ORGANIC LETTERS

2002
Vol. 4, No. 2
297−300

Reagent-Controlled Stereoselective Iodolactonizations

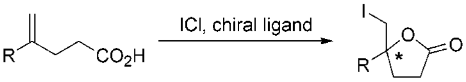
Jürgen Haas,[†,‡] Sandrine Piguel,[‡] and Thomas Wirth*[,†,‡]

Department of Chemistry, Cardiff University, P.O. Box 912, Cardiff CF10 3TB, U.K., and Institute of Organic Chemistry, University of Basel, Switzerland

wirth@cf.ac.uk

Received November 23, 2001

ABSTRACT



Iodocyclizations are important transformations and among stereocontrolled iodocyclizations mostly *substrate*-controlled versions using a chiral auxiliary have been successfully investigated. This work reports on stereoselective *reagent*-controlled iodolactonizations applying a new method using a combination of ICl and a primary amine leading to the highest selectivities known so far.

Halocyclizations have been studied extensively, and this type of transformation serves as an important key reaction in a variety of syntheses.[1] The first examples of this reaction were described early in the last century,[2] and the reaction conditions developed at that time (aqueous solvent, base, iodine) are still widely used.

This is also true for many *substrate*-controlled stereoselective iodocyclizations, where an existing chiral moiety in the substrate controls the outcome of the reaction. This type of control has been investigated in detail[3] and applied to natural product syntheses[4] and to reactions on solid support.[5]

To our knowledge there are only two reports on *reagent*-controlled stereoselective halolactonizations.[6,7] Grossman and Trupp described a dihydroquinidine−iodine complex as the source of I^+ in a chiral environment,[6] while Brown and Cui investigated cyclizations of 4-penten-1-ol using pyridines as chiral ligands for Br^+.[7] The selectivities in the halolactones synthesized did not exceed an enantiomeric ratio (er) of 57:43. Chiral electrophilic fluorination reagents have been explored and have already been used in asymmetric synthesis.[8]

Prior to the work reported herein, we had previously prepared analogues of bis-(*sym*)-collidine−iodine−perchlorate (BCIP) for iodolactonizations.[9] In that work *sym*-collidine was replaced by a pyridine with a chiral moiety attached to the 2-position. This strategy was similar to that of Brown;[7] hence we could not obtain enantiomeric ratios exceeding 52:48.[9]

In reactions using BCIP, only one collidine molecule is coordinated to the I^+ during the addition step to alkenes.[10] Consequently, the second collidine ligand has to dissociate off before the reaction can take place. Additionally, it is known that the complex of ICl and pyridine is linear with one ICl molecule coordinated to the nitrogen atom.[11] Therefore, first experiments were performed using an equimolar ratio of I^+ and amine in the reactions.

[†] Cardiff University.

[‡] University of Basel.

(1) (a) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, 171. (b) Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 363. (c) Mulzer, J. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H. J., Braun, M., Krohn, K., Reissig, H. U., Eds.; VCH: Weinheim, 1991; p 157. (d) Rousseau, G.; Robin, S. *Tetrahedron* **1998**, *54*, 13681.

(2) (a) Stobbe, H. *Liebigs Ann. Chem.* **1902**, *321*, 119. (b) Fittig, R. *Liebigs Ann. Chem.* **1904**, *331*, 142. (c) Bougault, M. J. *Ann. Chim. Phys.* **1908**, *14*, 145.

(3) (a) Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317. (b) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (c) Hoffmann, R. W.; Stürmer, R.; Harms, K. *Tetrahedron Lett.* **1994**, *35*, 6263.

(4) (a) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2120. (b) Takano, S.; Murakata, C.; Imamura, Y.; Tamura, N.; Ogasawara, K. *Heterocycles* **1981**, *16*, 1291. (c) Shi, Y.; Peng, L. F.; Kishi, Y. *J. Org. Chem.* **1997**, *62*, 5666.

(5) Moon, H.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1992**, *57*, 6088.

(6) Grossman, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233.

(7) Brown, R. S.; Cui, X. L. *J. Org. Chem.* **2000**, *65*, 5653.

(8) Muñiz, K. *Angew. Chem.* **2001**, *113*, 1701; *Angew. Chem., Int. Ed.* **2001**, *40*, 1653.

(9) Haas, J. Diploma Thesis, University of Basel, 1999.

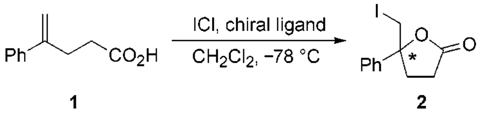
(10) Brown, R. S.; Neverov, A. A. *J. Org. Chem.* **1998**, *63*, 5977.

(11) Hassel, O.; Rømming, C. *Acta Chem. Scand.* **1956**, *10*, 696.

10.1021/ol0171113 CCC: $22.00

We chose the iodolactonization of **1** to **2** as a first model reaction, because **2** contains only one stereogenic center and the analysis of the product is straightforward (Scheme 1).[12]

Scheme 1. Stereoselective Lactonization Using ICl



A common side reaction of iodocyclizations, a subsequent HI elimination, is impossible in molecules of type **2**, because the $-CH_2I$ moiety is adjacent to a quaternary carbon atom.

To investigate conditions and possible chiral ligands for I^+, initial experiments included a variety of enantiomerically pure compounds such as carboxylic acids, alcohols, amino alcohols, or amino acids. Only by using primary amines was the iodolactone **2** obtained with some enantiomeric excess, especially using ligands similar to (*R*)-1-phenylethylamine **3**.[13]

We investigated I_2, IBr, and *N*-iodosuccinimide (NIS) as well as ICl as sources of I^+, whereas ICl proved to be the most efficient one. We therefore chose ICl as a convenient reagent because the highest selectivities have been obtained using this source of I^+ (Table 1). The ratio of I^+ and amine was optimized during the first experiments, and all subsequent experiments mentioned below are performed with a ratio of 1:2 (ICl:amine).

Table 1. Iodolactonization of **1** Using Amine **3** as a Chiral Ligand to ICl

source of I^+	**2** er (*S*:*R*)
NIS	50:50
I_2	53.5:46.5
IBr	54:46
ICl	62.5:37.5

Clearly, all the reactions decribed in Table 1 generate the same absolute configuration in **2** with different selectivities depending on the source of I^+.[14] Further optimization of the reaction conditions was then carried out by investigating temperature effects and solvent dependency as described below.

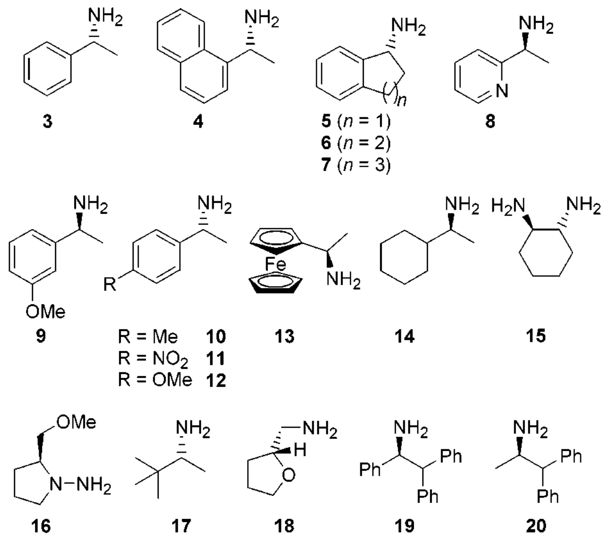


Figure 1. Primary amines used as ligands in the iodolactonization of **1** to **2**.

Figure 1 shows a selection of primary amines which were investigated as ligands. A variety of secondary and tertiary amines showed only very small selectivities in the reaction of **1** to **2**.[15]

During the optimization studies, it was found that after mixing the amine with ICl in CH_2Cl_2 it is essential to stir at room temperature for 30 min to form the most selective species (if this time exceeds 2 h, no reaction was observed). After the mixture was cooled to −78 °C, a solution of **1** was added. The lactonization of **1** is very fast; NMR investigations indicated a time scale below 2 min for the formation of **2** at −60 °C. The yields of the iodolactonizations described are typically around 80%.[16] Many screening experiments have, however, only been performed on an analytical scale without determination of yields. Further investigations to gain more insight on the structure of the reactive species were done by ^1H NMR. The amine **3** was titrated with ICl, and the results imply the formation of a 1:1 complex[17] similar to published investigations.[10] Ad-

---

[12] Spectroscopic data for **2**. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.44-2.82$ (m, 4H), 3.63 (s, 2H), 7.35−7.41 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.3, 29.2, 33.9, 86.0, 124.8, 128.6, 128.8, 140.6, 175.2$. MS (EI, 70 eV): *m*/*z* (%) 302 (1), 175 (46), 161 (100), 133 (8), 105 (38), 91 (34), 77 (22), 51 (13). The enantiomeric excess was determined by HPLC (hexane:2-propanol = 9:1). Chiralcel OD: 0.5 mL min^{-1}; 270 nm; $R_f(S) = 37.6$ min; $R_f(R) = 43.0$ min.

[13] *R*)-*N*-Methyl-1-phenylethylamine and (*R*)-*N*,*N*-dimethyl-1-phenylethylamine are much less efficient (**2**: er 51.5:48.5 and 50:50, respectively).

[14] The absolute configuration of **2** was determined by comparison of the optical rotation after radical deiodination of **2** to the known 5-methyl-5-phenyl-dihydrofuran-2-one: Albinati, A.; Bravo, P.; Ganazzoli, F.; Resnati, G.; Viani, F. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1405.

[15] Secondary and tertiary amines used as ligands in the iodolactonization of **1**: (*R*)-1-(1-phenylethyl)pyrrolidine (**2**: 52.5:47.5 *S*:*R*), (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (**2**: er 50:50), sparteine (**2**: er 50:50), sparteinesulfate (**2**: er 50:50), (*S*)-1,1′-binaphthalenyl-2,2′-diamine (**2**: er 50:50), (*S*)-glutamic acid (**2**: er 50:50), (*R*,*R*)-*N*,*N*′-1,2-cyclohexanediylbis(4-methyl-benzenesulfonamide) (**2**: er 50:50), (*S*)-alaninol (**2**: er 50:50); the ratio of these amines to I^+ was 1:1, because of the minor selectivities observed they have not been repeated using optimized conditions.

[16] A 1 M solution of ICl in CH_2Cl_2 (0.58 mmol, 0.58 mL) was added dropwise to a solution of **6** (1.15 mmol, 169 mg) in CH_2Cl_2 (10 mL) at room temperature. The resulting orange solution was stirred for 30 min before cooling to −78 °C. A solution of **1** (0.28 mmol, 49 mg) in CH_2Cl_2 (3 mL) was then added. The reaction mixture was stirred for 15 min at −78 °C before quenching with 10% aqueous $Na_2S_2O_3$. After extraction with CH_2Cl_2 (2 × 40 mL) the combined organic layers were washed with brine and dried ($MgSO_4$). Removal of the solvent in vacuo and purification by column chromatography on silica (pentane:methyl-*tert*-butyl ether 2:1) afforded 69 mg of (*R*)-**2** (0.23 mmol, 82%) with an er of 27.5:72.5.

[17] The quadruplett of the benzylic proton in **3** was shifted to a higher field, up to a ratio of 1:1, then to lower field.

Table 2. Results of the Stereoselective Iodolactonization Using Different Primary Amines as Ligands

amine	**2** er (*S*:*R*)	amine	**2** er (*S*:*R*)
3	62.5:37.5	**12**	54.5:45.5
4	35:65	**13**	40.5:59.5
5	41:59	**14**	57:43
6	27.5:72.5	**15**	57:43
7	45:55	**16**	57:43
8	51.5:48.5	**17**	50:50
9	37:63	**18**	50:50
10	62:38	**19**	52.5:47.5
11	53:47	**20**	51.5:48.5
11·HCl	50:50		

ditional UV experiments signify the formation of a 1:1 complex as well.[18] Further experiments are needed to clarify whether the active chiral electrophilic species is an amine: ICl complex or an amine:I^+ complex with Cl^- already dissociated from the complex.

Table 2 shows that amines with a structure similar to that of **3** result in better selectivities than others. Substitution of the aromatic moiety of **3** as well as altering the size of the anellated ring (**5**, **6**, **7**) have been investigated. It can be seen that substitution at the 4-position of the aromatic ring (**10**−**12**) results in a smaller enantiomeric ratio in **2**. An anellated five-membered (**5**) or seven-membered ring (**7**) also resulted in a decrease of the enantiomeric excess. In case of amine hydrochlorides (e.g., **11**·HCl) racemic iodolactone **2** was obtained independent of the amine. The ferrocene moiety in **13** did not enhance the selectivity.

Interestingly, a substituent in *ortho*-position to the chiral amino moiety is changing the absolute configuration of iodolactone **2**. With amine **3**, iodolactone (*S*)-**2** is generated, whereas iodolactone (*R*)-**2** is obtained using amine **4** or the amines **5**, **6**, or **7** with an anellated aliphatic ring system. A study on skeletal alterations of **3** revealed that using (*S*)-1,2,2-triphenylethylamine **19** with two phenyl groups at the 2-position or (*S*)-1,1-diphenyl-2-aminopropane **20** did result in significantly lower selectivities (er (*S*:*R*) 52.5:47.5 and 51.5:48.5, respectively).

Obviously an aromatic moiety in the amine is not necessary (**14**) to induce a stereoselective iodolactonization, although the selectivity is lower than that using aromatic amines.

We then investigated the effect of the solvent and have used the most successful ligand **6** as well as amine **3**. A small selection of different solvents is shown in Table 3.

Whereas all solvents led to the formation of product **2**, we found that methylene chloride gave the highest selectivity in the iodolactonization of **1**. Another promising solvent was benzene at room temperature, leading to an er of 35:65 of **2** compared to 27.5:72.5 of **2** in methylene chloride at −78 °C. Mixtures of benzene and methylene chloride did not lead to higher selectivities.

Table 3. Solvent Dependency of the Stereoselective Iodolactonization to **2** (−78 °C, ICl, 2 equiv of Amine)

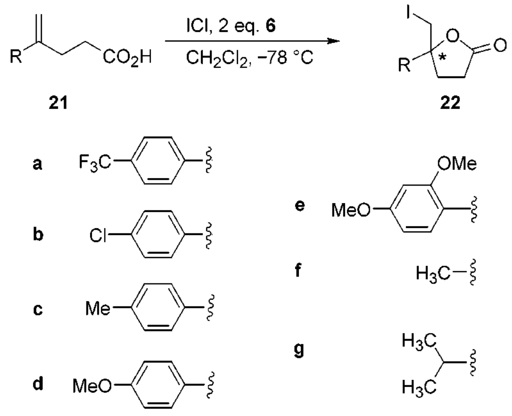
solvent	**2** er (*S*:*R*) (using amine **3**)	**2** er (*S*:*R*) (using amine **6**)
Et_2O	53:47	50:50
CH_3CN	52.5:47.5	47.5:52.5
C_6H_6[a]	53:47	35:65
$CHCl_3$	57.5:42.5	42.5:57.5
CH_2Cl_2	62.5:37.5	27.5:72.5
CCl_4	51.5:48.5	43.5:56.5

[a] Reaction performed at room temperature.

The influence of the substrate on the selectivity of the iodolactonization was then investigated by a series of different substituted unsaturated carboxylic acids of type **21**.

Compounds **21** have been synthesized by Suzuki reactions[19] using 4-bromo-4-pentenoic acid ethyl ester[20] and appropriate boronic acids and subsequent basic cleavage of the ethyl ester. The different acids and the iodolactonizations leading to compounds **22** are shown in Scheme 2.

Scheme 2. Stereoselective Lactonization of Substituted Carboxylic Acid Derivatives **21**



From the results described in Table 4 it is obvious that electron-withdrawing substituents at the 4-position of the aromatic moiety lead to an increase in selectivity. The intermediate iodonium ion is less stabilized and more reactive. This finding can be rationalized with an altered

Table 4. Substituted Carboxylic Acids **21** in Iodolactonization Reactions

acid	**22** er	acid	**22** er
21a	26:74	**21d**	36.5:63.5
21b	25.5:74.5	**21e**	45:55
1	27.5:72.5	**21f**	50:50
21c	29.5:70.5	**21g**	50:50

---

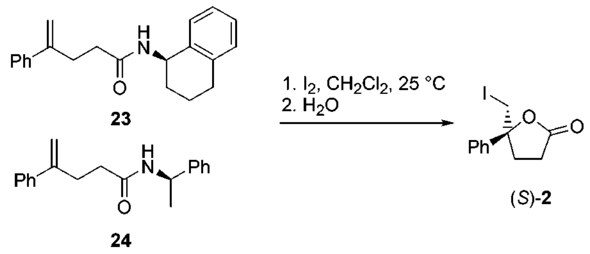
[18] The formation of a 1:1 complex was found by generating a Job plot by continuous variation of concentration. (a) Job, P. *Ann. Chem.* **1928**, *9*, 113. (b) MacCarthy, P. *Anal. Chem.* **1978**, *50*, 2165.

geometry of the intermediate iodonium ion formed,[21] which obviously affects the orientation of the chiral reagent and influences the selectivity. Unsaturated carboxylic acids with an aliphatic substituent (**21f**, **21g**) only led to racemic iodolactone in the cyclization reactions.

Finally, we prepared the unsaturated chiral amides **23** and **24** (Scheme 3). Using these compounds in *substrate*-controlled iodocyclizations, we could demonstrate that the induction is smaller (er 55.5:44.5 and 65:35, respectively, of (*S*)-**2**) than using the reagent complex ICl:amine described above. It is interesting to see the opposite absolute configuration in iodolactone **2** synthesized from **1** using **6** as a chiral ligand (Table 2, amine **6**) and from amide **23** using the same amine as a chiral auxiliary.

In conclusion, we have developed a new protocol for *reagent*-controlled stereoselective iodolactonizations. This method uses commercially available primary amines as the chiral source together with ICl as a powerful source of I^+. The nature of the reactive complex and further studies to optimize the reaction are in progress.

Scheme 3. Chiral Amides **23** and **24** in Substrate-Controlled Iodocyclizations



Acknowledgment. We thank Prof. Olaf G. Wiest (University of Notre Dame) and Martin Spichty (University of Basel, Switzerland) for discussing theoretical aspects of this project and the Swiss National Foundation for financial support.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0171113

---

(19) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(20) Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447.

(21) De La Mare, P. B. D. In *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1976.