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# Temperature-Controlled Diene Cyclization Toward Trifluoromethyl Biphenyl Derivatives: Synthetic and Computational Study

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## ABSTRACT

A temperature-controlled palladium-catalyzed cyclization of polyfluorinated dienes provides direct access to both functionalized 1,3,5-conjugated trienes and trifluoromethylated biphenyls. These dienes are readily accessible via Heck coupling of fluorinated vinyl iodides prepared through atom transfer radical addition (ATRA) of hydrofluoroolefins (HFOs). At elevated temperatures, the dienes undergo transformation into trifluoromethylated biphenyl derivatives—a pathway not previously described. Detailed mechanistic investigation, including intermediate isolation, $^{19}$F NMR monitoring, and computational studies, suggests a sequence involving $\beta$-fluoro elimination to a triene intermediate, followed by electrocyclization and aromatization. Experimental data support that the triene intermediate cyclizes through a free triene pathway, though the palladium-mediated triene cyclization remains possible. Control experiments confirm that phosphine ligands play a dual role as both stabilizing ligands and reductants. The reaction can be tuned by modulating temperature and reductant conditions, enabling stepwise access to either diene or biphenyl products. This dual-stage Pd-mediated transformation expands the synthetic utility of fluorinated building blocks and offers new opportunities in designing functionalized aromatic frameworks via in situ generated triene intermediates.

## 1 | Introduction

The construction of biaryl scaffolds as an important structural motif in active pharmaceutical ingredients and advanced materials has relied on transition-metal-catalyzed cross-couplings [1], most commonly on the Suzuki–Miyaura reaction [2]. While these classical palladium-catalyzed methods remain main synthetic tools in the pharmaceutical sector due to their robustness [3], alternative methods are still in the focus of synthetic chemistry. To circumvent the required pre-functionalization of coupling partners, step-economical direct C—H arylation has evolved from directed metal-catalyzed reactions to recent breakthroughs in nondirected functionalization [4]. Recently, biaryl syntheses based on mild, highly sustainable visible-light-driven photoredox catalysis were also developed, and these strategies enable the construction of complex biaryls using inexpensive organic promoters

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without the use of transition metals, harsh thermal conditions, and stoichiometric oxidants [5, 6]. Additionally, the in situ generation and trapping of highly reactive benzyne intermediates have emerged as a powerful alternative strategy, enabling the rapid, often metal-free assembly of the desired biaryl systems (Scheme 1a) [7].

Trifluoromethyl-containing compounds have garnered significant attention due to their broad applications in agriculture, pharmaceuticals, and organic synthesis [7–10]. Incorporation of a trifluoromethyl (—$CF_3$) group into biphenyl scaffolds has proven particularly valuable for tuning the physicochemical and biological properties of bioactive molecules [11–13]. Over the past 2 decades, fluorine has played a pivotal role in drug development, with more than 50% of FDA-approved best-selling drugs incorporating fluorinated functional groups. Among these, the trifluoromethyl aryl moiety is especially prominent, contributing to improved pharmacokinetics and therapeutic efficacy across a wide spectrum of diseases [9]. Interestingly, the trifluoromethyl (—$CF_3$) group is virtually absent in natural products, despite fluorine's relative abundance in the Earth's crust. This biochemical "unnaturality" underscores the synthetic origin and structural uniqueness of $CF_3$-containing pharmaceuticals, which have no direct natural analogs and reflect a distinctly human-driven innovation in medicinal chemistry [14, 15].

Considering the importance of $CF_3$ group in medicinal chemistry, several methods were developed for the introduction of this group into organic scaffolds [16, 17]. These include the industrially widely used Swarts method, which involves chlorination followed by reaction with HF under harsh conditions, a protocol considered unsuitable for the synthesis of functionalized organic moieties [18]. Moreover, several protocols have emerged, such as halogen substitution with $CF_3$ via transition-metal-mediated processes using Pd and Cu [19–22], Cu-catalyzed protocols for converting boron-bearing compounds into aryl-$CF_3$ [22–29], direct C—H functionalization via introduction of a $CF_3$ radical to the aromatic C—H bonds [30–38], and a Sandmeyer-type method that converts an aromatic amino group directly to $CF_3$ (Scheme 1b) [39].

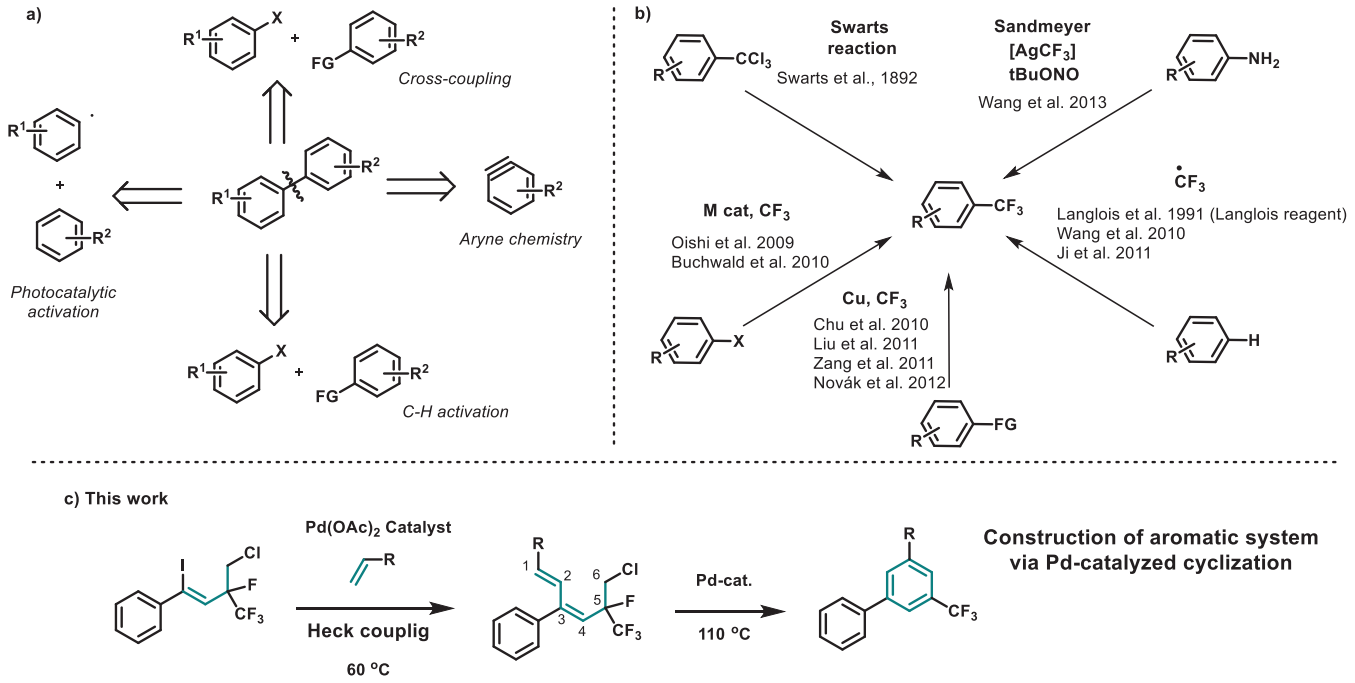
Additionally, conjugated trienes are highly reactive intermediates that engage in pericyclic and transition-metal-mediated reactions, including electrocyclization, under thermal or photochemical conditions to rapidly generate molecular complexity [40–46]. Various synthetic protocols for 1,3,5-trienes have been reported in the literature, such as microwave-accelerated Ru-catalyzed hydrovinylation of enynes [47], nucleophile-intercepted Beckmann fragmentation reaction (NuBFr) of tropone oxime tosylate in the presence of NaHMDS base [48], and Rh-catalyzed triene formation upon the reaction of acetylene with an alkene [49]. Despite these advances, a single-step dehalogenation of a vicinal F/Cl pair in complex substrates has not been reported. Obtaining a 1,3,5-hexatriene from a mixed-halide diene in a one-pot reaction would therefore be synthetically valuable.

Our group recently developed a photochemical atom-transfer radical addition (ATRA) reaction [50] of terminal alkynes and hydrofluoroolefin-based fluoroalkyl iodide to prepare fluorinated vinyl iodides, as valuable substrates for palladium-catalyzed cross-coupling reactions [51–53] such as Suzuki–Miyaura and Sonogashira couplings. Based on the results of our studies, we aimed to expand the functionalization strategies to Heck coupling towards preparing fluorinated butadienes and study the possibility of palladium-catalyzed $\beta$-fluoro elimination [54–58] step for the formation of conjugated trienes. The triene can readily cyclize and aromatize once sufficient activation energy is provided, leading to the formation of a new aryl-$CF_3$ framework (Scheme 1c) [59–64]. Herein, we report a one-pot protocol that converts 5-fluoro-6-chloro-1,3-diene derivatives directly into their corresponding 1,3,5-hexatrienes under mild conditions. Our protocol merges the dechlorination and defluorination processes in a single reaction to accomplish net elimination of Cl—F across C5–C6 (see Scheme 1c) while preserving the 1,3-diene moiety, achieving in one step what the literature suggests must be staged (hydrodechlorination followed by dehydrofluorination) [65–74]. This dual-stage process, Pd-catalyzed triene formation followed by cyclization, highlights the broader synthetic potential of harnessing in situ generated polyenes for controlled cyclization.

## 2 | Results and Discussion

For the comprehensive optimization study, we used fluorinated vinyl iodide **1a** and ethyl acrylate **2a** as coupling partner, $Pd(OAc)_2$ as catalyst and the Heck couplings were achieved in DMF in the presence of various bases and tetrabutylammonium bromide (TBAB) (Table 1). The influence of key reaction parameters such as the stoichiometry of reagents (X, W, Z, Y), base, temperature, and reaction time was systematically explored. We found that the modification of the amount of $K_2CO_3$, the alkene and TBAB had no significant influence on the reaction (Entries 1–4), and biphenyl **4aa** was formed as the major product, alongside the alkyne side product **5aa**, which formed via base-catalyzed elimination at 110°C. When the reaction was performed in the absence of palladium catalyst, vinyl iodide underwent only elimination, and the alkyne side product was accounted for 25% of the reaction mixture. This experiment highlights the importance of palladium catalyst (Entry 5).

In the next series of experiments, we aimed to find reaction conditions to achieve the diene synthesis without the formation of the biphenyl system (Entries 6–15). In the presence of 10 mol% $Pd(OAc)_2$, 1.2 equivalents of alkene, 1 equivalent of TBAB, and 2 equivalents of base ($K_2CO_3$ and diisopropylethylamine), we performed the coupling over a reaction-temperature range (25°C–100°C). We found that the coupling took place even at RT, and provided the diene product with nearly complete selectivity after 24 h (Entries 6 and 7). Increasing the temperature to 40°C or 60°C shortened the reaction time with the exclusive formation of the fluorinated diene (Entries 8–11). Further increasing the temperature, the cyclization of the diene occurred at 80°C (Entries 12 and 13) and became dominant at 100°C (Entries 14 and 15). Reduction of the palladium catalyst loading to 2 mol% enabled the coupling with full conversion and resulted in selective formation of the diene, which was isolated in 75% yield (Entry 16), and provided optimal reaction conditions for the extension of the substrate scope. To achieve the cyclization and synthesize the biphenyl derivatives efficiently, we increased the reaction temperature of the second step to 110°C, increasing the amount of alkene and additional base for the second step were also necessary (Entries 17–19). These reaction conditions enabled the synthesis of the




**SCHEME 1** | (a–c) Representative synthetic strategies for the construction of biaryl and trifluoromethyl aryl frameworks. (a) In situ generation and trapping of benzyne intermediates for biaryl synthesis. (b) Selected strategies for the introduction of $CF_3$ groups into aromatic compounds. (c) This work: Pd-catalyzed formation of a conjugated triene from fluorinated diene derivatives, followed by cyclization and aromatization to afford an aryl-$CF_3$ framework.

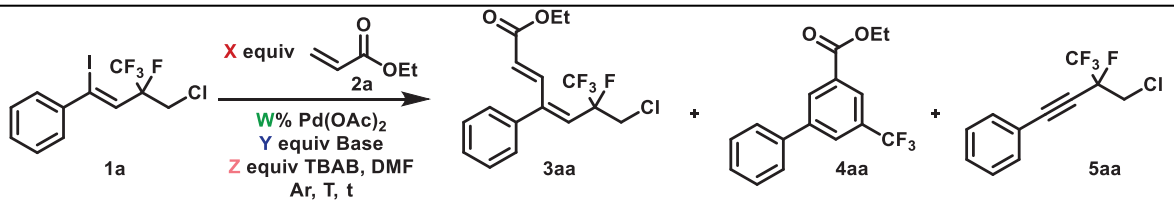
trifluoromethylated biphenyl in 73% yield in a one-pot manner (Entry 19).

After finding the optimal reaction conditions for both reaction steps, we studied the scope of the Heck coupling of our vinyl iodides with acrylonitrile and ethyl acrylate. As representative examples (Scheme 2), we executed the coupling on five phenylacetylene derivatives at 60°C to avoid cyclization and isolate the corresponding dienes as novel compounds. The coupling of the unsubstituted **1a** and *para*-substituted vinyl iodide substrates (methyl **1b**, fluorine **1c**, and methoxy **1d**) gave the desired product in over 85% yield under the optimized reaction conditions. The *ortho*-methyl substituted butadiene compounds (**3ea** and **3eb**) were isolated only in 68% and 60% chemical yield, showing some steric constraints on the reaction.

For the cyclization step, we developed a one-pot sequential coupling-elimination-cyclization procedure without isolation of the diene intermediate. After completing the initial Heck coupling under the previously described conditions, the reaction mixture was heated directly to 110°C and an additional two equivalents of base were added to promote the cyclization-elimination-aromatization sequence. Under these one-pot conditions, the ethyl-acrylate derivatives **3aa**, **3ba**, **3ca**, and **3da** performed well and gave the corresponding biphenyls in excellent 73%–89% yields. The cyanoacrylates **3ab**, **3bb**, **3cb**, and **3db**, on the other hand, gave diminished results and the desired products could only be prepared in 51%–59% yield range. For further extension of the cyclization step, we transformed vinyl iodides bearing electron-withdrawing group such as $CF_3$, CN, Cl to biaryl systems by performing the reaction at 110°C, and obtained the corresponding products **4fa**, **4ga**, and **4ha** in 54%, 44%, and 35% yield, respectively. We also demonstrated that heterocyclic vinyl iodide can be cyclized to 2-aryl-benzofuran (**4ia**) in 27% yield. Interestingly, in these additional cases, the Heck coupling was not complete at 60°C, and at higher temperatures we could not stop the reaction in the diene stage, therefore, we achieved the coupling and the cyclization in one step at 110°C. However, it is worth noting that except for compounds **4aa** and **4ab**, the obtained products are novel compounds. Importantly, for characterization and mechanistic studies, the diene intermediates could also be isolated after the first step and subsequently subjected to the cyclization conditions (heating to 110°C with fresh $K_2CO_3$), confirming that the transformation proceeds through the same pathway. Interestingly, an ortho-methyl substituent on the aromatic ring does not impede the coupling, but the subsequent cyclization did not occur in either the case of the ethyl-acrylate **3ea** or the cyanoacrylate **3eb**, suggesting that steric hindrance plays a critical role in the cyclization step.

To investigate the role of the individual reaction components in the diene cyclization step, a series of control experiments were executed. As the first step is considered a straightforward palladium-catalyzed cross-coupling [75], attention was directed toward the second step. A greater amount of the diene intermediate was isolated, and the reaction conditions required for its transformation into the biphenyl product were examined. Initially, to determine which components are essential for the transformation, different reagents were systematically excluded, and palladium-free conditions were employed. These control experiments revealed that all components, including palladium, TBAB, and the base, are required for the transformation to proceed. Therefore, the cyclization step could be confidently identified as a palladium-mediated reaction, as only a trace

**TABLE 1** | Optimization of Heck-reaction conditions.[a]




| Entry | X | W | Z | Y | Base | *T*, °C | *t*, h | 1a, % | 3aa, % | 4aa, % | 5aa, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1.5 | 10 | 1 | 2 | $K_2CO_3$ | 110 | 4 | 0% | 0% | 80% | 20% |
| 2 | 1.5 | 10 | 1.5 | 2 | $K_2CO_3$ | 110 | 4 | 0% | 0% | 83% | 17% |
| 3 | 1.5 | 10 | 1 | 3 | $K_2CO_3$ | 110 | 4 | 0% | 0% | 81% | 19% |
| 4 | 2.0 | 10 | 1 | 2 | $K_2CO_3$ | 110 | 4 | 0% | 18% | 73% | 9% |
| 5 | 1.5 | 0 | 1 | 2 | $K_2CO_3$ | 110 | 4 | 75% | 0% | 0% | 25% |
| 6 | 1.2 | 10 | 1 | 2 | $K_2CO_3$ | RT | 24 | 10% | 87% | 0% | 3% |
| 7 | 1.2 | 10 | 1 | 2 | DIPEA | RT | 24 | 0% | 99% | 0% | 1% |
| 8 | 1.2 | 10 | 1 | 2 | $K_2CO_3$ | 40 | 4 | 0% | 99% | 0% | 1% |
| 9 | 1.2 | 10 | 1 | 2 | DIPEA | 40 | 4 | 0% | 97% | 0% | 3% |
| 10 | 1.2 | 10 | 1 | 2 | $K_2CO_3$ | 60 | 4 | 0% | 95% | 0% | 5% |
| 11 | 1.2 | 10 | 1 | 2 | DIPEA | 60 | 4 | 0% | 98% | 1% | 1% |
| 12 | 1.2 | 10 | 1 | 2 | $K_2CO_3$ | 80 | 4 | 0% | 75% | 16% | 7% |
| 13 | 1.2 | 10 | 1 | 2 | DIPEA | 80 | 4 | 0% | 90% | 6% | 3% |
| 14 | 1.2 | 10 | 1 | 2 | $K_2CO_3$ | 100 | 4 | 0% | 18% | 68% | 13% |
| 15 | 1.2 | 10 | 1 | 2 | DIPEA | 100 | 4 | 0% | 22% | 75% | 3% |
| 16 | **2.0** | **2** | **1** | **2** | **$K_2CO_3$** | **60** | **4** | **0%** | **99%(75%)** | **0%** | **1%** |
| 17 | 1.2 | 2 | 1 | 2 + 2 | $K_2CO_3$ | 60->110 | 4 + 24 | 0% | 0% | 100%(63%) | 0% |
| 18 | 1.5 | 2 | 1 | 2 + 2 | $K_2CO_3$ | 60->110 | 4 + 24 | 0% | 0% | 100%(54%) | 0% |
| 19 | **2.0** | **2** | **1** | **2 + 2** | **$K_2CO_3$** | **60->110** | **4 + 24** | **0%** | **0%** | **100%(73%)** | **0%** |

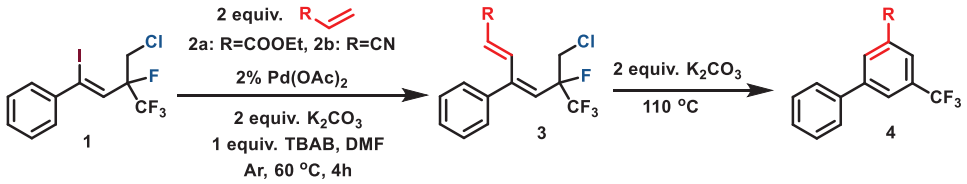
[a]The optimization of the coupling reaction. Conversions were determined by GC-MS. Preparative yields are in parentheses. The amounts marked by + signs indicate additional amounts after elevating the temperature. Best reaction condition was highlighted with bold (Entry 16).

amount of the biphenyl product was observed in its absence (Table 2).

To further investigate the role of phosphine ligands in the cyclization step, a series of experiments were conducted using various palladium sources and phosphines. While our optimized preparative reactions employ ligand-free Jeffery conditions [76–78], it was found that the addition of phosphine ligand accelerates the cyclization step, specifically, in the presence of one equivalent of $PPh_3$, the diene-to-biphenyl conversion reached completion within 1 h, compared to 4–24 h under ligand-free conditions (Section S4 for detailed kinetic data). This observation indicated that the phosphine functions not only as a ligand but also as a reductant in the reaction. It is well known that phosphines can reduce palladium species into Pd(0) in catalytic cycles [79]. Notably, the use of $PPh_3$ also led to the formation of difluoromethylated by-product (observed in up to 23% yield under these conditions, see Supporting Information), which, while mechanistically informative, caused synthetic challenges and prompted us to retain ligand-free conditions for preparative purposes. These experimental observations guided the design of our computational studies, in which a Pd-phosphine model system was employed.

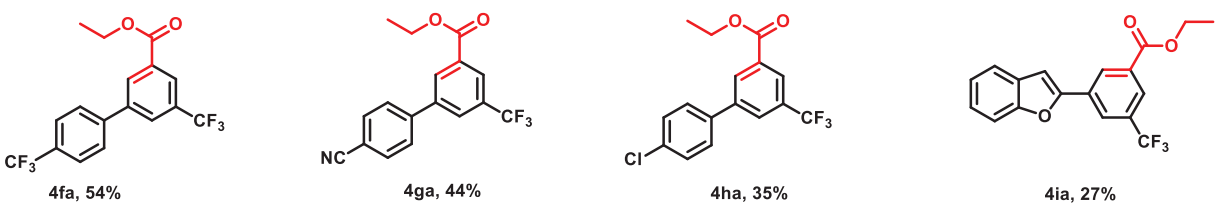
## 2.1 | Theoretical Study

The experimental results indicated that while phosphine ligands are not required for the reaction to proceed under the optimized conditions, their addition significantly accelerates the cyclization step (see Supporting Information for detailed kinetic studies). This observation combined with the well-documented role of phosphines as both stabilizing ligands and reductants in palladium catalysis [79], prompted us to investigate the mechanism using a well-defined Pd-phosphine model system. Although the preparative reactions were conducted under ligand-free Jeffery conditions [76–78], a common approach in Heck-type couplings, the inherent complexity of such systems, poses significant challenges for computational modeling. Under these conditions, the system is not perfectly homogeneous due to gradual palladium precipitation leading to the formation of ill-defined coordination environments and multiple potential palladium species [80]. These characteristics complicate both experimental and theoretical mechanistic analysis. To obtain a chemically meaningful and computationally tractable mechanistic picture, we chose to model the catalytic cycle using $Pd(PPh_3)_2$ as a representative catalyst. This approach allows us to capture the essential features of the transformation, including




| Entry | Starting material | Coupling product (3)[b] | Yield%[b] | Cyclization product (4)[c] | Yield% |
|---|---|---|---|---|---|
| 1 | 1a | | 3aa, R: $CO_2Et$ 92%<br>3ab, R: CN 86% | | 4aa, R: $CO_2Et$ 73%<br>4ab, R: CN 57%, 51% |
| 2 | 1b | | 3ba, R: $CO_2Et$ 92%<br>3bb, R: CN 84% | | 4ba, R: $CO_2Et$ 89%<br>4bb, R: CN 57% |
| 3 | 1c | | 3ca, R: $CO_2Et$ 90%<br>3cb, R: CN 85% | | 4ca, R: $CO_2Et$ 87%<br>4cb, R: CN 59% |
| 4 | 1d | | 3da, R: $CO_2Et$ 86%<br>3db, R: CN 87% | | 4da, R: $CO_2Et$ 88%<br>4db, R: CN 57% |
| 5 | 1e | | 3ea, R: $CO_2Et$ 68%<br>3eb, R: CN 60% | | 4ea, R: $CO_2Et$ 0%<br>4eb, R: CN 0% |

Additional products



4fa, 54% 4ga, 44% 4ha, 35% 4ia, 27%

[a] Isolated after the first step
[b] Isolated yield, NMR yield
[c] two step synthesis from vinyl iodide without the isolation of 3

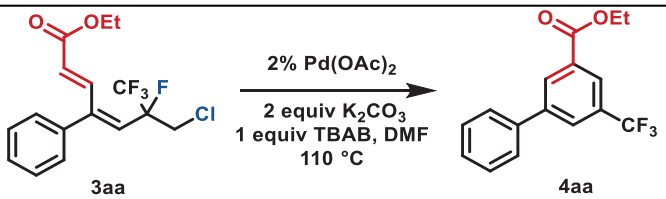
**SCHEME 2** | Scope of Heck coupling and subsequent cyclization reaction.

oxidative addition, $\beta$-fluoro elimination, and triene cyclization, while maintaining a well-defined electronic structure suitable for high-level quantum chemical calculations. Importantly, control experiments confirmed that the same reactivity pattern, namely, diene formation followed by cyclization to the biphenyl product, is observed both in the presence and absence of phosphines, albeit with different kinetics (Section S3). Thus, the Pd-phosphine model serves as a reliable surrogate to elucidate the fundamental mechanistic steps, and the conclusions drawn are expected to be transferable to the experimentally relevant ligand-free conditions.

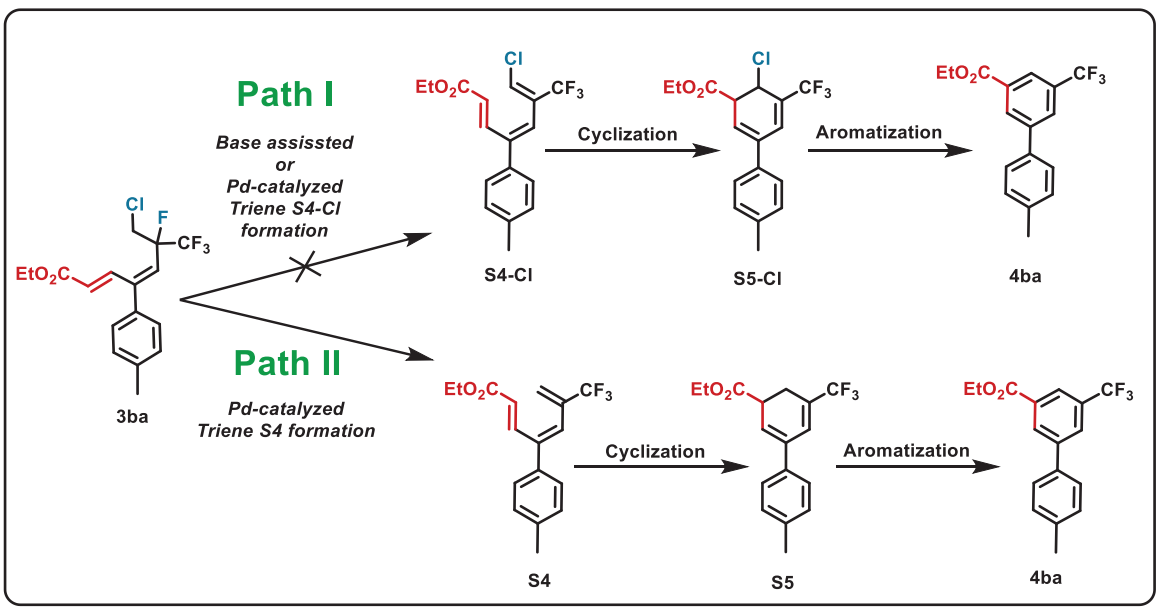
## 2.2 | Computational Details

Relaxed potential energy scan for the newly formed bonds is performed using the extended tight-binding method xTB [81] to

**TABLE 2** | Evaluation of individual reaction components.




| Entry | $Pd(OAc)_2$ | Base | TBAB | Conversion (4 h), % | Conversion (18 h), % |
|---|---|---|---|---|---|
| 1 | — | — | — | 0 | 0 |
| 2 | — | + | — | 3 | 5 |
| 3 | — | + | + | 0 | 7 |
| 4 | + | — | — | 0 | 0 |
| 5 | + | + | — | 0 | 8 |
| 6 | + | — | + | 2 | 7 |
| 7 | + | + | + | 31 | 72 |




**SCHEME 3** | Diene **3ba** cyclization reaction stages. Path I involves prohibitively high barriers (see Supporting Information, excluded Mechanisms Section). Path II represents the full reaction profile shown in Figure 1.

probe initial reaction coordinates. Transition states were located using the simple zero-temperature string (sZTS) method [82]. For a rapid exploration of chemical space to find low-energy conformers, the Conformer-Rotamer Ensemble Sampling Tool CREST program [83] is used. In case of transition states, conformational searches are applied with geometrical constraints. The analytical linearized Poisson–Boltzmann (ALPB) solvation model is used for semiempirical GFN2-xTB level in initial optimization and CREST conformational search [84]. Conformer ensembles found with CREST are fed into *Commandline Energetic Sorting* program CENSO following CENSO-light protocol [85, 86] afterward for further structural refinement at DFT level and calculating entropy correction term. Reactants, transition states, and products lowest energy conformers obtained are optimized with B97-3c method [87] using the ORCA 6.0.0 program [88, 89]. Vibrational frequencies were calculated to confirm that optimized structures are either transition states or global minimum structures. Thermal correction is calculated at the reaction temperature (383.15 K). For optimized structures, accurate single-point energies are calculated with local natural orbital coupled-cluster (LNO-CCSD(T)) [90–93] method using MRCC package [94, 95]. The energy extrapolation scheme def2-TZVPP/def2-QZVPP has been used to reach complete basis set limit CBS [96–98]. The conductor-like polarizable continuum solvation model CPCM is used to calculate solvent correction at ωB97M-V/def2-TZVPP level of theory [97, 99]. We have applied a sophisticated computational workflow based on conformational analysis and local correlation methods, developed and experimentally validated in our laboratory [86, 100, 101].

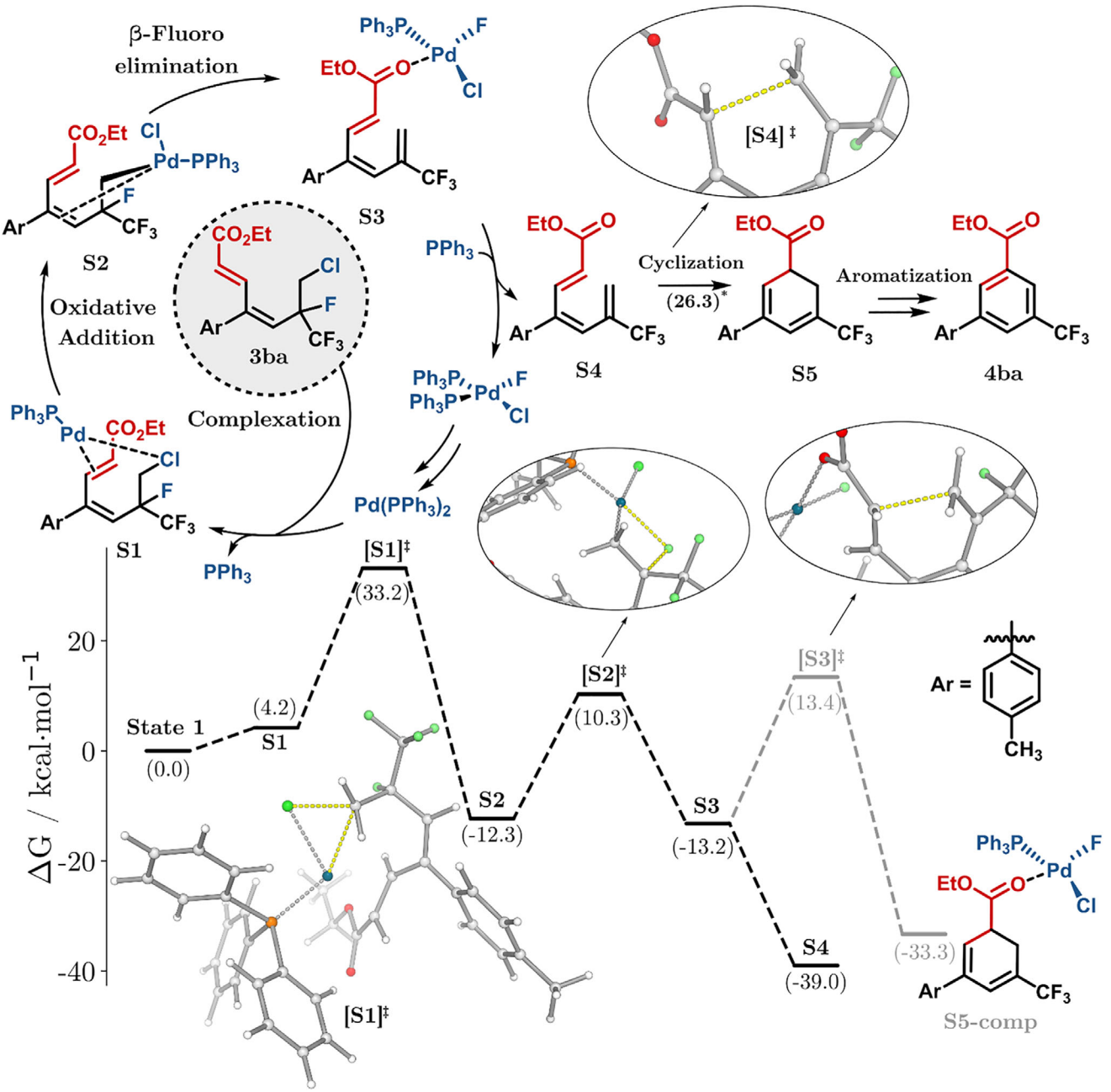



**FIGURE 1** | Experimentally and computationally supported catalytic cycle of the Pd-assisted diene **3ba** cyclization and its corresponding reaction free-energy profile computed at the LNO–CCSD(T)/CBS//B97-3c level. *Activation barriers in parentheses are in kcal/mol. For full 3D transition-state structures see Supporting Information.

## 2.3 | Mechanistic Investigation

A computational study is conducted to investigate the cyclization of polyfluoro diene **3ba**. Based on the experimental findings, a mechanism involving Pd-assisted triene formation step followed by electrocyclization that obtains biphenyl product **4ba** is proposed. To study the proposed mechanism, the cyclization process is divided into three stages, Pd-catalyzed triene formation, Pd-free triene cyclization, and cyclic diene aromatization (Scheme 3). It is hypothesized initially that the reaction could take place through different trienes, namely, triene **S4-Cl**, and **S4** as shown in path I and path II respectively. Since in both cases the triene cyclizes readily as soon as it is formed, the limiting step is the triene formation. However, barriers of **S4-Cl** pathway were found to be prohibitively high and were excluded (See Supporting Information, Section 8.5 Mechanisms Section). Reasonable barriers have been found for **S4** formation via Pd-catalyzed process. Therefore, it is concluded that the reaction is more likely to take place through path II, which is also supported by experimental findings.

The full reaction profile for the cyclization of diene **3ba** through path II is shown in Figure 1. Initially, a ligand exchange takes place between diene **3ba** and $Pd(PPh_3)_2$ catalyst producing

complex **S1** in a slightly endergonic step. The resulting diene-Pd complex **S1** undergoes oxidative addition of the C—Cl bond to the palladium center via **[S1]**‡ ($\Delta G$ = 33.2 kcal/mol). The produced $Pd^{II}$ complex **S2** ($\Delta G$ = −12.3 kcal/mol) then undergoes $\beta$-fluoro elimination with relative barrier of 22.6 kcal/mol via **[S2]**‡ ($\Delta G$ = 10.3 kcal/mol) producing Pd-triene complex **S3** ($\Delta G$ = −13.2 kcal/mol). The Pd-triene complex **S3** can dissociate to release the free triene **S4** ($\Delta G$ = −39.0 kcal/mol) which subsequently undergoes cyclization with a relative barrier of 26.3 kcal/mol via **[S4]**‡ producing **S5**, followed by aromatization that produces biphenyl product **4ba** [59–64].

An alternative reaction pathway is that **S3** can cyclize while the triene is still coordinated to the palladium center with a relative barrier of 26.6 kcal/mol relative barrier via **[S3]**‡ ($\Delta G$ = 13.4 kcal/mol) forming the cyclic diene-Pd complex **S5-comp** ($\Delta G$ = −33.3 kcal/mol), which then readily dissociates before undergoing aromatization obtaining the final biphenyl product **4ba**. It is apparent from Figure 1 that the free triene cyclization path has lower-lying intermediate prior to cyclization which results in lower energy span [102].

The electrocyclization of triene **S4** is examined both in the presence and the absence of palladium catalyst, as the possibility of trace amounts of palladium in the isolated triene cannot be ruled out [103]. To address this, in addition to calculating the cyclization barrier of the triene, various scenarios involving palladium-assisted cyclization were explored, including the $\eta^4$–$\eta^6$ Pd-triene complexes (see Figure S8), and the palladium-triene complex **S3** (Figure 1). Ultimately, results indicate that triene cyclization occurs either as a free triene **S4** with an energy barrier of 26.3 kcal/mol or as complexed triene **S3** with a barrier of 26.6 kcal/mol which indicates no significant difference between the two scenarios. Given the low palladium concentration, the Pd-free reaction is more probable, but due to the comparable values and the computational accuracy, the Pd-catalyzed reaction cannot be excluded [80]. It is worth noting that various computational methods and solvation models were tested and compared. The results revealed only negligible differences among them; detailed data are provided in Table S2.

## 3 | Conclusion

In summary, a novel temperature-controlled palladium-mediated cyclization route that transforms polyfluorinated diene intermediates obtained by vinyl iodides Heck-coupling into trifluoromethylated biphenyl derivatives is introduced. A combination of control experiments and computational analysis revealed a mechanistic pathway involving initial Heck coupling, $\beta$-fluoro elimination to triene intermediate, and subsequent electrocyclization followed by aromatization. Key control experiments revealed the dual role of phosphine ligands as stabilizing agent and reductant. Computational studies corroborated the feasibility of both palladium-bound and Pd-free triene cyclization mechanisms, with similar barrier height. This temperature-dependent, two-stage transformation not only enhances the synthetic utility of fluorinated vinyl iodides derived from HFOs but also broadens access to functionally diverse, $CF_3$-substituted biphenyls. These findings pave the way for further exploration of transition-metal-mediated transformations in the synthesis of highly functionalized fluorinated aromatics.

## 4 | Experimental Section

General methods for Heck coupling: Into a screwcap vial measure $Pd(OAc)_2$ (0.008 mmol, 1.8 mg), TBAB (0.4 mmol, 133 mg), $K_2CO_3$ (0.8 mmol, 111 mg) and vinyl iodide (0.4 mmol) from the photoaddition. Then seal the vial and change the atmosphere to argon by evacuating and back-filling three times. Then add dry DMF (4 mL) and the olefin (0.8 mmol). Stir at 60°C for 4 h. After the completion of the coupling, pour into a separating funnel and add ethyl acetate (20 mL) and water (20 mL). Separate the aqueous layer and wash with Ethyl acetate two times. Then wash the combined organic layers with brine, and dry using $Na_2SO_4$. Purify using flash column chromatography with a gradient of hexanes and ethyl acetate.

General methods for the Heck coupling followed by cyclization: Into a screwcap vial measure $Pd(OAc)_2$ (0.008 mmol, 1.8 mg), TBAB (0.4 mmol, 133 mg), $K_2CO_3$ (0.8 mmol, 111 mg) and vinyl iodide (0.4 mmol) from the photoaddition. Then seal the vial and change the atmosphere to argon by evacuating and back-filling three times. Then add dry DMF (4 mL) and the olefin (0.8 mmol). Stir at 60°C for 4 h. After the completion of the coupling (determined by GC-MS), add another portion of $K_2CO_3$ (0.8 mmol, 111 mg) then stir at 110°C until the completion of the cyclization (determined by GC-MS). Then pour the mixture into a separating funnel and add ethyl acetate (20 mL) and water (20 mL). Separate the aqueous layer and wash with Ethyl acetate two times. Then wash the combined organic layers with brine, and dry using $Na_2SO_4$. Purify using flash column chromatography with a gradient of hexanes and ethyl acetate.

### Author Contributions

**Bálint Varga:** methodology, investigation, and writing – original draft. **Khaled T. Jaradat:** methodology, software, writing – original draft, and writing – review and editing. **Martin Polyák:** methodology and investigation. **János Kele-Jókuthy:** methodology and investigation. **Attila Herczegh:** methodology and investigation. **Andras Kotschy:** conceptualization and writing – review and editing. **Zoltán Novák:** conceptualization, methodology, project administration, resources, supervision, writing – original draft, and writing – review and editing. **János Daru:** conceptualization, methodology, supervision, writing – original draft, and writing – review and editing.

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## Conflicts of Interest

The authors declare no conflicts 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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## Supporting Information

Additional supporting information can be found online in the Supporting Information section.

**Supporting File 1**: cctc71064-sup-0001-SuppMat.pdf **Supporting File 2**: cctc71064-sup-0002-SuppMat.zip