

Cycloadditions

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Photosensitized [2+2]-Cycloadditions of Alkenylboronates and Alkenes

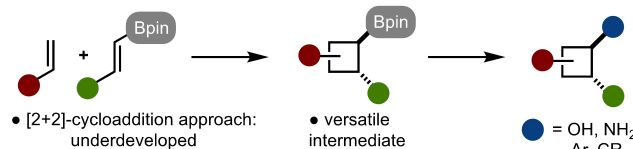
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Abstract: A new strategy for the synthesis of highly versatile cyclobutylboronates via the photosensitized [2+2]-cycloaddition of alkenylboronates and alkenes is presented. The process is mechanistically different from other processes in that energy transfer occurs with the alkenylboronate as opposed to the other alkene. This strategy allows for the synthesis of an array of diverse cyclobutylboronates. The conversion of these adducts to other compounds as well as their utility in the synthesis of melicodenine C is demonstrated.

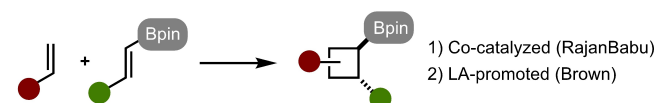
Cyclobutanes are important intermediates due to their ease of functionalization, presence in many natural products and bioactive molecules, and crucial role in medicinal chemistry. While numerous methods are available for their synthesis, [2+2]-cycloadditions have been established as a principal method for synthesis of cyclobutanes because readily available alkenes serve as the starting materials.^[1]

To aid in the synthesis of diverse cyclobutanes, cyclobutylboronates are versatile intermediates due to the ease with which the C–B bond can be elaborated to other functional groups (Scheme 1A).^[2] Established methods for cyclobutylboronate synthesis include, hydro- di- or carboboration of cyclobutenes,^[3,4] ring expansion of bicyclobutenes,^[5] electrocyclization,^[6] C–H functionalization,^[7] and [2+2]-cycloaddition.^[8–11] The final strategy is particularly attractive as readily available alkenylboronates and alkenes can be used (Scheme 1A). To date, several approaches have been described, including Co-catalyzed,^[8] Lewis-acid promoted,^[9] or photochemical-[2+2]-cycloadditions^[10] (Scheme 1B/C). Known photochemical [2+2]-cycloadditions operate by energy transfer from an excited state sensitizer to the alkene not bearing the boron, which is typically an electron deficient alkene (Scheme 1C).^[10,12] [2+2]-Cycloaddition reactions that oper-

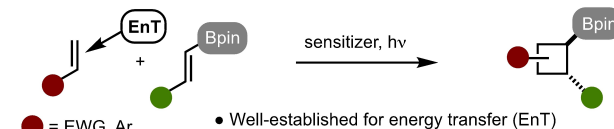
A) Diverse Cyclobutane Synthesis via Cyclobutylboronates



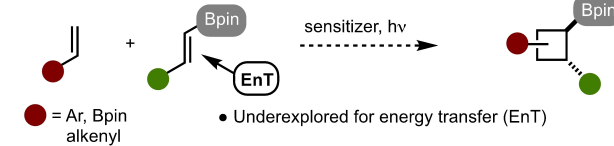
B) Non-photochemical [2+2]-Cycloaddition with Alkenylboronate



C) Photochemical [2+2]-Cycloaddition with Alkenylboronate



D) This Work: Energy Transfer (EnT) to AlkenylBpin



Scheme 1. Synthesis of Cyclobutylboronates by [2+2]-Cycloaddition.

ate by energy transfer to the alkenylboronate are not known (Scheme 1D). Development of such a process would be enabling as entirely different sets of cyclobutylboronates could be accessed. For these reasons, and based on the general interests of our lab in [4+2]/[2+2]-cycloadditions^[13] and borylation reactions,^[14] we targeted [2+2]-cycloadditions with alkenylboronates for development.

In 2018, Watson and Gilmour established that energy transfer to alkenylboronates is possible (in the context of alkene isomerization reactions).^[15] However, for [2+2]-cycloaddition to proceed by the design outlined in Scheme 1D, bimolecular quenching of the triplet state of the alkenylboronate is necessary.^[16,17] One factor that could be important is that the Bpin unit alters the photophysical properties of the attached alkene such that energy transfer is more facile relative to the other alkene component. In the absence of selective energy transfer, complex mixtures of products might be expected that result from different photoexcited substrates undergoing various non-desired product forming reactions. Based on calculations, it was

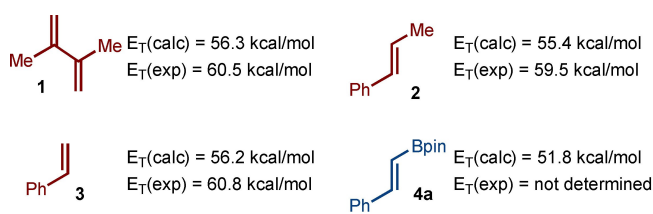
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determined that the Bpin unit lowers the triplet energy (52 kcal mol⁻¹ for **4a**) relative to other alkenes (55–56 kcal mol⁻¹ for **1–3**) that could be used in the [2+2]-cycloaddition (Scheme 2). It should be noted that the calculated triplet energies are lower than the experimentally determined values.^[18] While the triplet energy of **4a** has not been experimentally determined, it is likely greater than 52 kcal mol⁻¹. While many factors influence the efficiency of energy transfer, based on triplet energy alone, it was deemed plausible that a sensitizer could be identified to allow for energy transfer to the alkenylboronate in preference to other alkene.

An initial evaluation of various photosensitizers in the presence of 2,3-dimethylbutadiene (**1**) and alkenylboronate **4a** led to encouraging initial results (Table 1, entries 1–8). In particular, *fac*-Ir(ppy)₃ emerged as a promising photosensitizer (Table 1, entry 7). Optimization of the solvent and concentration allowed for synthesis of **5** in 82 % yield (10:1 dr). While in these reactions, photoisomerization was detected by the observation that *Z*-**4a** was formed, it does not appear to affect the outcome, as *Z*-**4a** is equally efficient in providing the same products (Table 1, entry 11). Finally, other substituents were explored such as BMIDA (**4b**),



Scheme 2. Experimental and Calculated Triplet Energies (E_T) of Various Alkenes. $E_T(\text{calc})$: Calculated triplet energies, CH₂Cl₂, electronic energy, ω B97XD/aug-cc-pVTZ. $E_T(\text{exp})$: experimentally determined triplet energies.^[18]

Table 1: Optimization of Reaction Conditions.

entry	R	sensitizer	E_T (kcal/mol)	Conc. (M)	yield ^a
1	Bpin (4a)	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆	60.4	0.4	38%
2	Bpin (4a)	[Ir(dF(CF ₃)ppy) ₂ (dtbbpy)]PF ₆	60.2	0.4	45%
3	Bpin (4a)	<i>fac</i> -Ir(dFppy) ₃	60.1	0.4	49%
4	Bpin (4a)	<i>fac</i> -Ir(<i>p</i> -Fppy) ₃	58.6	0.4	60%
5	Bpin (4a)	<i>fac</i> -Ir(<i>p</i> -CF ₃ ppy) ₃	56.4	0.4	62%
6	Bpin (4a)	[Ir(dFppy) ₂ (dtbbpy)]PF ₆	55.4	0.4	41%
7	Bpin (4a)	<i>fac</i> -Ir(ppy) ₃	55.2	0.4	71%
8	Bpin (4a)	[Ir(ppy) ₂ (dtbbpy)]PF ₆	49.2	0.4	28%
9	Bpin (4a)	<i>fac</i> -Ir(ppy) ₃	55.2	0.1	56%
10 ^b	Bpin (4a)	<i>fac</i> -Ir(ppy) ₃	55.2	0.8	82%
11 ^b	Bpin (<i>Z</i> - 4a)	<i>fac</i> -Ir(ppy) ₃	55.2	0.8	82%
12	BMIDA (4b)	<i>fac</i> -Ir(ppy) ₃	55.2	0.8	<10%
13	SiMe ₃ (4c)	<i>fac</i> -Ir(ppy) ₃	55.2	0.8	<10%
14	Me (2)	<i>fac</i> -Ir(ppy) ₃	55.2	0.8	<10%

[a] Yield was determined by ¹H NMR analysis of the unpurified reaction mixture with an internal standard (0.1 mmol scale).

[b] 0.2 mmol scale.

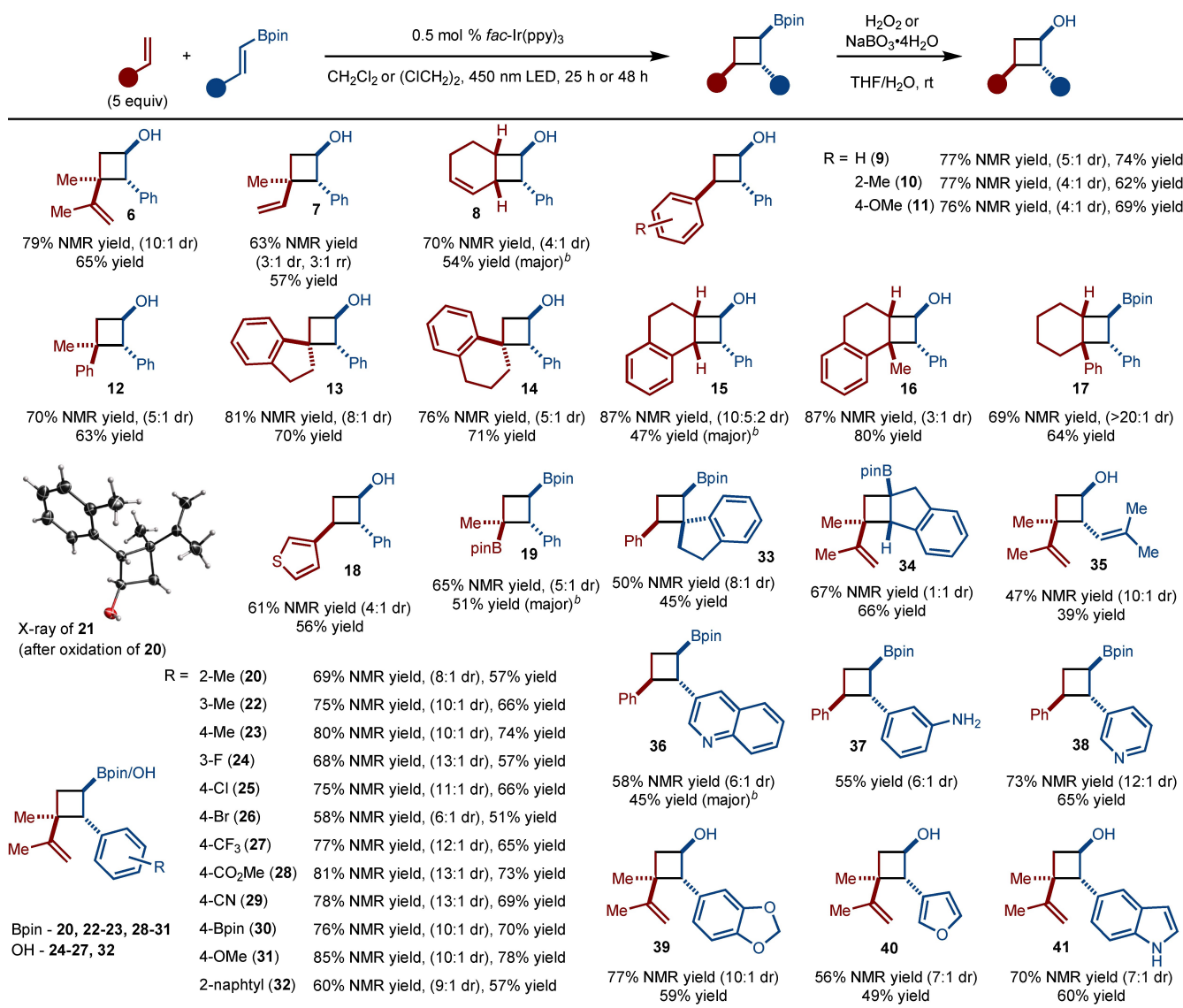
SiMe₃ (**4c**), and Me (**2**), which only led to product formation in low yield, thus demonstrating the importance of the Bpin unit. In all of these cases, photoisomerization was detected, thus indicating that quenching can occur, yet productive cycloaddition reaction does not proceed.

Evaluation of the alkene scope revealed that other dienes were permitted such as isoprene (product **7**) and 1,3-cyclohexadiene (product **8**) (Scheme 3). The reaction also tolerates the use of alkenyl arenes. For example, use of styrene allowed for the formation of **9** in good yield and selectivity. Other derivatives resulted in the formation of products with similar levels of selectivity (products **10** and **11**). Disubstituted and trisubstituted alkenyl arenes also functioned well in the reaction. For example, α -substituted styrenes allowed for the synthesis of a quaternary carbon (products **12–14**). In the case of 1,2-dihydronaphthalene, product **15** was formed in low selectivity; however, use of 1-methyl-1,2-dihydronaphthalene restored high levels of selectivity (product **16**). Particularly noteworthy is the example that led to the formation of **17** as a single observable diastereomer. Finally, isopropenyl-Bpin could also be coupled to generate **19** in good selectivity and yield, thus allowing for the synthesis of polyborylated products. In addition, reactions with unactivated alkenes or alkenes that bear electron-withdrawing substituents failed to deliver the products.

In the case of alkenylboronates, broad tolerance of various functional groups on the aryl unit was observed. In particular, halogens (products **24–26**), esters (product **28**), boronic esters (product **30**), nitriles (product **29**), and unprotected amines (product **37**) all allowed for product formation. Sterically demanding substituents also did not impede the reaction (product **20**). Various heterocycles such as pyridine (product **38**), quinoline (product **36**), indole (product **41**), and furan (product **40**) were also tolerated, thus demonstrating the applicability of this method to medicinal chemistry. Substitution of the alkenylboronate was also tolerated, as evidenced by the formation of **33** and **34**. In the case of the former, the yield suffered due to dimerization, whereas poor diastereoselectivity was observed in the latter. Finally, the aryl group was not necessary as a borylsubstituted diene could be used to generate **35**. However, the efficiency of this reaction is lower, likely due to a higher triplet energy of the diene (relative to **4a**). Attempted reaction with only alkyl-substituted alkenylboronates did not result in product formation, likely due to a high triplet energy.

The reaction could be carried out on 5 mmol scale. In the synthesis of **6**, prolonged reaction time (130 hrs) was necessary to achieve full conversion with our standard reaction setup (Scheme 4A). However, for more challenging examples (e.g., synthesis of **17**) that required 48 hrs of reaction time on small scale (0.2 mmol) the use of the Integrated Photochemical Reactor (IPR)^[19] was employed. On a 5 mmol scale, preparative amounts of product **17** can be easily obtained in 48 hrs (Scheme 4A).

The products generated by this method are useful intermediates for chemical synthesis, primarily due to the ability to functionalize the C–B bond. As illustrated in

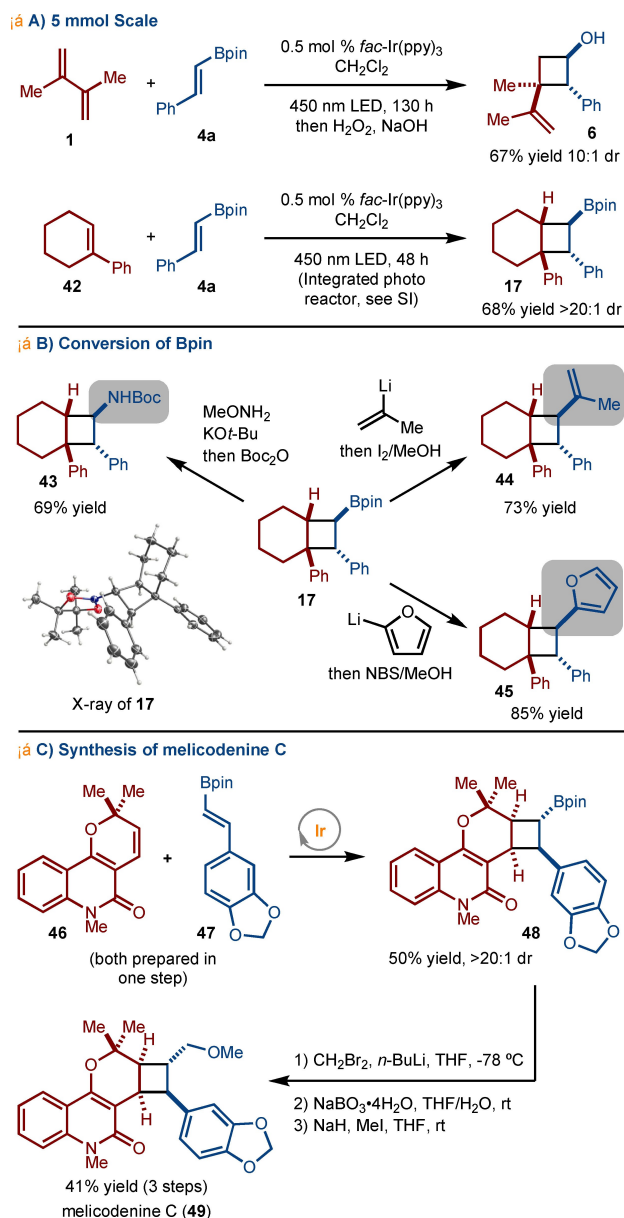


Scheme 3. Substrate Scope. ^aNMR yield refers to yield determined by ¹H NMR analysis of the unpurified reaction mixture of the Bpin product except for 8–11, 13, 15, 16, which was determined after oxidation. Diastereomeric ratio (dr) determined of the unpurified reaction mixture by ¹H NMR analysis. Yield is of isolated, purified product. In some cases, oxidation of the Bpin was conducted to facilitate purification. ^bIsolated in >20:1 dr.

Scheme 4B, application of amination,^[20] Zweifel,^[21] and cross-coupling^[22] protocols allowed for conversion to amine (43), alkene (44), and furan (45) containing products, respectively. To further underscore the utility of the method, a short synthesis of melicodenine C (49) was undertaken (Scheme 4C).^[23] The requisite starting materials (46 and 47) were prepared in one step from commercially available materials. Subjection of 46 and 47 to the standard reaction conditions (*fac*-Ir(ppy)₃, 450 nm LED, CH₂Cl₂) resulted in the formation of 48 in 50% yield as a single observable diastereomer, demonstrating that the use of a complex and sterically demanding alkene (46) was tolerated. Simple elaboration of the Bpin unit to the methyl ether by application of a Matteson homologation,^[24] oxidation, and etherification sequence allowed for the synthesis of melico-

denine C in five steps. A notable aspect of this route is that the Bpin unit can serve as a handle for further transformation in the construction of derivatives. Closely related structures to melicodenine C have shown promise as agonists of the human TLR4 receptor.^[23c]

To probe the mechanism of the reaction, Stern–Volmer luminescence quenching experiment was first conducted. A linear correlation with respect to alkenylBpin concentration was observed, thus demonstrating that 4a is an effective quencher ($K_{sv} = 120.8 \text{ M}^{-1}$, Figure 1). Additional quenching studies with 2,3-dimethyl butadiene (1, $K_{sv} = 9.0 \text{ M}^{-1}$), styrene (3, $K_{sv} = 4.1 \text{ M}^{-1}$) and other coupling partners (Figure S2) confirmed that they are less effective quenchers of *fac*-Ir(ppy)₃(T₁). Even given the use of 5 equiv. of 2,3-dimethyl butadiene, alkenylBpin (4a) is still a more effective



Scheme 4. Application in Synthesis.

quencher, when considering initial concentrations (See the Supporting Information for details).

To look for evidence of electron transfer versus triplet energy transfer, transient absorption spectra of $fac\text{-Ir(ppy)}_3$ in the presence of **4a** were measured at 100 ns, 1 μs , and 5 μs (Figure 2). At 100 ns, there is a broad transient absorption extending from 484 nm to beyond 800 nm. There is also a small bleach centered at 408 nm. Both of these features decay over the subsequent 5 μs . The transient spectra of excited $fac\text{-Ir(ppy)}_3$ in the absence of any quencher displays the same features (Figure S7). In addition, when compared to the spectrum for $[\text{Ir(ppy)}_3]^+$ we do not observe the strong bleach at 380 nm or the large, positive transient absorbance at 350 nm that are characteristic of the Ir^{IV} species.^[25] Taken together, this strongly supports an energy transfer mechanism instead of an electron transfer mechanism.

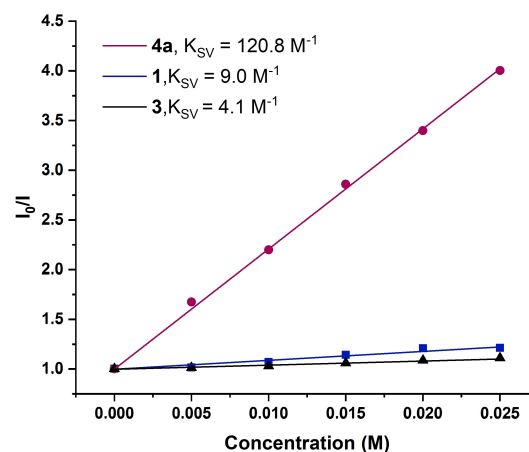
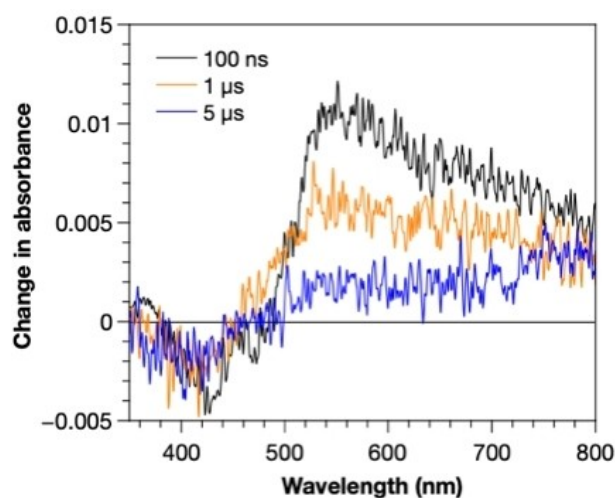
Figure 1. Stern–Volmer Luminescence Quenching of $fac\text{-Ir(ppy)}_3$.

Figure 2. Transient spectra at 100 ns (black), 1 μs (orange), and 5 μs (blue) for 100 mM of **4a** and 35 μM of Ir(ppy)_3 . The transient absorption at 520 nm and bleach at 408 nm are consistent with excited Ir(ppy)_3 and inconsistent with $[\text{Ir(ppy)}_3]^+$.

In addition, quenching experiments were conducted with $fac\text{-Ir(dFppy)}_3$, which has a higher triplet energy than $fac\text{-Ir(ppy)}_3$ and results in a lower yielding cycloaddition (Table 1, entry 3). In this case, quenching with diene **1** and boronate **4a** were closer to unity ($K_{\text{sv}}(\text{4a})/K_{\text{sv}}(\text{1})=2.1$, Table 2, Figure S3). Based on simple kinetic modelling with the initial concentrations, diene **1** quenches the triplet state

Table 2: Comparison of Stern–Volmer Luminescence Quenching.

	$fac\text{-Ir(ppy)}_3$	$[\text{Ir(dFppy)}_2\text{dtbbpy}]\text{PF}_6$	$fac\text{-Ir(dFppy)}_3$
yield of [2+2] ^a	71%	41%	49%
E_T (kcal/mol) ^b	55.2	55.4	60.1
$K_{\text{sv}}(\text{4a})$ (M^{-1})	120.8	232.1	999.7
$K_{\text{sv}}(\text{1})$ (M^{-1})	9.0	67.1	476.8
$K_{\text{sv}}(\text{4a})/K_{\text{sv}}(\text{1})$	13.4	3.5	2.1

[a] Condition: **4a** (0.2 mmol, 1.0 equiv), **1** (5.0 equiv), $[\text{Ir}]$ (1.0 mol %) in CH_2Cl_2 (0.4 M), 450 nm, 24 h. [b] ref. [27].

of *fac*-Ir(dFppy)₃ ≈ 2 × more effectively than alkenylBpin **4a** (See the Supporting Information for details). Compare this with the case of *fac*-Ir(ppy)₃ in which $K_{sv}(\mathbf{4a})/K_{sv}(\mathbf{1}) = 13.5$ (Table 2) and when considering the initial concentrations, alkenylBpin **4a** quenches the excited state of *fac*-Ir(ppy)₃ (T_1) ≈ 3 × more effectively compared to diene **1**. Finally, quenching studies with [Ir(dFppy)₂dtbpy]PF₆ were also conducted, because it has a similar triplet energy as *fac*-Ir(ppy)₃, yet results in a lower yield (Table 1, compare entries 6 and 7). Despite the similar triplet energies, the quenching between **4a** and **1** only slightly prefers **4a** ($K_{sv}(\mathbf{4a})/K_{sv}(\mathbf{1}) = 3.5$, Table 2, Figure S3). In addition, the efficacy of energy transfer is not purely linked to the triplet energy of the respective components as size of sensitizer^[26] and homoleptic versus cationic complexes likely play a major role. Based on the data shown in Table 2, selective quenching of the alkenylBpin relative to the other alkene component appears to be important for high yielding [2+2]-cycloaddition to occur. Increased quenching of the diene leads to polymerization, which results in lower yield.

Based on the mechanism studies, the reaction is proposed to occur by Dexter energy transfer from the photoexcited triplet state of *fac*-Ir(ppy)₃ to alkenylboronate **4a** to result in the T_1 state **50** (Scheme 5).^[15,16] Addition of the α -boryl radical (**50**) to the alkene (**1**) results in formation of diradical **51**. Intersystem crossing and bond formation then occurs to generate product **5**.

In conclusion, a versatile method for the synthesis of cyclobutylboronates is demonstrated. The [2+2]-cycloaddition reaction likely operates by energy transfer to the alkenylboronate, which is an underexplored pathway in photochemistry. By harnessing this type of reactivity, a range of synthetically useful cyclobutylboronates can be prepared, which has been demonstrated in the synthesis of various functionalized cyclobutanes and the natural product melicodenine **C**.^[28]

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Conflict of Interest

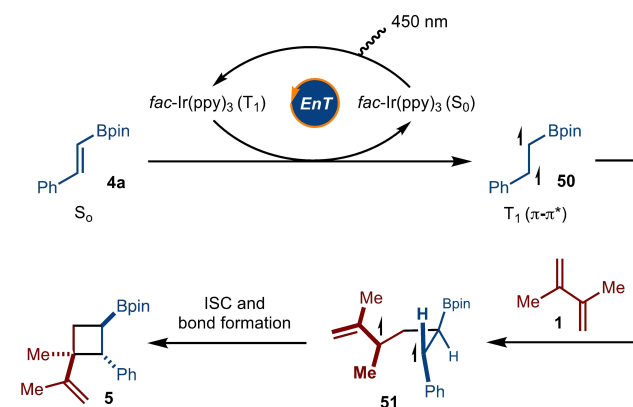
The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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Scheme 5. Proposed pathway of the reaction.

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