Flow Chemistry

Deutsche Ausgabe: DOI: 10.1002/ange.201504454
Internationale Ausgabe: DOI: 10.1002/anie.201504454

[2+2] Photocycloaddition of Cinnamates in Flow and Development of a Thiourea Catalyst**

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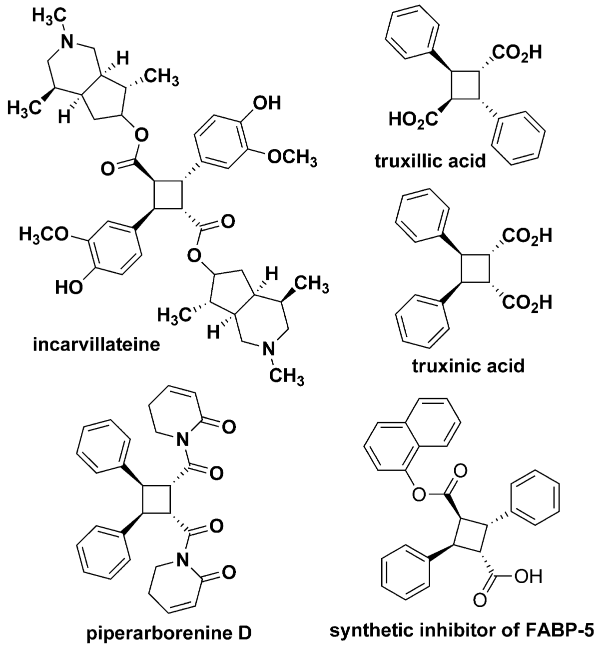
Abstract: *Cyclobutanes derived from the dimerization of cinnamic acids are the core scaffolds of many molecules with potentially interesting biological activities. By utilizing a powerful flow photochemistry platform developed in our laboratory, we have evaluated the effects of flow on the dimerization of a range of cinnamate substrates. During the course of the study we also identified a bis(thiourea) catalyst that facilitates better reactivity and moderate diastereoselectivity in the reaction. Overall, we show that carrying out the reaction in flow in the presence of the catalyst affords consistent formation of predictable cyclobutane diastereomers.*

Cinnamic acid derivatives are the building blocks for many cyclobutane-containing natural products.[1] Truxillic and truxinic acids are dimers of cinnamic acid,[2] and there are a number of related molecules, such as natural products piperarborenine and incarvillateine and synthetic derivatives, that exhibit a range of biological activities (Scheme 1).[3–5]



Scheme 1. Cyclobutanes with cinnamic acid derived cores.

One of the most common and synthetically direct methods for the synthesis of cyclobutanes is photochemical [2+2] cycloaddition.[6] However, cinnamate dimerization can pose a challenge as a consequence of the kinetically favored isomerization of olefins.[7] Efforts by Lewis et al. revealed that the addition of Lewis acids (BF_3OEt_2 or $SnCl_4$) could facilitate the dimerization of cinnamic acid, but with modest selectivity and very long reaction times.[8] Some of the greatest successes in dimerizing cinnamic acid derivatives have been achieved by carrying out the photochemical reaction in the solid state.[9,10] More recently, Ramamurthy and co-workers designed host–guest systems to facilitate dimerization through templating effects.[11–13] There have also been a number of tethering approaches to facilitate dimerization to afford head-to-head cyclobutanes.[14]

We recently developed a flow photochemistry platform[15] which utilizes a xenon(Hg) source that is collimated into a two-inch beam (Figure 1).[16–18] Through the introduction of commercially available lenses and UV and IR filters, we are able to effectively focus the beam with specific wavelengths onto a reactor. To best take advantage of this UV source we designed a cone reactor that would allow for even irradiation

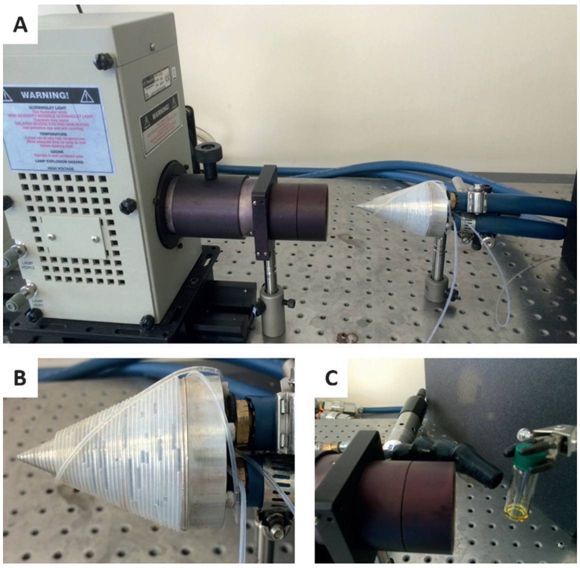


Figure 1. A) Xenon(Hg) UV source with collimating lens and UV filter. B) Conical flow device attached to a glycol recirculating chiller. C) Batch reaction vial cooled by a Venturi air gun.

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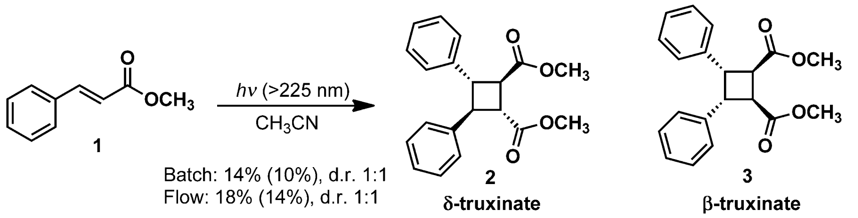
[**] Financial support from Boston University is gratefully acknowledged. We thank Dr. Norman Lee (Boston University) for high-resolution mass spectrometry data. NMR (CHE-0619339) and MS (CHE- 0443618) facilities at Boston University are supported by the NSF.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201504454.

and could be temperature-controlled by a circulating chiller. The reactor is wrapped with fluorinated ethylene propylene (FEP) tubing which sits in small grooves that promote heat transfer.[15] The cone reactor can be irradiated for long periods of time while maintaining a set temperature (5–30 °C). Batch reactions may also be carried out by placing a reaction vial in front of the beam. In this case we are able to maintain temperatures utilizing a Venturi cold air gun.

We began evaluating the reactivity of methyl cinnamate with our photochemical platform. In batch, we found that the irradiation (> 225 nm) of methyl cinnamate in acetonitrile for 11 h afforded the head-to-head dimers, β-truxinate and δ-truxinate,[14b] as a 1:1 mixture (14 % conversion, 10 % yield of isolated product; Scheme 2). In flow, a minor increase in efficiency was observed after 8 h residence time (18 % conversion, 14 % isolated product). In both reactions, the remaining material was an approximate 1:1 mixture of the starting material and the corresponding *Z* isomer. We did not observe alternative head-tail dimers or dimers incorporating the *Z* isomer.[8b]



Scheme 2. Photochemical dimerization of methyl cinnamate.

To better understand the photochemical reaction parameters we evaluated the effect of the wavelength on the dimerization in the flow reactor. We observed that the reactivity declines at wavelengths greater than 320 nm (Table 1), which correlates well with the observed UV absorbance of the substrate.[15] We also evaluated the output power of the UV source and observed similar results with 300–500 Watts and a drop to 10 % conversion at 200 Watts (Table 1). Temperatures of 0–40 °C did not have an effect on the conversion or diastereoselectivity (data not shown).

Table 1: Photochemistry parameters and temperature effects.[a]

T [°C]	Power [W]	λ [nm]	Conv. [%][b]	d.r. (δ/β)[c]
15	500	no filter	18	1:1
15	500	> 305	20	1:1
15	500	> 320	16	1:1
15	500	> 370	3	1:1
15	200	> 305	10	1:1
15	300	> 305	18	1:1
15	400	> 305	21	1:1
0	500	> 305	29	1:1

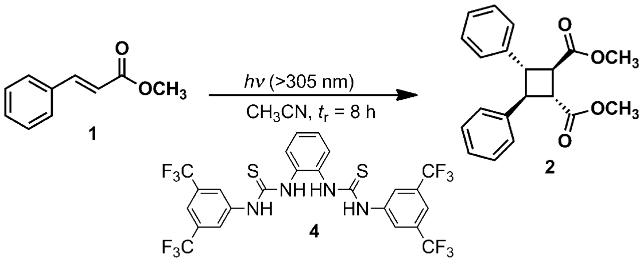
[a] Reactions were carried out in the flow reactor with an 8 h residence time. [b] Conversion was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. [c] Diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures.

With an eye toward developing a controlled dimerization of cinnamic esters we considered methods that might facilitate the process. On the basis of results with macromolecular host–guest systems[11] and solid-state photodimerization[9] we postulated that a dual hydrogen-bonding catalyst[19] might be capable of templating two substrates to facilitate dimerization. Thus, we began evaluating a number of bis(thioureas)[20] for the [2+2] cycloaddition of methyl cinnamate.[15] We were pleased to see that thiourea **4** afforded a moderate increase in conversion (24 %) after 2 h residence time and a notable increase in diastereoselectivity (3:1, δ/β).

Initial optimization of the reaction in flow indicated that we could decrease the loading of thiourea **4** to 8 mol % with a moderate increase in conversion. As expected, increasing the residence time and concentration resulted in higher conversions.[15] We also evaluated alternative solvents, but CH_3CN was the most effective.[15] We attribute this, in part, to poor solubility of either methyl cinnamate or the bis(thiourea) in a number of solvents.

Evaluation of the photochemical reaction parameters indicated some loss of conversion at wavelengths greater than 320 nm, but selectivity was maintained (Table 2). Notably, there was a dramatic loss of conversion and diastereoselectivity at wavelengths greater than 370 nm, which corresponds to the absorbance of thiourea **4**.[15] We also observed a significant effect of the power of the UV source, in contrast to the uncatalyzed reaction (Table 2).

Table 2: Photochemical conditions for the catalyzed cycloaddition of methyl cinnamate.[a]



Power [W]	λ [nm]	Reactor	Conv. [%][a]	d.r. (δ/β)[b]
500	no filter	flow	72	3:1
500	> 305	flow	76 (60)	3:1
500	> 320	flow	59	3:1
500	> 370	flow	16	1:1
200	> 305	flow	19	3:1
300	> 305	flow	39	3:1
400	> 305	flow	48	3:1
500	> 305	batch	25 (20)	2:1

[a] Conversion was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. [b] Diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures.

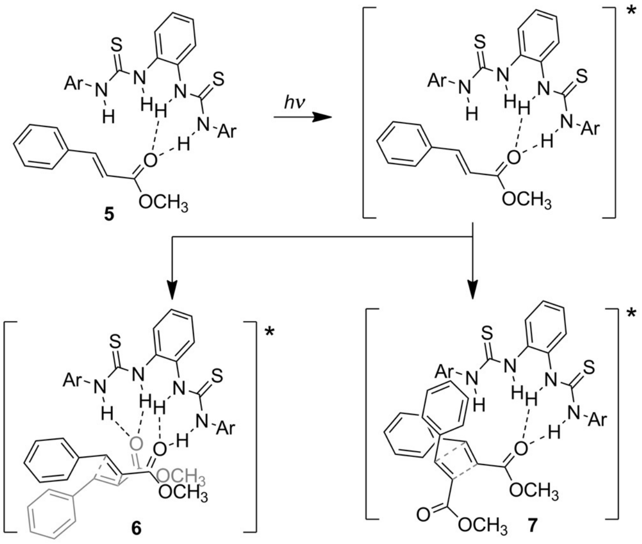
Overall, optimization of the thiourea-promoted reaction in flow with methyl cinnamate resulted in 76 % conversion

(60 % yield of isolated product) and moderate diastereoselectivity (d.r. 3:1). The optimized conditions were 8 h residence time (> 305 nm) in CH_3CN (0.8 M) and 8 mol % bis(thiourea) **4**. In batch, we observed a notable loss of conversion (25 % conversion, 20 % yield of isolated product) and lower diastereoselectivity (Table 2).

The observed sensitivity to wavelength and power in the thiourea-promoted reaction suggested a potential triplet sensitization effect. To better understand these effects[21] we screened a number of triplet sensitizers. We found that acetophenone promotes the reaction with 38 % conversion and 2:1 selectivity after 8 h irradiation in flow.[15] These results are poorer than those observed with bis(thiourea) **4**, but suggest that the reactivity and selectivity of the thiourea-promoted reactions may be attributed, in part, to triplet sensitization.[22]

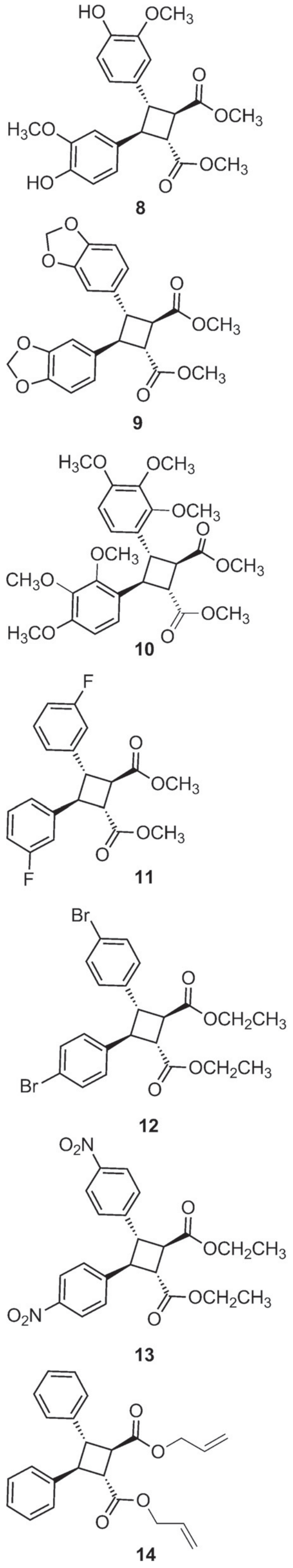
To evaluate whether bis(thiourea) **4** was actively coordinating with the substrate we carried out studies in solution by NMR spectroscopy.[23] ^{1}H NMR analysis of compound **4** and methyl cinnamate (1:2 ratio) in both acetone and acetonitrile showed significant sharpening of the NH signals, thus indicating strong hydrogen bonding.[15] We also looked for evidence of intermolecular interactions by utilizing NOESY.[24] We observed signals corresponding to the interaction of the thiourea NH protons with the methyl ester, alkene, and phenyl protons of methyl cinnamate.[15] We also observed interactions between the *ortho* hydrogen atoms of the phenyl moiety of the photocatalyst and the cinnamate aromatic hydrogen atoms.[15]

Based on these preliminary results, we propose that thiourea **4** functions through initial hydrogen bonding of methyl cinnamate to afford complex **5** (Scheme 3). The interaction can promote potential excitation by lowering the HOMO/LUMO gap.[25] Also, potential triplet sensitization by the bis(thiourea) **4** may be facilitated by a proximity effect as a result of the coordination.[26] Ultimately, a second molecule



5 6 7

Scheme 3. Potential reaction pathway through hydrogen bonding of bis(thiourea) **4**. Facial approach affording both β isomer **2** (complex **6**) and the δ isomer **3** (complex **7**) are illustrated.



8

Batch no thiourea: 27%, d.r. 1:2
Batch thiourea: 28%, d.r. 1:2
Flow no thiourea: 50%, d.r. 1:2
Flow thiourea: 67%, (49%) d.r. 1:1

9

Batch no thiourea: 46%, d.r. 1:2
Batch thiourea: 48%, d.r. 1:2
Flow no thiourea 58%, d.r. 1:2
Flow thiourea: 62% (59%), d.r. 3:1

10

Batch no thiourea: 17%, d.r. 1:3
Batch thiourea: 20%, d.r. 1:1
Flow no thiourea: 64%, d.r. 1:3
Flow thiourea: 71% (69%), d.r. 2:1

11

Batch no thiourea: 16%, d.r. 1:2
Batch thiourea:19%, d.r. 1:1
Flow no thiourea: 56%, d.r. 1:1
Flow thiourea: 74%(56%), d.r. 2:1

12

Batch no thiourea: 20%, d.r. 1:1
Batch thiourea: 29%, d.r. 1:1
Flow no thiourea: 27%, d.r. 2:3
Flow thiourea: 40%(19%), d.r. 3:2

13

Batch no thiourea: 74%, d.r. 1:1
Batch thiourea: 69%, d.r. 2:1
Flow no thiourea: 85%, d.r. 1:2
Flow thiourea: 80%(69%), d.r. 5:3

14

Batch no thiourea: 14%. d.r. 1:1
Batch thiourea: 20%. d.r. 2:1
Flow no thiourea: 15%, d.r. 1:1
Flow thiourea: 41%(31%), d.r. 4:1

Scheme 4. Evaluation of cinnamate derivatives. For clarity the δ isomer is shown. Reactions were conducted for 8 h in CH_3CN. The conversion was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. Yields of isolated products in parentheses refer to material purified by flash chromatography. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures.

proceeds to react through either unaided approach (**7**) or possibly by hydrogen bonding to the second thiourea (**6**).

We wanted to assess the effect of catalyst **4** on [2+2] photocycloaddition with a number of cinnamate substrates in batch and flow. The first aryl-substituted cinnamate we evaluated was the natural product ferulic acid methyl ester.[27] In batch, we observed similar results with and without thiourea **4** (27 % and 28 % conversion) and both reactions favored the β isomer (2:1). In flow, the conversion increased to 50 % and the selectivity remained the same. With addition of catalyst **4** in flow, the conversion increased to 67 % and we observed an increase in the δ isomer **8** (d.r. 1:1; Scheme 4).

Electron-rich pyrinyl and trimethoxy[28] cinnamates also afforded moderate conversion in favor of the β isomer in batch with and without thiourea **4**. In flow in the absence of **4**, the conversion was significantly higher (58 % and 64 %). However, in flow with thiourea **4**, there was increased conversion and moderate selectivity, now favoring the δ isomers (**9** and **10**, 3:1 and 2:1, respectively). *m*-Fluoro and *p*-bromo cinnamates had similar reactivity, each resulting in a significant increase in conversion in flow and favoring the δ isomer (**11**, **12**) in the presence of catalyst **4**. Although *p*-nitro ethyl cinnamate has been shown to be highly reactive in batch[22] and was similarly reactive in all of our reactions, we observed an increased selectivity for the δ isomer **13** in the presence of thiourea **4**. The reaction with allyl cinnamate occurred with low conversion and no selectivity without thiourea **4**. In the presence of **4** in flow, there was significant improvement in the conversion (41 %) and good selectivity (4:1) for the δ isomer **14**. We did not observe cycloaddition of the allyl olefin.

We have demonstrated that a flow photochemical platform with a novel cone reactor can facilitate significant improvement of the [2+2] photocycloaddition of cinnamate derivatives. We have also discovered a bis(thiourea) that significantly increases the conversion and diastereoselectivity with a number of substrates. This study highlights the impact that flow chemistry can have on photochemical reactions and will serve as a foundation for the development of the next-generation catalysts for highly diastereoselective and enantioselective intermolecular [2+2] cycloadditions of cinnamates.

Keywords: cinnamates · cyclobutanes · flow chemistry · photochemistry · truxinates

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 11521–11525
Angew. Chem. **2015**, *127*, 11683–11687

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Received: May 18, 2015