BODIPY-Labeled Cyclobutanes by Secondary C(sp3)H Arylations for Live-Cell Imaging

BODIPY-Labeled Cyclobutanes by Secondary C(sp^3)–H Arylations for Live-Cell Imaging

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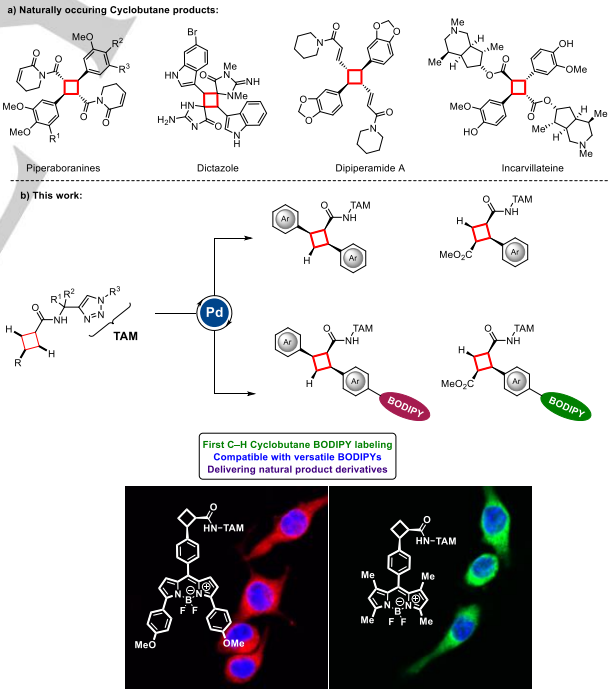
Abstract: Arylated cyclobutanes were accessed by a versatile palladium-catalyzed secondary C(sp^3)–H activations exploiting chelation assistance by modular triazoles. The C−H arylation led to cyclobutane natural product derivatives in a highly regioselective fashion, setting the stage for the rapid access to novel fluorogenic BODIPY-labeled probes for live-cell imaging.

Cyclobutanes represent important building blocks for complex natural molecules with relevant biological activities, and found as a core motifs in several natural products (Scheme 1a).[1] For instance, pipercyclobutanamides, piperchabamides, nigramides, and dipiperamides are tetrasubstituted cyclobutanes of relevance to traditional medicines.[2] Specifically, pipercyclobutanamide A and dipiperamide E belong to a family of molecules that selectively inhibit CYP2D6 and CYP3A4, the two main cytochrome P450 isoenzymes responsible for drug metabolism.[3] In nature, the strained cyclobutane ring is constructed via the coupling of the monomeric olefins. However, this approach is not applicable in the laboratory due to the by-products originated from the [2+2] photocycloaddition strategy.[4] In this context, C−H activations can be considered as an unconventional alternative to classical approaches, such as the intermolecular photocycloaddition to access unsymmetrical cyclobutane derivatives. Despite undisputable progress,[5] the functionalization of inert C(sp^3)–H bond, the most ubiquitous chemical bonds in nature, continues to be challenging. Hence, the formation of C−C bonds from unactivated secondary C(sp^3)–H bonds continues to be rare and most of the reported examples are limited to specific substrates or favored by entropically-biased intramolecular reactions.[6] Notable progress has been witnessed by palladium-catalyzed C(sp^3)–H activations as reported by Corey,[7] Kazmaier,[8] Chen,[9] Daugulis,[10] Shi,[11] Yu[12] and Ackermann,[13] among others[14] using auxiliaries such as 8-aminoquinoline[15] or picolinamide[16] bidentate directing groups as well as perfluoroaryl containing directing groups.[17] These approaches offer unique opportunities for overcoming the longstanding challenge constituted by the stereocontrolled synthesis of structurally complex cyclobutanes. Baran indicated the power of palladium(II/IV) catalysis towards methylene C−H activation.[18] As part of our program on sustainable C–H activations,[19] we have now devised the first example of triazole-assisted C–H functionalization of cyclobutanes (Scheme 1b).[20] Triazole-based TAM groups can be easily accessed under mild reaction conditions in a highly modular fashion via 1,3-dipolar Huisgens cycloaddition reaction.[21] Moreover, isosteric triazoles have been frequently utilized in bioactive peptidomimetics as powerful amide surrogates.[22] Our strategy led not only to arylated cyclobutanes with high regio- and stereo-selectivity. Indeed, cyclobutane BODIPYs[23] were prepared for the first time as effective biorelevant molecules for live-cell imaging studies. Notable features of our approach include 1) efficient triazole-assisted secondary C(sp^3)–H cyclobutane arylations, 2) access to natural product derivatives, 3) transformative fluorophore labeling in a stereo- and regioselective fashion, and 4) novel cyclobutane-BODIPY molecules for fluorescence-based live-cell imaging.



Scheme 1. Secondary C(sp^3)–H arylation for BODIPY-cyclobutanes.

We initiated our studies by probing various reaction parameters for the envisioned C(sp^3)–H arylation of cyclobutane **1a** (see Supporting Information). After considerable preliminary experimentation, we identified *o*-xylene as the optimal solvent, AgOAc and Pd(TFA)$_2$ as the base and catalyst of choice (Scheme 2). Thereby, the desired secondary C(sp^3)–H functionalization occurred with high catalytic efficacy and complete

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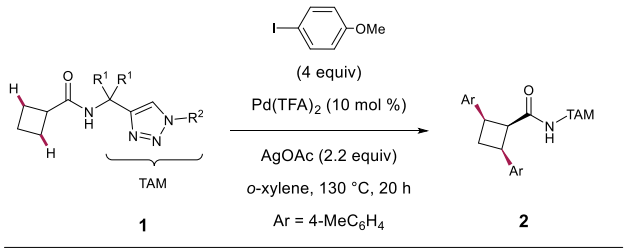
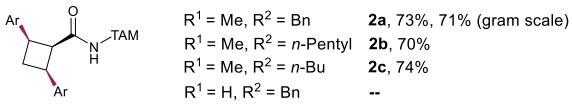
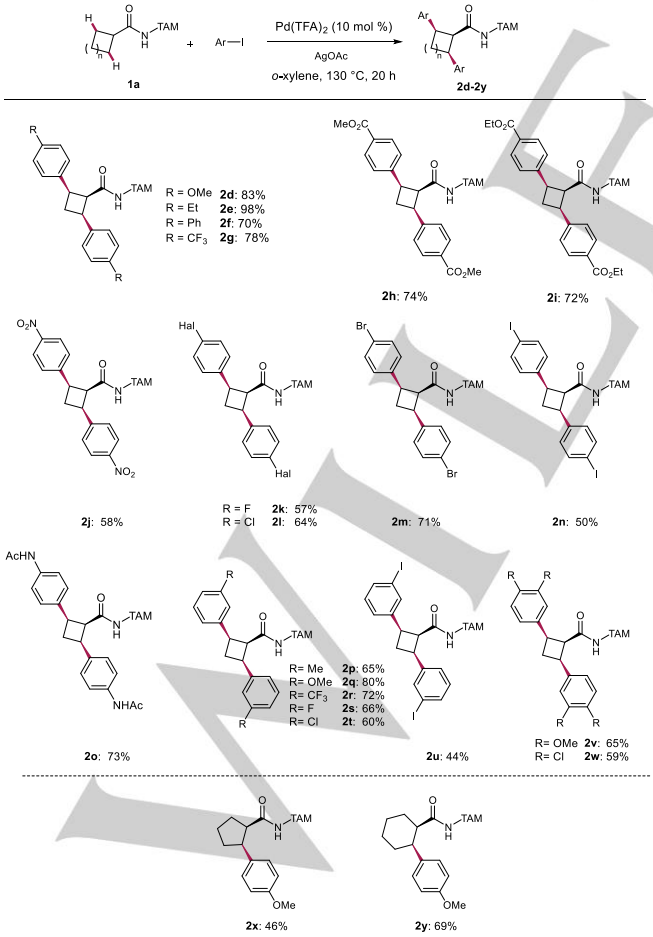
diastereoselectivity. (see Table S1 to S7 in the Supporting Information).





Scheme 2. Optimized triazole-assisted secondary C(sp^3)–H arylation.

The diarylated compounds **2** were obtained selectively as the all-*cis*-diastereomers when employing an excess of the electrophilic aryl iodides. Encouraged by these results, we tested the versatility of the optimized catalyst (Scheme 2). The C(sp^3)–H arylation proved to be widely applicable and was found to be compatible with valuable electrophilic functional groups, such as fluoro, chloro, amide and ester substituents (**2h**, **2i**, **2k**, **2l**, **2o**, **2s**, **2t**, **2w**). Interestingly, mono-arylated products **2x**, **2y** were selectively obtained when five- or six-membered cycloalkanes were employed, again featuring complete *cis*-selectivity.



Scheme 3. Scope of secondary C(sp^3)–H arylation.

The mechanism of the activation of C(sp^3)–H bond of cyclobutane was studied by means of density functional theory (DFT) calculations at the PW6B95-D3(BJ)/def2-TZVP+COSMO (*o*-xylene)//TPSS-D3(BJ)/def2-TZVP level of theory (Figure 1). Our findings highlight a facile formation of the palladacycle **im4** by carboxylate-assisted[24] secondary C(sp^3)–H activation.

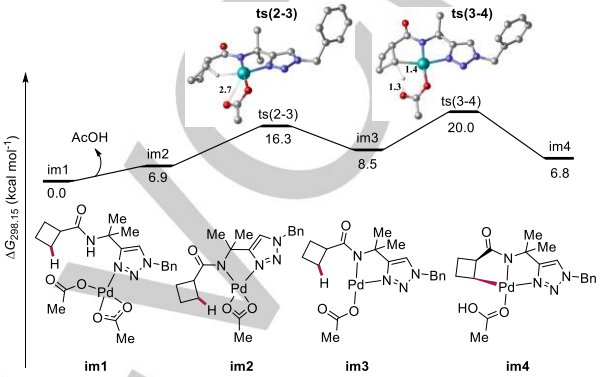
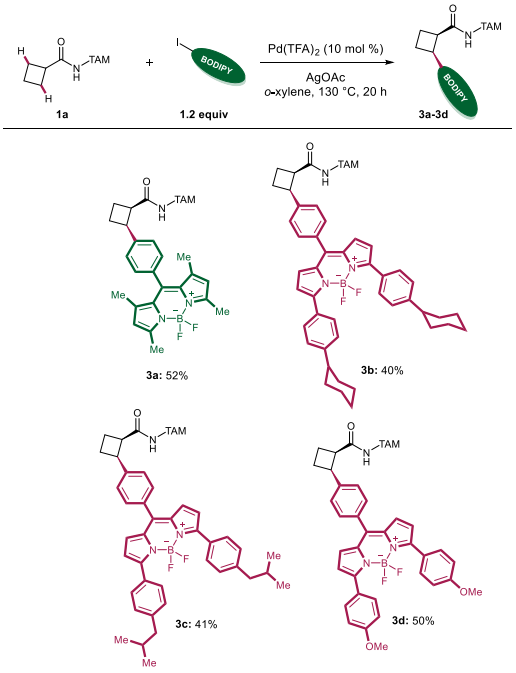


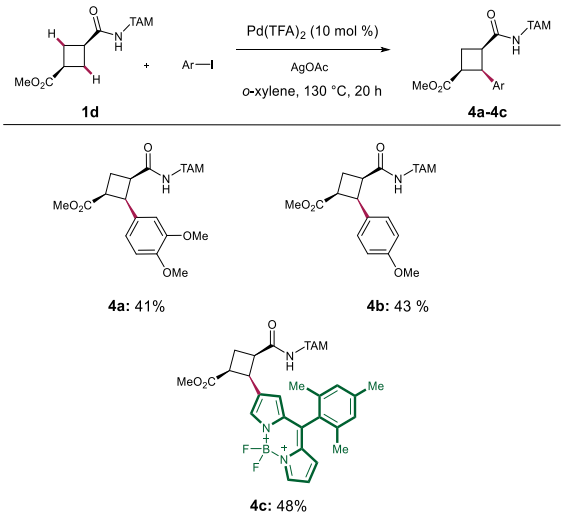
Figure 1. Computed relative Gibbs free energy profile in kcal mol^{-1} for the secondary C(sp^3)–H activation at the PW6B95-D3(BJ)/def2-TZVP+COSMO (o-xylene)//TPSS-D3(BJ)/def2-TZVP level of theory. Non-relevant hydrogen atoms were omitted for clarity in the transition state geometries.

Intrigued by the unique potential of BODIPYs[25] as biocompatible fluorescent probes, we explored BODIPY labeling by testing different BODIPYs in our secondary C(sp^3)–H activation process (Scheme 4). We were thus pleased to discover the unprecedented BODIPY fluorescence labeling on the desired cyclobutane with *cis* stereochemistry to furnish the mono functionalized BODIPY cyclobutanecarboxamide **3**.



Scheme 4. BODIPY labeling of cyclobutanes by secondary C(sp^3)–H activation.

Next, we applied our strategy to the cyclobutane-1-carboxylate **1d**, further substantiating the robustness towards natural product analogs (Scheme 5). These studies also enabled the preparation of BODIPY labeled cyclobutane-1-carboxylate **4c**, as an unprecedented fluorescent core of natural product derivatives, such as piperarborenine B, Santiaguine and Piplartine.



Scheme 5. Cyclobutanes-1-carboxylate derivatives by secondary C(sp^3)–H activation.

Considering that cyclobutane natural products display significant anticancer activity, we evaluated the biological activity of the non-fluorescent cyclobutane **4a** and a BODIPY fluorescent analogue **3a**. Cell viability measurements in human cervical cancer cells indicated similar trends for both on their dose-dependent cytotoxicity (Figure 2), which suggests that BODIPY-labeled cyclobutanes may retain some of the properties on the unlabeled cores.

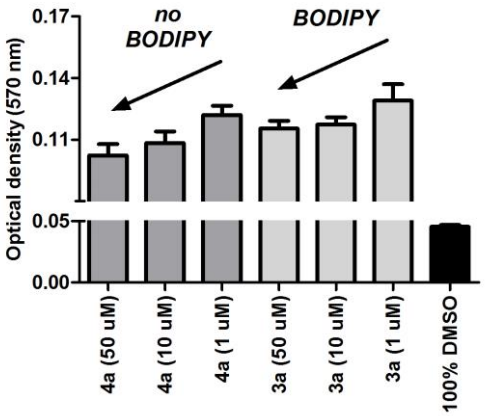
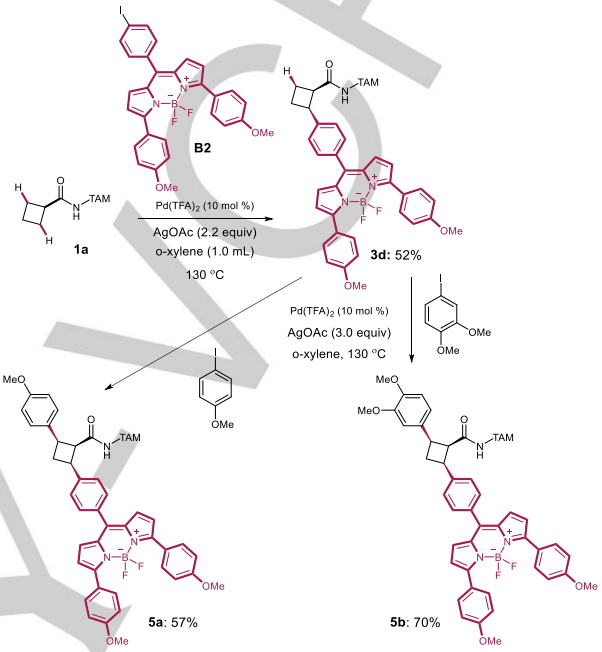


Figure 2. Anticancer activity assays. Cell viability after incubation with different concentrations of compounds **3a** and **4a** were measured, using cells incubated with only DMSO as a positive control for cell death. Values are represented as means (n=3) and error bars as s.d.

To further modify the BODIPY labeled cyclobutane core, the mono BODIPY-labeled compound **3d** was transformed into the bi-functionalized products **5a** and **5b** in an iterative C–H activation fashion (Scheme 6). In particular, the double C–H activation led to unsymmetrical cyclobutanes containing one aryl moiety and one red fluorescent BODIPY dye, featuring mimics of biorelevant natural products. Indeed, these compounds are structural mimics of the naturally occurring cyclobutanecarboxamide piperarborenine B, highlighting an additional fluorescent BODIPY scaffold.



Scheme 6. Two-fold C(sp^3)–H BODIPY labeling and arylation of cyclobutanes.

Given the novelty of the cyclobutane-BODIPY hybrids, we analyzed their spectral and biological properties for live-cell imaging. The tetramethyl BODIPY derivative **3a** emitted in the green visible range ($\lambda_{exc.}$: 495 nm, $\lambda_{em.}$: 510 nm), whereas the extended *p*-methoxyaryl derivative **3d** showed bright fluorescence emission in the red region ($\lambda_{exc.}$: 580 nm, $\lambda_{em.}$: 620 nm). These results indicate that cyclobutane labeling does not affect the excitation and emission profiles of conventional BODIPY structures. Next, we analyzed the emission in different organic solvents and the environmentally-sensitive properties of compounds **3a** and **3d**, and compared them to a tetramethyl BODIPY-aryl (BA) structure devoid of the cyclobutane ring. We measured their fluorescence emission both in aqueous buffer in hydrophobic liposome suspensions to observe that compounds **3a** and **3d** showed a stronger fluorogenic behavior than BA, which highlights a notable increase in environmental sensitivity due to the cyclobutane motif (Figures 3 and S3 and Table S8). Next, we used compounds **3a** and **3d** for fluorescence imaging of live-cell RAW264.7 macrophages. Both green and red cyclobutane-BODIPY derivatives were permeable and brightly stained macrophages, to a similar extent than BA when used at nanomolar concentrations (Figure S2). We also acquired high magnification fluorescence images of RAW264.7 macrophages after incubation with compounds **3a** and **3d** and commercial the intracellular markers Hoechst 33342-nuclei, LysoTracker-lysosomes as well as MitoTracker-mitochondria (Figure 3). From these experiments, we can conclude that both BODIPY labeled

cyclobutanes localize in the cytoplasm, but do not preferentially accumulate in the lysosomes or in the mitochondria.

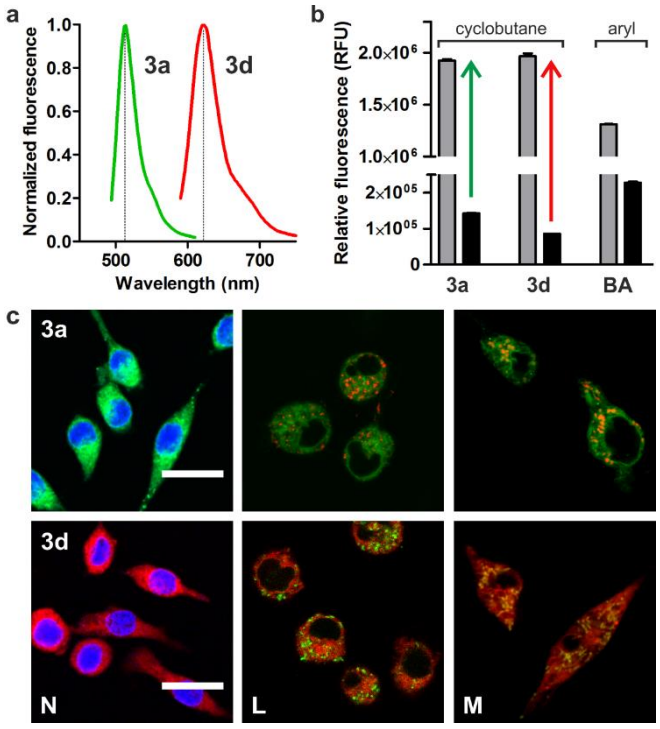


Figure 3. a) Fluorescence emission spectra of compounds **3a** and **3d**. b) Fluorogenic response of compounds **3a**, **3d** and BODIPY-aryl (BA) after incubation in liposome suspensions (grey bars) and in phosphate buffer saline (black bars). c) Fluorescence confocal microscopy of live RAW264.7 macrophage cells after treatment with compound **3a** (green, top panels) and compound **3d** (red, bottom panels), both at 250 nM. Cells were counterstained with Hoechst 33342 (blue) for nuclei (N), Lysotrackers (red in top panel, green in bottom panel) for lysosomes (L), and MitoTrackers (red in top panel, green in bottom panel) for mitochondria (M). Scale bars: 10 μm.

In conclusion, we have reported on the unprecedented secondary C(sp^3)–H arylation by TAM assistance to provide efficient access to functionalized cyclobutane natural product analogs. The robustness of our secondary C(sp^3)–H activation was reflected by an excellent functional group tolerance and ample substrate scope. The synthetic utility of our strategy was further validated by preparing the first cyclobutane-BODIPY derivatives, which paves the way for new approaches in the chemical derivatization of natural products with fluorescent labels.[26]

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Keywords: C(sp^3)–H activation • cyclobutane • labeling • BODIPY • triazoles

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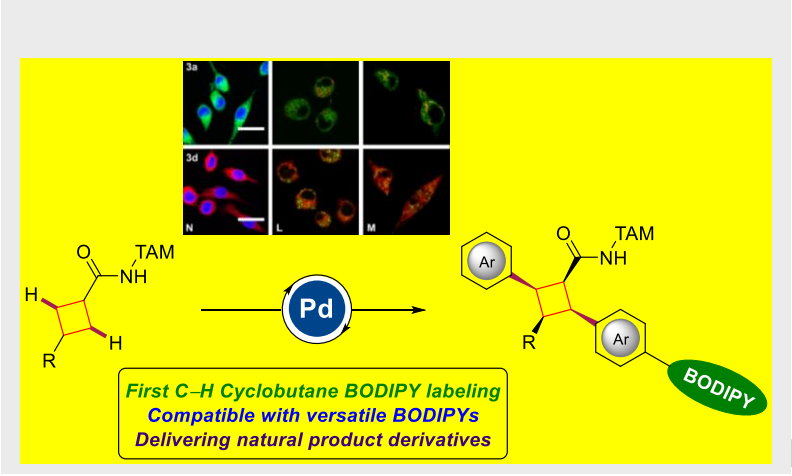

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BODIPY-Labeled Cyclobutanes by Secondary C(sp^3)–H Arylations for Live-Cell Imaging