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Asymmetric Iodolactonization Utilizing Chiral Squaramides

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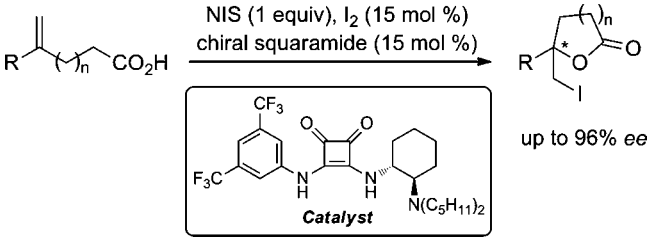
ABSTRACT



Asymmetric iodolactonization of γ- and δ-unsaturated carboxylic acids has been explored in the presence of six different chiral organocatalysts 5−8. The catalyst 6b was found to facilitate the cyclization of 5-arylhex-5-enoic acids 1 to the corresponding iodolactones 2 with up to 96% *ee*. By this protocol, unsaturated carboxylic acids are converted enantioselectively to synthetically useful δ-lactones in high yields using commercially available NIS. Apparently, both hydrogen bonding and aryl/aryl interactions are important for efficient stereodifferentiation.

Halolactonization, the intramolecular cyclization that ensues as proximally unsaturated acids react through an incipient halonium ion, is a powerful synthetic transformation.[1] Approximately 60 years ago, Woodward and Singh demonstrated its relevance in total synthesis by staging halolactonization as a linchpin feature in the synthesis of the natural product *allo*-patulin.[2] During the intervening time, several eminent examples have appeared in the literature,[3] and halolactonization is now a well-established tool in total synthesis.[4,5] Over the past 30 years, development of asymmetric versions of halolactonization, in terms of substrate controlled reactions, has been met with considerable success.[6] However, asymmetric versions under reagent control, in particular catalytic processes, have proven more difficult to realize.[7] Although good asymmetric induction can be achieved when chlorine or bromine is involved,[8] the catalytic enantioselective iodolactonization has only recently been communicated.[9]

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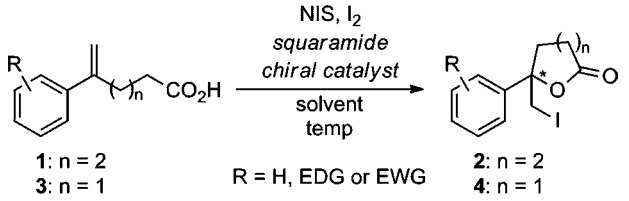
Preceding the rendition given here, the highest level of stereocontrol had been obtained based on a tentative H-bonding motif being present in the organocatalyst, which used a urea scaffold.[9c] The increased attention on squaramides as a novel H-bonding catalophore for asymmetric synthesis[10−13] prompted us to investigate their ability to promote enantioselective iodolactonization (Scheme 1).

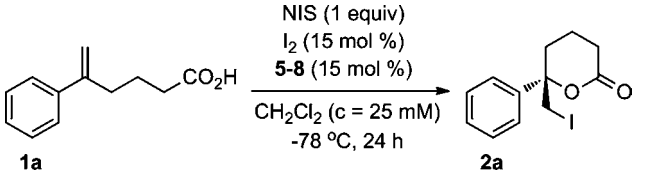
Scheme 1. Development of Asymmetric Iodolactonization Utilizing Chiral Squaramide Organocatalysts



In our study of iodolactonization, δ-unsaturated acid **1a** (R = H) was selected as a model substrate for protocol development (Table 1). A collection of squaramides **5**−**8** was prepared (see Supporting Information) and subjected to screening (Figure 1). Having prenominated dichloromethane as the reference solvent, the reactions were run at −78 °C for 24 h with a fixed starting concentration of 25 mM. Equimolar amounts of substrate and *N*-iodosuccinimide (NIS) were used, while the catalyst loading and the I_2 additive were both held at 15 mol %.

Based on the initial findings, it was evident that squaramide **6a** and **6b** were practically equipotent and provided the best asymmetric induction (entries 3 and 4). Conversely, among the squaramides **5**−**6**, the presence of a benzyl motif proved vastly inferior to the aryl motif (entries 1 and 2). Further insight into the catalytic activity of the catalophore was gained by subsequently omitting or modifying certain structural features. In the absence of a benzyl or a phenyl motif, squaramide **7** displayed some weak intrinsic asymmetric induction conferred by the chiral diamino

Table 1. Catalyst Screening of Squaramides **5**−**8** in the Reaction between δ-Unsaturated Acid **1a** and NIS/I_2



1a 2a

entry[a]	catalyst	yield (%)[b]	*ee* (%)[c]
1	**5a**	83	8
2	**5b**	84	10
3	**6a**	74	43
4	**6b**	81	42
5	**7**	15	11
6	**8**	85	0

[a] The reactions were performed on a 0.2 mmol scale. [b] Isolated material. [c] Determined by HPLC analysis using commercial chiral columns.

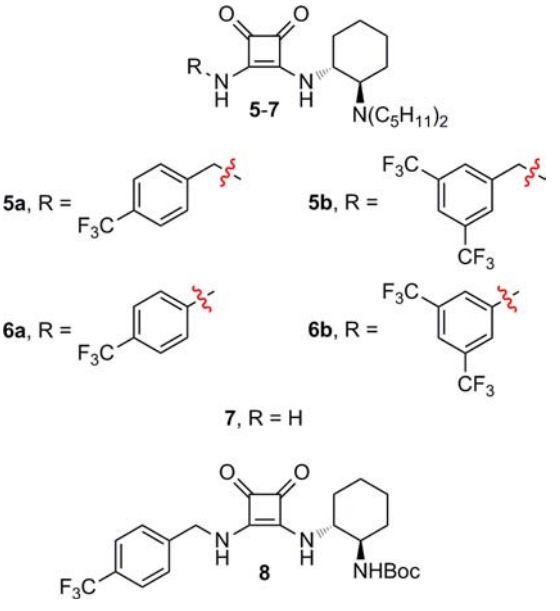


Figure 1. Squaramide catalysts investigated in this study.

functionality (entry 5). On the other hand, when the chiral diamino moiety itself was altered, interchanging the tertiary amine for a carbamate, racemic **2a** was obtained (entry 6).

Having identified seemingly suitable catalysts, the enantioselectivity was subsequently examined in terms of solvent effects (Table 2). In the first run (entries 1−12), squaramide **6a** was assessed. Among the solvents tested it was found that, whereas acetone was conducive for obtaining higher *ee*-values (entry 9), dichloromethane provided a better chemical yield (entry 1). By combining the two solvents it was possible to retain the achieved *ee*-value

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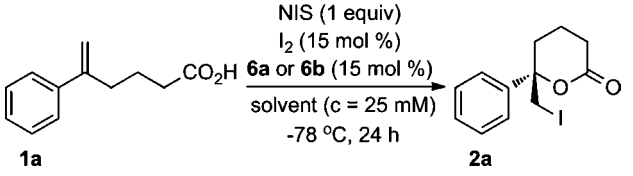
while increasing the chemical yield (entry 12). However, it became clear that squaramide **6a** could not be easily swayed to deliver iodolactone **2a** beyond 54% *ee*. Thus, in a second run, squaramide **6b** was assessed (entries 13−16). Gratifyingly, when the reaction was performed in acetone (entry 14), the difference between the catalysts was demonstrable, as iodolactone **2a** could be obtained in 80% *ee*, albeit in moderate chemical yield. Employing the precognized solvent combination of acetone/dichloromethane effectively enhanced the chemical yield (entry 15).

Table 2. Solvent Screening in the Squaramide Catalysed Asymmetric Reaction of δ-Unsaturated Acid **1a** with NIS/I_2



entry[a]	catalyst	solvent	yield (%)[b]	*ee* (%)[c]
1	**6a**	CH_2Cl_2	74	43
2	**6a**	$CHCl_3$[d]	72	21
3	**6a**	toluene	75	37
4	**6a**	hexane	0	n.d.
5	**6a**	DMF[d]	0	n.d.
6	**6a**	THF	11	41
7	**6a**	Et_2O	8	9
8	**6a**	EtOAc	65	45
9	**6a**	acetone	56	53
10	**6a**	EtOH	9	7
11	**6a**	*i*-PrOH	0	n.d.
12	**6a**	acetone/CH_2Cl_2 1:1	86	54
13	**6b**	CH_2Cl_2	81	42
14	**6b**	acetone	60	80
15	**6b**	acetone/CH_2Cl_2 1:1	84	81
16	**6b**	acetone/toluene 1:1	74	80

[a] The reactions were performed on a 0.2 mmol scale. [b] Isolated material. [c] Determined by HPLC analysis using commercial chiral columns. [d] The reaction was performed at −61 °C.

Finally, a screening was performed in order to examine the effects of concentration, additives, and catalyst loading (Table 3). The best result was achieved when the concentration was quadrupled, using 1:1 acetone/dichloromethane (entry 9), yielding iodolactone **2a** in 87% *ee* and 83% chemical yield.

The constellation of *N*-iodoimides and I_2 in the presence of protic acid has been shown to render a triiodide cation,[14] which promotes the iodolactonization at low temperature.[9c] For our purpose, commercial NIS and I_2 was sufficient to achieve the desired transformation within 24 h. Nonetheless, the reaction proved to be sensitive in one respect; the ratio between NIS, I_2, and catalyst was of importance. Deviation from the established conditions

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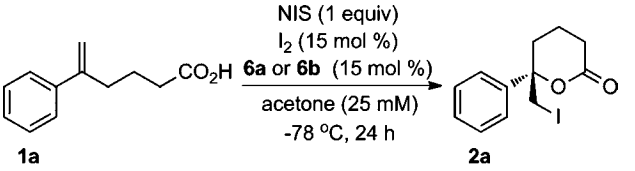
Table 3. Screening of Conditions in the Squaramide Catalyzed Asymmetric Reaction of δ-Unsaturated Acid **1a** with NIS/I_2



entry[a]	catalyst	conditions	yield (%)[b]	*ee* (%)[c]
1	**6a**	30 mol % cat.	30	57
2	**6a**	2.0 equiv NIS	53	47
3	**6b**	30 mol % cat.	60	87
4	**6b**	1 mol % I_2	6	71
5	**6b**	30 mol % I_2	81	70
6	**6b**	*c* = 0.1 M	74	87
7	**6b**	*c* = 0.2 M	72	87
8	**6b**	30 mol % cat., *c* = 0.1 M	70	87
9	**6b**	*c* = 0.1 M, 50% v/v CH_2Cl_2	83	87
10	**6b**	as entry 9 but w. 100 mol % cat.	64	85
11	*ent*-**6b**	*c* = 0.1 M, 50% v/v CH_2Cl_2	79	82[d]

[a] The reactions were performed on a 0.2 mmol scale. [b] Isolated material. [c] Determined by HPLC analysis using commercial chiral columns. [d] Antipodal **2a** was formed with opposite stereochemistry.

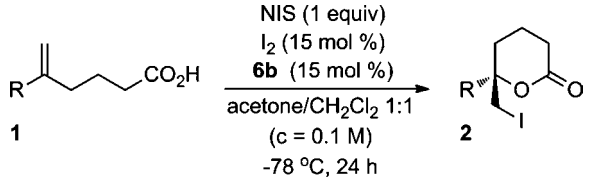
was generally followed by a decrease in *ee* (entries 2, 4, and 5).

At the outset, it was found that squaramides **5**−**6** only dissolved poorly in a range of organic solvents. This raised the question as to whether the reaction at low temperature proceeded in a heterogeneous or homogeneous fashion. However, when δ-unsaturated acid **1a** was added to a suspension of squaramide **6b** in acetone/dichloromethane, instantaneous dissolution occurred. Thus, the aggregate of substrate and catalyst is highly soluble. Presumably, δ-unsaturated acid **1a** and squaramide **6b** form an ion pair through an acid/base reaction. This is substantiated by the fact that squaramide **6b** also dissolves easily in acetic acid and acidified acetone. To corroborate whether the catalyst was indeed performing at its optimum under the given conditions, a 1:1 mixture of δ-unsaturated acid **1a** and squaramide **6b** was subjected to reaction. The good correspondence between the catalytic and stoichiometric experiments (entries 9 and 10) instilled confidence in the procedure.

After having established satisfactory conditions for the asymmetric conversion of δ-unsaturated acid **1a** to the corresponding iodolactone, the scope of the protocol was tested against a series of different substrates (Table 4). As the results were accrued a causal connectivity became evident, demonstrating that the enantioselectivity was subject to electronic modulation.

When δ-unsaturated acid **1** contained an electron-deficient aryl moiety, the asymmetric induction was elevated compared to the reference substrate and iodolactones **2e**−**2g** were obtained in 90 to 96% *ee*. Juxtaposed, an electron-rich aryl moiety caused the level of asymmetry to

Table 4. Asymmetric Reaction of δ-Unsaturated Acid **1** with NIS/I_2 Catalyzed by Squaramide **6b**



entry[a]	R-groups in **1** and **2**	yield of **2** (%)[b]	*ee* of **2** (%)[c]
1	**1a**, **2a**: phenyl	83	87
2	**1b**, **2b**: 2-naphthyl	91	92
3	**1c**, **2c**: *p*-tolyl	80	86
4	**1d**, **2d**: *p*-anisyl	87	12
5	**1e**, **2e**: *p*-fluorophenyl	83	90
6	**1f**, **2f**: *p*-chlorophenyl	78	96
7	**1g**, **2g**: *p*-bromophenyl	73	91
8	**1h**, **2h**: *i*-propyl	77	16

[a] The reactions were performed on a 0.2 mmol scale. [b] Isolated material. [c] Determined by HPLC analysis using commercial chiral columns.

be severely demoted and **2d** was obtained in only 12% *ee*. Interestingly, while the presence of a *p*-tolyl moiety in δ-unsaturated acid **1** was comparable to a phenyl, 86% *ee* for **2c** and 87% *ee* for **2a** respectively, the presence of a 2-naphthyl caused the level of asymmetry to rise to 92% *ee* for **2b**. Whether the latter can be attributed to steric encumbrance or aryl/aryl interaction between the substrate and catalyst is an open question. It was observed, however, that the replacement of an aryl group with an isopropyl group was detrimental to the enantioselectivity, with only 16% *ee* for **2h**. This could be taken to indicate the necessity of aryl/aryl interactions for efficient stereodifferentiation.

Next, we turned our attention toward applying squaramide **6b** to γ-unsaturated acid **3** (Table 5). For kinetic reasons,[15,16] the transition from δ-iodolactone **2** to γ-iodolactone **4** was anticipated as a more challenging asymmetric transformation, in view of the poor induction obtained with reactive substrate **1d** (*vide supra*).

As the experiments were conducted, this premonition was echoed in the results. Thus, when γ-unsaturated acid **3** only contained a phenyl group, the stereochemical outcome was diminutive, with 7% *ee* for **4a**. The result was somewhat ameliorated when γ-unsaturated acid **3** carried an electron-deficient aryl moiety, yielding 14% *ee* for **4b**. However, based on these findings, the constellation of substrate and catalyst clearly needs to be evaluated anew in order to deliver γ-iodolactones **4a** and **4b** with

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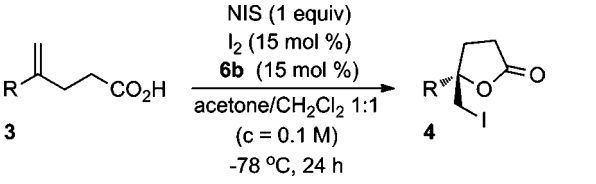
Table 5. Asymmetric Reaction of γ-Unsaturated Acid **3** with NIS/I_2 Catalyzed by Squaramide **6b**



entry[a]	R-groups in **3** and **4**	yield of **4** (%)[b]	*ee* of **4** (%)[c]
1	**3a**, **4a**: phenyl	86	7[d]
2	**3b**, **4b**: *p*-chlorophenyl	85	14

[a] The reactions were performed on a 0.2 mmol scale. [b] Isolated material. [c] Determined by HPLC analysis using commercial chiral columns. [d] Apparent inversion of configuration by HPLC analysis.

acceptable enantioselectivity. The lack of a rigid fit between the substrate and catalyst in the stereodifferentiating step is borne out by an apparent configurational inversion of iodolactone **4a** relative to iodolactone **4b**. Yet, the assignment of iodolactones **4a** and **4b** is substantiated by a previous report of the compounds.[9c]

Bromolactonization of δ-unsaturated acids **1** catalyzed by squaramide **6b** is currently under investigation. The preliminary findings have revealed a more sluggish reaction with moderate asymmetric induction: Cyclization of acid **1a** in the presence of *N*-bromosuccinimide (NBS) afforded the corresponding δ-bromolactone in 58% *ee* and 30% chemical yield after 24 h. Thus, the protocol featured in this communication does not translate directly to efficient asymmetric bromolactonization.

In conclusion, we have developed a highly enantioselective protocol for iodolactonization of δ-unsaturated acids by the use of the novel squaramide **6b** as an efficient organocatalyst. Our approach compares favorably with those already published in terms of enantioselectivity,[9a,b,d] substrate concentration, reaction time, and simplicity of execution.[9c]

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Supporting Information Available. Experimental procedures and characterization data, $^1H-^{13}C$ NMR, MS, and HRMS spectra as well as chromatograms of HPLC and GLC analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.