N-Heterocyclic Carbene-Catalyzed Conjugate Umpolung for the Synthesis of \( \gamma \)-Butyrolactones

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Dedicated to the memory of Professor Nabi Magomedov and his family.

Abstract: The N-heterocyclic carbene-catalyzed conjugate Umpolung of differently substituted \( \alpha,\beta \)-unsaturated aldehydes, e.g. cinnamaldehydes, \( \alpha \)-methylcinnamaldehydes, and crotonaldehydes, is described. Coupling of these compounds with a variety of electrophilic aldehydes and ketones results in the selective formation of highly substituted \( \beta \)- and \( \gamma \)-butyrolactones.

Key words: carbenes, Umpolung, lactones, heterocycles, cyclization

Introduction

The inversion of the commonly accepted reactivity pattern of a functional group, the Umpolung,\(^1\) is a versatile and fertile concept that allows new chemical transformations. Stoichiometric\(^2\) as well as catalytic methods for Umpolung have been known for a long time, and have become standard tools in organic synthesis. The catalytic Umpolung of electrophilic aldehydes upon addition of nucleophilic catalysts like cyanide or thiazolium carbenes is an extraordinarily attractive approach.\(^3\) The resulting nucleophiles can react with aromatic aldehydes (benzoin condensation\(^4\)) or with electron-poor, polarized olefins (Stetter reaction\(^5\)). In contrast to this \( \text{a}^1\)-to-\( \text{d}^1\)-Umpolung, the term ‘conjugate’ Umpolung describes the transformation of \( \alpha,\beta \)-unsaturated aldehydes into \( \text{d}^3\)-nucleophiles (homoenolate equivalents\(^6\)) upon attack of a suitable nucleophilic catalyst on the aldehyde function (Scheme 1). Here we report an organocatalyzed, chemo- and stereoselective reaction of \( \alpha,\beta \)-unsaturated aldehydes with a variety of different aldehydes and ketones to give substituted \( \beta \)-lactone and \( \gamma \)-butyrolactone products.\(^7\)

Aromatic Aldehydes as Electrophiles

Our investigation commenced with the reaction of cinnamaldehyde with 4-chlorobenzaldehyde. The Umpolung of these two compounds can lead to a variety of different products: benzoin products, Stetter products and the products arising from conjugate Umpolung (Scheme 2). Many different catalysts were screened and it became obvious that the catalyst has a dramatic influence on the outcome of this transformation. Using a combination of the commercially available thiazolium salt 2 (Figure 1) and an equimolar amount of base resulted in the formation of the corresponding benzoin products only, with no \( \gamma \)-butyrolactone being formed. Interestingly, employing potassium cyanide (30 mol%) in combination with 18-crown-6 (10 mol%) gave lactone 1a, albeit in low yield (Scheme 3, Table 1, entry 2).
Recently, imidazolium derived N-heterocyclic carbenes (NHCs) have found numerous applications as ligands in transition metal catalysis and as organocatalysts. In parallel, we and Bode et al. were the first to find that 1,3-dimesityl-2,3-dihydro-1H-imidazol-2-ylidene (IMes) (Figure 1) is a competent catalyst for the conjugate Um- polung of \( \alpha,\beta \)-unsaturated aldehydes resulting in the formation of \( \gamma \)-butyrolactones. Under optimized conditions, a 1:1 mixture of cinnamaldehyde and the benzaldehyde derivative in tetrahydrofuran was treated with IMes (prepared in situ from IMes·HCl and excess KOt-Bu) and stirred at ambient temperature for 16 hours (Scheme 3). A variety of differently substituted \( \gamma \)-butyrolactones was formed from aromatic aldehydes in yields

Biographical Sketches

**Christian Burstein** received his diploma in 2003 from the Universität Duis- burg, where he worked in the laboratory of Prof. D. Döpp. His Ph. D. work under the guidance of Prof. F. Glorius commenced at the Max-Planck-Institut für Kohlenforschung in 2003 and was completed at the Universität Marburg in 2006. His main research interests are modern organocatalytic methods, N-heterocyclic carbenes, and organometallic chemistry.

**Serena Tschan** was born in Hamburg, Germany, in 1981. She obtained her diploma degree in chemistry from Philipps-Universität Marburg in 2006 under the direction of Professor Frank Glorius, where she carried out her graduate work in the area of organocatalyzed reactions for the synthesis of \( \beta \)- and \( \gamma \)-lactones.

**Xiulan Xie** was born in Fujian, China, in 1964. She has supervised the NMR centre in the Faculty of Chemistry, Philipps-Universität Marburg since 2002. Her main interest is structure determination by using modern NMR spectroscopic techniques in solution.

**Frank Glorius** was educated in chemistry at the Universitität Hannover, Stanford University (Professor Paul A. Wender), Max-Planck-Institut für Kohlenforschung and Universität Basel (Prof. Andreas Pfaltz), and Harvard University (Professor David A. Evans). In 2001 he began his independent research career at the Max-Planck-Institut für Kohlenforschung in Mühlheim, Germany. In 2004 he became Professor of Organic Chemistry at the Philipps-Universität Marburg. The purpose of his research program is to significantly facilitate organic synthesis by developing new concepts for catalysis. At present his group focuses on the design of new N-heterocyclic carbenes, challenging cross-coupling reactions, asymmetric hydrogenations, and organocatalyzed umpolung reactions.
ranging from 30% to 70% with, generally, hardly any benzoin or Stetter product being produced.16 With the exception of 2-chlorobenzaldehyde (Table 1, entry 10), the cis-diastereomer was formed predominantly in all cases (Table 1).17 The typical cis/trans ratio was 80:20, and the diastereomers were separated by column chromatography.

**Scheme 2** Possible products of the Umpolung of an α,β-unsaturated aldehyde and another aldehyde

**Mechanism**

A plausible mechanism for the conjugate Umpolung to give γ-butyrolactones is depicted in Scheme 4. Reaction of the N-heterocyclic carbene with the α,β-unsaturated aldehyde gives rise to a zwitterionic structure 3 that isomerizes by protonation/deprotonation to give the conjugated dienamine 4. Nucleophilic attack of 4A or its zwitterionic homoenolate tautomer 4B18 onto the electrophilic aldehyde or ketone results in the formation of alkoxide 5, followed by isomerization to the corresponding tautomer 6. Related activated carboxylates are thought to be intermediates in N-heterocyclic carbene catalyzed transesterification reactions, leading to ester formation when attacked by alcohol nucleophiles.8 In analogy, intramolecular attack of the alkoxide of 6 or its protonated form onto the carbonyl group leads to the closing of the lactone ring and the regeneration of the nucleophilic catalyst.

It is tempting to speculate that the steric demand of IMes is key to its success by modulating the reactivity of the nucleophilic species. Namely, the former aldehyde carbons of benzaldehyde and cinnamaldehyde are significantly shielded by the catalyst leading to reduced nucleophilicity of the amine carbon nearby. In contrast, the conjugate position does not suffer from this shielding and can still react with the electrophile (Figure 2).

**Table 1** IMes-Catalyzed Coupling of Cinnamaldehyde with Aromatic Aldehydes*  

<table>
<thead>
<tr>
<th>Entry</th>
<th>R 1</th>
<th>Yield (%)</th>
<th>Ratio$^b$ cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-CIC₆H₄</td>
<td>a</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>4-CIC₆H₄</td>
<td>a</td>
<td>33$^{d,e}$</td>
</tr>
<tr>
<td>3</td>
<td>4-CIC₆H₄</td>
<td>a</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>4-BrC₆H₄</td>
<td>b</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>4-MeOCC₆H₄</td>
<td>c</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>4-F₃CC₆H₄</td>
<td>d</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>3-FC₆H₄</td>
<td>e</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>3-CIC₆H₄</td>
<td>f</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>3-BrC₆H₄</td>
<td>g</td>
<td>66</td>
</tr>
<tr>
<td>10</td>
<td>2-CIC₆H₄</td>
<td>h</td>
<td>32$^{a}$</td>
</tr>
</tbody>
</table>

* General reaction conditions: IMes·HCl (0.05 mmol), KOr-Bu (0.1 mmol), THF (3 mL), then cinnamaldehyde (1 mmol), R 1CHO (1.0 mmol), THF, r.t., 16 h. Isolated combined yield of separately isolated diastereomers.

$^b$ Determined by GC-MS.

$^c$ Instead of IMes·HCl, thiazolium salt 2 was used as the catalyst.

$^d$ Instead of IMes·HCl, KCN (0.3 mmol) and 18-crown-6 (0.1 mmol) were employed.

$^e$ Isolated as mixture of diastereomers.

**Figure 2** Possible sterical influence of the catalyst on the nucleophilicity
Another Useful Class of Electrophiles: Ketones

For a long time, no efficient benzoin condensation with ketones as electrophiles was known. Only recently, reports appeared describing the use of ketones in intramolecular benzoin condensations.\textsuperscript{10a,b,d} We were pleased to find that for the first time ketones could be employed as intermolecular electrophiles in the conjugate Umpolung (Scheme 5).\textsuperscript{7c,j} The IMes catalyzed reaction of cinnamaldehyde with one equivalent of \(\text{a},\text{a},\text{a}\)-trifluoraceto-phenone smoothly proceeded to give the corresponding \(\gamma\)-butyrolactone \(7a\), which bears a valuable quaternary stereocenter, in 70\% yield. Using a twofold excess of the ketone significantly improved the yield to 84\% (Table 2, entry 1). The reaction could be scaled up to 30 mmol without a deterioration of the yield (Table 2, entry 2). In addition, the use of 1,8-diazabicyclo[5.4.0]undec-7-ene instead of potassium tert-butoxide often resulted in superior results, improving the yield by roughly 10\% and in addition simplifying the reaction set up (Table 2, entry 3). Methyl benzoylformate and 1-phenylpropane-1,2-dione were also found to be suitable ketone electrophiles in this reaction resulting in the formation of the corresponding \(\gamma\)-butyrolactones in good yields (Table 2, entries 10–13).

In many cases, the like and unlike diastereomer could be separated by column chromatography. The stereochemistry of \(\nu\)-7b was unequivocally determined by an X-ray structural analysis.\textsuperscript{17}

Asymmetric Conjugate Umpolung

Recently, chiral triazolium salt derived N-heterocyclic carbenes were successfully used in highly enantioselective benzoin condensation\textsuperscript{10} and Stetter reactions.\textsuperscript{11} Interestingly, triazolium salts 8\textsuperscript{10c} and 9\textsuperscript{11a} and imidazolium salt 10\textsuperscript{19} are unsuitable catalysts for the synthesis of \(7a\) under standard conditions (Table 2, entries 4–6, 0\%, 10\%, and 0\% yields, respectively). In contrast, the N-heterocyclic carbone derived from imidazolium salt 11\textsuperscript{19} (Table 2, entry 7) is a competent catalyst for this transformation. Using 5 mol\% of 11 provides \(7a\) in 70\% yield\textsuperscript{10a,d,e} with an improved \(l/u\) ratio of 74:26 and an enantiomeric excess of 12\% and 25\%, respectively.

Conjugated Umpolung of Substituted Crotonaldehyde Derivatives: Synthesis of \(\gamma\)-Butyrolactones

Initially, we reasoned that the aromatic group of cinnamaldehydes would be crucial for success in the conjugate Umpolung.\textsuperscript{20} However, we were pleased to find that alkyl-substituted \(\alpha,\beta\)-unsaturated aldehydes can also be successfully used in the conjugate Umpolung (Scheme 6). Using activated ketones as electrophiles, high yields of...
γ-butyrolactones were obtained under our standard conditions. In many cases the diastereomeric ratios were improved compared to the use of cinnamaldehyde (see Table 3), the best was 93:7 favoring the product 12c-I. In comparison, reduced selectivities were obtained in the cases using methyl benzoylformate.17

Conjugated Umpolung of Substituted Crotonaldehyde Derivatives: Synthesis of β-Lactones

Under some reaction conditions, an isomeric side product was obtained. Structural investigation revealed the β-lactone structure of this compound. Interestingly, using the same substrates and the same catalyst, but changing the base, the solvent, and the reaction temperature allowed this reaction to be controlled (Scheme 7). Under optimized reaction conditions, β-lactone 13c formed in 48% yield (Table 4, entry 3). The use of less polar solvents, higher temperatures, and triethylamine as a base were optimal for this reaction. Methyl benzoylformate could also be employed as an electrophile after slightly modifying the reaction conditions.

Mechanistically, we reason that for the formation of β-lactones a protonation/deprotonation sequence transforms homoenoate 4 into enolate 14 (Scheme 8). Reduced nucleophilicity and a longer lifetime of homoenoate equivalent 15 would favor this process. Finally, attack of the electrophilic carbonyl component, followed by cyclization to the β-lactone liberates the N-heterocyclic carbene catalyst.
N-Heterocyclic Carbene-Catalyzed Conjugate Umpolung to Synthesize γ-Butyrolactones

FEATURE ARTICLE

Umpolung of α-Methylcinnamaldehydes

γ-Butyrolactones are ubiquitous motifs in naturally occurring compounds, many of which bear an α-substituent at C3 (Figure 4).21 Therefore, the reactivity of α-methylcinnamaldehydes was of special interest. Does the conjugate Umpolung tolerate an α-substituent?

Table 4  β-Lactone Formation by Conjugate Umpolung

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>13</th>
<th>Yield (%)</th>
<th>Ratio&lt;sup&gt;b&lt;/sup&gt; l/u</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>a</td>
<td>34</td>
<td>60:40</td>
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<td>2</td>
<td>Pr</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>b</td>
<td>45</td>
<td>55:45</td>
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<tr>
<td>3</td>
<td>i-Pr</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>c</td>
<td>48</td>
<td>62:38</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>d</td>
<td>30</td>
<td>70:30</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>e</td>
<td>22&lt;sup&gt;c&lt;/sup&gt;</td>
<td>71:29</td>
</tr>
</tbody>
</table>

<sup>a</sup> General reaction conditions: IMes·HCl (0.05 mmol), Et<sub>3</sub>N (2.0 mmol), toluene (2.5 mL), α,β-unsaturated aldehyde (1.0 mmol), ketone (1.0 mmol), 60 °C, 16 h.
<sup>b</sup> Determined by GC-MS.
<sup>c</sup> IMes·HCl (0.1 mmol), DBU (0.1 mmol).

Under conditions optimized for the previously mentioned reactions using IMes as the catalyst, the use of α-methylcinnamaldehyde and trifluoroacetophenone did not result in the formation of the desired product. It is reasonable to assume that the α-methyl substituent would exhibit an unfavorable steric interaction with the mesityl rings in conjugated intermediate 16 (Figure 5). Consequently, the use of N-heterocyclic carbenes with smaller groups was investigated. Whereas thiazolium salt 2 failed once again to provide lactone products, the precatalysts 1-mesityl-3-methylimidazolium iodide (17) and 1,3-dimethylimidazolium iodide (18) resulted in the formation of small amounts of product. Gratefully, 1,3-dimethylbenzimidazolium iodide (19), electronically slightly different from 18, resulted in the formation of the highly substituted γ-butyrolactones 20 (Scheme 9, Table 5). Using N,N-dimethylformamide as the optimal solvent and α-methylcinnamaldehyde as the substrate, product 20<sup>a</sup> was formed in 83% yield (Table 5, entry 8). Of the four possible diastereomers, mainly 20-I and 20-II were obtained (Figure 6). In these two major diastereomers the methyl group at C3 is oriented trans relative to the R<sup>1</sup> substituent at C4. In agreement with the results obtained for cinnamaldehyde or crotonaldehyde derivatives, 20-I is formed predominantly in most cases. However, when 2-methyl-5-phenyl-penta-2,4-dienal, an α,β-unsaturated aldehyde containing an alkene as R<sup>1</sup> substituent, was used as a substrate, diastereomer 20-II was obtained in excess (Table 5, entry 11).17

Figure 4  Natural products with α-substituted γ-lactone substructure

Figure 5  Unfavorable steric interactions in hypothetical intermediate 16 and precatalysts 17, 18, and 19
Another interesting observation was made when using 4-chlorocinnamaldehyde as the substrate. In this case, only a small amount (20%) of the expected product 20 was obtained. In addition, the isomeric product 21 was formed in 46% yield (Figure 7). This product could result from a protonation/reprotonation sequence analogous to the one shown in Scheme 8.

Figure 6  Diastereomers of 20

Another interesting observation was made when using 4-chlorocinnamaldehyde as the substrate. In this case, only a small amount (20%) of the expected product 20 was obtained. In addition, the isomeric product 21 was formed in 46% yield (Figure 7). This product could result from a protonation/reprotonation sequence analogous to the one shown in Scheme 8.

Figure 7 21

Table 5  Reaction of α-Methylcinnamaldehydesa

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>20</th>
<th>Yield (%)</th>
<th>drb</th>
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<tr>
<td>1</td>
<td>Ph</td>
<td>2</td>
<td>THF</td>
<td>a</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>IMes</td>
<td>THF</td>
<td>a</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>IMes</td>
<td>DMF</td>
<td>a</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>17</td>
<td>DMF</td>
<td>a</td>
<td>traces</td>
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</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>18</td>
<td>THF</td>
<td>a</td>
<td>traces</td>
<td>–</td>
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<td>6</td>
<td>Ph</td>
<td>19</td>
<td>THF</td>
<td>a</td>
<td>37b</td>
<td>66:28:5:1</td>
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<tr>
<td>7</td>
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<td>19</td>
<td>MeCN</td>
<td>a</td>
<td>24b</td>
<td>64:27:7:2</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>19</td>
<td>DMF</td>
<td>a</td>
<td>83</td>
<td>62:30:6:2</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>19</td>
<td>DMF</td>
<td>a</td>
<td>85c</td>
<td>63:29:6:2</td>
</tr>
<tr>
<td>10</td>
<td>4-ClC6H4</td>
<td>19</td>
<td>DMF</td>
<td>b</td>
<td>71</td>
<td>63:29:6:2</td>
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<tr>
<td>11</td>
<td>CH=CHPh</td>
<td>19</td>
<td>DMF</td>
<td>c</td>
<td>82</td>
<td>32:66:2:0</td>
</tr>
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</table>

a General reaction conditions: α,β-unsaturated aldehyde (0.5 mmol), ketone (1.0 mmol), solvent (2.5 mL), catalyst (0.05 mmol), DBU (0.05 mmol), 75 °C.

b Determined by GC-MS.
c 10 mmol scale.

Intramolecular Reaction

The aforementioned intermolecular reactions generate a γ-butyrolactone with up to three contiguous stereocenters. For a number of reasons an intramolecular variant of this reaction would be attractive. First of all, less reactive electrophiles, namely unactivated ketones, might become suitable reaction partners, thereby significantly expanding the scope of this transformation. Second, in the course of the intramolecular lactone formation an additional ring would be formed, leading to bicyclic products. Finally, an existing stereocenter could influence the reaction leading to the highly selective formation of the lactone products. However, frequently the use of an elaborate, multistep substrate synthesis decreases the attraction of intramolecular approaches.

Consequently, our investigation commenced with the design of readily accessible cyclization precursors. But-2-ene-1,4-diol was identified as an ideally suited building block, allowing the synthesis of the cyclization substrates in only two steps. In this sequence, one hydroxy group of the diol was used for a highly regioselective opening of an epoxide, followed by the parallel oxidation of both hydroxy groups of the resulting diol with Dess–Martin periodinane in good yield (Scheme 10).

The IMes-catalyzed cyclization of 22 and 23 resulted in the formation of γ-butyrolactones with an annulated tetrahydrofuran ring (Table 6, entries 1 and 2). Interestingly, only a single diastereomer was formed. Moreover, for the first time nonactivated, enolizable ketones proved to be suitable electrophiles in the conjugate Umpolung. Especially, the synthesis of the tricyclic product 28 is rather...
complex and demonstrates the potential of this new synthetic method.

Another class of substrates for an intramolecular homoenolate addition, leading to the formation of six-membered rings, was synthesized. Substrates 24, 25, and 26 were easily prepared in two, four, and five steps, respectively (Schemes 11 and 12).22 Once again, IMes allows the conjugate Umpolung of the unsaturated aldehyde, followed by attack onto the nonactivated ketone and the concluding cyclization. In these cases, besides the formation of the γ-butyrolactone, a tetralin or tetrahydroquinoline ring system formed. Impressively, the cyclization of 24 resulted in the formation of the trans-diastereomer 29, only (Table 6, entry 3). The stereochemical assignment of compounds 27–31 was based on elaborate NMR experiments, described in the experimental section.

Table 6 Intramolecular Homoenolate Addition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
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<tr>
<td>1a</td>
<td>22</td>
<td>27</td>
<td>36</td>
</tr>
<tr>
<td>2b</td>
<td>23</td>
<td>28</td>
<td>41</td>
</tr>
<tr>
<td>3c</td>
<td>24</td>
<td>29</td>
<td>55</td>
</tr>
<tr>
<td>4d</td>
<td>25</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>5e</td>
<td>26</td>
<td>31</td>
<td>26</td>
</tr>
</tbody>
</table>

a IMes·HCl (0.07 mmol), KOt-Bu (0.06 mmol), THF (14 mL), then substrate (0.34 mmol), 60 °C, 16 h.

b IMes·HCl (0.11 mmol), KOt-Bu (0.1 mmol), THF (20 mL), then substrate (0.55 mmol), 60 °C, 5 h.

c IMes·HCl (0.030 mmol), KOt-Bu (0.028 mmol), THF (4 mL), then substrate (0.2 mmol), 60 °C, 16 h.

d IMes·HCl (0.036 mmol), DBU (0.03 mmol), THF (15 mL), then substrate (0.30 mmol), 60 °C, 16 h.

e IMes·HCl (0.036 mmol), DBU (0.03 mmol), THF (6 mL), then substrate (0.285 mmol), 60 °C, 16 h.

Conclusion

The organocatalyzed conjugate Umpolung of α,β-unsaturated aldehydes allows the direct, intermolecular, and cross-linking of an α,β-unsaturated aldehyde with another aldehyde or ketone, resulting in a flexible one-step synthesis of substituted γ-butyrolactones. In intramolecular cases, the use of nonactivated ketones as an electrophilic reaction partner is described, leading to the formation of multicyclic products. In addition, variation of the reaction conditions allows the formation of β-lactones in some cases.
All commercially available compounds were used as received and all reactions were performed under an atmosphere of argon. The solvents used were purified by distillation over the drying agents indicated and were transferred under argon: THF (Na), CHCl₃ (CaH₂), toluene (CaH₂). For flash chromatography, Merck silica gel 60 (230–400 mesh) was used. NMR spectra were recorded on an ARX 300 or DRX 400 spectrometer (Bruker) in the solvents indicated; chemical shifts are relative to TMS. For the stereochemical assignment of lactones 27–31, NMR spectra were recorded on Bruker DRX-500 and AVANCE-600 spectrometers in CDCl₃ at concentration of about 0.3 M. Complete signal assignments were carried out on all of the compounds based on 1H, 13C, HSQC, DQF-COSY, and HMBC spectra. Routine pulse sequences with gradients were used. The pulse sequence DPPFGSE-NOE of Shaka[8] was used for the selective transient NOE experiments. Gaussian-shaped pulse was applied for the selective excitation, whose length was optimized for each measurement. Mixing time in the range of 1.0 to 2.0 s was used. 1D-NOE spectra were recorded with 256 scans and a typical experiment time was about 20 min. IR spectra were recorded on a Bruker IFS 88. EI-MS were recorded on a Varian CH 70 (70 eV) and HRMS were recorded on a Finnigan LTQ FT or TSQ 700. For MS data of the diastereomeric mixtures a Agilent Technologies System (GC: 6890N, column: HP-5MS (0.25 mm × 30 m × 0.25 mm); Agilent G1701D GC/MS ChemStation) with a 5973 Network Mass Selective Detector at 70 eV was used. Method 70 20: 70 °C for 3 min; gradient: 20 °C/min to 280 °C; 280 °C for 3.5 min. Method 50 20: 50 °C for 3 min; gradient: 20 °C/min to 280 °C; 280 °C for 3.5 min.

Conjugate Umpolung: Typical Procedures

Methyl 4-(5-Oxo-3-phenyltetrahydrofuran-2-yl)benzoate (1c);

**Typical Procedure for Table 1**

Generation of the catalyst soln (for multiple reactions): Under an atmosphere of argon, IMes·HCl (17.0 mg, 0.050 mmol) was dissolved in THF (5 mL). The soln was stirred at r.t. for 16 h, after which MeOH (2 mL) was added and the soln stirred for a further 15 min. The solvent was evaporated in vacuo, and the residue was distilled in a Kugelrohr apparatus (5 × 10²⁻ mbar, 150–200 °C). Purification of the distillate by column chromatography (silica gel, 2.5 cm × 12 cm, MTBE–hexane 1:3) yielded cis-1c (164 mg, 56%) and, after crystallization (CH₂Cl₂–hexane), trans-1c (41 mg, 14%) as colorless solids.

4-Methyl-5-phenyl-5-(trifluoromethyl)tetrahydrofuran-2-one (12a);

**Typical Procedure for Tables 2 and 3**

Under an atmosphere of argon, IMes·HCl (17.0 mg, 0.050 mmol) was dissolved in THF (2.5 mL) in a septum capped vial and crotonaldehyde (35.0 mg, 0.50 mmol) and a,a,a-trifluoroacetophenone (174 mg, 1.0 mmol) were added. DBU (7.60 mg, 0.05 mmol) was added and the soln stirred at r.t. for 16 h. After this time the solvent was evaporated and the residue purified by column chromatography (silica gel, 2.5 cm × 12 cm, hexane–MTBE, 40:1) to give 12a as a colorless oil; yield: 100 mg (82%).

3-Isobutyl-4-phenyl-4-(trifluoromethyl)oxetan-2-one (13c);

**Typical Procedure for Table 4**

Under an atmosphere of argon, IMes·HCl (17.0 mg, 0.050 mmol) was dissolved in toluene (2.5 mL) and 4-methyl-2-pentenal (116 µL, 1.0 mmol) and a,a,a-trifluoroacetophenone (174 mg, 1.0 mmol) were added. Finally, Et₃N (280 µL, 2.00 mmol) was added and the soln stirred at 60 °C for 16 h. After this time the solvent was evaporated and the residue purified by column chromatography (silica gel, 2.5 cm × 12 cm, pentane–CH₂Cl₂, 15:1) to give 13c as a colorless oil; yield: 130 mg (48%).

3-Methyl-4,5-diphenyl-5-(trifluoromethyl)tetrahydrofuran-2-one (20a);

**Typical Procedure for Table 5**

Under an atmosphere of argon, 19 (13.7 mg, 0.050 mmol) was dissolved in DMF (2.5 mL) in a septum capped vial and (E)-2-methyl-3-phenylprop-2-enal (73.1 mg, 0.50 mmol) and a,a,a-trifluoroacetophenone (174 mg, 1.0 mmol) were added dropwise. Then DBU (7.60 mg, 0.050 mmol) was added and the soln stirred at 75 °C for 16 h. The solvent was then removed by rotary evaporation and the residue was purified by column chromatography (silica gel, 2.5 cm × 12 cm, hexane–MTBE, 40:1) to give 20a as a mixture of diastereomers; yield: yielding 132 mg (83%).

**Stereochemical Assignment**

**Table 1, Products 1**

1H NMR signals for the ring protons of the lactones 1 are very similar within the cis and trans series. Thus, based on an X-ray structural analysis of cis-1d, comparison of the 1H NMR data allows the assignment of the relative stereochemistry. In addition, some aromatic protons in the cis-diastereomer show a significant upfield shift, because they lie in the anisotropic cone of the other aromatic ring. Furthermore the retention times in the GC-MS are consistent, i.e. the like-diastereomer has always a shorter retention time than the unlike-diastereomer.

**Table 2, Lactones 1**

As for the lactones 1, the NMR signals of the ring protons are very similar within the I and II series. Based on an X-ray structural analysis of 7a–c, the relative configuration could be assigned. For compounds 7a–c the chemical shift in the 19F NMR of the CF₃ group is also typical. The signal of the CF₃ group in the like-diastereomer has a upfield shift compared to the unlike-diastereomer. Furthermore the retention times in the GC-MS are consistent, i.e. the like-diastereomer has always a shorter retention time than the unlike-diastereomer.

**Table 3, Products 1**

As for the lactones 1, the NMR signals of the ring protons are very similar within the I and II series. Based on an X-ray structural analysis of 12c–I, the relative configuration was assigned. For diastereomer I of each compound a significant upfield shift of some aliphatic protons (am Rest R) can be observed, because they lie in the anisotropic cone of the aromatic ring. For compounds 12a–c the chemical shift in the 19F NMR of the CF₃ group is also typical. The signal of the CF₃ group in diastereomer I has a upfield shift compared to the diastereomer II. Furthermore the retention times in the GC-MS for diastereomer I are always shorter than the retention times for diastereomer II.

**Table 4, β-Lactones 13**

The stereochemical assignment of the β-lactone products is based on the assignment of the γ-lactones as shown above. First of all, in the series assigned to be like, the CH group of the substituent on C3 of the β-lactone ring experienced a significant upfield shift (anisotropic cone of the phenyl group). This is supported by NOESY experiments, showing an NOE between this CH group and the phenyl ring. This was not observed for the compounds of the other diastereomeric series. Furthermore, the like-isomers exhibit shorter GC retention times and are less polar based on column chromatography.

**Table 5, γ-Lactones 20**

As for the aforementioned lactones, assignment was made based on an X-ray structural analysis of 20c–II and comparison of the NMR data. Furthermore the coupling constants of the lactone ring protons
are similar to those reported for a comparable structure. Again, the relative GC retention times of the diastereomers and the chemical shift of the CF3 group allow the stereochemical assignment.

**Table 6, Products 27–31**

Both 1H and 13C spectra reveal that the isolated compounds consist of a single diastereomer only. The one-dimensional NOE experiments with pulsed field gradients for the observation of selective transient NOEs delivered high quality spectra. These methods enable the observation of weak NOE enhancements and even can provide quantitative distance information. The configuration of the compounds was thus determined using selective NOE techniques.

Methylene protons in molecules containing chiral centers are diastereotopic and often show resolved NMR signals. In this study we used diastereotopic protons as reference points to deduce the spatial arrangement of the products. Protons attached to the stereocenters were selectively excited resulting in distinct NOE contacts with the diastereotopic methylene protons. The observed NOE contacts allow to predict the configurations for 27, 29, and 30 (Table 7).

**Scheme 13**

Relative configurations given as determined by NMR; numbering used in Table 7

The determination of the conformation of 28 is more complicated. For 28, which contains three stereocenters, four pairs of enantiomers are possible and two of them might exist in two different favorable conformations. Protons on axial positions of the cyclohexane ring served as reference points. Furthermore, NOE contacts were used in combination with coupling constants. The coupling constant J_5a–6ax is equal to 9.1 Hz, which reveals the axial orientation of H_{5a}. The NOE contacts detected are given in Table 7. Of the possible configurations, only the one shown for 28 corresponds to the NMR observation and it is thus determined to be the correct configuration of compound 28.

**α,β-Unsaturated Aldehyde Substrates for the Conjugate Umpolung**

(E)-4-(2-Hydroxy-2-phenylethoxy)but-2-en-1-ol

Styrene oxide (1.14 mL, 10.0 mmol, 1 equiv) was added to a stirred and heated (60 °C) mixture of KOH (30 mL). The mixture was stirred for 2 h and then it was poured into a mixture of ice water (100 mL) and toluene (100 mL). The soln was acidified to pH 1 with concd HCl and the layers were separated. The aqueous layer was basified to pH 10–11 using K2CO3, then extracted with CH2Cl2 (3 × 100 mL). The combined extracts were washed with H2O (3 × 50 mL) and dried (MgSO4) and the solvent was removed on a rotary evaporator. The residue was purified by column chromatography (CH2Cl2–MeOH, 40:1) to afford a colorless oil; yield: 1.45 g (70%).

**Table 7**

<table>
<thead>
<tr>
<th>Lactone</th>
<th>Diastereotopic Protons</th>
<th>NOE</th>
<th>Config</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>H_{4α}, H_{4β}; H_{6α}, H_{6β}</td>
<td>H_{3α}−H_{5α} (s), H_{3α}−H_{4α} (s), H_{3α}−H_{6α}; H_{3β}−H_{5β}; H_{3β}−H_{6β} (s)</td>
<td>unlike</td>
</tr>
<tr>
<td>28</td>
<td>H_{4α}, H_{4β}; H_{6α}, H_{6β}</td>
<td>H_{3α}−H_{4α} (s), H_{3α}−H_{6α}; H_{3α}−H_{6α}; H_{3β}−H_{5β}; H_{3β}−H_{6β}; H_{5α}−H_{6α} (s), H_{5α}−H_{6α}; H_{5α}−H_{6α}; H_{5β}−H_{6β} (s)</td>
<td>as shown in Scheme 13</td>
</tr>
<tr>
<td>29</td>
<td>H_{4α}, H_{4β}</td>
<td>H_{3α}−CH_{3} (w), H_{3α}−H_{4α}; CH_{2}−H_{8β}</td>
<td>like</td>
</tr>
<tr>
<td>30</td>
<td>H_{4α}, H_{4β}</td>
<td>H_{3α}−CH_{3} (w), H_{3α}−H_{4α}; CH_{2}−H_{8β}</td>
<td>unlike</td>
</tr>
</tbody>
</table>

^a^ The subscripts are positional descriptors.

^b^ *s* is strong, ’w’ = weak, ’ax’ = axial, ’eq’ = equatorial.
A soln of 2-[((E)-3-Hydroxyprop-1-enyl)phenylamino]propan-2-one
1-Chloropropan-2-one (463 mg, 5.0 mmol, 1.5 equiv) was added to a mixture of (E)-3-aminophenylprop-2-en-1-ol (500 mg, 3.35 mmol, 1 equiv), KHCO₃ (335 mg, 3.35 mmol, 1 equiv), and KI (110 mg, 0.67 mmol, 0.2 equiv) in acetone (10 mL). The mixture was stirred at 50 °C for 24 h, then silica gel was added and the solvent removed on the rotary evaporator. The powder was purified by column chromatography (pentane–EtOAc, 1:1) to afford the product as a yellow solid; yield: 472 mg (69%).

Rₛ = 0.11 (pentane–EtOAc, 1:1).

IR (KBr): 3413, 1722, 1601, 1574, 1504, 1453, 1359, 1295, 1185, 1147, 1098, 1013, 958, 751, 608, 531, 498, 466 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.27–7.25 (m, 1 H), 7.20–7.14 (m, 1 H), 6.76–6.70 (m, 2 H), 6.48 (d, J = 8.1 Hz, 1 H), 6.25 (dt, J = 5.7, 15.7 Hz, 1 H), 4.78 (s, 1 H), 4.35 (d, J = 5.7 Hz, 2 H), 4.01 (s, 2 H), 2.26 (s, 3 H).

13C NMR (75 MHz, CDCl₃): δ = 204.1, 143.9, 131.3, 128.8, 127.8, 126.4, 123.4, 117.9, 110.9, 63.9, 54.3, 27.4.

MS (EI): m/z (%) = 205 [M⁺] (21), 162 (55), 146 (14), 145 (11), 144 (100), 143 (29), 133 (10), 132 (92), 131 (20), 130 (90), 118 (22), 117 (40), 116 (16), 115 (31), 91 (20), 77 (16).

HRMS (EI): m/z [M⁺] calcd for C₁₂H₁₅NO₂: 205.1103; found: 205.1095.

(E)-3-[2-(Oxobutyl)phenyl]prop-2-en (25)
1-[2-(E)-3-Hydroxyprop-1-enyl]phenylamino)propan-2-one (821 mg, 4.0 mmol, 1 equiv) was dissolved in EtOAc (50 mL) and 2-iodobenzonic acid (IBX; 3.36 g, 12.0 mmol, 3 equiv) was added. The mixture was stirred at 50 °C for 24 h, then silica gel was added and the solvent removed on the rotary evaporator. The powder was purified by column chromatography (pentane–EtOAc, 1:1) to afford an orange solid; yield: 630 mg (78%). The product was stored under an argon atmosphere in the fridge.

Rₛ = 0.45 (pentane–EtOAc, 1:1).

IR (KBr): 3422, 1718, 1668, 1602, 1567, 1503, 1454, 1413, 1366, 1334, 1291, 1262, 1231, 1190, 1161, 1146, 1130, 1075, 962, 757 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.90 (d, J = 7.7 Hz, 1 H), 7.66 (d, J = 15.7 Hz, 1 H), 7.42 (d, J = 7.8 Hz, 1 H), 7.30 (m, 1 H), 6.78 (t, J = 7.5 Hz, 1 H), 6.66 (dd, J = 7.7, 15.7 Hz, 1 H), 6.55 (d, J = 8.2 Hz, 1 H), 5.07 (br s, 1 H), 4.06 (d, J = 4.1 Hz, 2 H), 2.30 (s, 3 H).

13C NMR (75 MHz, CDCl₃): δ = 203.0, 193.8, 147.7, 145.3, 132.6, 128.8, 128.9, 119.7, 118.1, 112.1, 53.8, 27.4.

MS (EI): m/z = 203 [M⁺] (21), 160 (73), 132 (57), 131 (20), 130 (100), 118 (29), 117 (51), 115 (12), 103 (12), 77 (20).
HRMS (EI): m/z [M⁺] calcd for C₁₅H₁₂NO₂: 203.0947; found: 203.0938.

-N-[2-[E]-3-Oxoprop-1-enyl(phenyl)]-N-(2-oxopropyl)acetamide (26)
A few drops of pyridine and AcCl (220 μL, 3.08 mmol, 1.25 equiv) were added to a soln of (E)-3-[2-oxopropylaminopheno]prop-2-enal (500 mg, 2.46 mmol, 1 equiv) in toluene (10 mL). The mixture was stirred at 80 °C for 30 min, then H₂O (10 mL) was added. The organic layer was washed with H₂O (5 mL) and dried (MgSO₄) and the solvent was removed on the rotary evaporator. The residue was purified by column chromatography (hexane–EtOAc, 1:1) to afford a colorless resin; yield: 178 mg (30%).

Rₚ = 0.06 (hexane–EtOAc, 1:1).

IR (film): 3064, 3032, 2929, 1783, 1594, 1491, 1455, 1409, 1318, 1302, 1173, 1144, 1030, 1010, 980, 879, 795, 731, 701, 514 cm⁻¹.


cis-5-(4-Bromophenyl)-4-phenyltetrahydrofuran-2-one (cis-1b)
Colorless oil; yield: 118 mg (37%).

Rₚ = 0.10 (hexane–EtOAc, 7:1).

IR (film): 3088, 3064, 3032, 2929, 1783, 1594, 1491, 1455, 1409, 1318, 1302, 1173, 1144, 1030, 1010, 980, 879, 795, 731, 701, 514 cm⁻¹.


trans-5-(4-Bromophenyl)-4-phenyltetrahydrofuran-2-one (trans-1b)
Light yellow oil; yield: 37 mg (12%).

Rₚ = 0.22 (hexane–EtOAc, 7:1).

IR (film): 3063, 3031, 2924, 1786, 1594, 1491, 1455, 1416, 1268, 1194, 1142, 1071, 1035, 1004, 880, 808, 760, 699, 637, 504 cm⁻¹.

cis-4-Phenyl-5-[4-(trifluoromethyl)phenyl]tetrahydrofuran-2-one (cis-1d)
Colorless solid; yield: 108 mg (35%).

IR (KBr): 3063, 3034, 2926, 1775, 1759, 1693, 1540, 1487, 1375, 1279, 1261, 1254, 1247, 1236, 1223, 1216, 1206, 1098, 1089, 981, 895, 839, 729, 710, 604, 516 cm⁻¹.

trans-4-Phenyl-5-[4-(trifluoromethyl)phenyl]tetrahydrofuran-2-one (trans-1d)
Colorless oil; yield: 27 mg (9%).

IR (film): 3065, 3034, 2929, 1787, 1716, 1616, 1593, 1490, 1454, 1419, 1270, 1195, 1146, 1035, 1003, 967, 907, 875, 789, 759, 699, 522 cm⁻¹.

cis-5-(3-Fluorophenyl)-4-phenyltetrahydrofuran-2-one (cis-1e)
Colorless solid; yield: 119 mg (46%).

IR (KBr): 3079, 3051, 2962, 2927, 1775, 1765, 1756, 1591, 1489, 1455, 1382, 1304, 1273, 1197, 1148, 1139, 1082, 1027, 986, 969, 866, 791, 777, 729, 705, 693, 522 cm⁻¹.

HRMS (EI): m/z (%) = 296 [M⁺] (9), 265 (2), 191 (1), 165 (2), 133 (3), 115 (2), 104 (100), 78 (7).
cis-5-(3-Bromophenyl)-4-phenyltetrahydrofuran-2-one (cis-1g)

Purification by Kugelrohr distillation (5 x 10^{-4} mbar, 130–150 °C), followed by column chromatography (hexane–MTBE, 5:1); colorless solid; yield: 155 mg (49%).

IR (KBr): 3064, 3030, 2927, 1773, 1756, 1598, 1570, 1495, 1476, 1454, 1434, 1430, 1303, 1261, 1177, 1145, 1073, 1028, 980, 937, 882, 781, 738, 702, 676, 508, 433 cm⁻¹.


Diastereomeric mixture, colorless solid; yield: 310 mg (92%).

IR (film): 3064, 3030, 2927, 1773, 1756, 1598, 1570, 1495, 1476, 1454, 1434, 1430, 1303, 1261, 1177, 1145, 1073, 1028, 980, 937, 882, 781, 738, 702, 676, 508, 433 cm⁻¹.


trans-5-(3-Bromophenyl)-4-phenyltetrahydrofuran-2-one (trans-1g)

Colorless oil; yield: 53 mg (17%).

IR (film): 3064, 3030, 2927, 1773, 1756, 1599, 1570, 1495, 1476, 1454, 1434, 1430, 1303, 1261, 1177, 1145, 1073, 1028, 980, 937, 882, 781, 738, 702, 676, 508, 433 cm⁻¹.


6-Chlorophenyl-4-phenyltetrahydrofuran-2-one (1h)

Diastereomeric mixture; yield: 87 mg (32%).

IR (film): 3064, 3030, 2927, 1773, 1756, 1599, 1570, 1495, 1476, 1454, 1434, 1430, 1303, 1261, 1177, 1145, 1073, 1028, 980, 937, 882, 781, 738, 702, 676, 508, 433 cm⁻¹.


2-(Chlorophenyl)-4-phenyltetrahydrofuran-2-one (1h)

Diastereomeric mixture; yield: 87 mg (32%).

IR (film): 3064, 3030, 2927, 1773, 1756, 1599, 1570, 1495, 1476, 1454, 1434, 1430, 1303, 1261, 1177, 1145, 1073, 1028, 980, 937, 882, 781, 738, 702, 676, 508, 433 cm⁻¹.


5-(2-Chlorophenyl)-4-phenyltetrahydrofuran-2-one (1h)

Diastereomeric mixture; yield: 87 mg (32%).

IR (film): 3064, 3030, 2927, 1773, 1756, 1599, 1570, 1495, 1476, 1454, 1434, 1430, 1303, 1261, 1177, 1145, 1073, 1028, 980, 937, 882, 781, 738, 702, 676, 508, 433 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.75–7.01 (m, 5 H), 6.78–6.71 (m, 2 H), 6.67–6.60 (m, 2 H), 4.25 (dd, J = 9.5 Hz, 6.2 Hz, 1 H), 3.71 (s, 3 H), 3.32–3.22 (m, 1 H), 2.77–2.68 (m, 1 H).

13C NMR (100 MHz, CDCl₃): δ = 173.8, 159.1, 131.3, 129.6, 129.2, 128.8, 127.8, 126.9, 124.6 (q, J = 286 Hz), 113.8, 88.5 (s, J = 29 Hz), 55.2, 45.2, 36.6.

19F NMR (282 MHz, CDCl₃): δ = –76.9.


IR (KBr): 3062, 3038, 3005, 2963, 2935, 2843, 1801, 1614, 1582, 1518, 1452, 1411, 1314, 1292, 1183, 1156, 1131, 1030, 922, 888, 798, 767, 725, 699, 530 cm⁻¹.

IR (film): 3065, 3037, 3005, 2984, 2891, 1716, 1496, 1455, 1410, 1353, 1176, 1140, 1088, 1061, 1030, 992, 969, 754, 698 cm⁻¹.

IR (KBr): 3062, 3038, 3005, 2963, 2935, 2843, 1801, 1614, 1582, 1518, 1452, 1411, 1314, 1292, 1183, 1156, 1131, 1030, 922, 888, 798, 767, 725, 699, 530 cm⁻¹.

IR (film): 3065, 3037, 3005, 2984, 2891, 1716, 1496, 1455, 1410, 1353, 1176, 1140, 1088, 1061, 1030, 992, 969, 754, 698 cm⁻¹.

IR (KBr): 3062, 3038, 3005, 2963, 2935, 2843, 1801, 1614, 1582, 1518, 1452, 1411, 1314, 1292, 1183, 1156, 1131, 1030, 922, 888, 798, 767, 725, 699, 530 cm⁻¹.

IR (film): 3065, 3037, 3005, 2984, 2891, 1716, 1496, 1455, 1410, 1353, 1176, 1140, 1088, 1061, 1030, 992, 969, 754, 698 cm⁻¹.

IR (KBr): 3062, 3038, 3005, 2963, 2935, 2843, 1801, 1614, 1582, 1518, 1452, 1411, 1314, 1292, 1183, 1156, 1131, 1030, 922, 888, 798, 767, 725, 699, 530 cm⁻¹.

IR (film): 3065, 3037, 3005, 2984, 2891, 1716, 1496, 1455, 1410, 1353, 1176, 1140, 1088, 1061, 1030, 992, 969, 754, 698 cm⁻¹.

IR (KBr): 3062, 3038, 3005, 2963, 2935, 2843, 1801, 1614, 1582, 1518, 1452, 1411, 1314, 1292, 1183, 1156, 1131, 1030, 922, 888, 798, 767, 725, 699, 530 cm⁻¹.
Methyl 3-(4-Methoxyphenyl)-5-oxo-2-phenyltetrahydrofuran-2-carboxylate (7f)
Diastereomeric mixture (D1 = like, D2 = unlike), colorless solid; yield: 153 mg (94%).

HRMS (ESI): m/z [M + Na+] calcld for C_{14}H_{18}NaO_{3}: 319.0941; found: 319.0934.

5-Phenyl-4-propyl-5-(trifluoromethyl)tetrahydrofuran-2-one (12b)
Diastereomeric mixture (D1 = like, D2 = unlike), colorless oil; yield: 123 mg (90%).

HRMS (ESI): m/z [M + Na+] calcld for C_{14}H_{18}NaO_{3}: 349.1046; found: 349.1040.
Methyl 5-Oxo-2-phenyl-3-propyltetrahydrofuran-2-carboxylate (12e)
Diastereomeric mixture (D1 = like, D2 = unlike), colorless oil; yield: 93 mg (71%).

\[ R_f = 0.25 \] (hexane–MTBE, 4:1).

\[ R_f = 0.70 \] (D1) 11.84 min (D2).

IR (film): 3566, 2959, 2873, 2065, 1794, 1740, 1493, 1450, 1436, 1227, 1164, 1116, 1052, 1029, 906, 738, 701 cm⁻¹.

\[ R_f = 0.70 \] (D1) 11.28 min (D2).

IR (film): 3566, 2959, 2873, 2065, 1794, 1740, 1493, 1450, 1436, 1227, 1164, 1116, 1052, 1029, 906, 738, 701 cm⁻¹.

\[ R_f = 0.25 \] (hexane–MTBE, 4:1).

HRMS (ESI): \[ m/z \] 295.0916; found: 295.0915.

**u-12c** (single diastereomer obtained from crystallization (CH₂Cl₂–hexane). 

\[ R_f = 0.32 \] (hexane–MTBE, 9:1).

\[ \tau_f = 70.20 \] 9.84 min.

IR (KBr): 2962, 2880, 1798, 1495, 1471, 1451, 1294, 1270, 1244, 1196, 1168, 1124, 1092, 1063, 1016, 943, 768, 730, 709 cm⁻¹.

\[ \tau_f = 70.20 \] 10.34 min (D2).

HRMS (ESI): \[ m/z \] 295.0916; found: 295.0915.

Methyl 3-Methyl-5-oxo-2-phenyltetrahydrofuran-2-carboxylate (12d)
Diastereomeric mixture (D1 = like, D2 = unlike), colorless solid and oil; yield: 101 mg (87%).

\[ \tau_f = 0.70 \] (hexane–MTBE, 9:1).

IR (KBr): 2959, 1794, 1737, 1489, 1448, 1383, 1266, 1212, 1162, 1109, 1027, 996, 832, 704, 632 cm⁻¹.

\[ \tau_f = 10.99 \] (D1) 11.34 min (D2).

HRMS (ESI): \[ m/z \] 295.0916; found: 295.0915.

Methyl 5-Oxo-2-phenyl-3-propyltetrahydrofuran-2-carboxylate (12e)
Diastereomeric mixture (D1 = like, D2 = unlike), colorless oil; yield: 93 mg (71%).

\[ R_f = 0.25 \] (hexane–MTBE, 4:1).

\[ \tau_f = 70.20 \] 11.84 min (D1), 12.18 min (D2).

IR (film): 3566, 2959, 2873, 2065, 1794, 1740, 1493, 1450, 1436, 1227, 1164, 1116, 1052, 1029, 906, 738, 701 cm⁻¹.

\[ R_f = 0.25 \] (hexane–MTBE, 4:1).

HRMS (ESI): \[ m/z \] 295.0916; found: 295.0915.

**u-12c** (single diastereomer obtained from crystallization (CH₂Cl₂–hexane). 

\[ R_f = 0.32 \] (hexane–MTBE, 9:1).

\[ \tau_f = 70.20 \] 9.84 min.

IR (KBr): 2962, 2880, 1798, 1495, 1471, 1451, 1294, 1270, 1244, 1196, 1168, 1124, 1092, 1063, 1016, 943, 768, 730, 709 cm⁻¹.

\[ \tau_f = 70.20 \] 10.34 min (D2).

HRMS (ESI): \[ m/z \] 295.0916; found: 295.0915.
The given document contains data on the synthesis of γ-butyrolactones using N-heterocyclic carbene-catalyzed conjugate umpolung. The text includes 1H and 13C NMR spectra, HRMS data, and IR data for various compounds. Here is a structured representation of the key findings:

**3-Isobutyl-4-phenyl-4-(trifluoromethyl)oxetan-2-one (13c)**
- **IR (film):** 3066, 3034, 2930, 2854, 1499, 1452, 1329, 1268, 1177, 1077, 1045, 1025, 980, 948, 762, 715, 700 cm⁻¹.
- **HRMS (EI):** [M⁺] calcd for C₁₄H₁₁F₃O₂: 244.0711; found: 244.0710.

**3-Benzyl-4-phenyl-4-(trifluoromethyl)oxetan-2-one (13d)**
- **IR (film):** 3066, 3034, 2930, 2854, 1499, 1452, 1329, 1268, 1177, 1077, 1045, 1025, 980, 948, 762, 715, 700 cm⁻¹.

**3-Butyl-4-phenyl-4-(trifluoromethyl)oxetan-2-one (13b)**
- **Diastereomeric mixture, colorless oil; yield: 122 mg (45%).**

**1-3c**
- **Rf = 0.22 (pentane–CH₂Cl₂, 10:1).**

**1-3c**
- **IR (film, mixture of diastereomers):** 2963, 2936, 2875, 1853, 1470, 1452, 1310, 1267, 1217, 1177, 1130, 1077, 1045, 1025, 980, 948, 762, 715, 700 cm⁻¹.

**3-Benzyl-4-phenyl-4-(trifluoromethyl)oxetan-2-one (13d)**
- **Diastereomeric mixture, colorless oil; yield: 130 mg (48%).**

**1-3c**
- **Rf = 0.08 (pentane–CH₂Cl₂, 10:1).**

**1-3c**
- **IR (film, mixture of diastereomers):** 2963, 2936, 2875, 1853, 1470, 1452, 1310, 1267, 1217, 1177, 1130, 1077, 1045, 1025, 980, 948, 762, 715, 700 cm⁻¹.

**3-Butyl-4-phenyl-4-(trifluoromethyl)oxetan-2-one (13b)**
- **Diastereomeric mixture, colorless oil; yield: 122 mg (45%).**

**1-3b**
- **Rf = 0.15 (pentane–CH₂Cl₂, 10:1).**

**1-3b**
- **IR (film, mixture of diastereomers):** 2962, 2935, 2875, 1854, 1451, 1384, 1333, 1271, 1178, 1153, 1125, 1077, 1049, 970, 948, 806, 763, 719, 700 cm⁻¹.

**3-Benzyl-4-phenyl-4-(trifluoromethyl)oxetan-2-one (13d)**
- **Diastereomeric mixture, colorless oil; yield: 130 mg (48%).**

**1-3b**
- **Rf = 0.08 (pentane–CH₂Cl₂, 10:1).**

**1-3b**
- **IR (film, mixture of diastereomers):** 2963, 2936, 2875, 1853, 1470, 1452, 1310, 1267, 1217, 1177, 1130, 1077, 1045, 1025, 980, 948, 762, 715, 700 cm⁻¹.
Methyl 3-Isobutyl-1-oxo-2-phenylexane-2-carboxylate (13e)

Diastereomeric mixture [D1 = diastereomer II, D2 = diastereomer I] (see Figure 6), colorless solid and oil; yield: 126 mg (71%).


3-Methyl-5-phenyl-4-styryl-5-(trifluoromethyl)tetrahydrofuran-2-one (20c-II)

Diastereomeric mixture [D1 = diastereomer I, D2 = diastereomer II] (see Figure 6), colorless solid and oil; yield: 142 mg (82%).

Rf (70_20): 13.02 (D1), 13.32 min (D2).

IR (KBrs): 3063, 3030, 2980, 2938, 1803, 1496, 1450, 1315, 1284, 1258, 1227, 1171, 1134, 1069, 1024, 941, 758, 735, 721 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 7.71–7.65 (m, 4 H), 7.55–7.27 (m, 16 H), 6.70 (d, J = 15.6 Hz, 1 H, D2), 6.66 (d, J = 15.9 Hz, 1 H, D1), 6.47–6.38 (m, 1 H, D2), 5.54 (dd, J = 15.7, 9.5 Hz, D1), 3.34 (dd, J = 11.9, 9.6 Hz, D1), 3.17 (t, J = 11.0 Hz, 1 H, D2), 2.99–2.89 (m, 1 H, D1), 2.51–2.42 (m, 1 H, D1), 1.30 (m, 3 H, D1), 1.28 (d, J = 7.2 Hz, 3 H, D2).
2.95–2.86 (m, 1 H), 2.56 (dd, 1032, 976, 910, 679, 651, 599, 548 cm–1.

19F NMR (282 MHz, CDCl3); δ = −73.8.

MS (EI); m/z (%) = 346 [M'] (6), 215 (1), 202 (2), 144 (100), 129 (75), 115 (9), 105 (7), 89 (2), (77) (8), 65 (2).

HRMS (ESI); m/z [M + Na+] calc for C23H14F2NaO2: 369.1073; found: 369.1070.

3-(2-Chlorobenzyl)-5-phenyl-5-(trifluoromethyl)tetrahydrofur-2-one (21)

Diastereomeric mixture, yellowish oil; yield: 81 mg (46%).

Rf = 0.13 (hexane–MTBE, 40:1).


13C NMR (75 MHz, CDCl3); δ = 175.6, 175.0, 135.4, 135.4, 135.3, 134.0, 134.0, 131.0, 130.9, 129.9, 128.9, 129.5, 128.7, 127.2, 127.2, 126.3, 126.1, 125.5, 123.3, 121.7, 83.1 (q, J = 30.6 Hz), 83.1 (q, J = 30.2 Hz), 39.4, 38.8, 35.7, 34.8, 34.7, 33.5.

19F NMR (282 MHz, CDCl3); δ = −79.5 (D), −79.6 (D).

IR (film); 3013, 2949, 1767, 1489, 1452, 1384, 1348, 1319, 1287, 1222, 1189, 1115, 1074, 1045, 972, 931, 899, 770, 741 cm–1.

1H NMR (300 MHz, CDCl3); δ = 7.43–7.34 (m, 5 H), 4.31 (d, J = 10.7 Hz, 1 H), 4.21 (dd, J = 7.0, 9.5 Hz, 1 H), 3.95 (d, J = 3.3, 9.6 Hz, 1 H), 3.88 (d, J = 10.7 Hz, 1 H), 3.17–2.10 (m, 1 H), 2.95–2.86 (m, 1 H), 2.56 (dd, J = 2.4, 18.4 Hz, 1 H).

1^3C NMR (75 MHz, CDCl3); δ = 175.3, 138.9, 128.8, 128.3, 124.6, 95.5, 80.4, 76.1, 47.6, 34.7.

MS (EI); m/z (%) = 204 [M'] (36), 146 (31), 105 (100), 77 (29).

HRMS (EI); m/z [M'] calc for C12H12O2: 204.0877; found: 204.0874.

(3aR*,6aS*)-6a-Phenyltetrahydrofurano[3a,b]furan-2(3H)-one (27)

A soln of IMes·HCl (23.3 mg, 0.0684 mmol, 0.2 equiv) and KOr-Bu (6.73 mg, 0.060 mmol, 0.17 equiv) in freshly distilled THF (14 mL) was stirred at r.t. for 30 min. (E)-4-(2-Oxo-2-phenyletheno)-but-2-enal (22, 69.8 mg, 0.342 mmol, 1 equiv) was added and the mixture was stirred at 60 °C for 16 h. Silica gel was added and the solvent removed on the rotary evaporator. The residue was purified by column chromatography (hexane–EtOAc, 4:1) to afford 27 as a yellowish solid; yield: 22 mg (35%).

Rf = 0.18 (hexane–EtOAc, 2:1).

IR (film); 3523, 3061, 2978, 2928, 2823, 1776, 1748, 1494, 1447, 1274, 1223, 1203, 1176, 1100, 1060, 1033, 951, 925, 760, 701 cm–1.

1H NMR (300 MHz, CDCl3); δ = 7.45–7.32 (m, 5 H), 4.30 (d, J = 10.7 Hz, 1 H), 4.22 (dd, J = 7.0, 9.5 Hz, 1 H), 3.95 (d, J = 3.3, 9.6 Hz, 1 H), 3.87 (d, J = 10.7 Hz, 1 H), 3.17–3.09 (m, 1 H), 2.95–2.86 (m, 1 H), 2.56 (dd, J = 2.4, 18.4 Hz, 1 H).

13C NMR (75 MHz, CDCl3); δ = 175.3, 138.9, 128.8, 128.3, 124.6, 95.5, 80.4, 76.1, 47.6, 34.7.

MS (EI); m/z (%) = 204 [M'] (36), 146 (31), 105 (100), 77 (29).

HRMS (EI); m/z [M'] calc for C12H12O2: 204.0877; found: 204.0874.
(3aR,9bR)-S-Acetyl-3a-methyl-3a,4,5b-tetrahydrofuro[2,3-c]quinolin-2(1H)-one (31)

IR (film): 1781, 1649, 1606, 1489, 1462, 1377, 1341, 1322, 1296, 117.0, 112.6, 80.3, 53.1, 45.6, 30.1, 18.2.

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References

(2) For example the use of deprotonated dithianes as masked carbonyl anion synthons has become a very popular stoichiometric approach, see: Seebach, D.; Corey, E. J. J. Org. Chem. 1975, 40, 231.


The stereochemistry of the lactones 1a–h is very similar within the cis and trans series. The stereochemistry of the products 1 was therefore assigned by comparison of the NMR data for these compounds with that of cis-1d, whose structure was unequivocally established by X-ray structural analysis. The stereochemistry of lactones 7, 12, and 20 was assigned in an analogous manner. CCDC-246600 (cis-1d), CCDC-250238 (a-7b), CCDC-603356 (12c-I) and CCDC-603357 (20c-II) contain the crystallographic data (excluding structure factors) for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk.

Bode et al. found that when using cis-cinnamaldehyde the same stereochemical outcome as with trans-cinnamaldehyde was observed. Moreover, stopping the reaction of cis-cinnamaldehyde prior to completion a significant amount of trans-cinnamaldehyde was observed, showcasing the importance of homoconelation resonance structure IIb; ref. 7d.


For the Cambridge Structural Database (2004), deposition numbers CCDC-246600 and 250238. (b) Harms, K. private communication to the Cambridge Structural Database (2006), deposition numbers CCDC-603356 and 603357.


Under a different set of reaction conditions (r-ButOH, DBU, THF) and using two equivalents of electrophilic aldehyde, Bode et al. reported improved yields: ref. 7d.

The stereochemistry of the lactones 1, 7, 12, and 20 was assigned by X-ray and NMR analysis. The 1H NMR data for