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pathway. Surprisingly, increasing the catalyst loading from 1 to 2 mol% did not improve the yield of 2a, but rather enhanced the formation of side-product 3a (entry 8). A limit experiment under highly diluted conditions (0.01 M) with a prolonged reaction time (60 h) showed a general decrease in reactivity (entry 9). Solvent evaluation revealed good reactivity in DMSO (entry 12) and a drastic drop of yield in DMF (entry 10) or apolar solvents like toluene (entry 11).

As part of the optimisation study, we investigated the role of different halogens in the mesolysis of the C–X bond and in the following cyclisation step (Table 2). As previously reported by Ishibashi and Curran, the nature of the radical precursor has an effect on the product distribution, and hence we assumed that the analogous mechanism using different catalytic systems could lead to the formation of the same radical intermediates (Scheme 4).

When α-bromoenamide 1a′ was tested under the optimised reaction conditions, a mixture of the expected cyclised product 2a along with the directly reduced side product 3a was obtained, accompanied by 24% of the cyclised-oxidative product 4a (entry 2).

When sodium iodide (2 equiv.) was added to the reaction mixture in order to *in situ* generate the iodide precursor 1a″, the reaction provided only traces of the desired product 2a, while a mixture of 3a (major product in 38% yield) and cyclised-oxidative products 4a and 5a was obtained. Taking note of the role of radical precursors in the product distribution, we began the synthesis of various α-chloroenamides in order to investigate the electronic and steric effects on the cyclisation reaction (Scheme 2).

Although the 5-endo-trig pathway is considered disfavoured, the reaction generally proceeded in moderate to good yields with a broad range of substrates with different substitution patterns. Remarkably, in almost all cases, only one diasteroisomer was formed. The product was obtained in

### Table 1 Optimisation of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Solvent</th>
<th>[mmol ml⁻¹]</th>
<th>2 [%]</th>
<th>3 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂N</td>
<td>MeCN</td>
<td>0.3</td>
<td>19</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>n-Bu₃N</td>
<td>MeCN</td>
<td>0.3</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>i-PrN(Et)₂</td>
<td>MeCN</td>
<td>0.3</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>Et₂N</td>
<td>MeCN</td>
<td>0.06</td>
<td>40</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>n-Bu₃N</td>
<td>MeCN</td>
<td>0.06</td>
<td>41</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>n-Bu₃N</td>
<td>MeCN</td>
<td>0.03</td>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>n-Bu₃N</td>
<td>MeCN</td>
<td>0.02</td>
<td>592 (48)</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>n-Bu₃N</td>
<td>MeCN</td>
<td>0.02</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>n-Bu₃N</td>
<td>MeCN</td>
<td>0.01</td>
<td>42</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>n-Bu₃N</td>
<td>DMF</td>
<td>0.02</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>n-Bu₃N</td>
<td>Toluene</td>
<td>0.02</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>n-Bu₃N</td>
<td>DMSO</td>
<td>0.02</td>
<td>69 (67)</td>
<td>17</td>
</tr>
</tbody>
</table>

*Reaction conditions: α-chloroenamide 1a (0.2 mmol), amine (0.4 mmol), PC = Ir(ppy)₂(dtbbpy)PF₆ (1 mol%), degassed solvent, blue LEDs (450 nm, 11 W), r.t., 22 h, NMR-yield (internal standard: mesitylene); the yield of the isolated product in parenthesis. 40 h reaction time. 60 h reaction time. α-Chloroenamide 1a (0.13 mmol).*
good yield when a heteroatom was introduced as part of the cyclohexane skeleton (1b), but slightly decreased when the substituents were placed in the 4,4’ positions (1c-e); in this particular case, the yield decreased along with the increasing bulkiness (2c, 2d and 2e). It is noteworthy to underline that when two methyl groups were placed in the 5,5’ position (1g) the reaction gave a comparable yield (2g) to the non-substituted one (2a). When the same pattern of substituents was arranged directly next to the olefin bond on the 3,3’ carbon atom (1f), the formation of product 2f dropped to 43% yield. This trend was also observed when a methyl group was placed alpha to the incoming radical (2h). Good yields were observed when different substituents were placed on the nitrogen atom (2i and 2j). Next, we wondered how the diastereoselectivity would be influenced by placing the chiral auxiliary (S)-1-phenethyl group as a removable protecting group in this position (2k). Although the yield was modest, only one diastereoisomer was formed (Scheme 2). The cleavage of the phenethyl group upon treatment with Na/NH3 in THF at -78 °C20 led to the optically pure lactam 6. The absolute configuration of lactam 6 was assigned as 3aR,7aR by comparison with the literature reported compound.20,21 The auxiliary mediated asymmetric induction furnishes a smooth access to the basic structural core of the angiotensin converting enzyme (ACE) inhibitor HOE 498 (Scheme 3).22 Furthermore, we also observed comparable reactivity for the opened-chain system giving 50% yield (2l).

Regarding the mechanism, we assume that irradiation with visible light triggers the photoredox catalytic cycle of Ir3+, whose stable and long-lived (557 ns for Ir(ppy)2(dtbbpy)+7) excited state Ir3+ acts as an oxidant towards trialkylamines (E1/2 = +1.0 V vs. SCE for triethylamine),23 generating the aminium radical cation A+ and Ir2+, which can reduce the α-chloroenamide 1 to the α-carbonyl radical B (Scheme 4). The latter species can then partition between the directly reduced product 3 and the 5-endo cyclised product 2.

However, the ratio between the cyclised product 2 and the directly reduced product 3 depends on the ability of the radical precursor 1 to react with C, either by direct electron transfer (ET) or by halogen atom transfer (AT), to give an acyliminium ion that leads to D after deprotonation. This pathway is particularly favoured for iodo precursors, since they can compete with the hydrogen donor A+, while chlorides cannot. For the iodides it was further reported that the high amount of the directly reduced product 3 can be attributed to the formation of HI during the reaction, which, if not consumed fast enough by an acid/base reaction with the stannane or silane (n-Bu3N in our case), might react ionically with 1 to form 3 and I2.

In conclusion, we developed a mild and tin-free method for the preparation of synthetically valuable γ-lactams24 in good yields and high diastereomeric ratios, using visible light photoredox catalysis. Therewith, we provide the first example of visible light mediated 5-endo-trig cyclisation of α-chloroenamides that, in spite of its synthetic utility, still remains a challenging transformation. Furthermore, the diastereoselective reaction resulted in the formation of a single diastereoisomer, which is of interest for the synthesis of enantiomerically enriched products. The use of α-chloroenamides for the generation of monocyclic γ-lactams is particularly appealing and further application of this photoredox catalysis methodology is currently under investigation.

Acknowledgements

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Notes and references


6 For reviews on thin-free radical reactions, see: (a) P. A. Baguley and J. C. Walton, Angew. Chem., Int. Ed., 1998, 37, 3072; (b) A. Studer and S. Amrein, Synthesis, 2002, 835.


Reaction conditions utilised: syringe pump addition of Bu3SnH (1.2 equiv.) to α-haloenamides at reflux in toluene.

