

# Blue Light-Induced 1,2-Aminochlorination of Olefins using Dichlorocarbamates

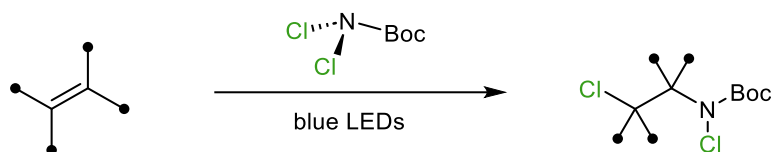
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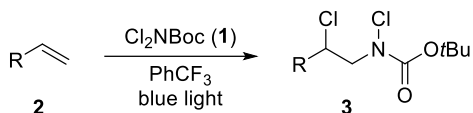
## Abstract:

Activation of *N,N*-dichlorocarbamates with blue light facilitates a direct 1,2-aminochlorination of unactivated olefins to yield 1,2-chloro-*N*-Cl-carbamates under ambient conditions. Mechanistic studies suggest that *N,N*-dichlorocarbamates undergo a photochemical excitation to yield a neutral nitrogen-centered radical, which rapidly reacts with olefins in an anti-Markovnikov fashion. Using the method, a range of functionally diverse substrates are successfully aminochlorinated to yield the corresponding 1,2-chloro-*N*-Cl compounds.

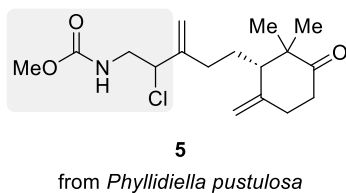
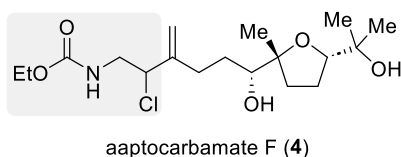
Direct aminochlorination of olefins has gained a lot of attention in the recent years, with the development of a range of organocatalytic, photochemical and metal catalyzed methods.<sup>1-9</sup> Our interest in 1,2-aminochlorinated compounds stems from their presence in recently isolated highly bioactive marine natural products, such as aptocabamate **4** and terpene alkaloid **5** (Scheme 1B).<sup>10,11</sup> When considering different entry points to access these alkaloids, we quickly focused on *N,N*-dichlorocarbamates. The utility of *N,N*-dichlorocarbamates in chemistry since 1960s has largely been limited by issues pertaining to functional group tolerance and complications related to their activation. Previously, *N,N*-

dichlorocarbamates of the type **1** have been applied to 1,2-dichlorination and aminochlorination of highly activated olefins (i.e. styrenes), metal catalyzed (Cr, Cu) amination reactions, and in rare cases photoactivated using UV irradiation under cryogenic and oxygen-free conditions.<sup>12–16</sup> Herein we demonstrate that Cl<sub>2</sub>NBoc (**1**) is much more useful reagent than previously thought, as it can be directly photoactivated with blue light – circumventing numerous prior issues related to generation of N-centered neutral radicals – to aminochlorinate unactivated olefins (**2**) to 1,2-chloro-N-Cl compounds **3** (Scheme 1A). The direct photochemical activation method using **1** does not require photocatalysts or additives, can be carried out under ambient conditions, and achieves broad-scope aminochlorination of unactivated olefins.

**A** Direct photochemical aminochlorination of unactivated olefins (*this work*)



**B** Chlorocarbamate natural products



**Scheme 1:** Photochemical aminochlorination of olefins and utility of chlorocarbamates.

The photochemical activation of N–Cl bonds is generally energetically out of scope for activation for blue light, and UV light is typically required.<sup>17,18</sup> Indeed, the absorption maxima for typical chloramine compounds, such as *N*-Cl piperidine and NHClBoc reside well in the UV region (see ESI for details on the UV/VIS-experiments). However, for the doubly chlorinated *N*-Boc reagent Cl<sub>2</sub>NBoc (**1**), an absorption band is displayed at 400 nm, an excitation wavelength achievable with blue LEDs. Inspired by this discovery, we reacted 1-hexene (**2**) with *N,N*-di-Cl-NBoc reagent **1** under blue LED irradiation in benzene to giving a 70%

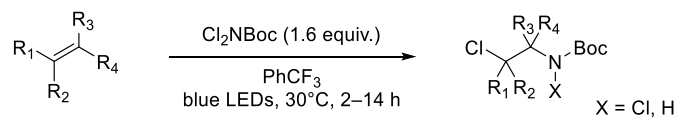
isolated yield of the corresponding anti-Markovnikov *N*-Cl aminochlorinated compound (**6**). Taking the discovery through extensive optimization (see ESI), the best yield (70%) was achieved using trifluorotoluene as the solvent with blue LED irradiation at 30°C. In particular, we noticed that lower temperatures start favoring the corresponding 1,2-dichlorination product over the desired 1,2-aminochlorinated one. The blue light was also required, as in control experiments without blue light or with thermal activation only traces (<5%) of the aminochlorinated product (**6**) was formed. The reaction is remarkably robust: it was not sensitive to either air or moisture, and all reactions could be carried out by simply loading the olefin, solvent and *tert*-butyl-dichlorocarbamate (**1**) into a vial and starting the irradiation. Drying the solvent and excluding air did not lead to marked changes in the isolated yield.

With the optimized reaction conditions at hand, we proceeded to screen a range of olefins (Scheme 2). Numerous aliphatic systems were well-behaved, and yields ranging from 31 to >99% were observed, with the same anti-Markovnikov pattern. The yields were somewhat varied, and under the same conditions, vinylcyclohexane gave a 36% isolated yield. Styrene-type systems were in general well behaved with styrene giving a 47% yield of **8**,  $\alpha$ -methylstyrene an almost quantitative yield (99%) of **9**, and *trans*-stilbene giving a 22% yield of **10** in 22% yield and dr = 50:50.

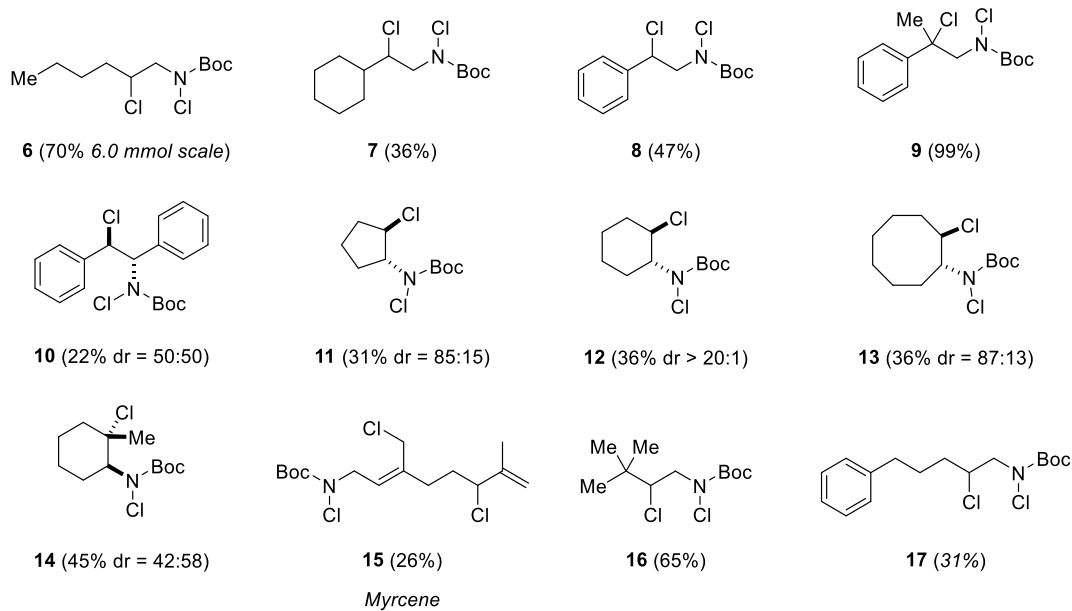
Cyclic olefins ranging from cyclopentene to cyclooctene gave slightly lower yields (31–45% yields) of the corresponding *trans* isomers **11** (31%, dr = 85:15), **12** (36%, dr > 20:1) and **13** (36%, dr = 87:13) as the major products – in contrast to the stilbene. The diastereoselectivity was exceptionally high in the case of cyclohexene **11** (36% dr >20:1) but significantly dropped with the introduction of a methyl group in **14** (45%, dr = 42:58). We were also slightly surprised to observe that myrcene underwent a facile 1,4-aminochlorination as well as a chloro-ene type reaction of the isopropenyl system – to yield polyfunctionalized compound **15** in 26% yield – showcasing that Cl<sub>2</sub>NBoc reagents can support multiple reaction modes. The reaction also tolerated increased steric bulk with **16** providing a 65% yield, but systems with benzylic sites are not as well tolerated as shown with **17** (31%).

With these promising results, we proceeded to study the broader functional group tolerance of the photochemical aminochlorination. The reaction tolerated halides albeit with a significant drop in yield (**18** 15%, **19** 8%). The lower yields could also be due to evaporative losses while removing trifluorotoluene from the crude reaction mixture. The aminochlorination reaction was also amenable to allyl trimethyl silane giving the 1,2,3-functionalized silane **20** in 30 % yield. Silyl protected alcohols were also excellently tolerated, and the TBDPS-protected **21** was isolated in 76% yield. The reaction was found to be remarkably tolerant towards carbonyl functionalities such as ketones (**22**, 66%) and ketoesters (**23**, 75%; **24** 53%). In

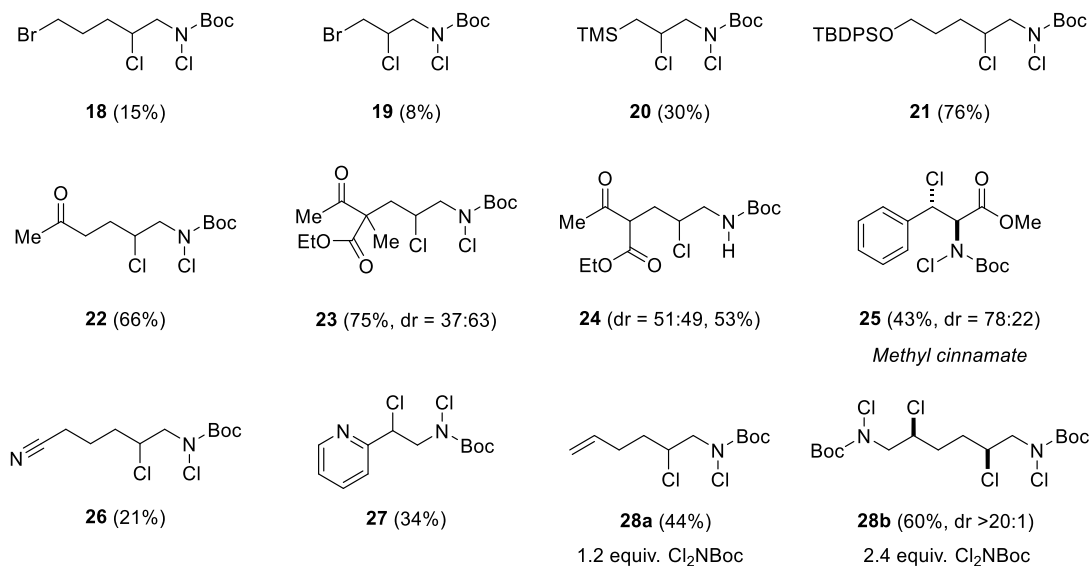
the case of systems containing alpha protons, such as **24**, N-dechlorination was also observed – likely because of an intramolecular 1,5-HAT reaction.<sup>19</sup> While most  $\alpha,\beta$ -unsaturated carbonyl systems we examined (such as cyclohexanone and aliphatic  $\alpha,\beta$ -unsaturated esters) failed to react, methyl cinnamate was amenable to the reaction, giving a 43% yield of **25** as a 78:22 mixture of diastereomers. With the promising results from carbonyl containing substrates, nitrile **26** was also found to be compatible albeit in lower 21% yield. To demonstrate the method with heterocycles, 2-vinylpyridine reacted to yield the corresponding pyridinyl derivative **27** in 34% yield. Finally, we also postulated that by controlling the loading of  $\text{Cl}_2\text{NBoc}$  (**1**), di-olefins could be selectively mono- or diaminochlorinated. With hexa-1,5-diene as the model diene and using 1.2 equivalents of  $\text{Cl}_2\text{NBoc}$  the monofunctionalized product **28a** was formed in 44% yield. Increasing the loading of  $\text{Cl}_2\text{NBoc}$  (**1**) to 2.4 equivalents, the diaminochlorinated product **28b** was formed in a very satisfactory 60% yield and with high diastereoselectivity (>20:1).



### A Hydrocarbons

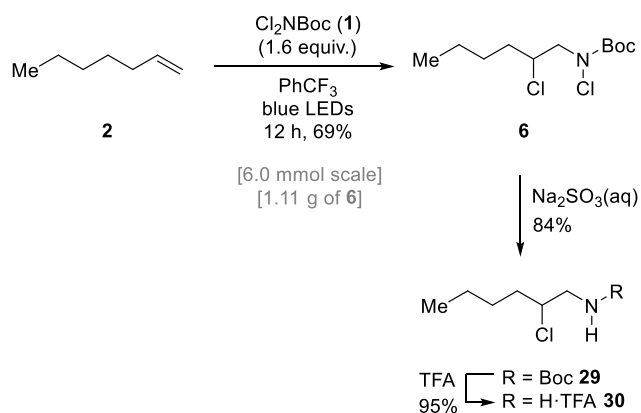


### B Functional group tolerance



**Scheme 2:** Scope of 1,2-aminochlorination. Reagents and conditions: olefin (0.5 mmol, 1.0 equiv.),  $\text{Cl}_2\text{NBoc}$  (0.8 mmol, 1.6 equiv.), 1.0 mL  $\text{PhCF}_3$ , irradiation 2–16 h.

To demonstrate the scalability of the method, aminochlorination of 1-hexene was successfully scaled up to 6.0 mmol scale to give 1.11 g of product **6** in 69% yield in a single batch. With access to large quantities of **6**, we explored utilizing the *N*-Cl aminochlorinated scaffolds by reducing them to corresponding 1,2-chloroamines by an aqueous wash of sodium sulfite (Scheme 3). Treating **6** with sodium sulfite gave the corresponding NHBoc compound **29** in 84% yield. The N-Boc protection was then removed with trifluoroacetic acid (TFA) resulting free chloramine as the trifluoroacetate salt **30** in a near-quantitative 95% yield.

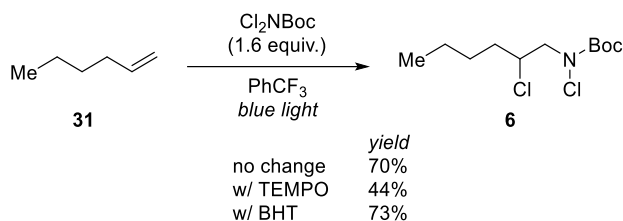


**Scheme 3:** Scale-up, N-dehalogenation and deprotection of **6**.

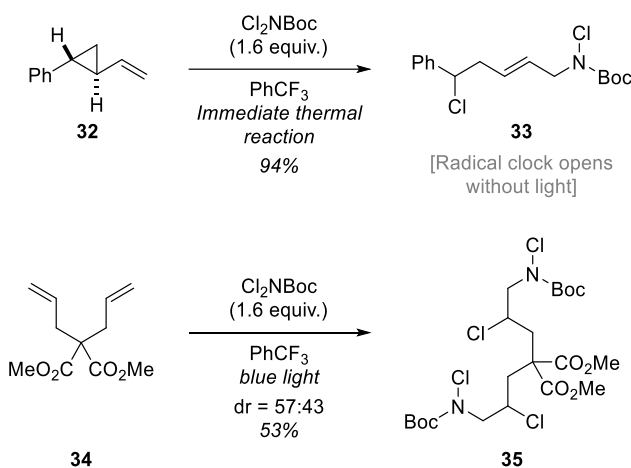
As the visible light activation of *N,N*-di-Cl-NBoc (**1**) systems have not precedence, we had to first differentiate between ionic and radical pathways. Carrying out the aminochlorination of 1-hexene (**31**) in the presence of TEMPO led to lower isolated yields (from 70% to 44% with TEMPO) but did not completely shut down the reaction (Scheme 4A) and with BHT the yield remained mostly unaffected. The experiments indicate that radical intermediates might be plausible but extremely short-lived due to lack of significant trapping and complete loss of yield. When the reaction was carried out with a radical clock substrate **32** the ring-opening reaction occurred immediately upon contact with **1** and without blue light to yield the product **33** in 94% yield as the sole product, which is a clear indication of a thermal radical mechanism. To select a more unreactive radical clock substrate, we prepared diallylic system **34** which did not show any thermal reaction (Scheme 4B).<sup>20</sup> Upon irradiation with blue light, the diolefin **34** delivers solely the mono and diaminochlorinated products with **35** being the major product. The radical 5-exo-trig cyclization product of **34** could not be detected even in trace amounts in NMR. This observation could be a result of an ionic aziridinium type pathway, or a rapid trapping of an initially forming C-radical with Cl. Finally, carrying out UV/VIS experiments on the *N,N*-dichloro-N-Boc reagent **1** and *N*-monochloro-NH-Boc reagent

revealed that the absorption maximum shifts drastically from 400 nm to 310 nm. This reactivity difference was further verified as the ClHNBoc reagent did not work in the photochemical aminochlorination (Scheme 4C), indicating that both chlorine atoms were essential for the observed photochemical reactivity.

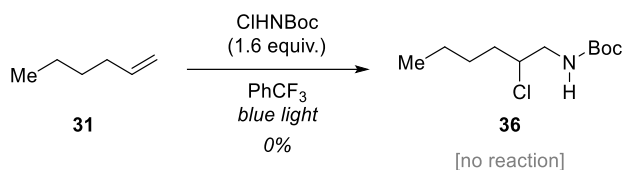
#### A Radical scavengers



#### B Radical clock experiments



#### C Control experiments



### Scheme 4: Mechanistic control experiments.

With these results, we proceed to probe the possible photochemical excitation pathways using computations. Density functional theory (DFT) computations at M062X/6-31+G(d,p) level of theory were carried out in Gaussian16. Gas-phase time-dependent density functional (TD-DFT) calculation performed on Cl<sub>2</sub>NBoc (**1**) indicated the S<sub>0</sub> to S<sub>1</sub> excitation to be dominated by a transition from an occupied π\*-type HOMO to σ\*<sub>N-Cl</sub> type LUMO (Scheme 5A). The calculated excitation energy corresponds to λ<sub>max,computed</sub> = 395.9 nm which agrees well with the experimental measurements (λ<sub>max,experimental</sub> = 400 nm) and falls in the

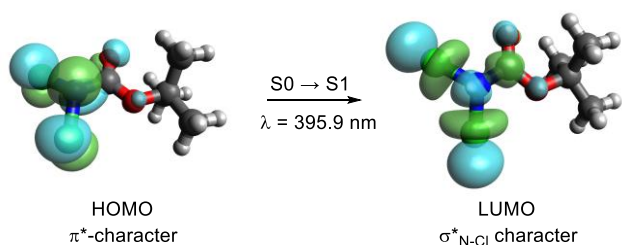
blue light regime of the visible spectrum (380–485 nm). The excited state decomposes to yield a N-centered radical and a Cl radical. Without the photochemical excitation, the N–Cl thermal bond dissociation energy is computed to be 36.9 kcal/mol.

To better understand why **1** has a particularly low-energy transition  $S_0$  to  $S_1$  transition, we applied qualitative molecular orbital theory. Analysis of the computed HOMO of  $\text{Cl}_2\text{NBoc}$  (**1**) showcases  $\pi^*$ -antibonding character arising from the contiguous  $3p_{\text{Cl}}-2p_{\text{N}}-3p_{\text{Cl}}$  arrangement, which suggests a significant antibonding effect to be present in the Cl–N–Cl system.<sup>21</sup> The occupied  $\pi^*$ -type orbital can therefore partially cancel out some of the  $\sigma$ -bonding in the N–Cl, weakening the N–Cl bond with respect to a typical N–Cl bond, making the  $\text{Cl}_2\text{NBoc}$  (**1**) reagent more reactive both photochemically as well as thermally. In addition, the effect lowers the photoexcitation energy by raising the HOMO of **1** significantly when compared to  $n_{\text{N},2p}$  type HOMO alone. This analysis is also in line with the control experiment in Scheme 4D where a single chlorine atom is not enough to achieve photochemical activation with blue light.

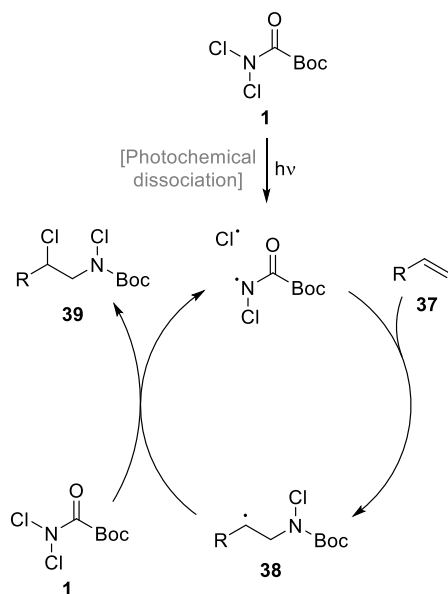
With the generated N-centered radical, we then computed the energetics for aminochlorination of **37** to contrast the cyclization vs. direct aminochlorination pathways. The initial N-radical attack **37**  $\rightarrow$  **38** to the olefin has a low barrier  $\Delta G = 8.2$  kcal/mol. The thus generated secondary radical has a significantly lower energy barrier for abstracting a chlorine from another  $\text{Cl}_2\text{NBoc}$  (**1**) ( $\Delta G = 5.1$  kcal/mol), than undergoing a cyclization ( $\Delta G = 11.2$  kcal/mol). Therefore, **38** + **1**  $\rightarrow$  **39** step regenerates the N-centered radical for another cycle. This rapid radical propagation step with  $\text{Cl}_2\text{NBoc}$  (**1**) is the likely reason that the more unreactive radical clock **34** aminochlorinated rather than cyclized, despite the Thorpe–Ingold effect imposed by the geminal dimethylester.



### A TDDFT computations



### B Proposed reaction mechanism



**Scheme 5:** Computational studies and the proposed mechanism.

In conclusion, we have demonstrated that blue light can highly effectively cleave the N–Cl bond of  $\text{Cl}_2\text{NBoc}$  (**1**) to yield a highly reactive N-centered radical. The photochemically generated NClBoc-radical successfully couples with a range of unactivated and activated olefins to yield 1,2-aminochlorination products. The thus obtained *N*-chlorocarbamates can be reduced and deprotected to yield 1,2-chloroamines. Computational studies indicate a highly facile photochemical N–Cl bond cleavage and very low-energy (<10 kcal/mol) pathways for the ensuing radical aminochlorination. In addition, a qualitative molecular orbital analysis seems to indicate that the N–Cl bond in **1** is weakened by the antibonding effect stemming from consecutive  $3p_{\text{Cl}}-2p_{\text{N}}-3p_{\text{Cl}}$  orbital arrangement. Further work on utilizing the photochemically generated N-centered radicals is currently ongoing in our laboratory.

## Acknowledgements

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