Novel Cyclization Approaches for the Syntheses of Sultones, Sultames and Cyclopropanes

Masterarbeit
zur Erlangung des akademischen Grades

Diplom-Ingenieurin
im Masterstudium

Technische Chemie

April 2017
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Eidesstattliche Erklärung

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Die vorliegende Masterarbeit ist mit dem elektronisch übermittelten Textdokument identisch.

Linz, April 2017

Christina Gaunersdorfer
Acknowledgement

I would like to express my sincere gratitude to my supervisor Prof. Dr. Mario Waser who supported me throughout the process of this master thesis. I am thankful for his motivation, great patience and friendly advice during the project work. Without his guidance and persistent help this thesis would not have been possible.

Furthermore, I would like to thank all members of the Department of Organic Chemistry who gave the permission to use the required equipment and the necessary materials to complete this thesis.
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Zusammenfassung

Das primäre Ziel dieser Masterarbeit war die Synthese von δ-Sultonen und δ-Sultamen via in situ gebildeter Sulfene über Cycloadditionsreaktionen unter Verwendung unterschiedlich substituierte Sulfonychloride, Metalltriflate sowie achiraler und chiraler Stickstoffbasen.

Ein weiteres Ziel war die Synthese von Trifluoroacetyl substituierten Cyclopropanen über Ammonium Ylide.


Bei Versuchen der asymmetrischen Synthese mithilfe chiraler Stickstoffbasen konnte kein Sulton synthetisiert werden.

Die Herstellung der δ-Sultame mit N-Tosylimin und Sulfonylchlorid bei gleichen Reaktionsbedingungen erwies sich als deutlich schwieriger realisierbar. Lediglich bei -80 °C in Dichlormethan mit DABCO und unter Indiumkatalyse konnten Spuren des erwünschten Produktes mittels ¹H-NMR detektiert werden.

Der letzte Teil dieser Arbeit beschäftigt sich mit der Synthese von neuartigen Cyclopropanen, die mittels Trifluorketon und unterschiedlicher Ammonium Ylide erfolgreich hergestellt werden konnten. Alle durchgeführten Reaktionen weisen einen
kompletten Umsatz und Ausbeuten von 36 bis 73 % auf, wobei jeweils zumindest zwei Diastereomere gebildet wurden, die teilweise mittels Säulenchromatographie voneinander getrennt werden konnten.
Abstract

The main target of this Master Thesis was the synthesis of δ-sultones and δ-sultames via in situ formed sulfenes by cycloaddition reactions using differently substituted sulfonylchlorides, metaltriflates as well as achiral and chiral nitrogen bases.

A further target was the synthesis of novel trifluoroacetyl substituted cyclopropanes using ammonium ylides.

For the synthesis of sultones, β-γ-unsaturated-α-ketoester, vinylketones, α-methylenketoester as well as fluoro substituted ketones were prepared, whereby the desired product could be isolated using one specific ketoester only.

Various Lewis acids were added to the reaction due to their activating effect and tested on the catalytic activity. In attempts with copper(I)-, copper(II)-, zinc(II)-, scandium(III)- and indium(III)triflate the last two resulted to be the most effective catalysts. In order to optimize reaction conditions the influence of the solvent on the synthesis was also investigated. The performance of the reaction in CH₂Cl₂ and THF resulted in highest yields.

Using DABCO as an achiral base and ethanesulfonylchloride the desired δ-sultone could be synthesized with a diastereomeric ratio of 3:1. Due to a simultaneously occurring rearrangement reaction of the double bond in the ring a diastereomerically pure second product was formed. The desired as well as the through rearrangement formed sultone could be isolated under catalysis with indium and scandium in THF at -15 °C in a ratio of 2:1 and 4:1 respectively with yields of 42 % (conversion ≥ 97 %).

Concerning asymmetric synthesis via chiral nitrogen bases no sultone could be synthesized.

The preparation of δ-sultames with N-tosylimine and sulfonylchloride at identical reaction conditions resulted to be more difficult to realize. Only at -80 °C in dichloromethane with DABCO and catalysed by indiumtriflate traces of the desired product could be detected with ¹H-NMR.

The last part of this work is about the synthesis of a new class of cyclopropanes which could be prepared successfully with trifluoroketone and various ammonium ylides. All of the performed reactions show full conversion and yields of 36 to 73 %, whereby at least two diastereomers were formed which could be separated partly via chromatographic purification.
1. Introduction

1.1. Sultones

In 1888 the term “sultone” appeared for the first time by Erdmann who defines them as cyclic esters of hydroxyl sulphonic acids which are therefore the analogues to lactones [1]. Many 4- to 6- ring sultones are known as well as a few larger ones [2]. These molecules are of high interest concerning natural product synthesis [3] and medical chemistry. They have been successfully applied in combats of diseases like human immunodeficiency virus type 1, HIV-1 [4]. Another application is their addition to electrolytes in lithium-ion batteries [5].

Preparation of sultones

- Via elimination

The first approaches for the synthesis of sultones were performed by Mustafa and Williams in the middle of the 20th century. As illustrated in Scheme 1 the product 2 could be isolated by distillation of sulfonic acids (1). The elimination of hydrogen halides or water occurred under reduced pressure whereby the sultone could be distilled due to lower molecular weight. Using this method a high number of saturated γ- and δ-sultones (2) as well as pentane-1, 5 sultone, a 7-ring sultone could be synthesized. [2, 6-8]

\[
\text{Scheme 1: Synthesis of sultones via distillation [2].}
\]

- Via Diels-Alder

Metz describes the synthesis of δ-sultones illustrated in Scheme 2 via Diels-Alder reaction. The cycloaddition can be performed in toluene at reflux with BHT or in CH₂Cl₂ under pressure of 12 kbar at room temperature. With a bulky group for R₂ the exo product (5) is preferably formed due to sterical reasons. For R₂ = Me products 5 and 6 are formed in a ratio of 4.7:1 respectively. For R₂ = SiMe₃ the exo product (5) is formed almost exclusively. Applying pressure would favor the formation of the endo
product (6) because of a more compact transition state but there is still a high impact of steric hindrance wherefore both diastereomers are formed. [9]

Scheme 2: Synthesis of δ-sultones via Diels-Alder reaction [9].

- Via sulfenes

Ketenes are frequently used in asymmetric catalysis due to their versatile applicability for stereoselective syntheses. Sulfenes, the sulfonyl analogues to ketenes, are interesting building blocks for the syntheses of enantiopure sulfonyl derivates which are important in medicinal chemistry. Nevertheless sulfenes have been hardly used due to their high instability. They tetramerize very rapidly so they cannot be isolated. [10] Their existence is only proven spectroscopically by IR at -196 °C [11].

The synthesis of β-sultones via sulfenes as illustrated in Scheme 3 can be performed in CH$_2$Cl$_2$ at -15 °C. Depending on the chirality of the base either a racemic diastereomerically pure mixture or products with excellent d.r. and good e.r. are obtained. In the first case 1 eq of quinuclidine as nucleophile or catalytic amounts of that base together with 1 eq of the non-nucleophilic iPr$_2$Net were added to educts 7 and 8 whereby yields of 76 to 89 % were obtained. Approaches with chiral bases resulted in yields of 2 to 23 % only and very low enantioselectivity. These values could be increased by the addition of Lewis acids as activating co-catalysts. Screening reactions showed highest yields and best e.r. values for the chiral catalyst (DHQ)$_2$PYR (hydrochinin 2,5-diphenyl-4,6-pyrimidinediyli diether), an equimolar amount of the base PMP (1,2,2,6,6-pentamethyipiperidine) and In(OTf) or Sc(OTf) as co-catalyst. Increasing the size of R of the sulfonylchloride from a methyl group to MeOC$_6$H$_4$O(CH$_2$)$_2$ resulted in higher e.r. values. [12-13]
Scheme 3: Syntheses of β-sultones [12].

The conditions found to be best for the synthesis of β-sultones when using chloral as starting material (Scheme 3) were also successfully applied for the reaction with ethyl glyoxylate as illustrated in Scheme 4 [12].

Concerning the cycloaddition there are two competitive mechanisms for the role of the amine proposed as illustrated in Scheme 5. Scenario I describes the formation of a sulfene-amine adduct (13) whereas the amine can also attack the chloral in order to generate a zwitterionic intermediate (15) as illustrated in scenario II. The formed chloral-amine adduct 15 reacts further with sulfonyl chloride 7 or the zwitterion 13. [12]
- **Via alkenols by photoredox catalysis**

Recent literature describes a synthesis for α-substituted trifluoromethylated sultones (18) via a photoredox catalyzed reaction as illustrated in Scheme 6. 4- to 7-ring sultones can be obtained in a one-step reaction using an alkenol (16), trifluorosulfonyl chloride and [Cu(dap)₂]Cl as catalyst in MeCN with an irradiation at 530 nm. The highest yields were obtained for γ- and δ-sultones with 64 % and 90 %, respectively. [14]
Applications of sultones

Sultones are mainly used as intermediates for ring-opening reactions. The addition of nucleophiles to the heterocycles leads to a cleavage of the carbon-oxygen bond wherefore they are of particular importance concerning the introduction of a sulfonic acid group. One example of an application for γ-sultones is the synthesis of α-phenyl-γ-hetero-substituted isopropyl sulphonates (22) reported by Enders and Iffland. As illustrated in Scheme 7 this asymmetric reaction can be performed in three steps. Adding different nucleophiles to the γ-sultone (19) in DMF or DMSO the enantiopure starting material undergoes a stereospecific ring-opening reaction. The sulfonate salts (20) are converted to sulfonic acids (21) under treatment with HCl and methanol. The following esterification step with triisopropyl orthoformate in dichloromethane results in sulphonates (22) in overall yields of 65-86 % as well as high de and ee values. [15]

\[
\text{Scheme 7: Synthesis of isopropyl sulphonates via ring-opening reactions [15].}
\]

Concerning β-sultones Koch and Peters describe the syntheses of β-hydroxysulfonyl derivates by regioselective ring-opening reactions using alcohols, amines and Grignard-reagents. These products are of high interest regarding their effects on deseases like diabetes, Alzheimer and vascular deseases. The reaction conditions for the synthesis of β-hydroxy-sulphonates (24, 27), -sulphonamides (28), -sulfones (23) and acids (29) are illustrated in Scheme 8. The trichlorogroup can be reduced...
partially with Bu$_3$SnH, increasing the use of chlorcontaining staring materials. With this approach Koch and Peters found an enantio- and diastereoselective method to synthesize enantioenriched β-hydroxysulfonyl derivates. [12]

**Scheme 8:** Synthesis of β-hydroxysulfonyl derivates by regioselective ring-opening reactions using β-sultones [12].

Furthermore Koch and Peters found methods for the chemoselective reductions of β-sultones (9). Due to high ring strain a cleavage of the S-O or the C-O bond is possible, synthesizing either β-hydroxy sulfinic acids (32) or allylsulfonic acids (31), respectively (Scheme 9). [16]

**Scheme 9:** Chemoselective reduction of -sultones [16].
1.2. Sultames

First approaches to synthesize β-sultams were carried out as illustrated in Scheme 10 with quinuclidine as nucleophilic achiral catalyst, an excess of the non-nucleophilic base iPr₂Net in CH₂Cl₂ at -80 °C and resulted in high yields of 88% and a cis-diastereoselectivity of 18:1 [17].

![Scheme 10: Enantioselective synthesis of β-sultams][1]

Products are obtained only under the addition of a nucleophilic base as catalyst. The proposed mechanism is illustrated in Scheme 11 [17].

![Scheme 11: Proposed mechanism for the synthesis of β-sultams][2]

Concerning an analogous asymmetric synthesis quinuclidine was exchanged by different chiral Cinchona alkaloid derivatives with highest yields and stereoselectivity for quinine (Q) and cinchonidine (Cd). As illustrated in Table 1 for R ≥ Et quinine works best regarding yield and diastereoselectivity whereas for ethanesulfonylchloride it is the nucleophilic base Q₂PYR. The structures of the used catalysts 40 and 41 are illustrated in Scheme 12.
Scheme 12: Catalysts for asymmetric synthesis of β-sultams [17].

Table 1: Synthesis of β-sultams using various sulfonyl chlorides [17].

<table>
<thead>
<tr>
<th>R</th>
<th>Catalyst</th>
<th>Yield / %</th>
<th>d.r.</th>
<th>ee / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Et</td>
<td>Q</td>
<td>82</td>
<td>20:1</td>
<td>79</td>
</tr>
<tr>
<td>2 Et</td>
<td>Cd</td>
<td>78</td>
<td>19:1</td>
<td>81</td>
</tr>
<tr>
<td>3 nPr</td>
<td>Q</td>
<td>81</td>
<td>18:1</td>
<td>91</td>
</tr>
<tr>
<td>4 nPr</td>
<td>Cd</td>
<td>70</td>
<td>18:1</td>
<td>91</td>
</tr>
<tr>
<td>5 (CH₂)₂Cl</td>
<td>Q</td>
<td>78</td>
<td>11:1</td>
<td>94</td>
</tr>
<tr>
<td>6 (CH₂)₂Cl</td>
<td>Cd</td>
<td>36</td>
<td>10:1</td>
<td>93</td>
</tr>
<tr>
<td>7 CH₂Ph</td>
<td>Q</td>
<td>94</td>
<td>21:1</td>
<td>94</td>
</tr>
<tr>
<td>8 (CH₂)₂OC₆H₄-p-OMe</td>
<td>Q</td>
<td>95</td>
<td>13:1</td>
<td>87</td>
</tr>
<tr>
<td>9 Me</td>
<td>Q₂PYR</td>
<td>80</td>
<td>17:1</td>
<td>-80*</td>
</tr>
</tbody>
</table>

*The (S,S)-enantiomer is formed.
1.3. Cyclopropanes

Cyclopropanes are the smallest cyclic molecules having a high significance as building blocks in natural and non-natural compounds [18-19].

Preparation of cyclopropanes

Some general strategies for cyclopropanation are the following reactions:

- Michael addition and ring closure

One possibility for the synthesis of cyclopropanes is the nucleophilic attack of a leaving group to an alkene bearing an electron withdrawing group. The ring closure is performed under expelling a leaving group (Scheme 13). [20]

\[
\begin{align*}
\text{EWG} \xrightarrow{\text{RCH-LG}} \text{EWG} & \quad \text{EWG} \quad \text{R} \\
\text{EWG} \quad \text{LG} & \quad \text{EWG} \quad \text{LG} \\
\end{align*}
\]

**Scheme 13:** Cyclopropanation via Michael addition [20].

- Simmons-Smith reaction

In this reaction illustrated in Scheme 14 diiodomethane and a zinc/copper mixture form an organozinc compound first, which reacts with an olefin (48) to generate a cyclopropane (49) and zinciodid (Scheme 15). [21, 22]

\[
\begin{align*}
\text{48} & \xrightarrow{\text{CH}_2\text{I}_2, \text{Zn(Cu)} \quad \text{Et}_2\text{O}} \quad \text{35 °C} \\
& \quad \text{48 %} \\
\end{align*}
\]

**Scheme 14:** Cyclopropanation via Simmons-Smith reaction [21].
• Via Corey-Chaykovsky Cyclopropanation

Starting from trimethylsulfoxonium iodide the sulfene 53 is generated in situ using a strong base. The first step of the Corey-Chaykovsky reaction is the addition of the ylide toward the double bond followed by ring closure to form the cyclopropane 55 (Scheme 16).

Scheme 16: Corey-Chaykovsky cyclopropanation [23].

CF₃-containing cyclopropanes

The incorporation of a trifluoromethyl group into organic molecules leads to a dramatic change in chemical, physical and biological properties due to the high electronegativity of fluorine which results in a strong C-F bond [18-19]. Recent literature describes the synthesis of trifluoroacetyl substituted cyclopropanes 58 as illustrated in Scheme 17 in ethylene dichloride at 60 °C for 12 hours via α-elimination of in situ generated 2-iodo-difluoroacetyl ethyl acetate (60). Therefore starting material 56 is treated with I₂ and benzoyl peroxide as oxidant, then deprotonated with a base to form the anion 61. The carbene 62 which is formed under expelling iodide reacts with the alkene 57 to form a cyclopropane (58). [24]

Scheme 17: Proposed mechanism for cyclopropane 58 [24].
Another example for the synthesis of trifluoroacetyl substituted cyclopropanes is illustrated in Scheme 18. DABCO is used as catalyst to form the ylide 65 which attacks the double bond of 63. Elimination of DABCO leads to the cyclopropane 67 in a yield of 57%. [25]

Scheme 18: Proposed mechanism for cyclopropane 67 [25].
2. Objectives

Only few studies have investigated the asymmetric synthesis of sulfonyl derivates which are of increasing importance concerning their applications as building blocks in medical chemistry. The preparation via sulfenes and ring-opening reactions of sultones or sultames could be a resource-efficient pathway.

In this context the synthesis of sultones and sultames is an interesting field in organic chemistry.

As already discussed in chapter 1.1 β-sultones and β-sultames can be synthesized as illustrated in Scheme 19.

Recent literature:

Scheme 19: Asymmetric synthesis of β-sultones and β-sultames.

The target of this work was the synthesis of δ-sultones and δ-sultames by reacting an in situ formed sulfene with an \( \alpha,\beta \)-unsaturated acceptor as illustrated in Scheme 20.

This work:

Scheme 20: Syntheses of δ-sultones and δ-sultames in this work.
In addition to versatile applications of cyclopropanes and a high interest in CF$_3$-containing molecules a further target of this work was the synthesis of a new class of trifluoroacetyl substituted cyclopropanes as illustrated in Scheme 21.

Scheme 21: Synthesis of CF$_3$-containing cyclopropanes using ammonium ylides.
3. Results and discussion

3.1. Preparation of starting materials

Preparation of \( \gamma \)-aryl-\( \beta \)-\( \gamma \)-unsaturated-\( \alpha \)-ketoesters (77a-c)

\[
\text{74a-c} + \text{75} \xrightarrow{\text{KOH (1.5 eq)}} \xrightarrow{\text{MeOH}} \text{76a-c} \xrightarrow{\text{Cl}^{-}(3 \text{ eq})} \xrightarrow{\text{MeOH}} \text{77a-c}
\]

Scheme 22: Synthesis of 77a-c.

Table 2: Synthesis of 77a-c.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Overall yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-H</td>
<td>77a</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>-OME</td>
<td>77b</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>-Br</td>
<td>77c</td>
<td>60</td>
</tr>
</tbody>
</table>

The syntheses of potassium salts (-) 77a-c illustrated in Scheme 22 and Table 2 could be performed as described in literature [26-27] with good yields of 72 % to 89 % compared to 83 % which are stated in literature [26-27]. The crude products were used without any further purification. The second step, the esterification, was carried out in analogy to literature [27] using 3 eq acetylchloride in methanol at a concentration of 2.4 mol L\(^{-1}\). Product 77a could be isolated after chromatographic purification with a very low overall yield of only 11 % compared to 41 % in [27]. Analysis by \(^1\)H-NMR showed very high purity for 77b and 77c which were obtained in overall yields of 45 % and 60 %, respectively. In comparison literature [26] using 11.5 eq acetylchloride in methanol with concentrations of 1.3 mol L\(^{-1}\) to 1.7 mol L\(^{-1}\) obtains products 77b and 77c in low overall yields of only 20 % and 17 %.

Preparation of \( N \)-tosyl imines (79a-b)

\[
\text{77a} \xrightarrow{\text{Et}_3\text{N}, \text{TiCl}_4} \xrightarrow{\text{CH}_2\text{Cl}_2} \text{79a-b}
\]

Scheme 23: Synthesis of 79a-b.
Table 3: Synthesis of 79a-b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Educt</th>
<th>R</th>
<th>Product</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77a</td>
<td>-COOMe</td>
<td>79a</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>77d</td>
<td>-Ph</td>
<td>79b</td>
<td>77</td>
</tr>
</tbody>
</table>

Syntheses of 79a and 79b, illustrated in Scheme 23 and Table 3, were carried out in analogy to literature [28]. The obtained yield of product 79a was quite high with 77 % whereas product 79b could be isolated in a low yield of 31 % only. Literature [28] states a yield of 54 % for the N-tosyl imin with a –COOEt group for R.

**Preparation of Phenyl vinylketon (81)**

![Scheme 24: Synthesis of 81.](image)

The elimination reaction, illustrated in Scheme 24, was performed as described in literature [29]. Analysis by $^1$H-NMR showed very high purity for the crude product 81 and a conversion of 100 %, so no further purification was needed.

**Preparation of α-methyleneketoester (84)**

![Scheme 25: Synthesis of 84.](image)

The Mannich α-methylenation of ethyl benzoylacetate (82), which is illustrated in Scheme 25, was carried out in analogy to literature [30]. The obtained yield of 75 % was somewhat lower compared to 99 % reported in literature [30].
Preparation of fluoro substituted ketones

Scheme 26: Synthesis of 70.

Scheme 26 illustrates the synthesis of starting material 70 for the syntheses of different sultones and cyclopropanes. This aldol reaction was carried out in analogy to literature [31]. The reported yields of 30 % to 60 % could not be reached, due to the volatility of the product during concentration under vacuum and problems concerning separation of not reacted benzaldehyde. Analysis by $^1$H-NMR of the crude product showed a conversion of 64 %. Product 70 could be isolated after chromatographic purification with a very low yield of 10 % only.

Scheme 27: Synthesis of 88.

The Knoevenagel condensation illustrated in Scheme 27 was performed as stated in literature [32]. Despite a reasonable conversion of 56 % only a very little amount of product 88 could be isolated due to decomposition during chromatographic purification.

Scheme 28: Synthesis of 93.
The reaction described in Scheme 28 was carried out in analogy to literature [33]. The reported yield of 74 % could not be reached. Due to problems concerning the purification step the product 93 could be obtained in 14 % only.

3.2. Attempted synthesis of sultones using a chalcone as an acceptor

![Scheme 29: Synthesis of sultone 94a.](image)

Table 4: Synthesis of sultone 94a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>DABCO / eq</th>
<th>Lewis acid</th>
<th>T / °C</th>
<th>Conversion / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>Sc(OTf)₃ (36 mol%)</td>
<td>-15</td>
<td>-</td>
</tr>
</tbody>
</table>

Scheme 29 illustrates the attempted syntheses of sultone 94a using chalcone (77d) and sulfonylchloride (7a) as starting material. These [4+2] cycloadditions were carried out in analogy to the conditions reported for 4-ring sultones published recently [12]. As shown in Table 4: Synthesis of sultone 94a, different conditions were chosen but no sultone was formed as indicated by ¹H-NMR. This was presumably the case because chalcone is maybe not reactive enough as an acceptor to undergo this reaction.

3.3. Synthesis of sultones using an α-ketoester-based acceptor

Reactions without using a lewis acid

![Scheme 30: Synthesis of sultone 94a.](image)
The second attempt to synthesize a sultone by this strategy was to use an α-ketoester (77a) as starting material due to its supposed higher reactivity compared to a chalcone. This was also first carried out in analogy to literature [12] but without using a lewis acid. The reaction and the chosen conditions are illustrated in Scheme 30 and Table 5 respectively. Analysis by \(^1\)H-NMR showed that no sultone had been synthesized.

Reactions using different lewis acids and reaction times

![Scheme 31: Synthesis of sultones 94a and 95a.](image)

Table 6: Synthesis of sultones 94a and 95a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfonylchloride / eq</th>
<th>Lewis acid (36 mol%)</th>
<th>T / °C</th>
<th>t / h</th>
<th>Conversion* / %</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>Sc(OTf)(_3)</td>
<td>-10</td>
<td>20</td>
<td>73</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>Sc(OTf)(_3)</td>
<td>-15</td>
<td>72</td>
<td>33</td>
<td>n. d.</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>Cu(OTf)(_2)</td>
<td>-15</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>Cu(OTf)(_2)</td>
<td>-15</td>
<td>96</td>
<td>traces</td>
<td>n. d.</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>Cu(OTf)</td>
<td>-15</td>
<td>96</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>Zn(OTf)(_2)</td>
<td>-15</td>
<td>20</td>
<td>19</td>
<td>n. d.</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>Zn(OTf)(_2)</td>
<td>-15</td>
<td>96</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Conversion refers to the quantity of α-ketoester (77a) used.

To enhance the reactivity of the acceptor the addition of lewis acids was tested next. Sultones 94a and 95a were formed under the use of Sc(OTf)\(_3\) as lewis acid and the reaction conditions illustrated in Scheme 31. Other triflates like copper- or zinc-based only showed little to no conversion as listed in Table 6, entries 4 and 6. Analysis by
$^1$H-NMR showed that two diastereomers of the expected product 94a were formed. Furthermore a diastereomerically pure second product (95a) was detected which was formed due to a simultaneously occurring rearrangement reaction of the double bond in the ring.

**Screening of different solvents**

Scheme 32: Synthesis of sultones 94a and 95a.

Table 7: Synthesis of sultones 94a and 95a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Solvent</th>
<th>T / °C</th>
<th>t / h</th>
<th>Conversion / %</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sc(OTf)$_3$; 36 mol%</td>
<td>CH$_2$Cl$_2$</td>
<td>-10</td>
<td>20</td>
<td>73</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>Sc(OTf)$_3$; 36 mol%</td>
<td>THF</td>
<td>-15</td>
<td>20</td>
<td>44</td>
<td>n. d.</td>
</tr>
<tr>
<td>3</td>
<td>Sc(OTf)$_3$; 36 mol%</td>
<td>DMSO</td>
<td>-15</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Sc(OTf)$_3$; 36 mol%</td>
<td>Acetonitril</td>
<td>-15</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Sc(OTf)$_3$; 36 mol%</td>
<td>CH$_2$Cl$_2$</td>
<td>-15</td>
<td>20</td>
<td>88</td>
<td>31</td>
</tr>
<tr>
<td>9</td>
<td>In(OTf)$_3$; 36 mol%</td>
<td>THF</td>
<td>-15</td>
<td>20</td>
<td>69</td>
<td>n. d.</td>
</tr>
<tr>
<td>10</td>
<td>Sc(OTf)$_3$; 36 mol%</td>
<td>Toluol</td>
<td>-15</td>
<td>20</td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>Sc(OTf)$_3$; 36 mol%</td>
<td>MTBE</td>
<td>-15</td>
<td>44</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>In(OTf)$_3$; 36 mol%</td>
<td>MTBE</td>
<td>-15</td>
<td>44</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>Sc(OTf)$_3$; 1 eq</td>
<td>MTBE</td>
<td>-15</td>
<td>44</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

In a next attempt different solvents were tested. The synthesis of sultones 94a and 95a using different solvents as listed in Table 7 shows that no reaction occurred in DMSO, acetonitrile or MTBE. The use of THF or toluene with 4 eq DABCO leads to moderate conversions of 44 % and 50 % respectively, whereas carrying out the reaction in CH$_2$Cl$_2$ at -15 °C a conversion of 88 % was found to be the most promising solvent.
Reactions using different sulfonyl chlorides

Scheme 33: Synthesis of sultones 94b – d and 95b – d.

Table 8: Synthesis of sultones 94b – d and 95b – d.

<table>
<thead>
<tr>
<th>Entry</th>
<th>DABCO / eq</th>
<th>R</th>
<th>Educt</th>
<th>Lewis acid</th>
<th>Conversion / %</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>6</td>
<td>Ph</td>
<td>In(OTf)$_3$; 1 eq</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>6</td>
<td>Et</td>
<td>In(OTf)$_3$; 1 eq</td>
<td>traces</td>
<td>n. d.</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>4</td>
<td>H</td>
<td>In(OTf)$_3$; 1 eq</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Scheme 33 illustrates the attempted synthesis using different sulfonyl chlorides (7a - b). As listed in Table 8 no sultone could be isolated if R = Ph, Et or H. This reaction does only work with a methyl group for R.

Reactions using different achiral and chiral nitrogen bases

Scheme 34: Synthesis of sultones 94a and 95a.

Table 9: Synthesis of sultones 94a and 95a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base 1</th>
<th>DIPEA</th>
<th>Conversion / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DABCO 1 eq</td>
<td>7 eq</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Base</td>
<td>Amount</td>
<td>Result</td>
</tr>
<tr>
<td>---</td>
<td>--------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>2</td>
<td>DABCO 2 eq</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Quinuclidin 2 eq</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Quinuclidin 1 eq</td>
<td>2 eq</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Quinuclidin 8 eq</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>DBU 8 eq</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Quinine 8 eq</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Quinine 1,5 eq</td>
<td>7 eq</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Quinine 0,25 eq</td>
<td>8 eq</td>
<td>-</td>
</tr>
</tbody>
</table>

Since screening of different lewis acids and solvents was performed successfully, in the next attempts of optimizing this reaction illustrated in Scheme 34: Synthesis of sultones 94a and 95a different bases were tested. Literature [12] describes the achiral synthesis of β-sultones with equimolar amounts of quinuclidine as well as catalytic amounts of that base together with 1 eq of the non-nucleophilic base iPr₂Net. As listed in Table 9 beside quinuclidine (entry 3-5) DABCO and DBU were tested also but no sultone was detected.

Concerning asymmetric synthesis literature [12] uses different quinine derivatives together with a non-nucleophilic base. Experiments with the chiral nitrogen base quinine and the non-nucleophilic base iPr₂Net (Table 9, entry 7-9) did not lead to any product.
Further optimization of the reaction conditions

Scheme 35: Synthesis of sultones 94a and 95a.

Table 10: Synthesis of sultones 94a and 95a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>DABCO / eq</th>
<th>Lewis acid</th>
<th>Solvent</th>
<th>T / °C</th>
<th>Conversion / %</th>
<th>94a:95a</th>
<th>Produkt 94a d.r.:</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>Sc(OTf)₃; 36 mol%</td>
<td>CH₂Cl₂</td>
<td>-10</td>
<td>73</td>
<td>6:1</td>
<td>3:1</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>Sc(OTf)₃; 36 mol%</td>
<td>CH₂Cl₂</td>
<td>-15</td>
<td>88</td>
<td>2:1</td>
<td>3:1</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>Sc(OTf)₃; 36 mol%</td>
<td>THF</td>
<td>-15</td>
<td>80</td>
<td>2:1</td>
<td>3:1</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>Sc(OTf)₃; 1 eq</td>
<td>THF</td>
<td>-15</td>
<td>98</td>
<td>2:1</td>
<td>3:1</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>In(OTf)₃; 1 eq</td>
<td>THF</td>
<td>-15</td>
<td>97</td>
<td>4:1</td>
<td>3:1</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>In(OTf)₃; 36 mol%</td>
<td>THF</td>
<td>-15</td>
<td>69</td>
<td>6:1</td>
<td>2:1</td>
<td>n. d.</td>
</tr>
</tbody>
</table>

Table 10 summarizes the best conditions for the synthesis of sultones 94a and 95a. There is a significant decrease of conversion rate concerning the synthesis illustrated in Scheme 35 by decreasing the amount of DABCO and Lewis acid. Using 4 eq of DABCO and 36 mol% of either In(OTf)₃ or Sc(OTf)₃ the conversion of products 94a and 95a was between 69 % and 88 % which could be increased significantly by using 8 eq DABCO and an equimolar amount of Lewis acid. Furthermore the ratio of the obtained diastereomers for product 94a was determined to be 3:1. The ratio of the two products 94a and 95a, whereby the second one is formed after a rearrangement step, depends on the used Lewis acid. Using Sc(OTf)₃ leads to a ratio of 2:1 of the two products 94a and 95a (Table 10, entry 4). In comparison the use of In(OTf)₃ suppresses the rearrangement reaction (Table 10, entry 5) so that product 95a forms 20 % of the obtained sultones only.
Use of other substrates

Scheme 36: Synthesis of sultones 96a – d and 97a – d.

Attempts of synthesizing a sultone using a methoxy substituted γ-aryl-β-γ-unsaturated-α-ketoester (77b) as illustrated in Scheme 36 with different sulfonyl chlorides (Table 11) and the reaction conditions which worked best for the synthesis of sultones 94a and 95a did not lead to any product.

Scheme 37: Synthesis of sultones 98a – d.

Table 11: Synthesis of sultones 96a – d, 97a – d and 98a – d.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conversion / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>-</td>
</tr>
</tbody>
</table>

In a next attempt phenyl vinylketone (81) was used as substrate for the synthesis of sultones 98a – d. The reaction illustrated in Scheme 37 was performed with different sulfonyl chlorides (Table 11) with 8 eq DABCO and 1 eq of Lewis acid in THF at -15 °C for 20 hours. For none of the chosen conditions sultone 98 was formed.
Scheme 38: Synthesis of sultones 99a-b.

Table 12: Synthesis of sultones 99a-b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conversion / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>-</td>
</tr>
</tbody>
</table>

Reaction of α-methyleneketoster (84) with different sulfonyl chlorides (Table 12) did not lead to any of the expected product 99a, b (Scheme 38).

3.4. Attempted synthesis of sultones using fluoro substituted ketones

Scheme 39: Synthesis of sultones 100.

Table 13: Synthesis of sultones 100 and 101.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base 1</th>
<th>Hünig-Base</th>
<th>Conversion / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chinuclidin 2 eq</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Chinuclidin 1 eq</td>
<td>2 eq</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Chinuclidin 8 eq</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>DABCO 8 eq</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>DABCO 1 eq</td>
<td>7 eq</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>DBU 8 eq</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Chinin 8 eq</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Chinin 1,5 eq</td>
<td>7 eq</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Chinin 0,25 eq</td>
<td>8 eq</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>DABCO 2 eq</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Due to high interest in CF$_3$-containing molecules attempts for the synthesis of sultones were performed using fluoro substituted ketones (70, 88 and 93) as illustrated in Schemes 39, 40 and 41. The reactions with ketones 70 and 93 and sulfonyl chloride 7a were performed with the achiral bases DABCO, quinuclidine and DBU with DIPEA as non-nucleophilic base. Concerning asymmetric catalysis quinine was tested as base (Table 13). For the reaction with substrate 88 one experiment was performed using the conditions which worked best for the synthesis of sultone 94a and 95a. No sultones were detected in any of the described reactions.
3.5. Attempted synthesis of sultames using N-Tosyl imines

![Chemical reaction](image.png)

Scheme 42: Synthesis of sultame 103.

<table>
<thead>
<tr>
<th>Entry</th>
<th>DABCO / eq</th>
<th>Lewis acid</th>
<th>T / °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>Sc(OTf)_3 (36 mol%)</td>
<td>-10</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Sc(OTf)_3 (36 mol%)</td>
<td>-80</td>
</tr>
</tbody>
</table>

Table 14: Synthesis of sultame 103.

The synthesis of sultame 103 using a tosyl protected imine 79b, illustrated in Scheme 42 did not work for the conditions listed in Error! Reference source not found..

![Chemical reaction](image2.png)

Scheme 43: Synthesis of sultame 104.

The product (104) of the reaction illustrated in Scheme 43 could not be isolated but analysis by ^1^H-NMR showed that the sultame 104 was formed in traces.
3.6. Synthesis of CF$_3$-containing cyclopropanes via ammonium ylids

![Scheme 44: Synthesis of cyclopropanes 72a – e and 73a – e.](image)

Table 15: Synthesis of cyclopropanes 72a – e and 73a – e.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Educt</th>
<th>R</th>
<th>Cs$_2$CO$_3$ / eq</th>
<th>Conversion / %</th>
<th>Crude product / %</th>
<th>a : b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>105a</td>
<td>-NEt$_2$</td>
<td>6</td>
<td>100</td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>105a</td>
<td>-OEt</td>
<td>2</td>
<td>100</td>
<td>42</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>105b</td>
<td>-Ph</td>
<td>2</td>
<td>100</td>
<td>66</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>105c</td>
<td>-C$_6$H$_4$Cl</td>
<td>2</td>
<td>100</td>
<td>64</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>105d</td>
<td>-C$_6$H$_4$OMe</td>
<td>2</td>
<td>100</td>
<td>48</td>
<td>1 : 1.2</td>
</tr>
<tr>
<td>6</td>
<td>105e</td>
<td>-C$_6$H$_4$OMe</td>
<td>2</td>
<td>100</td>
<td>73</td>
<td>1 : 3</td>
</tr>
</tbody>
</table>

The last target of this work was the synthesis of a new class of trifluoroacetyl substituted cyclopropanes (72a – e and 73a – e) illustrated in Scheme 44. The reactions were performed with different ammonium ylides (71a – e) and Cs$_2$CO$_3$ as base. Analysis by $^1$H-NMR showed the formation of two diastereomers which could be isolated after chromatographic purification for the products listed in Table 15, entries 5 and 6 with R = C$_6$H$_4$Cl, C$_6$H$_4$OMe with a ratio of 1:1.2 and 1:3 respectively.
4. Conclusion

It was shown that δ-sultones can be synthesized via in situ generated sulfenes using γ-aryl-β-γ-unsaturated-α-ketoester, ethanesulfonyl chloride, 8 eq of DABCO and 1 eq of Lewis acid in THF or CH₂Cl₂ at -15 °C. Two diastereomers of the expected sultone were formed in a ratio of 1:3. Furthermore a minor product was obtained due to a rearrangement reaction.

The preparation of δ-sultames with N-tosylimine and sulfonyl chloride at identical reaction conditions could not be realized. Only at -80 °C in CH₂Cl₂ with DABCO and catalysed by indiumtriflate traces of the desired product were detected.

The third target of this work, the synthesis of a new class of trifluoroacetyl substituted cyclopropanes, could be carried out successfully using trifluoroketone and various ammonium ylides. All of the performed reactions showed full conversion and yields of 36 to 73 %, whereby at least two diastereomers were formed.
5. Experimental part

5.1. Preparation of starting materials

Synthesis of methyl (E)-2-oxo-4-phenylbut-3-enolate (77a)

According to literature [26-27], potassium hydroxide (2.2 g, 39.3 mmol) in methanol (2 mL) was added dropwise to a solution of pyruvic acid (1.8 mL, 26.2 mmol) and benzaldehyde (2.7 mL, 26.2 mmol) in methanol (7 mL) over 30 minutes. The reaction was stirred at 40 °C for 1 hour and at 0 °C overnight. The precipitate was filtered off, washed with cold methanol and ether. Drying under vacuum gave the potassium salt 76a (4 g, 18.8 mmol, 72 %) as an intermediate. Acetyl chloride (4 mL, 56.1 mmol) was added dropwise to methanol (23.4 mL) at 0 °C followed by the potassium salt and the mixture was stirred for 30 minutes at 0 °C. The solution was then stirred for two hours at rt and then refluxed overnight. After concentration under vacuum, the residue was diluted with water (30 mL) and extracted twice with CH₂Cl₂. The combined organic layers were washed with water and brine, dried with Na₂SO₄, filtered and evaporated. Chromatographic purification (heptanes/EtOAc = 3/2) gave the ketoester 77a (811 mg, 4.3 mmol, 11 %) as a yellow solid.

Identification of 77a:

^1H-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): 3.94 (s, 3H, -CH₃), 7.38 (d, J = 16.15 Hz, 1H, -CH₂=CH₂-CO-), 7.41-7.50 (m, 3H, Ar-C), 7.60-7.68 (m, 2H, Ar-C), 7.89 (d, J = 16.15 Hz, 1H, Ar-CH₂=CH₂)
Synthesis of methyl (E)-4-(4-methoxyphenyl)-2-oxobut-3-enoate (77b)

According to literature [26-27], potassium hydroxide (2.2 g, 39.3 mmol) in methanol (6 mL) was added dropwise to a solution of pyruvic acid (1.8 mL, 26.2 mmol) and methoxybenzaldehyde (3.17 mL, 26.2 mmol) in methanol (6 mL) over 30 minutes. The reaction was stirred at 40 °C for 1 hour and at 0 °C overnight. The precipitate was filtered off, washed with cold methanol and ether. Drying under vacuum gave the potassium salt 76b as an intermediate. Acetyl chloride (4 mL, 56.1 mmol) was added dropwise to methanol (23.4 mL) at 0 °C followed by the potassium salt and the mixture was stirred for 30 minutes at 0 °C. The solution was stirred then for two hours at rt and then refluxed overnight. After concentration under vacuum, the residue was diluted with water (30 mL) and extracted twice with CH₂Cl₂. The combined organic layers were washed with water and brine, dried with Na₂SO₄, filtered and evaporated to give the ketoester 77b (2.58 g, 11.7 mmol, 45 %) as a yellow solid.

Identification of 77b:

¹H-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): 3.86 (s, 3H, -O-CH₃), 3.93 (s, 3H, -CO₂CH₃), 6.90-6.97 (m, 2H, Ar-C), 7.25 (d, J = 16.0 Hz, 1H, -CH₂=CH₂-CO-), 7.57-7.64 (m, 2H, Ar-C), 7.85 (d, J = 16.0 Hz, 1H, Ar-CH₂=CH₂-)
Synthesis of methyl (E)-4-(4-bromophenyl)-2-oxobut-3-enoate (77c)

Scheme 47: Synthesis of 77c.

According to literature [25-26], potassium hydroxide (1.75 g, 31.2 mmol) in methanol (7 mL) was added dropwise to a solution of pyruvic acid (1.45 mL, 21.1 mmol) and 4-bromobenzaldehyde (3.71 g, 20.1 mmol) in methanol (7 mL) over 30 minutes. The reaction was stirred at 40 °C for 1 hour and at 0 °C overnight. The precipitate was filtrated, washed with cold methanol and ether. Drying under vacuum gave the potassium salt 76c (5.2 g, 17.8 mmol, 88.6 %) as an intermediate. Acetyl chloride (3.8 mL, 53.3 mmol) was added dropwise to methanol (22.0 mL) at 0 °C followed by the potassium salt and the mixture was stirred for 30 minutes at 0 °C. The solution was stirred then for two hours at rt and then refluxed overnight. After concentration under vacuum, the residue was diluted with water (30 mL) and extracted twice with CH₂Cl₂. The combined organic layers were washed with water and brine, dried with Na₂SO₄, filtered and evaporated to give the ketoester 77c (3.23 g, 12.0 mmol, 60 %) as a yellow solid.

Identification of 77c:
¹H-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): 3.94 (s, 3H, -CH₃), 7.37 (d, J = 16.13 Hz, 1H, -CH₂=CH₂-CO-), 7.47-7.53 (m, 2H, Ar-C), 7.54-7.60 (m, 2H, Ar-C), 7.81 (d, J = 16.13 Hz, 1H, Ar-CH₂=CH₂-)

Synthesis of (E)-1,3-Diphenyl-N-tosylprop-2-en-1-imine (79b)

Scheme 48: Synthesis of 79b.
According to literature [28], Et₃N (0.58 mL, 4.1 mmol) and TiCl₄ (0.22 mL, 2.0 mmol) were added to a solution of chalcone (386 mg, 1.9 mmol) and p-toluenesulfonamide (317 mg, 1.9 mmol) in dry CH₂Cl₂ (23 mL) at 0 °C. The solution was refluxed for 20 hours, then cooled to room temperature and quenched with water (15 mL). It was extracted three times with CH₂Cl₂, dried with Na₂SO₄, filtrated and evaporated. Chromatographic purification (heptanes/EtOAc = 3/2) gave the imine 79b (492 mg, 1.4 mmol, 77 %).

Identification of 79b:

$^1$H-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): 2.43 (s, 3H, -Ar-CH₃), 7.07 (d, $J = 16.08$ Hz, 1H, -CH₂=CH₂-CN), 7.32 (d, $J = 8.14$ Hz, 2H, -Ar-H), 7.37-7.71 (m, 11H, Ar-C), 7.93 (d, $J = 7.80$ Hz, 2H, Ar-H)

Synthesis of methyl-4-phenyl-2-(tosylimino)but-3-enoate (79a)

According to literature [28], Et₃N (0.43 mL, 3.1 mmol) and TiCl₄ (0.16 mL, 2.0 mmol) were added to a solution of keto ester (262 mg, 1.4 mmol) and p-toluenesulfonamide (236 mg, 1.4 mmol) in dry CH₂Cl₂ (17 mL) at 0 °C. The solution was refluxed for 24 hours, then cooled to room temperature and quenched with water (15 mL). It was extracted three times with CH₂Cl₂, dried with Na₂SO₄, filtrated and evaporated. Chromatographic purification (heptanes/EtOAc = 3/2) gave the imine 79a (148 mg, 0.4 mmol, 31 %).

Identification of 79a:

$^1$H-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): 2.43 (s, 3H, -Ar-CH₃), 3.94 (s, 3H, O-CH₃), 6.83 (d, $J = 16.50$ Hz, 1H, -CH₂=CH₂-CN), 7.30-7.67 (m, 8H, Ar-H), 7.91 (d, $J = 8.35$ Hz, 2H, Ar-H)
Synthesis of 1-phenylprop-2-en-1-one (81)

According to literature [29], triethyl amine was added dropwise to 3-chloropropiophenone (80) in CHCl₃ and stirred for 18 hours at room temperature. The reaction mixture was extracted twice with HCl (0.1 N), twice with water, twice with NaHCO₃, once with brine, dried with Na₂CO₃, filtrated and concentrated under reduced pressure to give 81 in sufficient purity for further use.

Identification of 81:

1H-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): 5.75 (d, J = 10.70 Hz, 1H, -CH=CH₂), 6.30 (d, J = 17.11 Hz, 1H, -CH=CH₂), 7.03 (dd, J₁ = 17.06 Hz, J₂ = 10.57 Hz, 1H, -CH=CH₂), 7.25-7.45 (m, 3H, Ar-H), 7.76-7.86 (m, 2H, Ar-H)

Synthesis of ethyl-2-benzoylacrylate (84)

According to literature [30], a mixture of ethyl-3-oxo-3-phenylpropanoat (1.69 mL, 9.8 mmol), morpholine (0.26 mL, 30 mol%), glacial acetic acid (49 mL), paraformaldehyde (2.64 g, 88.0 mmol) and molecular sieves (4 Å) was stirred for 2 hours at 70 °C. The reaction was quenched with NaHCO₃, extracted three times with EtOAc, washed with NaCl, dried with Na₂SO₄, filtrated and evaporated to give 84 (1.49 g, 7.3 mmol, 75 %) in sufficient purity for further use.

Identification of 84:

1H-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): 1.07 (t, J = 7.14 Hz, 3H, -CH₂-CH₃), 4.16-4.21 (m, 2H, -CH₂-CH₃), 6.03 (d, J₁ = 0.60 Hz, 1H, -C=CH₂), 6.66 (d, J₁ = 0.60 Hz, 1H, -C=CH₂), 7.37-7.87 (m, 5H, Ar-H)
Synthesis of (E)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (70)

Scheme 52: Synthesis of 70.

According to literature [31], trifluoroacetone (1.8 mL, 20.1 mmol) in benzene (5 mL) was added dropwise to a solution of benzaldehyde (0.5 mL, 5 mmol), acetic acid (0.43 mL, 7.5 mmol) and piperidine (0.5 mL, 5 mmol) in benzene (5 mL) at 0 °C. It was stirred at this temperature for two hours and then at rt for 24 hours. The reaction mixture was quenched with saturated ammonium chloride solution, extracted three times with EtOAc (15 mL), washed with brine, dried with Na₂SO₄ and evaporated. Chromatographic purification (heptane/EtOAc = 5/1) gave the ketone 70 (100 mg, 10 %).

Identification of 70:

$^1$H-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): 7.02 (d, $J = 16.00$ Hz, 1H, -CH₂=CH₂-), 7.41-7.55 (m, 3H, Ar-C), 7.62-7.68 (m, 2H, Ar-C), 7.98 (d, $J = 16.00$ Hz, 1H, -CH₂=CH₂-)

$^{19}$F-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): -77.6 (s, CF₃)

Synthesis of 3-benzylidene-1,1,1,5,5,5-hexafluoropentane-2,4-dione (88)

Scheme 53: Synthesis of 88.

According to literature [32], a solution of benzaldehyde (2.44 mL, 24.0 mmol), hexafluoroacetone (5.0 g, 24 mmol) and acetic acid anhydride (24 mL) was stirred at 80 °C for 16 hours. Ac₂O and AcOH were removed by distillation. Concentration under vacuum gave the crude product 88 (6.3669 g, 27.0 mmol, 112 %).
Chromatographic purification (heptane/EtOAc = 2/1) gave the product 88 (12 mg, 0.05 mmol, 0.2 %).

Identification of 88:

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K, δ / ppm): 7.31-7.40 (m, 3H, Ar-C), 7.47-7.55 (m, 2H, Ar-C), 7.70 (s, 1H, -CH=CH=-)

$^{19}$F-NMR (300 MHz, CDCl$_3$, 298.0 K, δ / ppm): -71.0 (s, CF$_3$), -76.3 (s, CF$_3$)

Synthesis of 3-(2,2,2-trifluoroacetyl)-2H-chromen-2-one (93)

According to literature [33], acetic acid (1.74 μL) was added to piperidine (2.5 μL) in MeCN (10 mL) to generate piperidinium acetate (5 mol%). Salicylaldehyde (0.52 mL, 5.0 mmol) and ethyltrifluoroacetoacetone (0.73 mL, 5.0 mmol) were added and the solution was refluxed for 4 hours. The mixture was diluted with water (30 mL), the precipitate was filtered, washed with water (50 °C) and dried on air to give 92 (300 mg, 1.0 mmol, 20.0 %) as colorless crystals. The product 92 was refluxed with TsOH-H$_2$O (20.8 mg, 10 mol%) in chlorbenzene (10.4 mL) for 15 hours. Then the solvent was evaporated and the residue dissolved in toluene (30 mL) and extracted three times with water (10 mL). The solution was refluxed with a Dean-Stark trap for 5 hours and then evaporated to give 93 (158 mg, 0.7 mmol, 14 %) as yellow crystals.

Identification of 93:

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K, δ / ppm): 7.39-7.45 (m, 2H, Ar-C), 7.70-7.76 (m, 2H, Ar-C), 8.52 (s, 1H, =C-CH=C-) 

$^{19}$F-NMR (300 MHz, CDCl$_3$, 298.0 K, δ / ppm): -87.2 (s, CF$_3$)
5.2. Synthesis of sultones and sultames

General procedure

According to literature [12], a mixture of starting material 56 (1 eq), base (1 eq – 8 eq) and lewis acid (0.36 m% - 1 eq) in dry solvent was stirred for 5 minutes at room temperature. The reaction mixture was cooled down to -15 °C and stirred for 5 minutes. Sulfonylchloride 7 (2 eq) was added and it was stirred for 20 hours. The reaction was quenched with HCl (0.1 N), extracted three times with EtOAc, washed with NaCl, dried with Na₂SO₄, filtrated and concentrated under vacuum. Chromatographic purification (heptane/EtOAc = 5/1) gave the product 69.

Identification of 94a (major product):

1H-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): 1.44 (d, J = 6.9 Hz, 1H, -CH-CH₃), 1.62 (d, J = 6.7 Hz, 3H, -CH-CH₃), 3.63 (dd, J₁ = 9.0 Hz, J₂ = 3.5 Hz, 1H, -CH-CH-CH-), 3.84 (s, 4H, -O-CH₂-), 3.86-3.98 (m, 1H), 4.25-4.30 (m, 1H), 5.80 (d, J = 3.5 Hz, 1H), 6.00 (d, J = 2.5 Hz, 1H), 7.35-7.48 (m, 5H, Ar-H), 7.55-7.64 (m, 2H, Ar-H)

Identification of 95a (minor product):

1H-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): 1.71 (d, J = 6.9 Hz, 3H, -CH-CH₃), 3.84 (s, 3H, -O-CH₂-), 4.22 (dq, J₁ = 14.0 Hz, J₂ = 7.1 Hz, J₃ = 2.1 Hz, 1H, -CH-CH₃-), 6.14 (t, J = 7.18 Hz, 1H, -O-CH-CH-), 7.1 (d, J = 1.8 Hz, 1H, -O-CH-CH-), 7.35-7.48 (m, 5H, Ar-H)
### 5.3. Synthesis of cyclopropanes

#### General procedure B

![Chemical structure](attachment:structure.png)

To \((E)-1,1,1\text{-trifluoro-4-phenylbut-3-en-2-one}\) \(70\) \((20 \text{ mg}, 0.1 \text{ mmol})\) in \(\text{CH}_2\text{Cl}_2\) \((1 \text{ mL})\) a ylid \((71\text{a} - \text{e})\) \((0.1 \text{ mmol})\) and \(\text{Cs}_2\text{CO}_3\) \((0.2 - 0.6 \text{ mmol})\) were added. The mixture was stirred overnight at room temperature, diluted with \(\text{HCl}\) \((0.1 \text{ N}, 10 \text{ mL})\), extracted three times with \(\text{EtOAc}\) \((10 \text{ mL})\), dried with \(\text{Na}_2\text{SO}_4\), filtered off and concentrated under vacuum to give the crude product \((11 - 25 \text{ mg}, 0.04 - 0.07 \text{ mmol}, 36-73\%)\). Chromatographic purification (heptane/EtOAc = 10/1) gave the cyclopropanes \(72\text{a} - \text{e}\) and \(73\text{a} - \text{e}\).

#### Synthesis of cyclopropane \((72\text{a}, 73\text{a})\) using a diethylamide-ylide

![Chemical structure](attachment:structure2.png)

Following general procedure B, \(70\) \((20 \text{ mg}, 0.1 \text{ mmol})\) in \(\text{CH}_2\text{Cl}_2\) \((1 \text{ mL})\) with \(71\text{a}\) \((25.0 \text{ mg}, 0.1 \text{ mmol})\) and \(\text{Cs}_2\text{CO}_3\) \((66 - 196 \text{ mg}, 0.2 - 0.6 \text{ mmol})\) gave cyclopropane \(72\text{a}\) and \(73\text{a}\) \((11 - 13 \text{ mg}, 0.04 \text{ mmol}, 36-42\%)\) after chromatographic purification (heptane/EtOAc = 10/1) as one isomer.

#### Identification of \(72\text{a}\) and \(73\text{a}\):

- **\(^1\text{H-NMR}\) (300 MHz, CDCl\(_3\), 298.0 K, δ / ppm):** 2.23 (dd, \(J_1 = 13.5 \text{ Hz}, J_2 = 3.2 \text{ Hz}, 1\text{H}, -\text{CH-CH-CH-}\)), 3.40-3.50 (m, 1H, -\text{CH-CH-CH-}), 3.55-3.67 (m, 1H, -\text{CH-CH-CH-}), 7.27-7.70 (m, 5H, Ar\text{-H})
- **\(^{19}\text{F-NMR}\) (300 MHz, CDCl\(_3\), 298.0 K, δ / ppm):** -87.4 (s, CF\(_3\))
Synthesis of cyclopropane using a diethylster-ylide

Following general procedure B, 70 (20 mg, 0.1 mmol) in CH$_2$Cl$_2$ (1 mL) with 71b (23 mg, 0.1 mmol) and Cs$_2$CO$_3$ (65 mg, 0.2 mmol) gave cyclopropanes 72b and 73b (11 - 19 mg, 0.07 mmol, 66%) after chromatographic purification (heptane/EtOAc = 10/1) as one isomer.

Identification of 72b and 73b:
$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K, δ / ppm): 1.04 (t, $J_1$ = 7.18 Hz, 3H, -CH$_2$-CH$_3$), 2.89 (dd, $J_1$=10.11 Hz, $J_2$=4.70 Hz, 1H, -CH-CH-CH-), 3.22 (dd, $J_1$ = 10.12 Hz, $J_2$ = 5.88 Hz, 1H, -CH-CH-CH-), 3.44 (t, $J$ = 5.2 Hz, 1H, -CH-CH-CH-), 3.89 (d, $J_1$ = 7.18 Hz, $J_2$ = 1.00 Hz, 2H, -CH$_2$-CH$_3$), 7.21-7.34 (m, 5H, Ar-H)

$^{19}$F-NMR (300 MHz, CDCl$_3$, 298.0 K, δ / ppm): -78.7 (s, CF$_3$)

Synthesis of cyclopropane using an acetophenone-ylide

Following general procedure B, 70 (20 mg, 0.1 mmol) in CH$_2$Cl$_2$ (1 mL) with 71c (26 mg, 0.1 mmol) and Cs$_2$CO$_3$ (65 mg, 0.2 mmol) gave cyclopropanes 72c and 73c (20 mg, 0.06 mmol, 64%) after chromatographic purification (heptane/EtOAc = 10/1) as one isomer.
Identification of $72c$ and $73c$:

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K, $\delta$/ppm): 2.92-3.02 (m, 1H, -CH-CH-CH-), 3.45-3.54 (m, 1H, -CH-CH-CH-), 3.79-3.85 (m, 1H, -CH-CH-CH-), 7.11-7.24 (m, 4H, Ar-H), 7.30-7.64 (m, 4H, Ar-H), 7.93-8.00 (m, 2H, Ar-H)

$^{19}$F-NMR (300 MHz, CDCl$_3$, 298.0 K, $\delta$/ppm): -78.6 (s, CF$_3$)

**Synthesis of cyclopropane using a chloro substituted acetophenone-ylide**

Following general procedure B, $70$ (20 mg, 0.1 mmol) in CH$_2$Cl$_2$ (1 mL) with $71d$ (29 mg, 0.1 mmol) and Cs$_2$CO$_3$ (65 mg, 0.2 mmol) gave cyclopropanes $72d$ and $73d$ (17.0 mg, 0.05 mmol, 48 %). Chromatographic purification (heptane/EtOAc = 3/1) gave two diastereomers (1:1.2, 4.9 mg, 6 mg).

Identification of $72d$:

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K, $\delta$/ppm): 3.49 (dd, $J_1$ = 9.7 Hz, $J_2$ = 4.8 Hz, 1H, -CH-CH-CH-), 3.62 (dd, $J_1$ = 9.7 Hz, $J_2$ = 6.7 Hz, 1H, -CH-CH-CH-), 4.07 (dd, $J_1$ = 6.7 Hz, $J_2$ = 4.9 Hz, 1H, -CH-CH-CH-), 7.27-7.38 (m, 5H, Ar-H), 7.50-7.56 (m, 2H, Ar-H), 8.01-8.07 (m, 2H, Ar-H)

$^{19}$F-NMR (300 MHz, CDCl$_3$, 298.0 K, $\delta$/ppm): -79.1 (s, CF$_3$)

Identification of $73d$:

$^1$H-NMR (300 MHz, CDCl$_3$, 298.0 K, $\delta$/ppm): 3.46 (dd, $J_1$ = 10.1 Hz, $J_2$ = 5.0 Hz, 1H, -CH-CH-CH-), 3.76 (dd, $J_1$ = 10.2 Hz, $J_2$ = 4.9 Hz, 1H, -CH-CH-CH-), 3.83 (dd, $J_1$ = 5.3 Hz, 1H, -CH-CH-CH-), 7.10-7.25 (m, 5H, Ar-H), 7.42-7.48 (m, 2H, Ar-H), 7.88-7.93 (m, 2H, Ar-H)

$^{19}$F-NMR (300 MHz, CDCl$_3$, 298.0 K, $\delta$/ppm): -78.6 (s, CF$_3$)
Synthesis of cyclopropane using a methoxy substituted acetophenone-ylide

Scheme 62: Synthesis of 72e and 73e.

Following general procedure B, 70 (20 mg, 0.1 mmol) in CH₂Cl₂ (1 mL) with 71e (29 mg, 0.1 mmol) and Cs₂CO₃ (65 mg, 0.2 mmol) gave cyclopropanes 72e and 73e (25 mg, 0.07 mmol, 73%). Chromatographic purification (heptane/EtOAc = 3/1) gave two diastereomers (1:3, 5 mg, 16 mg).

Identification of 72e:

¹H-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): 3.47 (dd, J₁ = 9.7 Hz, J₂ = 4.8 Hz, 1H, -CH-CH-CH-), 3.61 (dd, J₁=9.7 Hz, J₂=6.7 Hz, 1H, -CH-CH-CH-), 3.91 (s, 3H, -CH₃) 4.08 (dd, J₁=6.7 Hz, J₂=4.9 Hz, 1H, -CH-CH-CH-), 6.99-7.05 (m, 2H, Ar-H), 7.27-7.38 (m, 5H, Ar-H), 8.06-8.13 (m, 2H, Ar-H)

¹⁹F-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): -79.1 (s, CF₃)

Identification of 73e:

¹H-NMR (300 MHz, CDCl₃, 298.0 K, δ / ppm): 3.41-3.50 (m, 1H, -CH-CH-CH-), 3.73-3.85 (m, 2H, -CH-CH-CH-), 3.87 (s, 3H, -CH₃), 6.90-6.96 (m, 2H, Ar-H), 7.08-7.25 (m, 5H, Ar-H), 7.91-7.99 (m, 2H, Ar-H)

¹⁹F-NMR (300 MHz, CDCl₃, 298.0 K, δ [ppm]): -78.6 (s, CF₃)
6. References


