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Access to cyclobutane-fused dihydrobenzothiophenes via gold-photocatalyzed [2+2]-cycloadditions

Ekaterina A. Martynova,[a] Vladislav V. Voloshkin,[a] Marco Villa,[b] Antonio Fiorentino,[b] Marek Beliš,[b] Kristof Van Hecke[a], Paola Ceroni[b] and Steven P. Nolan[a]

[a]Department of Chemistry and Centre for Sustainable Chemistry, Ghent University, Krijgslaan 281, S-3, 9000 Ghent, Belgium, E-mail: Steven.Nolan@Ugent.be

[b]Department of Chemistry "Giacomo Ciamician" and Center for Chemical Catalysis–C3, University of Bologna, Via Selmi, 2, 40126 Bologna, Italy, E-mail: ~~Paola.Ceroni@unibo.it~~marco.villa11@unibo.it

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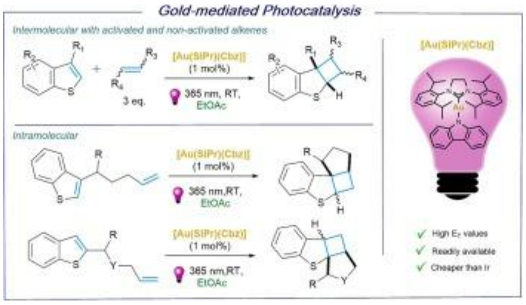
KEYWORDS: Photocatalysis; Gold; photosensitizers; benzothiophenes; [2+2] cycloadditions.

Abstract

The use of [Au(SIPr)(Cbz)] as photosensitizer in [2+2]–cycloaddition reactions between benzothiophenes and activated and non–activated alkenes is presented. Commonly used organic and Ir–photosensitizers proved inefficient in the reaction with non–activated alkenes. The study emphasizes the dependence on the nature of the alkene, a parameter that has previously received little attention. Under mild reaction conditions, a wide array of alkenes and benzothiophenes were successfully coupled, showcasing remarkable tolerance of diverse functional groups. Additionally, we present intramolecular [2+2]–cycloaddition reactions, including benzothiophenes featuring various alkene linkers at the C2 and C3 positions.

Graphical abstract



1. Introduction

Over the past two decades, the field of photocatalysis has undergone remarkable growth and has now become a powerful tool in the chemist's synthetic arsenal, [1], [2], [3], [4], [5] facilitating the construction of a plethora of molecular frameworks and enabling efficient late–stage functionalization. Photoredox catalysis [6], [7], [8], [9] has gained significantly more attention in comparison to energy transfer (EnT) photocatalysis, [10], [11], [12], [13] which still remains a relatively underexplored yet rapidly developing area.

Despite the existence and use of a wide range of organosensitizers [14], [15], [16], [17] and transition metal–based photocatalysts, [18], [19], [20], [21], [22], [23] in EnT photocatalysis, iridium photosensitizers remain the state–of–the–art [12], [24]. This can be attributed to the significantly long lifetimes of the excited triplet states, high quantum yields, and the diverse range of ligand modifications available to tailor catalyst properties. In addition, they possess high triplet energy (E_T) values, [25], [26] allowing their use in a wide variety of chemical transformations. However, Ir–photosensitizers have notable drawbacks, including low solubility in common organic solvents due to their cationic nature, which restricts solvent options [27]. Moreover, most of the Ir photosensitizers have triplet energy values below 64 kcal/mol, limiting the scope of substrates suitable for photocatalytic reactions. Additionally, their synthesis involves complex and multi–step procedures [28]. As a more cost–effective and efficient alternative to the state–of–the–art Ir–photosensitizers, Nolan and co–workers have recently reported [Au(SIPr)(Cbz)] (SIPr = [N,N–bis(2,6–diisopropylphenyl)imidazolin-2-ylidene]; Cbz = carbazolyl) and [Au(IPr)(Cbz)] (IPr = [N,N–bis(2,6-diisopropylphenyl)imidazol-2-ylidene]) photosensitizers, which exhibit high triplet energies of 67.9 and 67.6 kcal/mol, respectively [29], [30]. One of the notable advantages of gold photosensitizers is their facile synthesis, [30] which enhances their attractiveness in comparison to iridium photosensitizers. Noteworthy, both gold sensitizers reported by Nolan are now commercially available [31]. [Au(SIPr)(Cbz)] and [Au(IPr)(Cbz)] have permitted the previously unsuccessful (with Ir photocatalysts) intramolecular [2+2]–cycloaddition of unsubstituted indoles, resulting in the formation of products in remarkably short reaction times [29]. To explore the potential applications and inherent limitations of these gold–sensitizers, we have also reported other energy transfer (EnT) reactions successfully utilizing these catalysts [32], [33].

Benzothiophene and its derivatives have garnered significant attention, as this core framework exhibits a wide array of biological activities, rendering it valuable in the development of various pharmaceutical agents, including antimicrobial, anticancer, anti–inflammatory, antioxidant, antitubercular, antidiabetic, and anticonvulsant compounds, among others [34], [35]. Cyclobutane–containing molecules represent a class of organic compounds attracting substantial interest nowadays in the fields of medicinal chemistry and natural product synthesis [36], [37], [38], [39]. Given the significance of both scaffolds, we envisaged that a general synthetic access to cyclobutane–fused 2,3–dihydrobenzothiophenes in an efficient manner using readily accessible starting materials would be well–received as it represents a still unmet challenge.

The [2+2]–photocycloaddition is one of the most versatile and widely employed strategy for the synthesis of cyclobutanes [40], [41], [42], [43]. There is a limited number of reports published in the 1980s devoted to intermolecular cycloaddition between benzothiophenes and alkenes. One of these describes the formation of cyclobutane rings with 2,3–dichlorobenzo[*b*]thiophene and vinyl bromide as a solvent in the presence of benzophenone and 2,6–di–*tert*–butylcresol (Fig. 1a) [44]. In addition to the undesirable and wasteful use of 40–fold excess of the alkene, the reaction mixture was irradiated for 94 h with high pressure mercury lamp (450 W). Another report published by Ikeda and co–workers describes the [2+2]–photocycloaddition between benzo[*b*]thiophene and vinyl acetate in benzene, which yielded only 16% of the desired product after 30 h of irradiation with a Hg lamp (Fig. 1a) [45]. Several recent reports make use of EnT photocatalysis with iridium sensitizers to access this scaffold. However, in all reported studies a very specific substitution pattern either on benzothiophene or on the alkene proved essential to permit the transformation. An electron–withdrawing group positioned either at the C2 carbon of benzothiophene or one that is conjugated to the double bond of the alkene was found to be an unavoidable necessity. Additionally, a very limited number of examples (1 or 2) of such a transformation was reported in these contributions. It is worth mentioning that the reported triplet excited state energies of benzothiophene is relatively high, 68.7 kcal/mol [46]. Various substituents on benzothiophene or on the activated alkene are employed because the high E_T values of benzothiophenes supposedly impose photophysical limitations, even when utilizing the best Ir–photosensitizers.

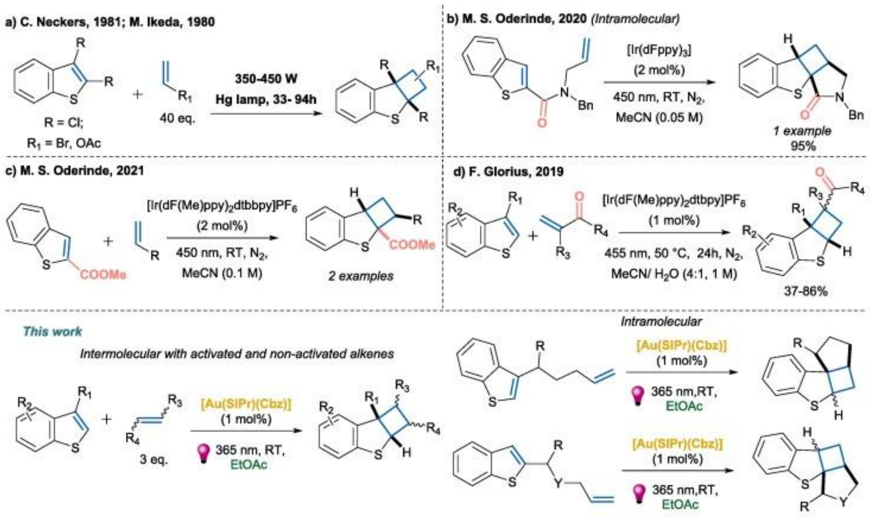


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Fig. 1. Overview of previously reported [2+2] photocycloadditions of benzothiophenes with alkenes.

The Oderinde group reported the [2+2]-cycloaddition of various heterocycles mainly focusing on indoles, but also included two examples of methyl benzo[b]thiophene–2–carboxylate with vinyltrimethylsilane and methyl acrylate [47]. The iridium complex [Ir(dF(Me)ppy)$_2$dtbbpy]PF$_6$ ($E_T \sim$ 62.9 kcal/ mol) was used as sensitizer (Fig. 1c). Baik and Meggers reported one example of [2+2]–photocycloadditions of benzothiophene functionalized at the C2–position with COOMe group with (E)–prop–1–en–1–ylbenzene, using 2 mol% of a Rh–photosensitizer [18]. In addition, Oderinde and co–workers reported intramolecular [2+2]-photocycloadditions of various 2–carboxamides, including one example of benzothiophene–2–carboxamides, utilizing 2 mol% of [Ir(dFppy)$_3$] (Fig. 1b)[48]. Glorius and co–workers reported “unforeseen energy transfer” based [2+2]-photocycloaddition of benzothiophenes with activated alkenes with the use of 1 mol% of [Ir(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ (E_T = 61.8 kcal/mol) (Fig. 1d) [49].

Therefore, as can be gauged by the existing literature reports, a general protocol for the construction of cyclobutane–fused 2,3–dihydrobenzothiophenes remains a challenge as their synthesis is up till now limited to activated substrates. Our working hypothesis was that this reaction proved likely inaccessible because of the E_T limitations of the commonly used Ir–photosensitizers. Given the higher E_T value of [Au(SIPr)(Cbz)] compared to most commonly used state–of–the–art Ir–photosensitizers, we deploy in the present study the novel gold photocatalysts as enablers for this challenging transformation.

2. Results and discussion

We began the reaction condition optimization by using benzothiophene and vinyltrimethylsilane as model substrates with 2 mol% of [Au(SIPr)(Cbz)] in EtOAc under irradiation with 365 nm 18 W LED lamp at room temperature. To our delight, we observed an 85% conversion of benzothiophene with 5 equivalents of alkene after 5 h. Interestingly, the use of 3 equivalents of alkene led to the same result (Table 1, entries 1, 2). Further prolongation of the reaction time, up to 24 h, did not lead to an increased conversion in both cases (see ESI, Table S1). When reducing the amount of alkene, the conversion also decreased to 59% when 2 eq. were used (Table 1, entry 3) and to 37% with 1 eq. (Table 1, entry 4). Therefore 3 eq. of the alkene were used as the optimization moved forward. Next, we screened a range of Au–NHC carbazolyl complexes (see ESI for full optimization). Noteworthy, [Au(IPr)(Cbz)] **(PS2)** performed somewhat less effectively when compared to [Au(SIPr)(Cbz)] **(PS1)**, leading to a 77% conversion (Table 1, entry 5). Other gold catalysts, bearing commonly used NHCs such as IMes, SIMes and ICy performed similarly as **PS2** (Table 1, entries 6–8). Surprisingly, [Au(I*t*Bu)(Cbz)] performed as well as [Au(SIPr)(Cbz)], which made it a potential candidate for this project (Table 1, entry 9). However, after longer reaction time decomposition of **PS6** was observed, making **PS1** the best catalyst among those tested in terms of performance, efficiency and (photo)stability.

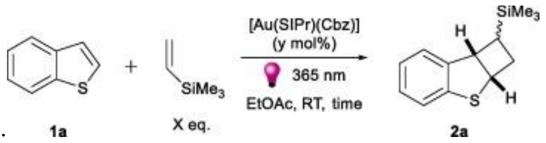

Table 1. Optimization of reaction conditions.

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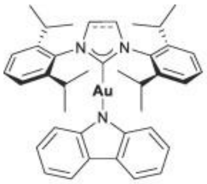
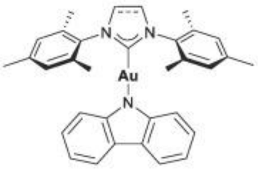
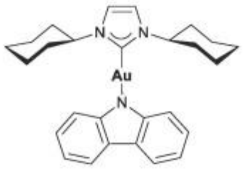
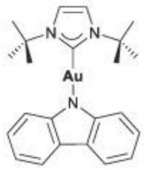
Entry	Catalyst	Cat. loading, (mol%)	Eq. of alkene	Time, h	GC yield, (%)
1	[Au(SIPr)(Cbz)] **(PS1)**	2	5	5	82
2	[Au(SIPr)(Cbz)] **(PS1)**	2	3	5	80
3	[Au(SIPr)(Cbz)] **(PS1)**	2	2	5	59
4	[Au(SIPr)(Cbz)] **(PS1)**	2	1	5	37
5	[Au(IPr)(Cbz)] **(PS2)**	2	3	5	77
6	[Au(IMes)(Cbz)] **(PS3)**	2	3	5	69
7	[Au(SIMes)(Cbz)] **(PS4)**	2	3	5	77
8	[Au(ICy)(Cbz)] **(PS5)**	2	3	5	73

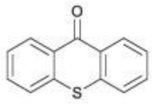
Entry	Catalyst	Cat. loading, (mol%)	Eq. of alkene	Time, h	GC yield, (%)
9	[Au(I^{t}Bu)(Cbz)] **(PS6)**	2	3	5	86
10	[Au(SIPr)(Cbz)] **(PS1)**	1	3	5	83
11	Thioxanthone **(PS7)**	2	3	24	NR
12	[Ir(dF(CF$_3$)ppy)$_2$(dtppy)]PF$_6$ **(PS8)**	2	3	24	NR
13	Acetophenone (**PS9**)	4	3	24	25
14	Benzophenone (**PS10**)	4	3	24	27

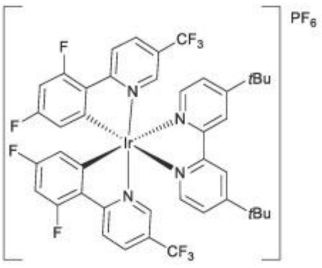

[Au(SIPr)(Cbz)] **(PS1)**
[Au(IPr)(Cbz)] **(PS2)**

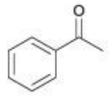

[Au(IMes)(Cbz)] **(PS3)**
[Au(SIMes)(Cbz)] **(PS4)**

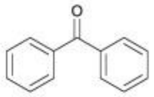

[Au(ICy)(Cbz)] **(PS5)**


[Au(*t*Bu)(Cbz)] **(PS6)**


Thioxanthone **(PS7)**


[Ir(dF(CF$_3$)ppy)$_2$(dtppy)]PF$_6$ **(PS8)**


Acetophenone **(PS9)**


Benzophenone **(PS10)**

We also examined an iridium sensitizer (**PS8**) possessing one of the highest E_T values among these routinely used complexes ($E_T \approx 62$ kcal/mol), along with an organic photosensitizer, thioxanthone (**PS7**) ($E_T \approx 66$ kcal/mol) (Table 1, entries 11 and 12). Notably, no products were detected in the final two sets of experiments, with only benzothiophene present in the reaction mixture after irradiation. Additionally, we conducted the same reactions using other organic sensitizers, namely acetophenone (**PS9**) (ET ≈ 74 kcal/mol) and benzophenone (**PS10**) (ET ≈ 69.1 kcal/mol). Both sensitizers successfully yielded the product, confirming that high triplet energy is essential for driving the transformation. However, even with extended reaction times of 24 h and an increased catalyst loading of 4 mol%, the product yields were limited to 25% and 27% for **PS9** and **PS10**, respectively (Table 1, entries 13, 14). This highlights that the examined [2+2]-photocycloaddition with alkenes, lacking an activating group, can be efficiently achieved under such mild reaction conditions only by employing a gold photosensitizer.

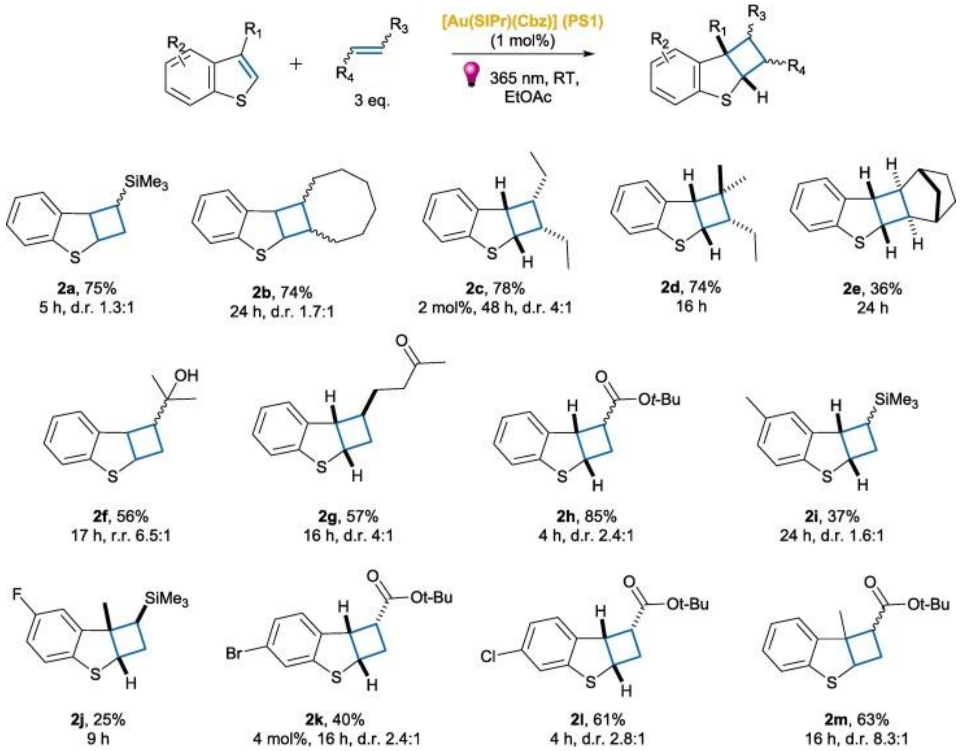
As further control experiments, the reactions with iridium and organo–photosensitizers were also performed with 405 nm irradiation, most commonly used for these, leading to the same negative outcome (see ESI, Table S3). The catalyst loading optimization was then addressed, 1 mol% of **PS1** proved as efficient as 2 mol% (Table 1, entry 10). A further decrease to 0.5 mol% of **PS1** led to a decrease in conversion. Control experiments in the absence of light and catalyst were also performed, no conversion to the desired product was observed in both cases (see ESI, Table S3). This finding conclusively demonstrates the need for both catalyst and light in the reaction.

During the course of the optimization, we noticed the formation of a second product in the reaction mixture. After careful investigation, we were able to confirm that this product was the product of the [2+2]–cycloaddition of two benzothiophene molecules (Fig. 2). The obtained side–product **7a** has an *anti*–head–to–head configuration. Interestingly, such product of homo cycloaddition was also observed in the [2+2]–cycloaddition of coumarins and non–activated alkenes recently reported by us.[32] Without the addition of alkene, a 68% conversion into this “dimer” was observed after 24 h. However, in contrast to the coumarin dimer, benzothiophene dimer could not be converted into product after prolonged reaction times (Table S1).

7a

Fig. 2. X–ray molecular structure of **7a** is presented showing thermal displacement ellipsoids at the 50% probability level. Two different orientations of the same structure are shown.

With optimized reaction conditions in hand, we began to explore the reaction scope. The model vinyltrimethylsilane yielded product **2a** as the sole regioisomer with 1:1.32 diastereomeric ratio in 75% isolated yield (Scheme 1). All other terminal alkenes examined in the study yielded the same regioisomer except for **2f**. *Cis*–cyclooctene afforded **2b** in 74% yield and *cis*–hex–3–ene afforded **2c** in 78%. Two pairs of diastereomers were isolated in both cases, with the d.r. ratio of 4:1 in the case of **2c** and 1.74:1 for **2b**. This is in contrast with previously reported [2+2]–cycloaddition with coumarin where the former alkene led to a mixture of all 4 possible diastereoisomers and the latter to 3 diastereomers.[32] Interestingly, 2–methylpent–2–ene and 2–norbornene afforded exclusively one diastereomer each, **2d** and **2e**, in 74% and 36% yields, respectively. The only case where two regioisomers were observed and isolated is when allylic alcohol was used as coupling partner (**2f**). For each regioisomer only one disastereomer was observed. Distal carbonyl group on the alkene was well tolerated, the product **2g** was obtained in 57 % yield. Catalyst **PS1** proved to be efficient not only with non–activated alkenes, but also with activated alkene, namely *tert*–butyl acrylate (Scheme 1, Scheme 2h). Noteworthy, for this specific example, full conversion was achieved after 4 h compared to the required 24 h previously reported with a Ir–photosensitizer [49]. The diastereomeric ratio of products observed was similar to the previously reported example, while yield with gold complex after shorter irradiation time is virtually the same (85% vs 86%).



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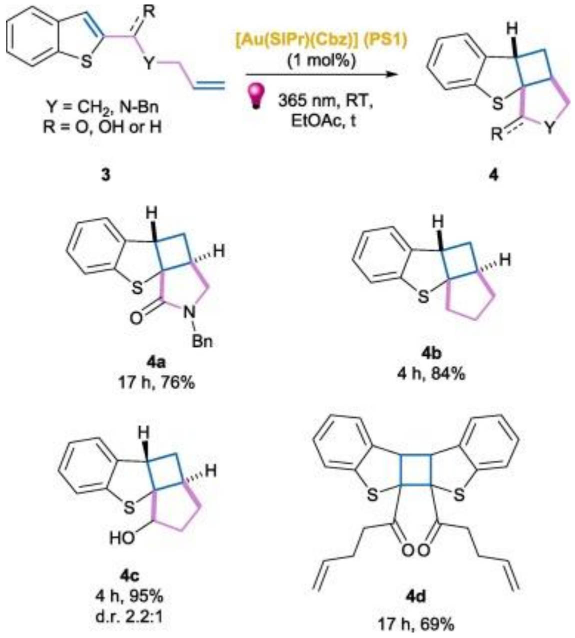
Scheme 1. Substrate scope. Yields of isolated products are reported as combined yields of both diastereomers; average of two runs. d.r. were determined by NMR of the crude. Structure of the major diastereomer/regioisomer is displayed where determined.



Scheme 2. The scope of intramolecular cycloaddition, linker at the C2 position.

Next, we explored the scope of various benzothiophenes using the model vinyltrimethylsilane as alkene. 5–methylbenzo[b]thiophene was successfully converted into the desired product **2i** in 37% yield. The d.r. value was found to be 1.65:1, but it was not possible to separate the two diastereomers due to their almost identical R_f values.

When attempting to extend our substrate scope with benzothiophenes substituted at C2 and C3 positions, we faced the increased formation of the corresponding homodimers similar to previously observed **7a** in the reaction mixtures. For instance, the use of 5–fluoro–3–methylbenzo[b]thiophene as a substrate led to 1:1 formation of the desired product and homodimer evidenced in ^{1}H NMR spectrum of the crude. Because of this side–reaction, the desired product **2j** was isolated in a 25 % yield only. You and co–workers reported that the presence of either phenyl or an ester group at the C2 position of indoles significantly lowered the E_T value of the substrate [50]. We hypothesized that the E_T value of the 5–fluoro–3–methylbenzo[b]thiophene is lower in comparison to non–substituted benzothiophene. Consequently, the formation of a homodimer becomes more favorable, especially considering the higher E_T of **PS1** compared to previously utilized Ir–photosensitizers.

To confirm our hypothesis 3–methylbenzo[b]thiophene **1m** and methyl benzo[b]thiophene–2–carboxylate **1x** were also tested as substrates. In the case of 3–methylbenzo[b]thiophene the ratio 8:1 of the dimer to the desired product was observed. For the other substrate **1x**, which has an electron–withdrawing group (COOMe) at the C2 position, only the formation of a homodimer was observed (Scheme S1). This is in contrast with the Oderinde work where the cyclobutane–fused product with vinyltrimethylsilane was isolated, using a Ir–photosensitizer [47]. Interestingly, when we performed the reaction with the same benzothiophene **1x** and the activated alkene, *tert*–butyl acrylate, we observed the formation of the product in a 4.4:1 ratio to the homodimer (See Table 2, entry 6). These surprising results, combined with the earlier observation that non–activated benzothiophenes formed products only with activated alkenes when using an Ir–photosensitizer, and our control experiment showing the Ir photocatalyst is ineffective with non–activated alkenes, led us to conclude that this process might depend on the nature of both the substrate and of the alkene, rather than just the benzothiophene substrate as previously thought.

Table 2. Comparison between the reaction yields and the Stern–Volmer quenching constants for **1a**, **1 k**, and **1x** with activated and non–activated alkenes.

Entry	**Substrate**	**Alkene**	**Yield**[a] **(%)**	**K_{SV} (M^{-1})**
1	**1a**	vinyltrimethylsilane	75	144
2	**1a**	*tert*–butyl acrylate	85	1.62×10^5
3	**1k**	vinyltrimethylsilane	NR	–[b]
4	**1k**	*tert*–butyl acrylate	40	115
5	**1x**	vinyltrimethylsilane	7	–[b]
6	**1x**	*tert*–butyl acrylate	69	425

a

The yield of [2+2]–cycloaddition product between corresponding benzothiophene and alkene.

b

No experimentally meaningful emission intensity change detected, not allowing to estimate K_{SV}.

Then we also turned our attention to benzothiophenes with substituents on the aromatic ring. When 6–bromobenzo[b]thiophene was used as the substrate with vinyltrimethylsilane, no reaction was observed, even with an increased catalyst loading of 4 mol%. Interestingly, no homodimer was formed either.

Considering our hypothesis that the nature of alkene can also affect the reaction, we used these 6–chloro- and 6–bromobenzothiophenes in the reaction with *tert*–butyl acrylate. Remarkably, in the case of 6–bromobenzo[b]thiophene with 4 mol% of catalyst loading, a 70% conversion was observed after 16 h. The desired product **2k** was isolated in 40% yield, with a diastereoisomer ratio of 2.4:1. When 6–chlorobenzo[b]thiophene was used as a substrate, after 4 h with 1 mol% of **PS1**, full conversion was observed and the desired product **2l** was isolated in a 61% yield.

To support our hypothesis concerning the effect of the alkene, we also tested [2+2]–photocycloaddition of 3–methylbenzo[b]thiophene with activated alkene. Again, after 16 h with 1 mol% of **PS1**, full conversion into the desired product **2m** was observed. Intriguingly, the formation of homodimer was not detected in this case, in striking contrast with the reaction involving vinyltrimethylsilane (*vide supra*). Inspired by all unexpected and previously unreported results, we initiated in–depth mechanistic investigations, which will be discussed in detail in a following section.

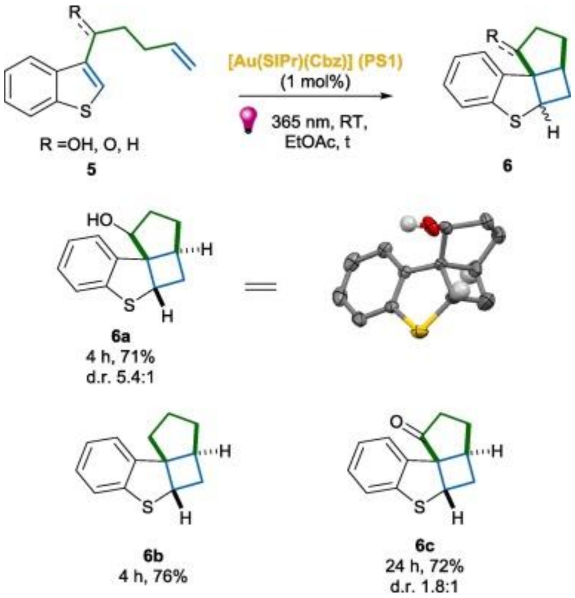
As mentioned above, few reports devoted to [2+2]–photocycloaddition of benzothiophenes with alkenes exist, and even fewer have focused on the [2+2] intramolecular photocycloadditions of benzothiophene derivatives. To the best of our knowledge, there is only one example of intramolecular photocycloaddition with benzothiophene using Ir photosensitizer reported in 2020 by Oderinde and co–workers [48].

We synthesized N-allyl-N-benzylbenzo[b]thiophene-2-carboxamide previously reported by Oderinde and co–workers to test the intramolecular cycloaddition under our optimized conditions with 1 mol% of **PS1** in EtOAc (Scheme 2). To our delight, the desired product **4a** was isolated as the sole diastereoisomer in 76% yield.

We next investigated a range of benzothiophene derivatives, characterized by the presence of alkene linkers at both the C2 and C3 positions. Based on our findings from the intermolecular [2+2] photocycloaddition and its sensitivity to the nature of the alkene, particularly the presence of activating groups, we synthesized various benzothiophene derivatives (see ESI for details).

Using the optimized conditions, after a short reaction time of 4 h, the desired products **4b** and **4c** were isolated in high yields, 84% and 95% respectively (Scheme 2). Remarkably, **4b** was obtained as the sole diastereoisomer, while for **4c**, two diastereoisomers were isolated in a ratio of 2.2:1. As anticipated, the benzothiophene with an activating acyl group at the C2 position yielded a homodimer **4d** and not the desired product. This finding is in line with our observations from the intermolecular [2+2]-photocycloaddition using methyl benzo[b]thiophene–2–carboxylate and a model alkene, where only the homodimer was formed. Notably, when an Ir sensitizer was employed in the intramolecular [2+2]–photocycloaddition of substrate **3c** less than 10 % conversion was observed, again showing the higher efficiency of our gold sensitizer under these conditions. Control experiments conducted with **3c** without light or without **PS1** demonstrated that both light and **PS1** are essential for the formation of the desired product (Table S4).

Subsequently, we moved to the exploration of benzothiophene derivatives featuring an alkene linker at the C3 position. Using the optimized reaction conditions: 1 mol% of **PS1** in EtOAc, the desired products were isolated in high yields (Scheme 3). Benzothiophene derivatives, characterized by the presence of C=O or OH functional groups in the alkene linker, yielded two diastereoisomers. In the case of **6a**, these isomers were isolated in a ratio of 5.4:1. The structure of **6a** was unambiguously confirmed with single crystal X–ray analysis (Scheme 3). The desired product **6b** was isolated in 76% yield as the sole diastereoisomer. In the case of **6c**, two diastereoisomers were isolated in the ratio of 1.8:1. Noteworthy, in the case of **6c** the formation of the homodimer was not observed, in contrast with **4d**, where only homodimer was isolated. We hypothesize that these results are most likely attributed to the higher E_T values of substrates, bearing an alkene linker at the C3 position.



1. Download: Download high-res image (217KB)
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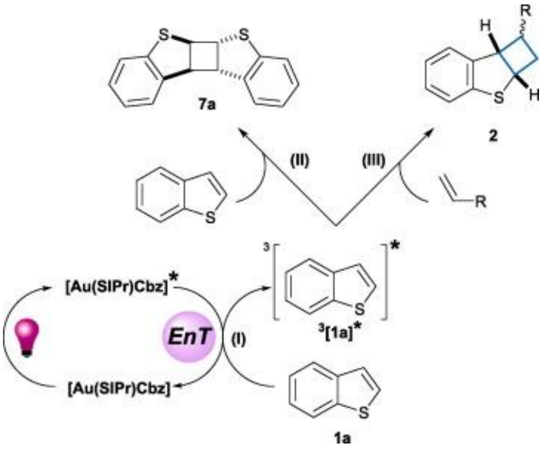
Scheme 3. The scope of intramolecular cycloaddition, linker at the C3 position. For the molecular X–ray structure of **6a**, thermal displacement ellipsoids are shown at the 50% probability level for the non–hydrogen atoms.

3. Mechanistic studies

To gain insights into the reaction mechanism and the reasons behind the unexpected reactivity, we revisited these unforeseen results and conducted photophysical studies with the substrates and alkenes involved. Namely, we investigated the benzothiophene **1a**, 6–bromobenzothiophene **1k** and methyl benzo[b]thiophenecarboxylate **1x** to understand the different reactivity in reactions with activated and non–activated alkenes (*tert*–butyl acrylate and vinyltrimethylsilane).

We began our investigations with the Stern–Volmer quenching studies of the photosensitizer **PS1** by the selected benzothiophenes and alkenes. All benzothiophenes **1a**, **1k** and **1x** quench the [Au(SIPr)(Cbz)] phosphorescence in degassed EtOAc solution (see Table S7), while vinyltrimethylsilane and *tert*–butyl acrylate do not, as we already reported.[32] The quenching rate constant for these benzothiophenes is in the range of 10^{8}–10^{10} M^{-1} s^{-1}, indicating an overall efficient quenching of the phosphorescent triplet state of the gold complex (process **(I)**, scheme 4). Previously, Glorius and co-workers observed the competitive oxidation of benzothiophene with the formation of its cation-radical by using a strongly oxidizing photocatalyst [49]. In our previous work we also determined the redox potentials for the [Au(SIPr)Cbz] complex [32]. Comparison of these values indicates that oxidation of the benzothiophene by gold sensitizer is not thermodynamically feasible, implying that energy transfer is the most probable quenching mechanism (see Table S11).



Scheme 4. Proposed energy transfer mechanism for the reaction between benzothiophene (**1a**) and an alkene.

To estimate whether triplet–triplet energy transfer from the photocatalyst to benzothiophenes is exergonic or endergonic, the triplet energies of **1a**, **1k** and **1x** were evaluated by measuring their phosphorescence spectra in rigid matrix at 77 K (Figure S4). The results evidence that the energy of the benzothiophenes **1a** and **1k** triplet excited states are slightly higher than [Au(SIPr)(Cbz)] (67.9 kcal/mol) (Table S6). Therefore, energy transfer between [Au(SIPr)(Cbz)] and them is slightly endergonic. However, productive endergonic energy transfer reaction was recently reported by the Glorius group [51] and one of us [32]. The triplet energy of **1x** was found to be significantly lower than that of the sensitizer, which indicates an exergonic nature of the EnT for this substrate.

Although endergonic in two cases, as indicated by the quenching constants, under the reaction conditions in which the benzothiophenes concentration is higher than 0.1 M, the quenching efficiency of the photocatalyst phosphorescent excited state is higher than 99.9% (Table S7). As this does not explain different reactivity, we assumed that it is necessary to determine the quenching constants of benzothiohenes lowest triplet excited state involved in the [2+2]–cycloaddition and homodimerization (Scheme 4, process **(II)** and **(III)**) by alkenes involved in a transformation [52], [53]. To achieve this, we evaluated the quenching constants of the lowest triplet excited state of the benzothiophenes by the activated and non–activated alkenes by recording the changes in the singlet oxygen emission, generated after energy transfer from the triplet state of benzothiophenes and bimolecular quenching with oxygen. Singlet oxygen is metastable and decay with a phosphorescent emission at 1270 nm (see SI for more details).

High quenching constant (9×10^9 $M^{-1}s^{-1}$, $K_{SV} = 1.62 \times 10^5$ M^{-1}) is observed for **1a** by *tert*–butyl acrylate, indicating efficient interaction between triplet state **1a*** and this alkene. This observation correlates well with the high yield of the product **2h**. In the cases of **1k** and **1x**, quenching constants by the same alkene are three orders of magnitude lower. We believe that such low quenching efficiency for **1x**, together with its lowest E_T make the dimerization reaction competitive with the formation of the desired product, as is observed experimentally (Scheme S1).

Interestingly, the quenching constant of **1k** by *tert*–butyl acrylate is even smaller than in the case of **1x**, which would make dimerization even more favorable. However, this was not observed experimentally, and we were able to isolate the product after increasing the catalyst loading and prolonging the reaction time. This indicates that there is another factor at play for this substrate. Previously we had observed that indole containing bromo–substituent showed no reactivity in [2+2]–cycloaddition [29]. We believe this can be attributed to the presence of a heavy atom in the structure, as it was shown that it could significantly decrease the lifetime of the triplet state of the substrate [54]. Such decreased lifetime can result in lower overall efficiency of productive [2+2]–cycloaddition and suppression of dimerization, which is in agreement with results for **2k**.

Interestingly, quenching of benzophiophenes with vinyltrimethylsilane was observed only for **1a** with a value of 8×10^{6} $M^{-1}s^{-1}$ (K_{SV} 144 M^{-1}), similar quenching is observed for **1k** and **1x** with activated alkenes. For compounds **1x** and **1k** no quenching was observed with non–activated alkenes. These results are again in good agreement with the experimental observations. We observed the formation of the homodimer during the optimization with **1a** and vinyltrimethylsilane, which seems to be competitive given the value of K_{SV}. In both cases with **1k** and **1x,** we did not observe formation of cyclobutane–fused dihydrobenzothiophenes with vinyltrimethylsilane. Once again the dimerization of **1k** was not observed, while full conversion into the dimer occurred for **1x**.

Therefore, our mechanistic studies indicate that apart from triplet energy of the substrate, several additional factors should be considered for a successful intermolecular [2+2]–cycloaddition between benzothiophenes and alkenes. One of these factors is the quenching constant of the triplet state of the substrate with the corresponding alkene. We identified that those quenching constants are much higher with activated *tert*–butyl acrylate than with non–activated vinyltrimethylsilane for identical benzothiophenes. Therefore self–quenching might begin to compete with low efficient quenching by alkene leading to the increased formation of the homodimer. This might explain why this transformation was possible with activated alkenes and not with non–activated ones while iridium catalysts are employed. Given the lower E_T of the iridium catalyst, we expect that much lower concentration of triplet state benzothiophene is generated, drastically increasing the reaction time with consequent absence of the desired product after 24 h. Activated alkenes, due to a more efficient quenching, could be converted to the desired products more easily. This leads to much slower reaction time (24 h) and the need for elevated temperature (50 °C), as reported in the literature [49], [53] and accounts for no reports with non–activated alkenes using these systems. Another factor which should be considered is the lifetime of the triplet state of the substrate, which should be sufficient to ensure the productive reaction to occur. Also, the heavy atom effect, such as when Br is present, can either decrease the efficiency or completely suppress the productive pathway.

4. Conclusions

We have reported the [2+2]–cycloaddition reactions between benzothiophenes and various activated and non–activated alkenes via gold–mediated photocatalysis. Our control experiments confirmed that utilizing a non–activated alkene is unattainable with state–of–the–art Ir–sensitizer or thioxanthone, making this type of transformation solely accessible with gold photosensitizer. Under mild reaction conditions, we have successfully achieved the coupling of a wide range of alkenes and benzothiophenes, demonstrating tolerance for various functional groups. Moreover, we have also performed the intramolecular version of this transformation under the same reaction conditions involving benzothiophenes with various alkenes linked to either C2 or C3 positions. The difference in reactivity between activated and non–activated alkenes has been investigated using quenching studies. It became evident that activated alkenes have significantly higher quenching constants of the triplet state of the same benzothiophenes than non–activated ones. This might explain why [2+2]–cycloaddition products with the latter were previously not accessible using iridium and organo–

sensitizers (which possess lower E_T than our gold sensitizers employed). Lowering the triplet energy of the benzothiophene and decreasing the quenching constant of its triplet state by the alkene favors the competitive homodimerization. Further studies aimed at employing these novel and efficient gold sensitizers in various transformations are ongoing in our laboratories.

Author contributions

EAM, VAV and SPN conceived and designed the project. EAM and VAV performed all optimization studies and photocatalytic reactions. Mechanistic studies were conducted by MV, AF and PC. Photochemical data were analysed by MV and PC. MB and KVH performed the XRD measurements and structure analysis. EAM, VAV, MV and SPN wrote the manuscript with input from all authors. All authors have given approval to the final version of the manuscript.

CRediT authorship contribution statement

Ekaterina A. Martynova: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation. **Vladislav V. Voloshkin:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation. **Marco Villa:** Supervision, Methodology, Investigation. **Antonio Fiorentino:** Methodology, Investigation. **Marek Beliš:** Methodology, Investigation. **Kristof Van Hecke:** Validation, Methodology, Investigation. **Paola Ceroni:** Validation, Methodology, Investigation. **Steven P. Nolan:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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