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**The first visible light mediated tin-free cyclisation of  $\alpha$ -chloroenamides leading to the synthesis of substituted  $\gamma$ -lactams with excellent stereoselectivity is reported. The protocol employs the single-electron reduction of activated C–Cl bonds, which are typically inert towards reduction.**

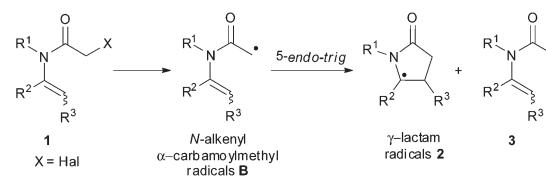
The opportunity to realise unique transformations has attracted the attention of the chemistry community and stimulated, among others, the development of protocols involving the formation of free radicals by single-electron transfer (SET) processes.<sup>1</sup> In particular, free-radical generation from organohalides represents a straightforward way to achieve reactive, open-shell carbon-centred radicals, which has found outstanding applications in natural product synthesis.<sup>2</sup>

However, the requirement of highly toxic radical reducing agents and initiators such as tin hydrides or AIBN, as well as specific and hard to manage equipment stimulated the development of new methods for the generation of free-radicals under benign conditions.<sup>3–6</sup> An alternative is represented by visible light photocatalysis<sup>7,8</sup> that, by means of transition-metal polypyridyl complexes or metal free photosensitizers, provides a valuable and green methodology for the single-electron reduction of carbon–halogen bonds. Yet, this approach seems to be limited to activated carbon–bromine/iodine bonds<sup>9</sup> while only a few examples are reported when the less reactive organochlorides are involved, due to a more negative reduction potential as a consequence of higher carbon–halide bond dissociation energy (BDE).<sup>10</sup> Specifically in the latter case, it is known that the BDE for the carbon–chlorine bond is significantly higher than those measured for the carbon–bromine/iodine bonds ( $\text{CH}_3\text{-Cl}$ , 83 kcal mol<sup>–1</sup>;  $\text{CH}_3\text{-Br}$ , 71 kcal mol<sup>–1</sup>;  $\text{CH}_3\text{-I}$ , 57 kcal mol<sup>–1</sup>),<sup>11</sup> and therefore the mesolysis

by SET often requires prohibitive energies for most of the common visible light photocatalysts.

Nevertheless, the stability of organochloride derivatives, often along with their low cost compared to the corresponding bromide/iodide precursors, stresses the importance of available methods able to overcome the energetic and selectivity issues associated with the functionalisation of this bond. In this context, we wondered if visible light photoredox catalysis can be applied as an alternative to the less favorable agent  $\text{Bu}_3\text{SnH}$  in the synthesis of  $\gamma$ -lactams through a formal 5-*endo*-trig cyclisation.<sup>12,13</sup> This is initiated by the reduction of the carbon–halogen bond of  $\alpha$ -haloenamide **1** to form the corresponding *N*-alkenyl  $\alpha$ -carbamoylmethyl radical **B** (Scheme 1).<sup>14</sup> Despite the stereoelectronic problems associated with this type of reaction (Baldwin–Beckwith's rule),  $\gamma$ -lactams are mainly formed compared to the directly reduced (non-cyclised) side-product **3**.

With these considerations in mind we started our investigation with  $\alpha$ -chloroenamide **1a** as a model substrate. In the course of the optimisation study we first tested a series of amines as suitable stoichiometric reductive quenchers. At a concentration of 0.3 M we noticed the reaction to proceed with good reactivity, with the predominant formation of **3a** after irradiation for 22 hours (Table 1, entries 1–3). Subsequently, we analysed the effect of more dilute concentrations on the product distribution, simultaneously increasing the reaction time from 22 to 40 hours. Low concentration mixtures (entries 5–7) encouraged the formation of the desired product **2a** in good yields along with the regression of the direct reduction



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Table 1 Optimisation of reaction conditions<sup>a</sup>

Entry	Amine	Solvent	[mmol ml <sup>-1</sup> ]	Yield [%]	
				2 [%]	3 [%]
1	Et <sub>3</sub> N	MeCN	0.3	19	43
2	n-Bu <sub>3</sub> N	MeCN	0.3	20	39
3	i-PrN(Et) <sub>2</sub>	MeCN	0.3	20	41
4 <sup>b</sup>	Et <sub>3</sub> N	MeCN	0.06	38	n.d.
5 <sup>b</sup>	n-Bu <sub>3</sub> N	MeCN	0.06	41	n.d.
6 <sup>b</sup>	n-Bu <sub>3</sub> N	MeCN	0.03	48	25
7 <sup>c</sup>	n-Bu <sub>3</sub> N	MeCN	0.02	592 (48)	9
8 <sup>b,d</sup>	n-Bu <sub>3</sub> N	MeCN	0.02	40	11
9 <sup>e</sup>	n-Bu <sub>3</sub> N	MeCN	0.01	42	7
10 <sup>c,f</sup>	n-Bu <sub>3</sub> N	DMF	0.02	11	14
11 <sup>c,f</sup>	n-Bu <sub>3</sub> N	Toluene	0.02	13	5
12 <sup>c,f</sup>	n-Bu <sub>3</sub> N	DMSO	0.02	69 (67)	17

<sup>a</sup> Reaction conditions:  $\alpha$ -chloroenamide **1a** (0.2 mmol), amine (0.4 mmol), PC = Ir(ppy)<sub>2</sub>(dtb-bpy)PF<sub>6</sub> (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. <sup>b</sup> 40 h reaction time. <sup>c</sup> 48 h reaction time. <sup>d</sup> 2 mol% PC. <sup>e</sup> 60 h reaction time. <sup>f</sup>  $\alpha$ -Chloroenamide **1a** (0.13 mmol).

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<sup>15</sup> and Curran,<sup>16</sup> the nature of the radical precursor has an effect on the product distribution, and hence we assumed that the analogous mechanism using different cata-

Table 2 Product distribution as a function of the radical precursor<sup>a</sup>

Entry	X	Additive	Yield [%]			
			2a [%]	3a [%]	4a [%]	5a [%]
1	Cl	—	69	17	—	—
2	Br	—	54	17	24	n.d.
3	Cl	NaI	<5	31	17	22

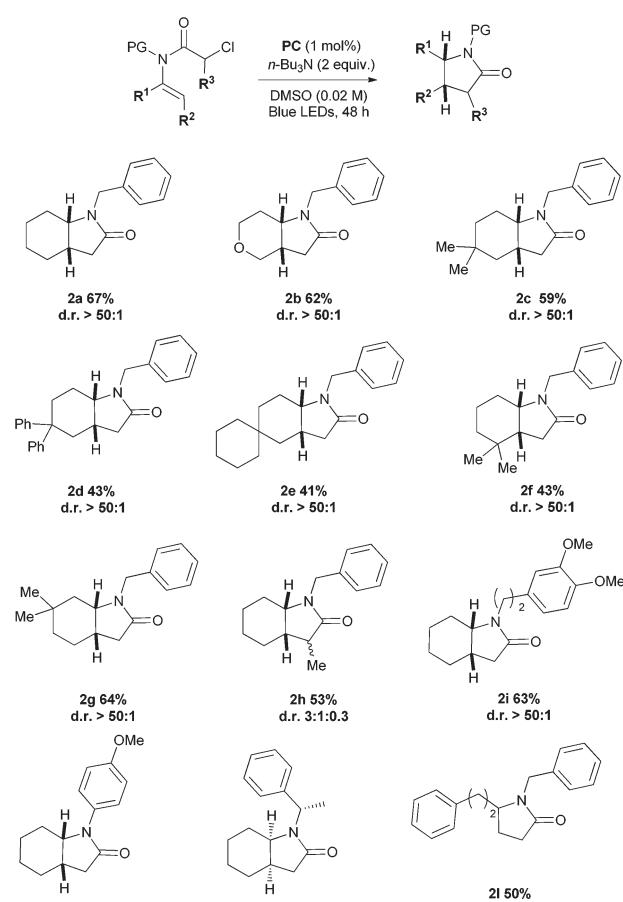
<sup>a</sup> Reaction conditions:  $\alpha$ -haloenamide **1** (0.13 mmol), amine (0.26 mmol), PC (1 mol%), degassed DMSO, blue LEDs (450 nm, 11 W), r.t., 48 h.

lytic systems could lead to the formation of the same radical intermediates (Scheme 4).<sup>17</sup>

When  $\alpha$ -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  $\alpha$ -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,<sup>18</sup> 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 diastereoisomer was formed.<sup>19</sup> The product was obtained in



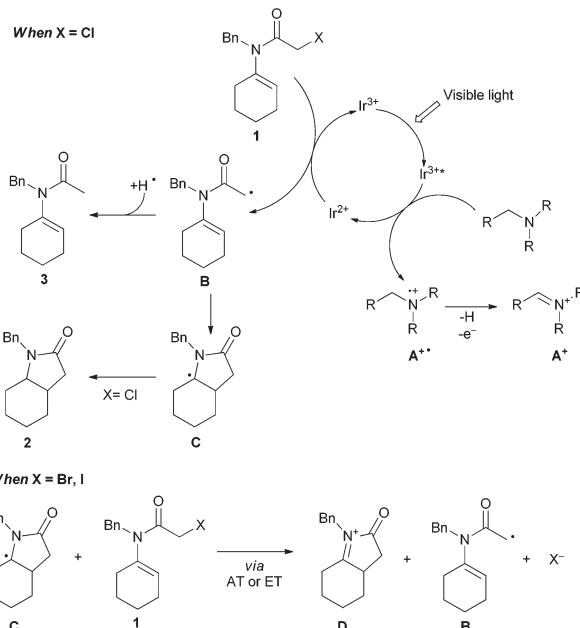
Scheme 2 Scope for the photoredox catalysed 5-*endo-trig* cyclisation of substituted  $\alpha$ -chloroenamides. Reaction conditions:  $\alpha$ -chloroenamide **1** (0.13 mmol), *n*-Bu<sub>3</sub>N (2 equiv.), PC (1 mol%), degassed DMSO, blue LEDs (450 nm, 11 W), r.t., 48 h; yield of the isolated product.



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**).<sup>20</sup> Although the yield was modest, only one diastereoisomer was formed (Scheme 2). The cleavage of the phenethyl group upon treatment with Na/NH<sub>3</sub> in THF at -78 °C<sup>20</sup> led to the optically pure lactam **6**. The absolute configuration of lactam **6** was assigned as 3*aR*,7*aR* by comparison with the literature reported compound.<sup>20,21</sup> 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).<sup>22</sup> 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 Ir<sup>3+</sup>, whose stable and long-lived (557 ns for Ir(ppy)<sub>2</sub>(dtbbpy)<sup>7j</sup>) excited state Ir<sup>3+</sup> acts as an oxidant towards trialkylamines (*E*<sub>1/2</sub> = +1.0 V vs. SCE for triethylamine),<sup>23</sup> generating the aminium radical cation A<sup>•+</sup> and Ir<sup>2+</sup>, which can reduce the  $\alpha$ -chloroenamide **1** to the  $\alpha$ -carbonyl radical **B** (Scheme 4). The latter species can then partition between the directly reduced product **3** and the 5-*endo* cyclised product **2**.

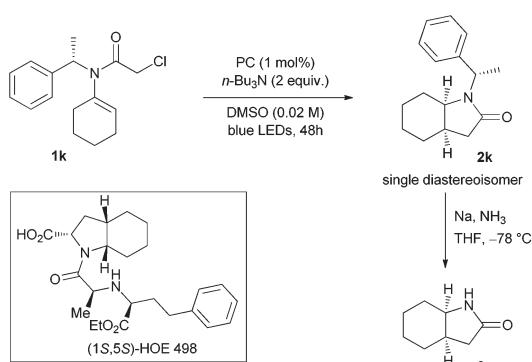
However, the ratio between the cyclised product **2** and the directly reduced product **3** depends on the ability of the radical precursor **1** to react with **C**, either by direct electron



Scheme 4 Postulated mechanism.

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 iodide precursors, since they can compete with the hydrogen donor A<sup>•+</sup>, 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*-Bu<sub>3</sub>N in our case), might react ionically with **1** to form **3** and I<sub>2</sub>.

In conclusion, we developed a mild and tin-free method for the preparation of synthetically valuable  $\gamma$ -lactams<sup>24</sup> 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  $\alpha$ -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  $\alpha$ -chloroenamides for the generation of monocyclic  $\gamma$ -lactams is particularly appealing and further application of this photoredox catalysis methodology is currently under investigation.



Scheme 3 Influence of the chiral auxiliary (*S*)-1-phenethyl group on the asymmetric induction.

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