032	2.989	2.878	3.094	3.044
HCN·ICl	2.850	2.780	2.727	2.822	3.951
NH ₃ ·ICl	2.711	2.601	2.567	2.613	2.602
sum of squares error		0.057	0.163	0.034	0.091
variance (r^2)		0.70	0.42	0.77	0.65

Results of statistical analysis showed that the B3LYP calculations with the modified basis set perform best among the DFT methods tested. Although MP2 performs best statistically, there is no constant trend in error (some bond lengths are overestimated, whereas others are underestimated). MP2 calculations, even on the small molecules, were found to be significantly more time-consuming than those carried out by using B3LYP. Therefore, MP2 methods were rejected in favor of B3LYP calculations with the modified basis set for iodine.

Ab initio calculations at different levels of theory (MP2/SDD, B3LYP/SDD, B3LYP/LANL2DZ, B3LYP/6–31G(d,p) with SDD+pd for iodine) were used to investigate species that could be involved in the formation of the chiral amine–ICl complexes. The formation of **5** is a straightforward donor–acceptor reaction between amine **3** and ICl. Species **6** involves a proton–iodine exchange on the nitrogen, which is likely to be facilitated by the formation of an HCl complex with another molecule amine. This explains the need for a second equivalent of amine, and is supported by the calculated energy of the amine–HCl complex. Experimentally, we found that the second equivalent of amine can be replaced by another base.^[7] The second molecule of ICl that is necessary to form **7** or **8** must originate from **5**, as all of the ICl is assumed to be used initially in the formation of **5**. This means that the reactions leading to **7** and **8** are side reactions. The formation of **7** can take place only if it is either assisted by the formation of an amine–HCl complex, or if the complexation energy of **7** is much higher than that of **5**. Transition states **A–D** connecting the different complexes have also been considered (Scheme 2).

Initial calculations were carried out by using methylamine–ICl complexes at various levels of theory. The geometries and energies at the MP2/SDD level and MP2/6–31G(d,p) levels (with SDD for iodine) are almost identical, and all subsequent calculations with the tetrahydronaphthyl



Scheme 2. Different amine-ICl complexes.

moiety were performed at the lower MP2/SDD level. The length of the N–I bond ranges from 2.14 to 2.52 Å. A slightly higher NBO^[20] charge was found on the iodine in **6** (0.3 *e*, direct N–I bond) compared to **5** (0.2 *e*, R*–NH₂–ICl). A rotational analysis around the carbon–nitrogen bond for complexes **5** and **6** was performed. Because the nitrogen atom in **6** is a chiral center, both diastereomers were investigated. The structures shown in Figure 4 represent the energetic

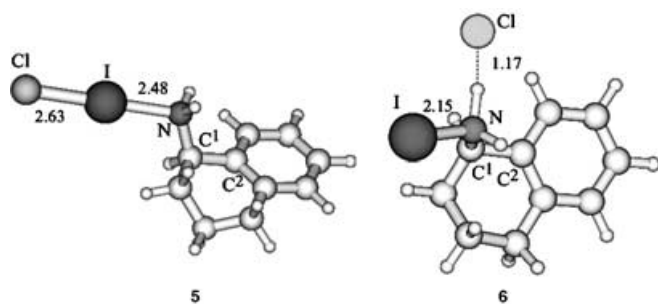


Figure 4. Calculated structures of **5** and **6**.

minima of all conformations calculated. Details can be found in the Supporting Information. At all levels of theory, the barrier to overcome **C** was too high to be achieved at room temperature, and **D** could not be located at all. The relative energies of complexes and transition states are given in Table 3.

Because the stereoselectivity of the iodolactonization can be influenced drastically by changing the solvent used in the reaction, the conductor polarizable continuum model

Table 3. Total energies (relative to free amine **3**) of complexes and transition states.

Total energies [kJ mol ^{−1}]	5	A	6	B	7	C	8
B3LYP/LANL2DZ	−88.6	29.5	−33.0	−0.2	−12.4	100.1	55.1
B3LYP/SDD	−92.0	29.5	−28.6	4.5	−2.7	105.9	63.5
MP2/SDD	−87.2	49.6	−46.3	−13.0	−44.9	— ^[a]	6.9
B3LYP/SDD + pd ^[b]	−72.5	79.1	−14.6 ^[c]	— ^[a]	−31.7	134.5	61.8

[a] Not available. [b] 6–31G(d,p) basis set used for all atoms apart from I.

[c] Relative energy of the amine–HCl complex is −60.8 kJ mol^{−1}.

(CPCM) was applied to the calculations of complexes **5** and **6**.^[21] The results obtained by using the CPCM model allow similar conclusions as the results obtained from the previous calculations. The energies of the complexes are lower, indicating a stabilization by the solvent. Solvents with a relatively high dielectric constant ϵ seem to stabilize the complexes most efficiently, as shown in Table 4.

Table 4. Total energies [kJ mol^{−1}] obtained (relative to free amine **3**) by using the CPCM solvent model.

	Benzene	Diethyl ether	Dichloromethane	Acetonitrile
ϵ [pF m ^{−1}]	2.25	4.36	8.93	36.64
5 total energy B3LYP/SDD	−107.1	−119.9	−119.6	−123.1
5 total energy B3LYP/SDD + pd	−87.8	−103.3	−106.0	— ^[a]
6 total energy B3LYP/SDD	−41.3	−52.1	−51.3	−54.1
6 total energy B3LYP/SDD + pd	−23.3	−33.9	−36.5	— ^[a]

[a] Not available.

The solvent plays an important role in the formation of the complexes and also in the subsequent addition to the alkene. The strong influence of the solvent on both reactivity and selectivity was already apparent from our preliminary experiments. Selectivity in the iodolactonization of **1** is thought to arise from complex **5** when the reaction mixture of ICl and **3** is cooled to −78 °C and the reaction is commenced immediately. When the mixture of ICl and **3** was stirred at room temperature for 30 min before the addition of **1** at −78 °C, which gave higher selectivities, **6** alone, or as a mixture together with **5**, may be the dominant source of selectivity. This hypothesis is supported by the isolation of α -tetralone after longer reaction times (> 30 min) for ICl and **3**. The α -tetralone might originate from **6** after elimination of an HI moiety to the imine and hydrolysis in the subsequent aqueous workup.

Based on the most successful 1,2,3,4-tetrahydro-1-naphthylamine scaffold, various compounds with similar structure (the enantiomerically pure amines **9**–**14**, Figure 5) were prepared and investigated in the iodolactonization reaction. Although secondary or tertiary amines led to racemic iodolac-

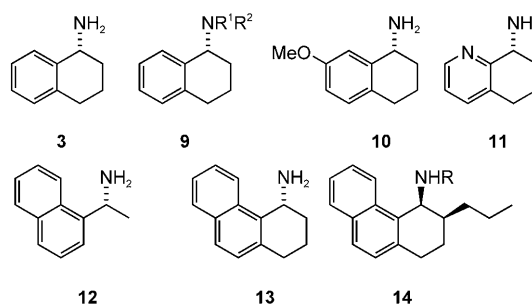


Figure 5. Enantiomerically pure amines **3** and **9**–**14**.

tone **2** in previous experiments, a series of *N*-monosubstituted and *N,N*-disubstituted derivatives **9** were investigated systematically.

Some selectivity was observed with the alkyl-substituted compounds **9a** and **9b**, but substituents on the nitrogen atom obviously strongly influence its ability to coordinate to iodine monochloride. Only racemic lactone was observed with amines **9c** and **9d** (Table 5). Amines **10** and **11**^[22] were

Table 5. Iodolactonizations of **1** obtained by using enantiomerically pure amines **9–14**.

Amine	2 (ee)	Amine	2 (ee)
3	45 % (<i>R</i>)	10	41 % (<i>R</i>)
4	26 % (<i>S</i>)	11	3 % (<i>R</i>)
9a (R ¹ =H, R ² =Me)	20 % (<i>R</i>)	12	30 % (<i>R</i>)
9b (R ¹ =R ² =Me)	13 % (<i>R</i>)	13	19 % (<i>R</i>)
9c (R ¹ =H, R ² =Boc)	0 %	14a R = <i>O</i> -menthyl	0 %
9d (R ¹ =H, R ² =Ts)	0 %	14b R = 3,5-dinitrobenzoyl	0 %

investigated as electronically modified derivatives of **3**. Amine **10** did show slightly reduced selectivities, whereas **11** interestingly led to almost racemic iodolactone. An interaction of the iodine atom with the ring-nitrogen atom might be the reason for an almost racemic product **2**.

To gain a better insight into the face-selectivity of the initial step, iodonium moieties of type **15** were calculated and optimized at a B3LYP/SDD level of theory. The more withdrawing (higher Hammett value) a substituent in the 4-position of the aromatic moiety of **1**, the shorter the bond between the iodine atom and the benzylic carbon atom (C¹–I) in the iodonium intermediates **15** (Figure 6). Interestingly,

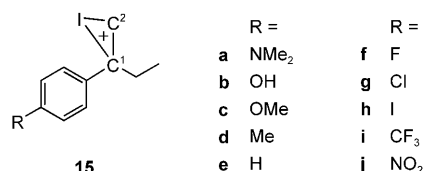
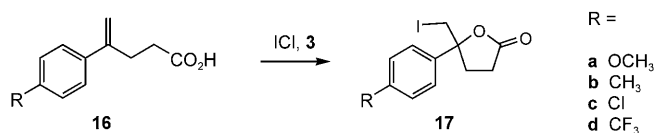


Figure 6. Differently substituted iodonium ions **15**.

this also correlates with higher selectivities observed in the iodolactonization of differently substituted, unsaturated carboxylic acids **1**. This iodolactonization appears, therefore, to be one of the rare examples in stereoselective synthesis in which only electronic factors of a substrate can remarkably influence selectivities. In most enantioselective reactions, steric factors play the major role, and electronic effects are only rarely studied.^[23]

All optimized geometries showed an unsymmetric iodonium ion **15** irrespective of the substituent R. The distance of C² to I remains constant at 2.24 Å, whereas the C¹–I bond lengths are significantly longer and vary from 2.97 to 3.04 Å, depending on the substituent R. Hammett correlations have been applied frequently to not only reaction rates, but also to NMR shifts, enantioselectivities, and vari-

ous thermodynamic properties.^[23c,d,24] The correlation of Hammett σ_p^+ constants with the calculated NBO charges at C¹ of iodonium ions **15** has an r^2 value of 0.86, which is much better than that obtained by using Hammett σ_p constants ($r^2=0.53$),^[25] and confirms a positive charge stabilized in the benzylic position (see Supporting Information for data). The correlation of the enantiomeric excess of iodolactonizations of unsaturated acids of type **16**, displaying different substituted aromatic moieties (Scheme 3), with the Hammett σ_p^+ values also shows a good correlation ($r^2=0.88$), as depicted in Figure 7.



Scheme 3. Iodolactonization of electronically modified acids **16**.

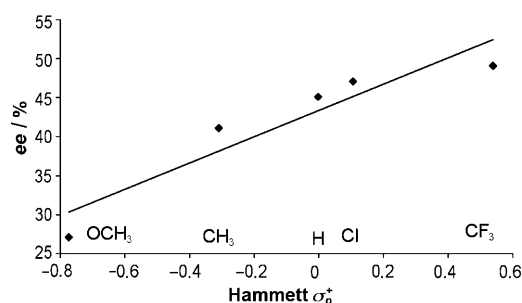


Figure 7. Correlation of Hammett σ_p^+ values with enantioselectivities in the iodolactonization of unsaturated acids **16**.

Because interactions between **1** and the amine–ICl complex might influence the selectivity, the cyclization of corresponding esters and amides was investigated. *tert*-Butyl ester **18** (Figure 8) could be cyclized only with ICl, but the expected lactone **2** was not formed by using the amine–ICl complex of the stereoselective protocol described above.^[7] The reactivity of the 2:1 amine–ICl complex is too low for the conversion of **18** into lactone **2**, but by changing to an amine:ICl ratio of 1:1.5, **2** was obtained in 66 % yield with 34 % *ee*. Only amide **19a** (Figure 8) was reactive when the stereoselective lactonization protocol was used (amine:ICl ratio of 2:1) to give **2** in 37 % *ee*, albeit in a low yield (43 %), which might be due to the low solubility of **19a** in dichloromethane. All other amide derivatives **19b–d** remained unreact-

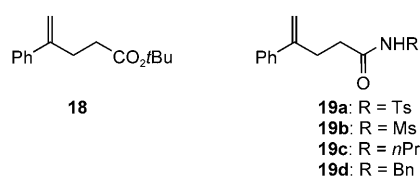
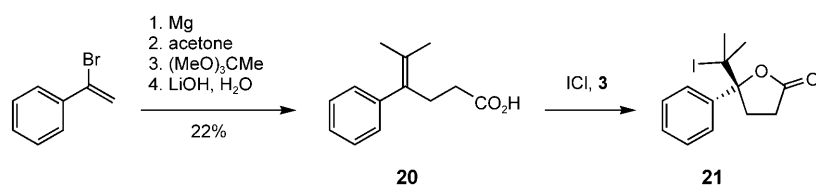


Figure 8. Ester **18** and amides **19** used in iodocyclizations.

ed when the stereoselective lactonization protocol was used, and only an iodine solution in aqueous THF could affect the lactonization.

The fact that ester **18** and amide **19** can be cyclized with selectivities comparable to the cyclization of the acid **1** ($R = Ph$) implies that the stereoselecting step is the face-selective attack of the double bond by the amine–ICl complex, rather than a precomplexation in an acid–base reaction prior to lactonization. A reaction of the solid amine–ICl complex and the carboxylic acid **1** in a solid-state reaction also led to lactone **2**. Grinding the two solids in a mortar produced lactone **2** with 14% *ee*, and the selectivity could be increased to 34% *ee* by cooling with liquid nitrogen.

The synthesis of the unsaturated acid **20** with a tetrasubstituted double bond was performed by using a Claisen rearrangement. The subsequent iodolactonization proceeded at a similar reaction rate and identical selectivities (45% *ee*) in the lactone **21** were obtained (Scheme 4).



Scheme 4. Synthesis and lactonization of acid **20** with a tetrasubstituted double bond.

Conclusion

The formation of chiral electrophilic complexes between primary amines and ICl was investigated, and the existence of two possible chiral complexes was hypothesized and supported by the results of *ab initio* and DFT calculations. By combining all the data obtained from NMR titrations, UV/Vis studies, crossover experiments, and ester as well as amide lactonizations, we conclude that the stereoselecting step is most likely to be the attack of the double bond without previous reagent–substrate interaction via the carboxylic acid moiety. The formation and the charge distribution of unsymmetric iodonium ions were successfully related to the Hammett substituent constants. This study should now lead to the development of new and more efficient chiral ICl complexes for a broad range of *reagent*-controlled stereoselective iodocyclizations.

Experimental Section

All reactions were performed under an argon atmosphere with anhydrous solvents. The 1H and ^{13}C NMR spectra were recorded in $CDCl_3$ by using TMS as an internal standard. Melting points are uncorrected. The enantiomerically pure amines **3**, **4**, and **12** are commercially available.

NMR titration of 1-phenyl-1-ethylamine **4 with ICl:** A solution of **4** (585 μL , 0.057 M in $CDCl_3$) was placed in an NMR tube. A solution of ICl (0.85 M in $CDCl_3$) was added in amounts of 10 μL and an NMR spectrum (300 MHz) was recorded after each addition.

General procedure for iodocyclizations: The enantiomerically pure amine (0.46 mmol) was dissolved in CH_2Cl_2 (3 mL) and stirred with ICl (0.23 mmol, 0.23 mL of a 1 M solution in CH_2Cl_2) for 35 min at 33 °C. After cooling to –78 °C, the unsaturated carboxylic acid **1** (0.115 mmol), dissolved in CH_2Cl_2 (1 mL), was added. After 10 min, aqueous $Na_2S_2O_3$ (10%) was added and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was extracted with CH_2Cl_2 (2 $\times$ 6 mL) and the combined organic layers were dried with $MgSO_4$. The product **2**^[26] was purified by performing preparative TLC (*tert*-butylmethyl ether/pentane 1:2).

General procedure for the synthesis of 4-aryl-4-pentenoic acid esters: The boronic acid (4 mmol), KF (12 mmol, 936 mg), and $[Pd_2(dba)_3]$ (0.06 mmol, 55 mg) were dissolved in THF (3 mL), then 4-bromo-4-pentenoic acid *tert*-butyl ester^[27] (4.4 mmol, 1.03 g) or 4-bromo-4-pentenoic acid ethyl ester^[28] (4.4 mmol, 911 mg), and tris-(*o*-tolyl)phosphine (0.16 mmol, 49 mg) were added. After 4–10 h, the reaction was filtered over celite. The celite pad was washed with diethyl ether (250 mL). After evaporation of the solvent, the crude product was purified by performing flash chromatography (silica gel, *tert*-butylmethyl ether/pentane 1:10). All products obtained were clear, colorless oils.

4-Phenyl-4-pentenoic acid (1**):** For spectral data, see reference [29].

5-Iodomethyl-5-phenyl-dihydrofuran-2-one (2**):** For spectral data, see Supporting Information of reference [7].

(R)-N-Methyl-1,2,3,4-tetrahydro-1-naphthylamine (9a**):** For preparation and spectral data, see reference [30].

(R)-N,N-Dimethyl-1,2,3,4-tetrahydro-1-naphthylamine (9b**):** For preparation and spectral data, see reference [31].

(R)-1,2,3,4-Tetrahydronaphthyl carbamic acid *tert*-butyl ester (9c**):** (*R*)-1,2,3,4-tetrahydro-1-naphthylamine (7 mmol, 1 g) and Et_3N (1.5 mL) were

dissolved in CH_2Cl_2 (10 mL), cooled to 0 °C, and di-*tert*-butyldicarbonate (9 mmol, 1.96 g) was added and allowed to warm to RT. After stirring for 10 h, the reaction was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 $\times$ 30 mL). After evaporation of the solvent and the performance of flash chromatography (silica gel, *tert*-butylmethyl ether/pentane 1:2), **9c** was obtained quantitatively (1.75 g, 100% yield). M.p. 76–78 °C; 1H NMR ($CDCl_3$, 400 MHz): δ = 1.95–1.86 (m, 1H), 1.95–1.86 (m, 1H), 2.73–2.57 (m, 2H), 4.75 (m, 2H), 6.96–6.92 (m, 1H), 7.09–7.02 (m, 2H), 7.26–7.21 ppm (m, 1H); IR: $\tilde{\nu}$ = 3328, 3054, 3013, 1694, 1494, 1454, 1391, 1174 cm^{-1} ; MS (EI): m/z (%): 248 (25) [$M+H^+$], 218 (45), 158 (50), 148 (100), 130 (55), 100 (78); HRMS: calcd for $C_{15}H_{22}O_2N$ [M^+]: 248.1644; found: 248.1644.

(R)-4-Methyl-N-(1,2,3,4-tetrahydronaphth-1-yl)benzenesulfonamide (9d**):** For preparation and spectral data, see reference [32].

(R)-1-Azido-7-methoxy-1,2,3,4-tetrahydronaphthalene: (*S*)-1-Hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalene^[33] (110 mg, 0.62 mmol) was dissolved in toluene (2.3 mL) and diphenylphosphoryl azide (166 mg, 0.68 mmol) was added. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (160 mg, 1 mmol) was then added and the reaction was stirred overnight at room temperature. The reaction mixture was then partitioned between CH_2Cl_2 and saturated NH_4Cl , washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting clear yellow oil was purified by performing flash chromatography (silica gel, *tert*-butylmethyl ether/pentane 1:9) to yield (*R*)-1-azido-7-methoxy-1,2,3,4-tetrahydronaphthalene (86 mg, 68% yield); 1H NMR ($CDCl_3$, 250 MHz): δ = 1.62–1.93 (m, 4H), 2.49–2.73 (m, 2H), 3.72 (s, 3H), 4.66 (t, J = 6.3 Hz, 1H), 6.58–6.74 (m, 2H), 6.89–7.02 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 19.4, 28.0, 29.2, 55.4, 59.7, 113.3, 114.8, 129.4, 130.4, 134.7, 157.8 ppm; IR (neat): $\tilde{\nu}$ = 2932, 2835, 2361, 2341, 2096, 1614, 1505, 1456, 1254, 1149, 1039, 808, 668 cm^{-1} ; MS (EI): m/z (%): 203 (10) [M^+], 174 (9), 161 (100), 146 (12), 128 (8), 115 (15), 89 (9), 74 (7), 51 (16); HRMS: calcd for $C_{11}H_{14}N_3$ [$M^+ + H$]: 204.2511; found: 204.2513.

(R)-7-Methoxy-1,2,3,4-tetrahydronaphthylamine (10):^[34] 1-Azido-7-methoxy-1,2,3,4-tetrahydronaphthalene (86 mg, 0.39 mmol) was dissolved in anhydrous methanol, and 10% palladium on charcoal (2 mg) was added. The solvent was then thoroughly degassed and saturated with H₂. The reaction mixture was stirred for 30 min. Purification by performing preparative TLC (ethyl acetate/MeOH 4:1) yielded 20 mg (38%) **10**; ¹H NMR (CDCl₃, 250 MHz): δ = 1.78–2.01 (m, 4H), 2.68–2.78 (m, 2H), 3.90 (s, 3H), 3.95 (t, J = 6 Hz, 1H), 6.76 (m, 1H), 7.00 ppm (m, 2H); ¹³C NMR: δ = 19.5, 28.4, 29.7, 31.8, 49.7, 55.4, 112.3, 114.2, 129.0, 130.1, 157.9 ppm.

(R)-8-Amino-5,6,7,8-tetrahydroquinoline (11): *rac*-8-Hydroxy-5,6,7,8-tetrahydroquinoline^[22] was separated into the enantiomers by performing HPLC (Daicel Chiracel OD, 21 mm × 250 mm), at 6 mL min^{−1} with 2-propanol/hexane 1:4 as eluent. R_f (S) = 18 min, R_f (R) = 24 min. The (S)-enantiomer was converted into amine **11** by following the procedure in reference [22].

1,2,3,4-Tetrahydrophenanthren-4-ol: NaBH₄ (62 mg, 1.68 mmol) was added to a solution of 2,3-dihydrophenanthren-4(1*H*)-one^[35] (300 mg, 1.53 mmol) in MeOH at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h. The solvent was evaporated and the residue was treated with saturated aqueous NH₄Cl (3 mL) and then extracted with CH₂Cl₂ (4 × 3 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure to yield 298 mg (98%) of 1,2,3,4-tetrahydrophenanthren-4-ol; ¹H NMR (CDCl₃, 400 MHz): δ = 1.68–2.04 (m, 3H), 2.11–2.20 (m, 1H), 2.71–2.89 (m, 2H), 5.31 (t, J = 3.3 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.34 (dt, J = 7.4, 0.7 Hz, 1H), 7.46 (dt, J = 7.0, 1.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 8.13 ppm (d, J = 8.5 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ = 17.2, 30.3, 31.7, 63.5, 123.4, 125.1, 126.6, 128.0, 128.2, 128.6, 132.0, 132.4, 132.6, 135.3 ppm; MS (EI): m/z (%): 198 (83) [M^+], 180 (100), 164 (62), 152 (27), 140 (77), 115 (38) 90 (26), 76 (21), 63 (25); HRMS: calcd for C₁₄H₁₈ON [M^+ +NH₄]: 216.1383; found: 216.1385.

4-Azido-1,2,3,4-tetrahydrophenanthrene: Mesyl chloride (50 μ L, 0.404 mmol) was added to a solution of 1,2,3,4-tetrahydrophenanthren-4-ol (20 mg, 0.101 mmol), 4-dimethylaminopyridine (DMAP) (74 mg, 0.606 mmol), and NaN₃ (328 mg, 5.05 mmol) in CH₂Cl₂ (3 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to room temperature and DMSO (1.5 mL) was added. The mixture was stirred for 3 d and then quenched with water. The aqueous phase was extracted with CH₂Cl₂ (3 × 3 mL) and the combined organic layers were washed with saturated aqueous NaCl (4 × 5 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the crude product was purified by performing flash chromatography (silica gel, diethyl ether/petroleum ether 2:1) to yield 17 mg (75%) of product. The racemate was separated by subjecting it to preparative HPLC (Daicel Chiracel OD, 21 mm × 250 mm, 5 mL min^{−1}, 15 °C), R_f (R) = 10.1 min, [α]_D²⁰ = +278 (c = 0.35, CHCl₃); R_f (S) = 18.8 min, [α]_D²⁰ = −276 (c = 0.35, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ = 1.82–2.05 (m, 3H), 2.22–2.38 (m, 1H), 2.77–2.98 (m, 2H), 5.04 (s, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.39 (dt, J = 5.6, 1.3 Hz, 1H), 7.48 (dt, J = 7.1, 0.6 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 8.0 ppm (d, J = 8.9 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ = 16.9, 28.6, 28.8, 53.9, 121.7, 124.3, 125.8, 126.1, 126.7, 127.6, 127.8, 131.1, 131.4, 135.1 ppm; IR (thin film): $\tilde{\nu}$ = 3051, 2938, 2094, 1626, 1602, 1510, 1430, 1292, 1263, 1233, 1190, 1058, 901, 848, 814, 743 cm^{−1}; HRMS: calcd for C₁₄H₁₃N₃ [M^+]: 223.1104; found: 223.1101.

(R)-1,2,3,4-Tetrahydrophenanthren-4-amine (13): (R)-4-Azido-1,2,3,4-tetrahydrophenanthrene (86 mg, 0.39 mmol) was dissolved in anhydrous methanol, and 10% palladium on charcoal (2 mg) was added. The solvent was then thoroughly degassed and saturated with H₂. The reaction mixture was stirred for 30 min. The solution was filtered through celite and the solvent was removed under reduced pressure. Purification by using preparative TLC with ethyl acetate/MeOH 4:1 yielded 20 mg (26%) **13**; [α]_D²⁰ = 22 (c = 1, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ = 1.7–2.05 (m, 4H), 2.76–2.90 (m, 2H), 4.64 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.34 (dt, J = 7.1, 0.9 Hz, 1H), 7.44 (dt, J = 7.0, 1.3 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 8.08 ppm (d, J = 8.5 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ = 17.1, 30.3, 31.9, 44.5, 123.3, 124.8, 126.4, 127.1, 128.2, 128.8, 132.0, 132.7, 133.9, 134.8 ppm; IR (thin film): $\tilde{\nu}$ = 2926, 2360, 1508, 1442, 1262, 806, 742, 668 cm^{−1}; MS: m/z (%): 198 (13) [M^+],

181 (25), 180 (100), 168 (33), 154 (31), 84 (16), 69 (15), 57 (16), 43 (21), 40 (25); HRMS: calcd for C₁₄H₁₆N [M^+ +H]: 198.1277; found: 198.1280.

(3*R*,4*R*)-trans-4-(3,5-Dinitrobenzamido)-3-propyl-1,2,3,4-tetrahydrophenanthrene (14b): (3*R*,4*R*)-trans-4-(3,5-Dinitrobenzamido)-3-propenyl-1,2,3,4-tetrahydrophenanthrene (500 mg, 1.15 mmol) was dissolved in a 1:1 mixture of dry THF/2-propanol (5 mL). Wilkinsons catalyst (0.5 mol %) was added and the mixture was stirred under hydrogen for 48 h. The solvent was removed under reduced pressure and the product was purified by performing flash chromatography (silica gel, petroleum ether/Et₂O 4:1); ¹H NMR (CDCl₃, 400 MHz): δ = 0.89 (t, J = 7.6 Hz, 3H), 1.14–1.31 (m, 1H), 1.41–1.72 (m, 4H), 1.92–2.04 (m, 2H), 2.94–3.10 (m, 2H), 5.98 (dd, J = 9.5, 3.4 Hz, 1H), 6.26 (d, J = 9.5 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.33 (t, J = 7.3 Hz, 1H), 7.43 (dt, J = 7.8, 1.1 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 8.73 (d, J = 2.0 Hz, 2H), 8.95 ppm (t, J = 2.1 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ = 14.8, 20.9, 24.0, 30.8, 34.9, 39.8, 48.1, 121.4, 132.0, 125.9, 127.5, 127.7, 128.1, 129.1, 130.9, 132.3, 132.8, 135.8, 138.2, 148.8, 162.2 ppm; IR (KBr): $\tilde{\nu}$ = 3339, 7632, 1541, 1526, 1345, 1083, 913, 804, 729 cm^{−1}; MS: m/z (%): 433.3 (37) [M^+], 432.3 (100), 210.1 (20), 166.8 (24), 62.0 (8); HRMS: calcd for C₂₄H₂₄N₃O₅ [M^+ +H]: 434.1710; found: 434.1715.

4-*p*-Tolyl-4-pentenoic acid ethyl ester: Yield: 34%, colorless oil; ¹H NMR (CDCl₃, 400 MHz): δ = 1.27 (t, J = 7.2 Hz, 3H), 2.38 (s, 3H), 2.50 (t, J = 7.8 Hz, 2H), 2.86 (t, J = 7.8 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 5.08 (s, 1H), 5.31 (s, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.34 ppm (d, J = 8.0 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ = 14.6, 21.9, 30.9, 33.8, 60.8, 112.4, 126.4, 129.5, 133.8, 139.4, 147.1, 173.6 ppm; IR (neat): $\tilde{\nu}$ = 3104, 3041, 2979, 1735, 1628, 1492, 1370 cm^{−1}; MS: m/z (%): 218 (42) [M^+], 145 (100), 129 (50), 115 (92), 91 (13), 77 (7), 55 (9); HRMS: calcd for C₁₄H₁₉O₂ [M^+ +H]: 219.1385; found: 219.1386.

4-*p*-Tolyl-4-pentenoic acid (16b): 4-*p*-Tolyl-4-pentenoic acid ethyl ester (1.28 mmol, 280 mg) was stirred in a 1 M LiOH solution in aqueous EtOH (60%) for 10 h. After evaporation, dilution with water, and extraction with CH₂Cl₂, the organic extracts were dried over MgSO₄. After evaporation of the solvent and recrystallization (petroleum ether), 90 mg (55% yield) of **16b** was obtained. For spectral data, see Supporting Information of reference [7].

4-(4-Chlorophenyl)-4-pentenoic acid *tert*-butyl ester: Yield: 60%, colorless oil; ¹H NMR (CDCl₃, 400 MHz): δ = 1.36 (s, 9H), 2.30 (t, J = 7.7 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 5.02 (s, 1H), 5.20 (s, 1H), 7.40–7.28 ppm (m, 4H); ¹³C NMR (CDCl₃, 100 MHz): δ = 28.1, 30.5, 34.2, 80.4, 113.2, 128.4, 129.0, 133.3, 139.2, 146.0, 178.4 ppm; IR (neat): $\tilde{\nu}$ = 3083, 2978, 1729, 1628, 1492, 1455, 1148 cm^{−1}; MS: m/z (%): 284 (40) [M^+ +NH₄], 228 (100), 194 (18), 165 (8), 108 (18), 91 (13); HRMS: calcd for C₁₅H₂₃ClO₂N [M^+ +NH₄]: 284.1417; found: 284.1426.

4-(4-Chlorophenyl)-4-pentenoic acid (16c): 4-(4-Chlorophenyl)-4-pentenoic acid *tert*-butyl ester (2 mmol, 500 mg) and silica (10 g) were refluxed in toluene (5 mL) for 2 h.^[36] After filtration over celite, a basic extraction with 1 N NaOH and extraction with CH₂Cl₂ after acidification with 1 N HCl yielded 250 mg (60%). For spectral data, see Supporting Information of reference [7].

4-(4-Trifluoromethylphenyl)-4-pentenoic acid *tert*-butyl ester: Yield: 64%, colorless oil; ¹H NMR (CDCl₃, 400 MHz): δ = 1.36 (s, 9H), 2.32 (t, J = 7.7 Hz, 2H), 2.75 (t, J = 7.5 Hz, 2H), 5.12 (s, 1H), 5.30 (s, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.49 ppm (d, J = 8.9 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ = 28.1, 30.5, 34.2, 80.4, 113.2, 124.5 (¹ J_{CF} = 260 Hz), 125.7, 126.9, 130.0 (² J_{CF} = 30 Hz), 144.8, 146.5, 172.6 ppm; IR (neat): $\tilde{\nu}$ = 3086, 3005, 2980, 1730, 1616, 1573, 1455, 1368, 1325, 1150 cm^{−1}; MS: m/z (%): 318 (100) [M^+ +NH₄], 262 (67), 228 (5), 199 (18), 115 (11), 77 (6.5); HRMS: calcd for C₁₆H₂₃F₃O₂N [M^+ +NH₄]: 318.1681; found: 318.1676.

4-(4-Trifluoromethylphenyl)-4-pentenoic acid (16d): 4-(4-Trifluoromethylphenyl)-4-pentenoic acid *tert*-butyl ester (1.1 mmol, 270 mg) and silica (10 g) were refluxed in toluene (5 mL) for 2 h.^[36] After filtration over celite, a basic extraction with 1 N NaOH and 1 N HCl yielded 280 mg (93%). For spectral data, see Supporting Information of reference [7].

Iodolactones (17): For spectral data, see Supporting Information of reference [7].

4-Phenyl-4-pentenoic acid *tert*-butyl ester (18): ^1H NMR (CDCl_3 , 400 MHz): δ = 1.38 (s, 9H), 2.42 (t, J = 7.8 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H), 5.38 (s, 1H), 5.58 (s, 1H), 7.18–7.38 ppm (m, 5H).

Procedure for the synthesis of 19a and 19b: 4-Phenyl-4-pentenoic acid **2** (400 mg, 2.27 mmol) was dissolved in THF (5 mL). Carbonyldiimidazole (368 mg, 2.27 mmol) was added dropwise in THF (5 mL). The reaction was stirred for 30 min, then heated to reflux for 30 min, and cooled to room temperature. *p*-Toluenesulfonamide (428 mg, 2.5 mmol) [methanesulfonamide 260 mg, 2.5 mmol] was added in one portion, and 1,8-diazabicyclo[5.4.0]undec-7-ene (339 μL , 2.27 mmol) dissolved in THF (2 mL) was added. The product was poured onto 1 M HCl and extracted with *tert*-butylmethyl ether (3 $\times$ 20 mL). The combined organic phases were dried over MgSO_4 and concentrated under reduced pressure. Flash chromatography with ethylacetate/pentane (1:2) and then CH_2Cl_2 /methanol (100:1) yielded **19a** (367 mg, 50%) [**19b**: 430 mg, 75%].

N-(4-Phenyl-4-pentenyl)-4-toluenesulfonamide (19a): M.p. 74–76°C; ^1H NMR (CDCl_3 , 300 MHz): δ = 2.39 (m, 5H), 2.71 (t, J = 8.4 Hz, 2H), 4.96 (s, 1H), 5.20 (s, 1H), 7.30–7.23 (m, 7H), 7.92 ppm (d, J = 8.4 Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): 21.5, 29.5, 29.5, 34.9, 113.1, 125.9, 127.6, 128.3, 128.8, 129.5, 135.4, 139.9, 145.0, 145.9, 170.7 ppm; IR: $\tilde{\nu}$ = 3346, 1826, 1712, 1496, 1428, 1440, 1340, 1477, 1086, 103, 91, 850, 815, 779, 704, 666 cm^{-1} ; MS: m/z (%): 330 (100) [M^+], 174 (38), 155 (25), 131 (28), 117 (22), 103 (10), 91 (58), 77 (20), 55 (26), 43 (18); HRMS: calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_3\text{S}$ [M^+ + H]: 330.1119; found: 330.1161.

N-(4-Phenyl-4-pentenyl)-methylsulfonamide (19b): M.p. 121–124°C; ^1H NMR (CDCl_3 , 300 MHz): δ = 2.46 (t, J = 7.8 Hz, 2H), 2.88 (t, J = 7.8 Hz, 2H), 3.21 (s, 3H), 5.12 (s, 1H), 5.34 (s, 1H), 7.41–7.26 ppm (m, 5H); ^{13}C NMR (CDCl_3 , 75 MHz): 29.9, 35.3, 41.5, 113.9, 129.1, 127.9, 128.6, 139.8, 146.1, 171.3 ppm; IR: $\tilde{\nu}$ = 3246, 3082, 3052, 3031, 2983, 2932, 2883, 1811, 1718, 1700, 1626, 1466, 1332, 1182, 1126, 980, 901, 894, 869, 779, 518, 509 cm^{-1} ; MS: m/z (%): 254 (100) [M^+], 174 (9), 159 (27), 131 (34), 117 (14), 91 (17), 89 (10); HRMS: calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_3\text{S}$ [M^+ + H]: 254.0851; found: 254.0851.

Procedure for the synthesis of 19c and 19d: DMAP (28 mg, 0.227 mmol) was dissolved in CH_2Cl_2 (2 mL), and *N*-(3-dimethylaminopropyl)-*N'*-ethyl-carbodiimide hydrochloride (EDCI) (436 mg, 2.27 mmol) dissolved in CH_2Cl_2 (5 mL) was added at 0°C. 4-Phenyl-4-pentenoic acid (400 mg, 2.27 mmol) dissolved in CH_2Cl_2 (5 mL) was added dropwise. Propylamide (205 μL , 2.27 mmol) [benzylamide 273 μL , 2.27 mmol] was added slowly to the reaction. The mixture was warmed to room temperature over 2 h, poured onto water, and extracted with CH_2Cl_2 (3 $\times$ 20 mL). The combined organic phases were washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. Flash chromatography with *tert*-butylmethyl ether/pentane (1:1) yielded **19c** (346 mg, 70%) [**19d**: 400 mg, 66%].

N-Propyl-4-phenyl-4-pentenamide (19c): M.p. 54–56°C; ^1H NMR (CDCl_3 , 300 MHz): δ = 0.89 (t, J = 8.1 Hz, 3H), 1.50–1.43 (m, 2H), 2.29 (t, J = 8.1 Hz, 2H), 2.85 (t, J = 8.1 Hz, 2H), 3.15 (q, J = 6.6 Hz, 2H), 5.09 (s, 1H), 5.29 (s, 1H), 5.74 (s, 1H), 7.41–7.23 ppm (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz): δ = 11.3, 22.7, 31.1, 35.3, 41.1, 112.9, 126.0, 127.5, 128.3, 140.4, 147.1, 172.2 ppm; IR: $\tilde{\nu}$ = 3303, 3079, 2958, 2872, 1956, 1894, 1798, 1638, 1542, 1492, 1444, 1372, 1339, 1263, 1232, 1169, 1025, 895, 777, 704 cm^{-1} ; MS: m/z (%): 218 (100) [M^+], 132 (16), 117 (7), 60 (13), 55 (12), 43 (34); HRMS: calcd for $\text{C}_{14}\text{H}_{20}\text{NO}$ [M^+ + H]: 218.1500; found: 218.1548.

N-Benzyl-4-phenyl-4-pentenamide (19d): M.p. 88–90°C; ^1H NMR (CDCl_3 , 300 MHz): δ = 2.30 (t, J = 7.5 Hz, 2H), 2.83 (t, J = 7.5 Hz, 2H), 4.32 (d, J = 5.4 Hz, 2H), 5.06 (s, 1H), 5.26 (s, 1H), 6.04 (s, 1H), 7.36–7.18 ppm (m, 10H); ^{13}C NMR (CDCl_3 , 75 MHz): δ = 31.0, 35.2, 43.4, 113.0, 126.0, 127.3, 127.5, 127.6, 128.3, 128.5, 138.2, 140.3 ppm; IR: $\tilde{\nu}$ = 3298, 3050, 2947, 1952, 1881, 1805, 1786, 1752, 1632, 1551, 1493, 1454, 1381, 1223, 1160, 1075, 1029, 996, 890, 778, 747, 695 cm^{-1} ; MS: m/z (%): 266 (80) [M^+ + H], 147 (5), 131 (10), 117 (7), 106 (11), 91 (9); HRMS: calcd for $\text{C}_{18}\text{H}_{20}\text{NO}$ [M^+ + H]: 265.1467; found: 265.1543.

Methyl 5-methyl-4-phenylhex-4-enoate: 2-Methyl-3-phenylbut-3-en-2-ol^[37] (799 mg, 4.9 mmol), trimethyl orthoformate (5.88 g, 49 mmol), and acetic acid (30 mg, 0.5 mmol) were heated to 125°C for 2 h. The temperature was increased to 140° for a further 6 h and the reaction mixture was

then concentrated under reduced pressure. After recrystallization, methyl 5-methyl-4-phenylhex-4-enoate was obtained (431 mg, 40% yield); ^1H NMR (CDCl_3 , 400 MHz): δ = 1.45 (s, 3H), 1.72 (s, 3H), 2.18 (t, J = 7.8 Hz, 2H), 2.61 (t, J = 7.8 Hz, 2H), 3.53 (s, 3H), 6.98 (m, 2H), 7.12 (m, 1H), 7.20 ppm (m, 2H); ^{13}C NMR (CDCl_3 , 62.5 MHz): δ = 20.5, 22.6, 30.0, 33.2, 51.8, 126.5, 128.3, 128.4, 129.0, 129.4, 129.5, 133.6, 143.2, 174.2 ppm.

5-Methyl-4-phenylhex-4-enoic acid (20): Methyl 5-methyl-4-phenylhex-4-enoate (280 mg, 1.28 mmol) was dissolved in a 5:1 mixture of THF and water. LiOH (118 mg, 2.82 mmol) was added and the mixture was heated to reflux for 16 h. The reaction mixture was neutralized with 5 N HCl and extracted with CH_2Cl_2 (3 $\times$ 10 mL). The combined organic layers were dried over MgSO_4 , the solvent removed under reduced pressure, and the product purified by performing column chromatography (petroleum ether/Et₂O 4:1) to obtain **20** in 97% yield (257 mg); ^1H NMR (CDCl_3 , 400 MHz): δ = 1.43 (s, 3H), 1.72 (s, 3H), 2.15 (t, J = 7.8 Hz, 2H), 2.61 (t, J = 7.8 Hz, 2H), 6.98 (m, 2H), 7.12 (m, 1H), 7.20 ppm (m, 2H); ^{13}C NMR (CDCl_3 , 62.5 MHz): δ = 20.1, 22.3, 29.4, 32.8, 126.2, 128.1, 129.1, 129.2, 132.9, 142.7, 180.1 ppm; IR (thin film): $\tilde{\nu}$ = 3074, 2909, 2360, 1709, 1490, 1441, 1295, 1214, 1122, 1072, 1026, 929, 768, 702 cm^{-1} ; MS: m/z (%): 204 (92) [M^+], 143 (68), 128 (100), 115 (71), 91 (45), 73 (32), 65 (28), 51 (37); HRMS: calcd for $\text{C}_{15}\text{H}_{16}\text{O}_2$ [M^+]: 204.2682; found: 204.2687.

5-(2'-Iodo-2'-methylethyl)-5-phenyldihydrofuran-2-one (21): This was synthesized from **20** by using the standard iodolactonization procedure; ^1H NMR (CDCl_3 , 400 MHz): δ = 1.8 (s, 3H), 2.03 (s, 3H), 2.36–2.52 (m, 2H), 2.67–2.79 (m, 2H), 7.28–7.39 ppm (m, 5H); ^{13}C NMR (CDCl_3 , 62.5 MHz): δ = 20.3, 20.8, 28.3, 32.5, 41.6, 83.2, 123.8, 127.3, 129.3, 139.7, 173.6 ppm.

Acknowledgements

We thank Prof. Barbara Alberts (University of Hamburg, Germany) for analytical data, Prof. Andrew N. French (Albion College, Michigan, USA) for valuable discussions and assistance in the synthesis of **14**, Dr. Sian Howard and Dr. David J. Willock (Cardiff University) for support in developing the SDD+pd basis set, Prof. Olaf G. Wiest (University of Notre Dame, South Bend, USA) for valuable discussions, and the CSCS Supercomputing Center, the CLRC, the University of Basel, and Cardiff University for support. We thank Regis Technology for the donation of the Whelk-O1 alkene. We also thank the EPSRC National Mass Spectrometry Service Centre, Swansea, for mass spectrometric data and the Swiss National Foundation (SNF) and EPSRC for funding this project.

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- [13] Similar results were obtained by using amine **4** for the UV/Vis experiment (isosbestic points at 231 and 286 nm).
- [14] After two equivalents of **4** were used to preform the complex with ICl , one equivalent of **3** was added at $-78^{\circ}C$ and the reaction was performed at $-78^{\circ}C$, which resulted in a selectivity of 15% *ee* (*S*)-**2**, instead of the expected 12% *ee* (*S*)-**2**. Reversing the order of the amines (first **3**, then **4**) resulted in 2% *ee* (*R*)-**2**.
- [15] The geometries of all species were obtained by conducting conformational analysis, optimized with no constraints, and the correct number of eigenvalues was confirmed by performing frequency calculations. Charges are given in elementary charge units, *e*. All calculations were performed by using Gaussian98 (Revision A.11.1), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh PA, **2001**.
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Received: May 5, 2005
Published online: July 22, 2005