Triarylmethyl Cation Catalysis: A Tunable Lewis Acid Organocatalyst for the Synthesis of Bisindolylmethanes

Nicholas G. Boekell
Trinity College

Dana J. Cerone
Trinity College, Hartford Connecticut

Maria M. Boucher
Trinity College, Hartford Connecticut

Wilfried B. Nganyak Tentchou
Trinity College, Hartford Connecticut

Christine G. Reavis
Trinity College, Hartford Connecticut

See next page for additional authors

Follow this and additional works at: http://digitalrepository.trincoll.edu/facpub
Part of the Chemistry Commons
Triarylmethyl Cation Catalysis: A Tunable Lewis Acid Organocatalyst for the Synthesis of Bisindolylmethanes

Nicholas G. Boekell
Dana J. Cerone
Maria M. Boucher
Phong K. Quach
Wilfried B. Nganyak Tentchou
Christine G. Reavis
Ifeanyi I. Okoh
Jordan O. A. Reid
Hayley E. Berg
Briana A. Chang
Cheyenne S. Brindle*

Trinity College, 300 Summit Street, Hartford, CT 06106, USA
cheyenne.brindle@trincoll.edu

Received: 29.06.2017
Accepted after revision: 07.08.2017
Published online: 22.08.2017

License terms: 

Abstract

Triarylmethyl cations serve as tunable organocatalysts for the synthesis of bisindolylmethanes. The catalyst structure can be modified to increase or decrease reactivity as needed to match the requirements of the substrate. High yields are achieved for a variety of substrates by using these green catalysts. Catalyst tuning allows for the use of less reactive electrophiles by increasing the reactivity of the catalyst. Acid-sensitive products can be isolated under these mild reaction conditions.

Key words antibiotics, carbocation, catalysis, electrophilic aromatic substitution, green chemistry, indoles, Lewis acids

The development of carbon-based catalysts, or organocatalysts, has flourished in recent years as alternatives to metal-based catalysts, which are frequently costly, sensitive to air and moisture, and toxic.1–4 The majority of these green chemistry efforts have focused on the creation of nucleophilic5,6 or Brønsted acid catalysts, such as proline7–9 and organophosphoric acids.10–12 Research focused on the development of organocatalytic Lewis acids has received far less attention, despite reports of the efficacy of triarylmethyl or trityl cation catalysis in the 1980s.13–15 Recent reports by Franzén and co-workers have revived interest in organocatalytic Lewis acids.16 Reports of their utility for Diels–Alder reactions, conjugate additions,17 α-halogenation, epoxide rearrangements, intramolecular ene reactions,18 and an unusual oxo-metathesis reaction19 have been described. Recently, the use of chiral counterions has allowed for enantioselective catalysis of a Diels–Alder reaction.20 These successes may portend the applicability of these organocatalysts as general Lewis acid catalysts for a wide range of applications.

One of the main advantages of this class of Lewis acids is the ability to tune their reactivity by changing the identity of the aryl substituents (Figure 1). Indeed, the stability of trityl cations has been shown to span over eight orders of magnitude.21 Electron-donating substituents stabilize the cation, reducing its reactivity toward nucleophiles. Conversely, adding electron-withdrawing groups decreases cation stability, increasing reactivity toward nucleophiles.

The development of carbon-based catalysts, or organocatalysts, has flourished in recent years as alternatives to metal-based catalysts, which are frequently costly, sensitive to air and moisture, and toxic.1–4 The majority of these green chemistry efforts have focused on the creation of nucleophilic5,6 or Brønsted acid catalysts, such as proline7–9 and organophosphoric acids.10–12 Research focused on the development of organocatalytic Lewis acids has received far less attention, despite reports of the efficacy of triarylmethyl or trityl cation catalysis in the 1980s.13–15 Recent reports by Franzén and co-workers have revived interest in organocatalytic Lewis acids.16 Reports of their utility for Diels–Alder reactions, conjugate additions,17 α-halogenation, epoxide rearrangements, intramolecular ene reactions,18 and an unusual oxo-metathesis reaction19 have been described. Recently, the use of chiral counterions has allowed for enantioselective catalysis of a Diels–Alder reaction.20 These successes may portend the applicability of these organocatalysts as general Lewis acid catalysts for a wide range of applications.

One of the main advantages of this class of Lewis acids is the ability to tune their reactivity by changing the identity of the aryl substituents (Figure 1). Indeed, the stability of trityl cations has been shown to span over eight orders of magnitude.21 Electron-donating substituents stabilize the cation, reducing its reactivity toward nucleophiles. Conversely, adding electron-withdrawing groups decreases cation stability, increasing reactivity toward nucleophiles.

This uniquely wide range of reactivity may allow for catalysis of reactions with very disparate activation barriers using the same molecular scaffold. This remarkable feature could lead to a general Lewis acid catalyst for a wide array
of nucleophile/electrophile combinations. This is especially useful in gaining specificity in situations when multiple reaction pathways are available. The ability to increase or decrease reactivity is also important to gain generality of reaction conditions across a wide scope of reaction partners. To probe these two features, we chose to look at the Friedel–Crafts reaction of indoles with aldehydes, with a wide array of electronic properties and chemical sensitivities, to investigate whether trityl cations can behave as selective and tunable organocatalysts. The products of these reactions, bisindolylmethanes, have a wide array of biological activities, including antibiotic and antitumor properties. This important family of compounds has garnered significant attention from synthetic chemists, and various successful methods have been disclosed, including several green methods. The proposed mechanism of the trityl-catalyzed Friedel–Crafts reaction begins with activation of the aldehyde by the trityl cation to give activated aldehyde which can eliminate trityl alcohol to give the unsaturated adduct. A second indole attack gives bisindolyl adduct and regenerates the catalyst and a molecule of water. The cation must release water to complete this last portion of the catalytic cycle. The ability to tune the catalyst will be essential to balance electrophile activation with stability toward nucleophilic attack by water. Therefore, this reaction is a good probe for the applicability of these tunable organocatalysts in synthesis.

Trityl cations are used commercially as dyes, and therefore the color of the reaction can serve as a visual cue to the state of the catalyst. When the catalyst is quenched by nucleophilic attack at the central carbon atom, conjugation is interrupted, and the molecule no longer absorbs visible light. This property is particularly applicable in the context of bisindolylmethane synthesis, due to the generation of a molecule of water as a by-product in the final step of the catalytic cycle. If regeneration of the catalyst does not occur from the trityl alcohol during the rearomatization step of adduct, the cation will function as a reagent rather than as a catalyst. This can be seen visually by a fading or complete disappearance of the reaction color. All intermediates in which the central carbon atom of the trityl catalyst is sp3-hybridized are expected to be colorless, but if any free catalyst is present, the color should persist. As these dyes can be detected visually, even at very low concentrations, active trityl catalyst should be visually apparent. This visual indication of catalyst performance is one of the benefits of using trityl cations as organocatalysts.

To test the effectiveness of trityl catalysts in the synthesis of bisindolylmethanes, we first investigated the reaction between indole and benzaldehyde. With no catalyst, only a trace amount of bisindolylmethane was present after 2 days. In contrast, triphenylmethyl tetrafluoroborate gave bisindolylmethane and benzaldehyde. Rearomatization delivers the final bisindolylmethane and regenerates the catalyst and a molecule of water. The cation must release water to complete this last portion of the catalytic cycle. The ability to tune the catalyst will be essential to balance electrophile activation with stability toward nucleophilic attack by water. Therefore, this reaction is a good probe for the applicability of these tunable organocatalysts in synthesis.

![Scheme 1](image-url) Proposed reaction mechanism for the trityl (Tr) cation catalyzed bisindolylmethane synthesis

Trityl cations are used commercially as dyes, and therefore the color of the reaction can serve as a visual cue to the state of the catalyst. When the catalyst is quenched by nucleophilic attack at the central carbon atom, conjugation is interrupted, and the molecule no longer absorbs visible light. This property is particularly applicable in the context of bisindolylmethane synthesis, due to the generation of a molecule of water as a by-product in the final step of the catalytic cycle. If regeneration of the catalyst does not occur from the trityl alcohol during the rearomatization step of adduct, the cation will function as a reagent rather than as a catalyst. This can be seen visually by a fading or complete disappearance of the reaction color. All intermediates in which the central carbon atom of the trityl catalyst is sp3-hybridized are expected to be colorless, but if any free catalyst is present, the color should persist. As these dyes can be detected visually, even at very low concentrations, active trityl catalyst should be visually apparent. This visual indication of catalyst performance is one of the benefits of using trityl cations as organocatalysts.

To test the effectiveness of trityl catalysts in the synthesis of bisindolylmethanes, we first investigated the reaction between indole and benzaldehyde. With no catalyst, only a trace amount of bisindolylmethane was present after 2 days. In contrast, triphenylmethyl tetrafluoroborate gave bisindolylmethane and benzaldehyde. Rearomatization delivers the final bisindolylmethane and regenerates the catalyst and a molecule of water. The cation must release water to complete this last portion of the catalytic cycle. The ability to tune the catalyst will be essential to balance electrophile activation with stability toward nucleophilic attack by water. Therefore, this reaction is a good probe for the applicability of these tunable organocatalysts in synthesis.
We next explored the substrate scope of the Friedel–Crafts reaction using the optimized conditions (Scheme 2). Electron-poor aromatic aldehydes are good substrates for the malachite green catalysis conditions, yielding the p-chloro substituted adduct 8b in 95% yield after 2 hours. Increasing the electron-withdrawing capacity further gave even better results, with the p-cyano 8c and p-trifluoromethyl 8d adducts obtained in 99.9% and 91% yield, respectively, after only 30 minutes. 2-Naphthaldehyde was also a good substrate, yielding 94% of adduct 8e after 1 hour. Electron-rich substrates were expected to give lower activity, and this was indeed the case. The p-methoxy adduct 8f was obtained in 96% yield after 3 hours, whereas the p-thiophenyl 8g adduct was isolated in 90% yield after 5 hours. Variation of the substitution pattern was investigated using o-, m-, and p-tolualdehyde. Adducts 8h–j were all isolated in high yield, but longer reaction times were necessary for the o-substitution pattern, presumably due to steric hindrance. This was also seen for the 2-trifluoromethyl adduct 8k, which was isolated in 95% yield after 1 day. Competitive binding of the catalyst by the pyridine nitrogen is possible during the synthesis of adduct 8l, which is likely the reason for the more sluggish reaction observed with the substrate. Despite the longer reaction time, useful yields can still be obtained despite the competitive binding that is expected to occur with the basic nitrogen of the 2-pyridine-carboxylic adduct and the product adduct 8l. The reaction methodology is also applicable for free OH and NH bonds, yielding adducts 8m and 8n in 91% and 96% yield, respectively. Aliphatic aldehydes are also tolerated, with isovaleraldehyde yielding adduct 8o in 90% yield after 2 hours. Increasing the steric hindrance greatly reduced activity. Valeraldehyde adduct 8p was obtained in only 52% yield after 1 day. As expected from the results of sterically hindered aldehydes, ketones were found to be very slow to react. Cyclohexanone derivative 8q was obtained in only 61% yield after 4 days.

Variation of the indole component was well-tolerated. 5-Bromindole yielded adduct 8r in 87% yield after 45 minutes. Adding electron-donating groups gave a very fast reaction, with 5-methoxyindole adduct 8s produced in 95% yield after only 15 minutes. An electron-withdrawing ester substituent was well-tolerated, giving 87% yield of adduct 8t after 1 hour. N-Alkylated adducts 8u, 8v, and 8w were obtained in 95%, 90%, and 86% yield, respectively. Interestingly, 2-methylindole was also a good substrate, yielding adduct 8x in 99% yield after only 30 minutes, despite steric hindrance near the reaction center. Adduct 8x was found to be unstable to silica gel, presumably due to the slight acidity of the chromatographic material. The product was isolated by using our recently developed bisulfite extraction protocol to purify the product away from the slight excess of aldehyde used in the reaction. After extraction, the product was pure by 1H NMR analysis, thereby avoiding the need for purification using silica gel chromatography. This result highlights both the mildness of the malachite green reaction conditions, and the mildness of the bisulfite work-up protocol, allowing for the application of these methods to sensitive substrates.

To improve the reactivity of poorly reactive substrates in the trityl-catalyzed Friedel–Crafts reaction, we increased the reactivity of the trityl cation employed (Scheme 3). Although malachite green is preferable as a catalyst due to its commercial availability and low cost, for certain substrates enhanced activation was required for the reaction to proceed at a satisfactory rate. Switching to the less electron-donating tri-p-methoxyphenylmethyl cation 2b increased the yield of o-pyridine adduct 8l to 95%. This triaryl alcohol is commercially available, but can also be readily synthesized in a single step from inexpensive commercial starting materials. Sterically hindered isobutyreraldehyde also participated effectively, giving adduct 8p in 99% yield. The reaction was also improved for ketone-derived adduct 8q, which was produced in 98% yield.

### Table 1 Tuning the Reaction Conditions for Bisindolylmethane Synthesis using Benzaldehyde and Indole

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>none</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>trace</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ph₂CBr₂</td>
<td>2c</td>
<td>CH₂Cl₂</td>
<td>RT</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(pMe₃C₆H₅)₂COH, HBF₄·OEt₂</td>
<td>2f</td>
<td>CH₂Cl₂</td>
<td>RT</td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(pMe₂C₆H₅)₂COH, HBF₄·OEt₂</td>
<td>2b</td>
<td>CH₂Cl₂</td>
<td>RT</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(pMe₃C₆H₅)₆C₆H₅</td>
<td>2a</td>
<td>CH₂Cl₂</td>
<td>RT</td>
</tr>
<tr>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(pMe₃C₆H₅)₆C₆H₅</td>
<td>2g</td>
<td>CH₂Cl₂</td>
<td>RT</td>
</tr>
<tr>
<td>7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(pMe₂C₆H₅)₆C₆H₅</td>
<td>2g</td>
<td>CH₂Cl₂</td>
<td>35</td>
</tr>
<tr>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(pMe₂C₆H₅)₆C₆H₅</td>
<td>2g</td>
<td>MeCN</td>
<td>RT</td>
</tr>
<tr>
<td>9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(pMe₃C₆H₅)₆C₆H₅</td>
<td>2g</td>
<td>MeCN</td>
<td>80</td>
</tr>
<tr>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(pMe₂C₆H₅)₆C₆H₅</td>
<td>2g</td>
<td>EA</td>
<td>RT</td>
</tr>
<tr>
<td>11&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(pMe₂C₆H₅)₆C₆H₅</td>
<td>2g</td>
<td>EA</td>
<td>75</td>
</tr>
<tr>
<td>12&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(pMe₂C₆H₅)₆C₆H₅</td>
<td>2g</td>
<td>EOH</td>
<td>RT</td>
</tr>
<tr>
<td>13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(pMe₂C₆H₅)₆C₆H₅</td>
<td>2g</td>
<td>EOH</td>
<td>75</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: indole 4 (0.2 M, 2 equiv), benzaldehyde 1a (1.1 equiv), catalyst (5 mol%), 5 h.
<sup>b</sup> Isolated yield.
<sup>c</sup> 4 days.
Trityl catalysis proves to be an effective and green solution to the challenge of bisindolylmethane synthesis. The tunability of these catalysts allowed for optimization with respect to catalyst stability toward the water generated as a by-product during the catalytic cycle. Malachite green is a convenient, commercially available organocatalyst that is applicable for most substrates tested, but the catalyst can be further optimized for less reactive substrates to enhance reaction rates. These results demonstrate the benefits of tunable Lewis acidic organocatalysts in synthesis.

### Funding Information

Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund for partial support of this research. We are grateful to the National Science Foundation (CHE-0619275 and CHE-0963165) for renovation and instrumentation grants that supported this research.
Supporting Information

Supporting information for this article is available online at Supporting Information.

References and Notes

(9) Mandalapu, D. Synlett 2015, 26, 707.
(23) Praveen, P. J.; Parameswaran, P. S.; Majik, M. S. Synthesis 2015, 47, 1827.
(26) General procedure for malachite green-catalyzed reactions: Indole (23.4 mg, 0.20 mmol), and malachite green (18.2 mg, 0.005 mmol) were added to a 1 dram vial equipped with a stir bar. Dichloromethane (0.5 mL, 0.2 M) was added, followed by the aldehyde (0.11 mmol; liquid aldehydes were directly injected, solid aldehydes were directly added as a solution in CH2Cl2) and the reaction was then heated to 35 °C. The reaction was stirred and the progress of the reaction was followed by TLC. The crude reaction was then purified by chromatography to isolate the product.

3.3′-(Phenylmethylene)bis(1H-indole) (8a): The reaction time was 5 hours and a 15–25% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a red foam (29.5 mg, 99% yield).

3.3′-(4-Chlorophenyl)methylene)bis(1H-indole) (8b): The reaction time was 2 hours and a 15–35% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a red foam (33.8 mg, 95% yield).

4-(Di(1H-indol-3-yl)methyl)benzonitrile (8c): The reaction time was 30 minutes and a 15–45% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a pink foam (34.5 mg, 99.9% yield).

3.3′-(4-(Trifluoromethyl)phenyl)methylene)bis(1H-indole) (8d): The reaction time was 30 minutes and a 15–25% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a red foam (34.6 mg, 91% yield).

3.3′-(Naphthalen-2-yl)methylene)bis(1H-indole) (8e): The reaction time was 1 hour and a 2–25% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a red foam (34.7 mg, 94% yield).

3.3′-(4-Methoxyphenyl)methylene)bis(1H-indole) (8f): The reaction time was 3 hours and a 15–40% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as an orange foam (33.7 mg, 96% yield).

3.3′-(4-(Methylthio)phenyl)methylene)bis(1H-indole) (8g): The reaction time was 5 hours and a 10–35% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a red oil (32.5 mg, 90% yield).

3.3′-(p-Tolylmethylene)bis(1H-indole) (8h): The reaction time was 1 hour and a 15–25% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a red foam (30.3 mg, 91% yield).

3.3′-(m-Tolylmethylene)bis(1H-indole) (8i): The reaction time was 2 hours and a 15–35% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a peach foam (33.5 mg, 99.7% yield).

3.3′-(o-Tolylmethylene)bis(1H-indole) (8j): The reaction time was 21 hours and a 15–30% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a white foam (31.4 mg, 99.4% yield).

3.3′-(2-(Trifluoromethyl)phenyl)methylene)bis(1H-indole) (8k): The reaction time was 24 hours and a 20–40% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a white foam (36.7 mg, 95% yield).

4-(Di(1H-indol-3-yl)methyl)phenol (8m): The reaction time was 3 hours and a 25–90% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as an orange foam (30.2 mg, 91% yield).

N-(4-(1H-indol-3-yl)methyl)phenylacetamide (8n): The reaction time was 1 hour and a 20–100% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a red-orange foam (36.6 mg, 96% yield).

3.3′-(3-Methylbutane-1,1-diyl)bis(1H-indole) (8o): The reaction time was 2 hours and a 15–35% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a light-brown foam (27.2 mg, 90% yield).

Phenylmethylene)bis(5-bromo-1H-indole) (8r): The reaction time was 45 minutes and a 5–45% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a white foam (82.0 mg, 96% yield).

Phenylmethylene)bis(5-methoxy-1H-indole) (8s): The reaction time was 15 minutes and a 5–30% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a white solid (70.1 mg, 93% yield).

Dimethyl (3.3′-(Phenylmethylene)bis(1H-indole-5-carboxylate) (8t): The reaction time was 1 hour and a 18–45% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a light-pink solid (74.0 mg, 87% yield).

Phenylmethylene)bis(1-methyl-1H-indole) (8u): This reaction was done on a 0.4 mmol scale. The reaction time was 1...
hour and a 2–10% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a pink foam (133.6 mg, 95% yield).

3,3′-(Phenylmethylene)bis(1-butyl-1H-indole) (8v): The reaction time was 15 minutes and a 5–20% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a red foam (38.6 mg, 90% yield).

3,3′-(Phenylmethylene)bis(1-isopropyl-1H-indole) (8w): The reaction time was 45 minutes and a 2–12% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a red film (69.0 mg, 86% yield).

3,3′-(Phenylmethylene)bis(2-methyl-1H-indole) (8x): The reaction time was 30 minutes and the mixture was then diluted with methanol and washed with sodium bisulfite to remove excess benzaldehyde. Ethyl acetate: hexanes (1:1) was then added to extract the organic layer, which was then dried (MgSO₄), filtered, and concentrated in vacuo to give the title compound as a pink foam (35.0 mg, 99% yield)


(28) General Procedure for Reactions using Tri-p-methoxyphenylmethanol as Precatalyst: Tri-p-methoxyphenylmethanol (0.011 mmol) was added to a 1 dram vial equipped with a stir bar and a cap fitted with a septum. Dichloromethane (0.2 mL) was added, followed by tetrafluoroboric acid diethyl etherate complex (1.4 μL, 0.010 mmol) to give a bright red-orange color. Aldehyde (0.11 mmol) was then added by using a syringe, followed by indole (23.4 mg, 0.20 mmol) as a solution in dichloromethane (0.2 mL, and a 0.1 mL rinse). The reaction was stirred and the progress of the reaction was followed by TLC. The crude reaction was then purified by chromatography to isolate the product.

3,3′-(2-Pyridinylmethylene)bis-(1H-indole) (8l): The reaction time was 16 hours and a 40–70% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a white amorphous solid (30.5 mg, 95% yield).

3,3′-(2-Methylpropylidene)bis(1H-indole) (8p): The reaction time was 16 hours and a 10–25% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a white foam (28.9 mg, 99% yield).

3,3′-(Cyclohexane-1,1-diyl)bis(1H-indole) (8q): The reaction time was 16 hours and a 10–25% ethyl acetate/hexanes gradient was used to purify the crude reaction mixture to give the title compound as a white foam (30.8 mg, 98% yield)