Dimeric cyclobutane formation under continuous flow conditions using organophotoredox catalysed [2+2]-cycloaddition

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Abstract: Radical cation-initiated dimerization of electron rich alkenes is an expedient method for the synthesis of cyclobutanes. By merging organophotoredox catalysis and continuous flow technology a batch versus continuous flow study has been performed providing a convenient synthetic route to an important carbazole cyclobutane material dimer t-DCzCB using less only 0.1 mol% of an organophotoredox catalyst. The scope of this methodology was explored giving a new class of functional materials, as well as an improved synthetic route to styrene based lignan dimeric natural products. The cyclobutane dimers could be isolated in higher chemical yields under continuous flow conditions and reaction times were reduced significantly compared to traditional batch reaction conditions.

INTRODUCTION

The dimerization of electron rich alkene building blocks, such as enamines and styrenes, provides a convenient synthetic route to valuable cyclobutane functional materials and natural products (scheme 1).\(^1\)

Vinyl carbazole (2, VCZ), a valuable monomer for the formation of conductive polymers, can serve as a precursor for 1,2-transdicarbazolylcyclobutane (1, t-DCzCB), a cyclobutane dimer used as a host material for blue electrophosphorescence and PhOLEDs.\(^2\) Similarly, naturally occurring styrenes such as E-asarone (4) can be seen as precursors of dimeric cyclobutyl natural products such as the anti-inflammatory lignan magnosalin (3), and its derivatives; presumably through a biomimetic light induced dimerization process.\(^3\)

The synthesis of cyclobutanes of this type are accomplished via a radical cation-induced [2+2]-cycloaddition (scheme 2).\(^10\) The key alkene radical cation intermediate (6) for these dimerizations can be generated using two methods; (i) through chemical oxidation or (ii) by utilizing photochemical methods (scheme 2A) of an electron rich alkene (5).\(^10\)\(^4\) The radical cation intermediate 6 then undergoes a [2+2]-cycloaddition with another equivalent of 5, giving the cyclobutyl radical cation 7 which is subsequently reduced providing the dimeric cyclobutane 8.

The homo [2+2]-cycloaddition of VCZ (2) has a rich history; chemical oxidation was first reported by Wang and co-workers using 2 with Fe(III) salts giving t-DCzCB (1).\(^10\)\(^a\) This transformation

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was further explored with 2 by Ledwith using both Fe(III) and Ce(IV)-salts. More recently, organomediated chemical oxidation using Heliquats (H4Qs) has also achieved the dimerization of 2 to t-DCzCB (1). Photochemical dimerization of 2 was first reported by Ellinger and Ledwith in 1965 using organophotosensitizers, and more recently a TiO2 photodimerization was achieved by Mizuno and co-workers.

With emergence of visible light photoredox catalysis, Yoon and co-workers demonstrated the effectiveness of Ru- and Ir-complexes in synthesizing symmetrical (and unsymmetrical) cyclobutanes from electron rich olefins. Nicewicz and co-workers then reported the dimerization of several classes of electron rich alkenes using a pyrillium organophotoredox catalyst (scheme 2B). The use of an organophotoredox catalysts (10) in these transformations has significant advantages over metal-based catalysts; including environmental, sustainability and cost factors. However, reaction times for the organophotoredox catalyzed dimerizations were excessive in some cases, cryogenic conditions were required for certain substrate classes, and the catalysis loadings (typically 3 mol%) were not as low those obtained using the Ru- and Ir-photoredox catalysed systems, where loadings of 0.025% could be employed. The use of continuous flow technology also has advantages in photoredox transformations. For examples transferring photochemical reactions from batch to continuous flow can lead to more efficient irradiation of the starting substrates, leading to higher conversions to the desired product. Recently, a heterogenous photoredox fixed bed flow chemical process using metal free polymeric carbon nitrides was reported providing a scalable route to cyclobutane dimers (scheme 2C).

Herein, we report a protocol that delivers cyclobutane functional materials and natural products by merging homogenous small molecule, sustainable, organophotoredox catalysis with continuous flow technology (scheme 3).

This work - merging organophotoredox and continuous flow

Scheme 3. Plausible cyclobutane dimer synthesis by the merging organophotoredox catalysis and continuous flow technology.

We began this study by undertaking a comparison of continuous flow versus the batch reaction conditions on commercially available VCZ (2, scheme 4). It was anticipated this may provide a convenient synthetic route to t-DCzCB (1) using continuous flow technology. Furthermore, we elected to use a commercial, off-the-shelf, continuous flow platform given their excellent useability together with their improved availability in recent years. In our hands, the batch synthesis of t-DCzCB was achieved using the organophotoredox catalysts 10 (3 mol%) and the conditions of Nicewicz, thereby providing 1 in 82% isolated yield (scheme 4). Significantly, this reaction required deoxygenated acetone, cryogenic temperatures, and extended reaction times to achieve optimal conversion to the desired cyclobutane dimer.

Optimization of the continuous flow synthesis of 1 was determined through HPLC-analysis using p-terphenyl as an internal standard (table 1). This required calibration of the 2 and 1, full details of which can be found in the supporting information. Optimal synthesis of 1 was realized at a flow rate of 0.5 mL.min⁻¹ (τ = 20 min) with a catalyst loading of 2 mol % (entry 1) with irradiation at 450 nm. A modest reduction in yield to 90% was observed at an increased catalyst (10) loading of 4.5 mol % (entry 2), while a reduction to 1 mol% of 10 resulted in a marginal reduction in yield of 93% (entry 3). To probe potential reversibility of the dimerization reaction in continuous flow we lowered the flow rate from 5 mL.min⁻¹ to 2 mL.min⁻¹, observing a noticeable reduction in yield to 79% using 2 mol% of 10 (entry 4); a comparable decrease in yield (82%) was observed using at 1 mol% of 10 (entry 5). This reduction in the formation of 1 was further exacerbated when the flow rate was reduced to 0.1 mL.min⁻¹ (τ = 100 min) where the yield of 1 dropped to a very modest 53% (entry 6). We also observed the formation of a significant amount carbazole under the reaction condition in entry 6, as confirmed by HPLC analysis. We attributed the formation of carbazole to background oxidation of 2 by adventitious oxygen within flow system. The extended reaction time and possible reversibility of the dimerization would increase the likelihood of 1O₂ oxidation of 2 to N-formylcarbazole, whose hydrolysis would give carbazole. The UV absorbance of the catalyst 10 led us to probe two further wavelengths, 405 nm, and 420 nm, both of which provided 1 in comparable yields to 450 nm irradiation at 0.5 mL.min⁻¹ (entries 7 and 8, respectively). The dimerization did not proceed in the absence of 10 (entry 9) nor in the absence of irradiation (entry 10). Finally, the dimerization was performed at 10 mmol scale of 2 using only 0.1 mol% of 10 at 0.5 mL.min⁻¹ providing t-DCzCB 1 in 79% isolated yield (entry 11). This catalyst loading is now greatly reduced compared to the batch conditions and is nearing the efficiencies of the Ru-based system reported by Yoon.
Having established robust continuous flow conditions for the formation of 1, an expansion of the cyclobutyl carbazole products available through this transformation was investigated. Surprisingly, given the importance of developing novel carbazole based photophysical host materials, there are very limited reports on the synthesis of t-DCzCBs possessing functional groups. Typically, functionalization is achieved through chemical modification of the parent t-DCzCB scaffold through electrophilic aromatic substitution, which can severely limit substrate scope (i.e., 3 and 6-positions). We therefore envisaged a superior approach could be realized through a vinylation / dimerization strategy of more heavily substituted carbazoles (scheme 5).

Our initial substrate scope examination was centered on synthesizing brominated t-DCzCB substrates. These substrates could be used as potential building blocks through existing transition metal cross coupling reactions. While vinyl carbazole (VCZ) is commercially available, the vinyl carbazoles necessary for our expanded substrate study required synthesizing. This was conveniently achieved using the method of Obora and coworkers providing each vinyl carbazole (12a-24a) in moderate to good yields. The only exception to this was 1-bromo-9-vinylcarbazole (15a), the isolation of which proved problematic and could only be achieved in very low yields.

Each bromo substituted vinylcarbazole was then dimerized using batch conditions and continuous flow conditions to ascertain a comparison between the two synthetic approaches (scheme 5). The solubility of all starting vinyl carbazoles in acetone proved challenging at the 0.4 M concentration used for the VCZ to t-DCzCB optimization. We therefore performed the continuous flow dimerization at a reduced concentration of 0.2 M in acetone which necessitated a review of the flow rate. The dimerization 3-bromo-9-vinylcarbazole (12a) under batch conditions provided the carbazole dimer 12b in 48% isolated yield. Unlike the batch dimerization of VCZ (2) to t-DCzCb (1), the dimerization of 12a required significant longer reaction times (5 days). Three flow rates were trialed for the continuous flow conditions with 12a with 0.2 mL min\(^{-1}\) (t = 50 min) providing 12b in an improved isolated yield of 64%. Batch dimerization of 13a provided the cyclobutane dimer 13b in 31% isolated yield. In contrast, using the continuous flow conditions at 0.2 mL min\(^{-1}\) gave an improved isolated yield of 13b of 71% in a considerably shorter time-period. Comparable batch versus flow reaction profiles were observed for 4-bromo-9-vinylcarbazole (14a) with the continuous flow conditions providing improved isolated yields of the dibromocyclobutane dimer 14b. In contrast, 1-bromo-9-vinylcarbazole (15a) proved a very challenging substrate to dimerize using both batch and continuous flow conditions with no observed cyclobutane product (15b) being detected by \(^1\)H NMR analysis. We examined the dimerization of two dibromo substituted vinyl carbazoles 16a and 17a. 3,6-Dibromo-9-vinylcarbazole (16a) could be dimerized in fair great efficiencies under continuous flow conditions, providing 16b in 65% isolated yields. In contrast, the observed disparity in isolated chemical yields was less apparent for 2,7-dibromo-9-vinylcarbazole (17a) with the batch reaction conditions slightly outperforming the continuous flow conditions to give 17b.

Generally, under the continuous flow reaction conditions completion could be attained in under 1h, whereas using the batch reaction conditions required significantly more time to affect dimerization. With the continuous flow conditions outperforming batch conditions, we next examined the performance of several mono- and disubstituted carbazoles solely using continuous flow. The 2-chloro (18a) and 2-methoxy-9-vinylcarbazoles (19a) could be cleanly dimerized using the continuous flow conditions to provide the carbazole cyclobutane dimers 18b and 19b in 61% and 45%, yield, respectively. The vinylation of 2-hydroxycarbazole gave the bis-vinylated product 20a in 62% yield. We anticipated that the organophotoredox conditions may provide an opportunity to undertake a chemoselective dimerization of this substrate, and this was indeed the case, as dimerization of 20a provided the cyclobutyl bis-enolether 21b, albeit in a modest isolated yield of 25%; the two enol ethers on 21b can be seen as synthetic handles for post modification or polymerization. Palladium mediated Suzuki coupling of 2-bromocarbazole with 4-methoxybenzene boronic acid and 4-fluorobenzene boronic acid, followed by vinylation provided the 2-arylated vinylcarbazoles 21a and 22a, respectively. The solubility 21a was poor in acetone and this was reflected in a moderate isolated yield of 22% for formation of the cyclobutane 21b. In contrast, the 4-fluoroarylated vinyl carbazole 22a displayed improved solubility in acetone and

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**Table 1. Optimization study**

| entry | variation from optimal conditions | yield (%)[^A] |
|-------|----------------------------------|--------------|
| 1     | none                             | 98           |
| 2     | 4.5 mol % cat. 10                | 90           |
| 3     | 1 mol % cat. 10                  | 93           |
| 4     | Flow rate 0.2 mL min\(^{-1}\)   | 79           |
| 5     | Flow rate 0.2 mL min\(^{-1}\) & 1 mol % cat. 10 | 82 |
| 6     | Flow rate 0.1 mL min\(^{-1}\) & 1 mol % cat. 10 | 53 |
| 7     | Flow rate 0.1 mL min\(^{-1}\) at 405 nm | 92 |
| 8     | Flow rate 0.1 mL min\(^{-1}\) at 420 nm | 94 |
| 9     | w/o cat. 10                      | -            |
| 10    | w/o irradiation                  | -            |
| 11[^C]| 0.1 mol % cat. 10                | 79[^D]       |

[^A]: The continuous flow reaction was performed at 1.00 mmol of 2 at 0.4 M in acetone using the flowrate, catalyst loading, and wavelength stated. [^B]: Determined by HPLC using p-terphenyl as an internal standard unless otherwise stated. [^C]: Performed on 10 mmol of 2. [^D]: Isolated yield.
consequently, the cyclobutane 22b was isolated 65% yield. In an analogous fashion, 3,6-di-tert-butylcarbazole was vinylated to give 23a in quantitative yields with subsequent dimerized to providing the tetra-alkyl substituted cyclobutyl dimer 23b in 57% yield. Finally, a two-fold Suzuki coupling of 3,6-dibromocarbazole with 4-fluorobenzene boronic acid, with subsequent vinylation provided the 3,6-bisarylated 9-vinyl carboxazoles 24a. Dimerization of 24a using these flow conditions, then provided the cyclobutane 24b in a modest yield of 50%.

The synthetic potential of the bromocyclobutane products was then briefly explored (scheme 6). A palladium mediated Suzuki cross-coupling of the 13b with 4-methoxybenzene boronic acid using the conditions of Kumar and Tao15 provided the cyclobutane 25 in a yield of 75%. Similarly, palladium mediated borylation using bis(pinacolato)diboron16 provided an expedient route to 26 in a modest yield of 36%.

Scheme 5. Vinylation / dimerization approach toward novel carbazole dimers using continuous flow; [A] see the supporting information for experimental conditions and full characterisation; [B] batch conditions: vinylcarbazole (1.00 mmol, 0.4 M acetone), 10 (5 mol%), 0° C, 450 nm (Kessil lamp) 5 days; [C] Continuous flow conditions: vinyl carbazole (1.00 mmol, 0.2 M, acetone), 10 (2 mol%), 0.2 mL.min⁻¹; (t = 50 min), 450 nm.

Scheme 6. Derivatisation of the bromo-disubstituted carbazole cyclobutane dimers 13b and 14b.
These two transformations demonstrate the potential of these brominated cyclobutylcarbazoles as viable synthetic building blocks, amenable to subsequent synthetic manipulation. Finally, we extended this continuous flow methodology by examining the performance of electron rich styrenes (scheme 7) Batch dimerization of these substrate types using organophotoredox had been realized by Nicewicz and co-workers. To facilitate dimerization the authors utilized a sub-stoichiometric amount of an electron relay (anthracene or diethylamline) which had partially suppressed the undesired polymerization of the starting styrene.

![Scheme 7: Dimerization of electron rich styrenes under continuous flow conditions](image)

Introduction of 4-methoxy styrene (27) into the continuous flow conditions provided the dimer 28 in a modest isolated yield 44%. As observed by Nicewicz and co-workers, introduction of an electron relay, anthracene, greatly improved product outcome. Practically, introduction of the electron relay (0.25 eq. of anthracene) was uncomplicated and was achieved by adding it to the starting solution of the styrene before introduction into the continuous flow apparatus. Styrene 29, in the presence of diethylamine as an electron relay, provided pellucidin A in an isolated yield of 22% using the continuous flow conditions. Finally, E-aserone (3) was then successfully dimerized, again using anthracene as an electron relay, on a 10 mmol scale providing the lignan magnosalin 4 in 40% isolated yield. In contrast to the traditional batch organophotoredox dimerization, the conditions used in scheme 7 did not require cryogenic temperatures and could be completed in significantly shorter time periods.

**CONCLUSION**

In summary, we have developed a continuous flow protocol for organophotoredox catalyzed dimerization of vinylcarbazoles and styrenes, giving high value cyclobutane materials and natural products. This protocol exploits traditional organophotoredox catalysis and a commercial continuous flow platform, dovetailing them to deliver a general, robust, and scalable route to a valuable carbazole host material. The advantage of our continuous flow protocol is demonstrated by comparison with traditional batch conditions, with reaction times and catalyst loadings reduced. The applicability of our methodology is demonstrated by the synthesis of a new family of cyclobutane carbazoles dimers, possessing functionality which should find them well placed to be exploited as novel functional materials. Finally, we were able to apply our continuous flow protocol to deliver a scalable synthesis of styrene based lignan dimeric natural product magnosalin. Our application of organophotoredox catalysis and continuous flow in the synthesis of new functional materials demonstrates the distinct advantages to traditional batch chemistry, such as scalability, and should find relevance to the synthesis new photophysical materials and natural products.

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**Conflict of Interest**

The authors declare no conflict of interest

**Keywords:** cyclobutane • photoredox • continuous flow • dimer • cycloaddition

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