# Selective 1,4-*syn*-Carboamination of Cyclic 1,3-Dienes via Hybrid Palladium Catalysis

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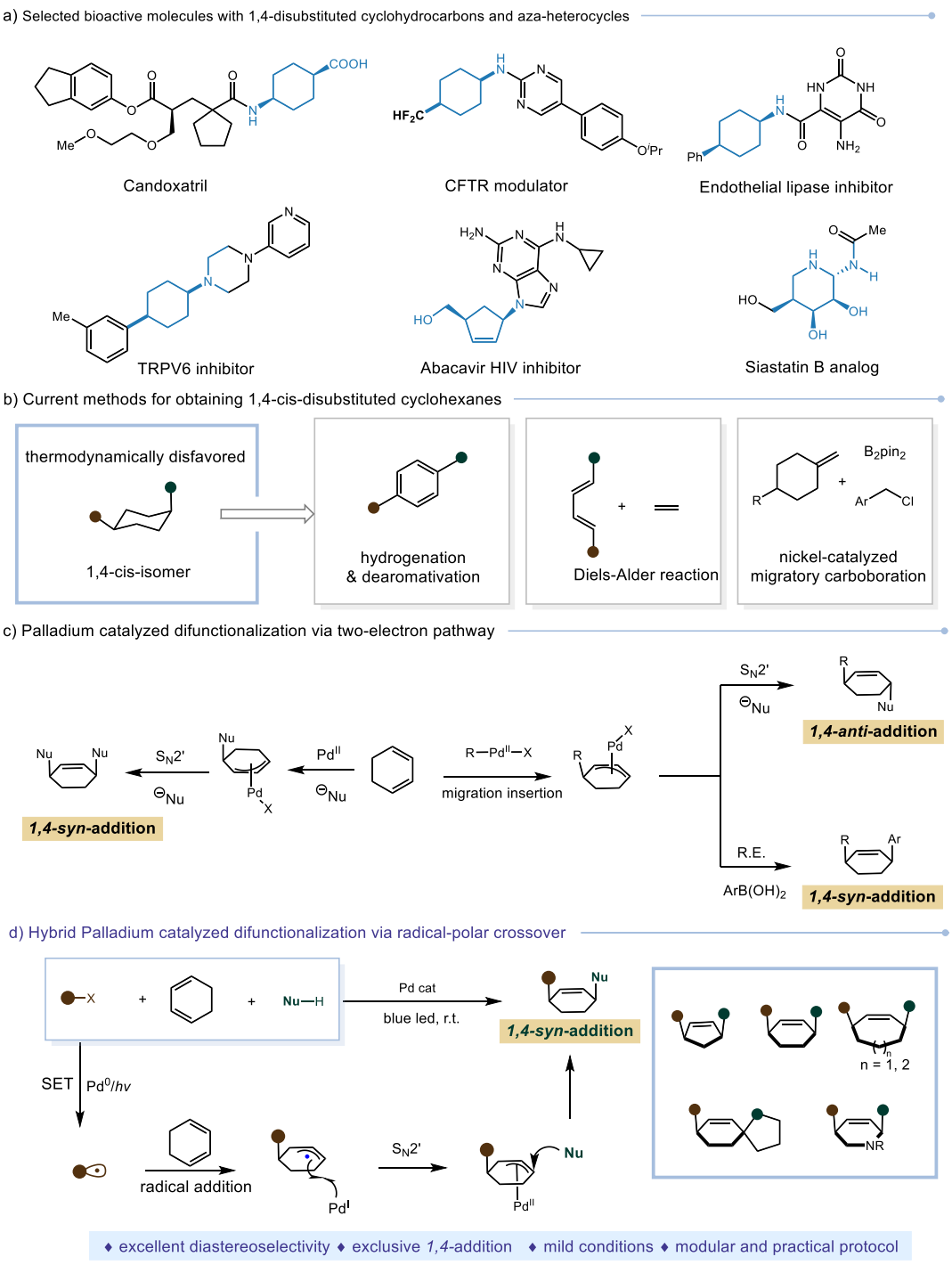
**ABSTRACT:** 1,4-*cis*-disubstituted cyclic compounds play a pivotal role in pharmaceutical development, offering enhanced potency and bioavailability. However, their stereoselective and modular synthesis remains a long-standing challenge. Here, we report an innovative strategy for accessing these structures via mild conditions employing cyclic 1,3-dienes/alkyl(aryl)halides and amines. This procedure exhibits a wide substrate scope that tolerates various functional groups. The utility of this method is demonstrated in the efficient synthesis of a TRPV6 inhibitor, CFTR modulator and other bioactive molecules. Combined experimental and computational studies suggest that the hybrid palladium-catalyzed radical-polar crossover mechanism is crucial for achieving the exceptional 1,4-syn-addition selectivity (dr > 20:1).

Contemporary drug discovery endeavors have increasingly focused on saturated compounds due to their intricate three-dimensional geometries, which often impart superior bioactivities and physical properties compared to their planar bioisosteres[1-3]. Given that a substantial majority of small-molecule pharmaceuticals feature at least one ring system, the development of efficient synthetic methodologies for stereospecific construction of saturated rings has garnered significant attention[4-6]. The 1,4-cis-disubstituted cyclic framework represents a pivotal structural motif within a wide spectrum of pharmaceutical molecules, including notable examples such as Candoxatril[7], CFTR modulator[8], Endothelial lipase inhibitor[9], TRPV6 inhibitor[10], Abacavir[11] and Siastatin B analog[12] (**Figure** 1a). Considerable effort has been devoted in selective constructing cyclic structures with energetically unfavorable 1,4-cis substitutions. However, the available methods are still limited to selective hydrogenation[13-15] and dearomatization of arenes[16], and the Diels-Alder reaction[17-19].

Multicomponent reactions, facilitating the rapid assembly of multifunctional molecules with structural diversity from readily accessible starting materials, stand out as highly efficient and practical synthetic strategies, characterized by their atom- and step-economical nature[20-21]. Recently, the Yin research group introduced an elegant approach for accessing thermodynamically disfavored substituted cyclohexanes through nickel-catalyzed migration functionalization of alkenes with a preinstalled substitution[22]. On the other hand, the transition metal-catalyzed difunctionalization of conjugated dienes has offered a dependable platform for the preparation of polysubstituted alkenes in a stereoselective manner. [23-44] For example, the Bäckvall group developed palladium catalyzed 1,4-syn-diacetoxylation of 1,3-dienes in the presence of LiCl.[45-46] Additionally, the Larock group developed a three-component coupling of aryl halides, 1,3-cyclohexadiene, and boronic acids to provide 1,4-syn-addition products.[47] However, these methods still suffered limited substrate scope. While using a general soft nucleophiles, the redox neutral transformation usually favor 1,4-trans isomer products or mixtures (**Figure** 1c), as they typically involve syn-migration addition and $S_N2'$ substitution, particularly with amines as nucleophiles.[48-50]Given the prevalence of 1,4-*cis*-difunctionalized cyclic scaffolds and the existing limitations in current synthetic approaches, new strategy for the modular synthesis of these thermodynamically disfavored isomers in a highly stereoselective and efficient manner is highly desirable, as it would significantly enrich the arsenal of organic synthetic chemists and expand the compound library available for drug discovery purposes.

**Figure 1.** The application and synthesis of 1,4-cis-disubstituented cyclic frameworks.

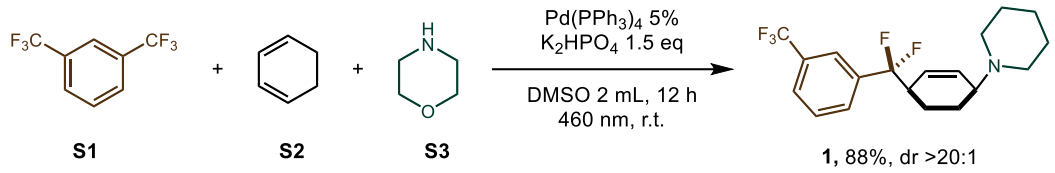


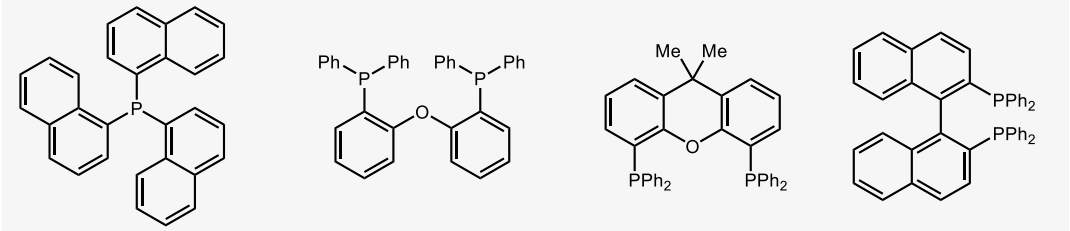

Recently, the hybrid palladium catalysis has exhibited outstanding reactivity by enabling the reduction of carbon-halogen (C-X) bonds and yielding carbon-centered radicals. Simultaneously, Pd(I) species have demonstrated the propensity to engage with subsequent allylic radicals, leading to the formation of allylic Pd(II) intermediates that offer the potential for robust regio- and enantioselectivity.[51-61] Nonetheless, achieving facial selectivity in cyclic conjugated dienes persists as an outstanding challenge.[53] We envisioned that achieving 1,4-*syn*-addition to cyclic 1,3-dienes could be accomplished through a formal stepwise migration addition, coupled with $S_N2'$ nucleophilic substitution (**Figure** 1d). Specifically, the photoexcited palladium catalyst harnesses visible light and donates an electron to the electrophilic partner, resulting in the formation of a carbon radical. This radical then engages in addition to the cyclic 1,3-diene to create an allylic carbon

radical. Considering the steric effect, we anticipate Pd(I) to effectively capture the allylic carbon radical from the less hindered back side. Proceeding with an $S_N2'$ type nucleophilic substitution finally yields the 1,4-syn-addition products. Herein, we present a dependable and modular protocol for the synthesis of 1,4-cis-substituted cyclic compounds via excited palladium-catalyzed multicomponent reactions, offering precise control of regio- and stereoselectivity. This method exhibits the capacity to efficiently assemble a broad array of amines, electrophiles, and cyclo-1,3-dienes into 1,4-*syn*-addition products, all characterized by excellent regio- and diastereoselectivity.

We initiated this investigation by selecting trifluoromethylated arene **S1**, cyclohexyl 1,3-diene **S2**, and morpholine **S3** as the model substrates (**Table 1**). Employing $Pd(PPh_3)_4$ as a catalyst at a 5 mol % loading in DMSO as the solvent led to a smooth reaction, yielding the desired product **1** in excellent diastereoselectivity and good yield (88%, **Table 1**). The introduction of external ligands proved ineffective and resulted in decreased yields. A solvent screening experiment revealed that only DMF provided comparable yields, while other solvents led to diminished yields (**Table 1**, entries 2-6). Substituting $Pd(PPh_3)_4$ with other catalysts either resulted in a halted reaction or a significant decrease in yield (**Table 1**, entries 7-9). Notably, reducing the catalyst loading to 2.5 mol % still lead to the desired product in high yield, at 86% (**Table 1**, entry 10). Conversely, increasing the catalyst loading to 10 mol % led to a slightly lower yield (**Table 1**, entry 11). Various bases were examined, with $K_2HPO_4$ identified as the optimal base for this transformation (**Table 1**, entries 12-16). Control experiments confirmed that both the presence of the catalyst and the exposure to light were essential for the success of this reaction (**Table 1**, entries 17-18).

**Table 1.** Optimization of conditions[a]




| Entry | catalyst | base | Solvent | Yield, *dr*[b] |
|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ 5 mol % | $K_2HPO_4$ | DMSO | 88%, >20:1 |
| 2 | $Pd(PPh_3)_4$ 5 mol % | $K_2HPO_4$ | DMF | 88%, >20:1 |
| 3 | $Pd(PPh_3)_4$ 5 mol % | $K_2HPO_4$ | Benzene | trace |
| 4 | $Pd(PPh_3)_4$ 5 mol % | $K_2HPO_4$ | Dioxane | trace |

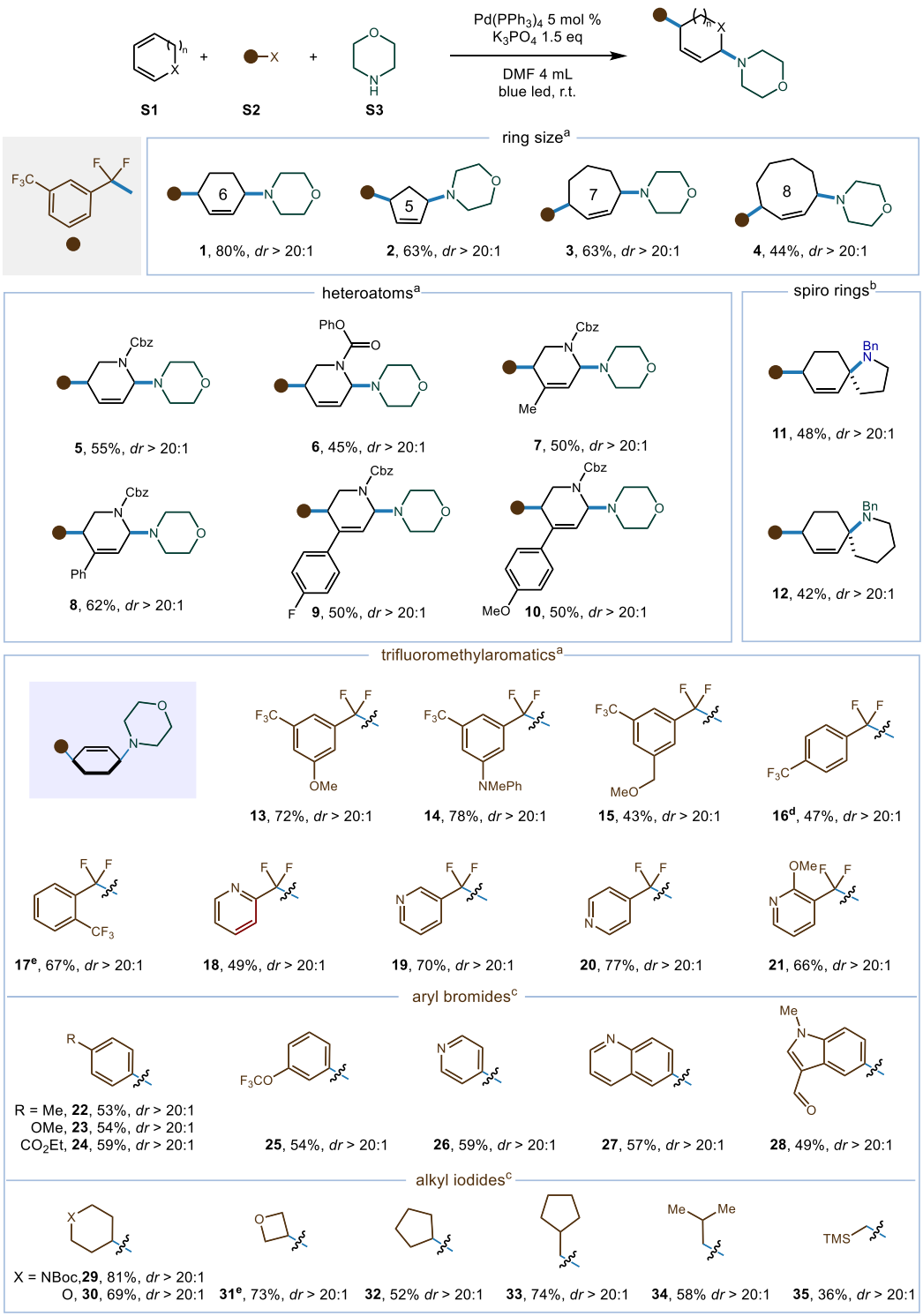
| | | | | |
|---|---|---|---|---|
| 5 | $Pd(PPh_3)_4$ 5 mol % | $K_2HPO_4$ | EA | 25%, >20:1 |
| 6 | $Pd(PPh_3)_4$ 5 mol % | $K_2HPO_4$ | DCE | trace |
| 7 | $Pd(OAc)_2$ 5 mol % | $K_2HPO_4$ | DMF | 0 |
| 8 | $Pd(acac)_2$ 5 mol % | $K_2HPO_4$ | DMF | 0 |
| 9 | $Pd(PPh_2)Cl_2$ 5 mol % | $K_2HPO_4$ | DMF | 13%, >20:1 |
| 10 | $Pd(PPh_3)_4$ 2.5 mol % | $K_2HPO_4$ | DMF | 86%, >20:1 |
| 11 | $Pd(PPh_3)_4$ 7.5 mol % | $K_2HPO_4$ | DMF | 71, >20:1 |
| 12 | $Pd(PPh_3)_4$ 5 mol % | NaOAc | DMF | 58%, >20:1 |
| 13[c] | $Pd(PPh_3)_4$ 5 mol % | $Na_2HPO_4$ | DMF | 40%, >20:1 |
| 14 | $Pd(PPh_3)_4$ 5 mol % | $Cs_2CO_3$ | DMF | 0 |
| 15 | $Pd(PPh_3)_4$ 5 mol % | $Na_2CO_3$ | DMF | 48%, >20:1 |
| 16 | $Pd(PPh_3)_4$ 5 mol % | $KHCO_3$ | DMF | 49%, >20:1 |
| 17 | No catalyst | $K_2HPO_4$ | DMF | NR |
| 18 [c] | $Pd(PPh_3)_4$ 5 mol % | $K_2HPO_4$ | DMF | NR |

[a] General conditions (unless otherwise indicated): 0.15 mmol **S1**, 0.15 mmol **S2**, 0.1 mmol **S3**, 5 mol% Pd $(PPh_3)_4$, 0.15 mmol base, solvent (2 mL), 460 nm (10 W), r.t., 30 h; [b] Yield determined by $^1$H-NMR and dr by $^{19}$F-NMR using 2,2,2-Trifluoro-N, N-dimethylacetamide as an external standard; [c] without light.

Subsequently, we turned our attention to exploring the versatility of this hybrid palladium-catalyzed reaction, initially assessing a range of cyclic 1,3-dienes with varying ring sizes (**Scheme 1**). Gratifyingly, cyclic dienes featuring 5 to 8-membered rings consistently delivered the desired products **1-4** with moderate to high yields and exceptional regio- and diastereoselectivity. Recognizing the significance of aza-heterocycles in medicinal chemistry, a diverse array of dihydropyridines was subjected to the established conditions, resulting in the formation of 1,4-cis-difunctionalized products **5-10** in moderate yields. Furthermore, conjugated cyclohexyldienes, equipped with preinstalled nucleophiles, demonstrated compatibility with the optimized reaction conditions, yielding diverse spirocyclic products **11-12** of varying sizes. Subsequently, an exploration of the scope of electrophiles was undertaken. Given the significance of gem-difluoromethylene unit in pharmaceutical discovery, our primary focus gravitated towards trifluoromethylaromatics. Various substituted trifluoromethylarenes including meta, para, and ortho di-trifluoromethylated arenes emerged as amenable substrates, delivering the desired products **13-17** in moderate to favorable yields, alongside the medicinally relevant trifluoromethylated pyridines **18-21** with diverse substitution patterns. Following this, we turned our attention to arylbromides. Both electron-rich and electron-deficient aryl bromides demonstrated the capability to yield corresponding aryl amination products **22-25** with moderate efficiency, albeit the

electron-rich aryl bromide **23** displayed a slightly reduced yield. Moreover, an array of heteroarenes, including pyridine **26**,

**Scheme 1.** Scope of 1,3-dienes and electrophiles

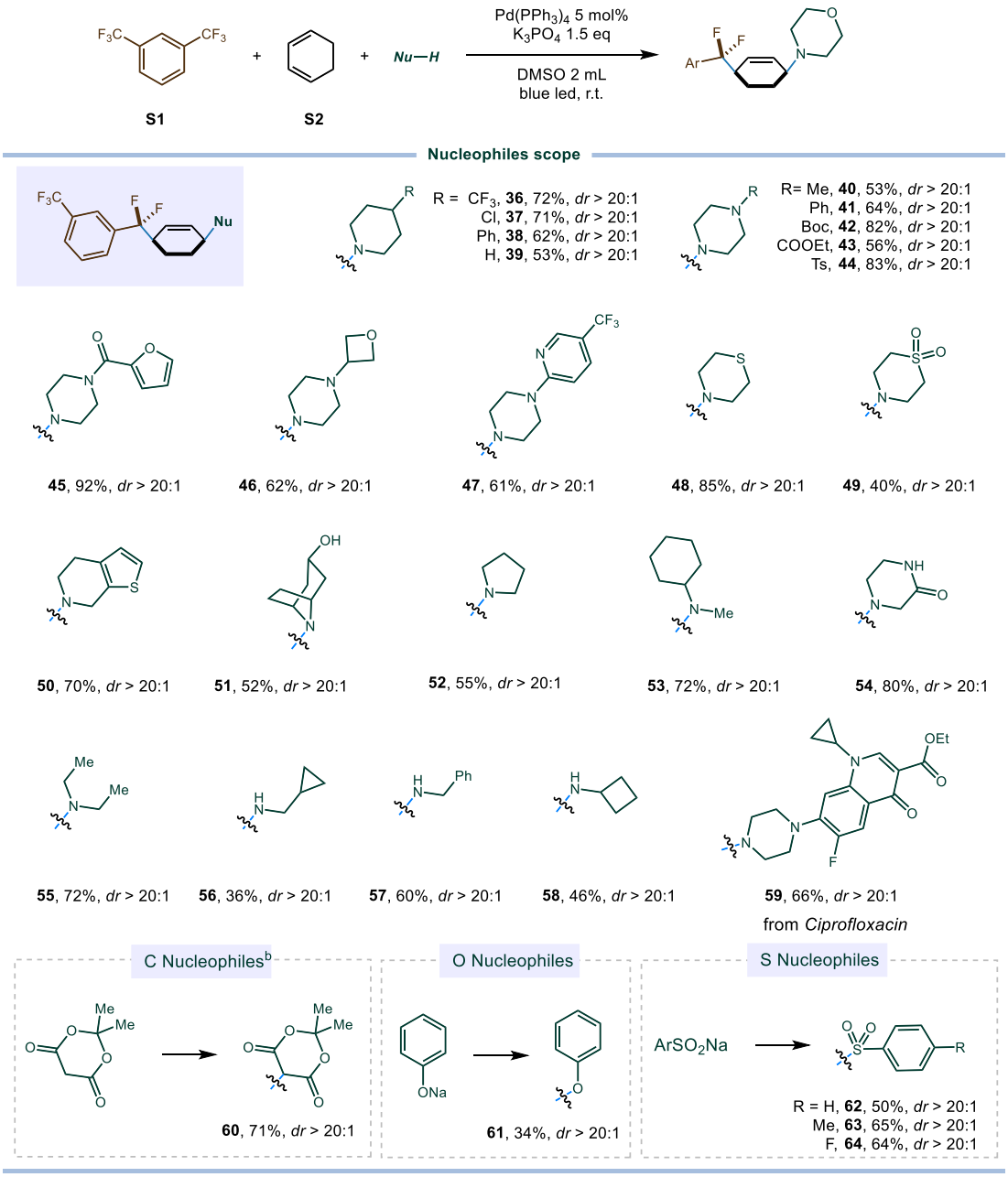



[a] 0.15 mmol **S1**, 0.15 mmol **S2**, 0.1 mmol **S3**, 5 mol% $Pd(PPh_3)_4$, 0.15 mmol $K_2HPO_4$, DMSO (2 mL), 460 nm (10 W), 25 °C, 30 h; [b] 0.15 mmol **S1**, 0.1 mmol amine-tethered diene, 5 mol% $Pd(PPh_3)_4$, 0.15 mmol $K_2HPO_4$, DMSO (2 mL), 460 nm (10 W), 25 °C, 30 h; [c] 0.15 mmol Ar-Br or alkyl-I, 0.45 mmol **S2**, 0.1 mmol **S3**, 10 mol% $Pd(PPh_3)_4$, 0.15 mmol $K_3PO_4$, DMSO (2 mL), 460 nm (10 W), 25 °C, 20 h; d1-(toluene-4-sulfonyl)-piperazine as nucleophile; ethiomorpholine as nucleophile.

quinoline **27**, and indole **28**, were proved to be suitable substrates for this transformation. Finally, the alkyl iodides were investigated as the electrophile in this transformation. Both secondary and primary alkyl iodides

were amenable to single electron reduction, yielding alkyl amination products **29**-**35** in moderate to good yields. Notably, in all cases, excellent regio- and diastereoselectivity were consistently observed, and the stereochemistry (**52**) was definitely confirmed by single-crystal x-ray crystallography.

**Scheme 2.** Scope of Nucleophiles[a]

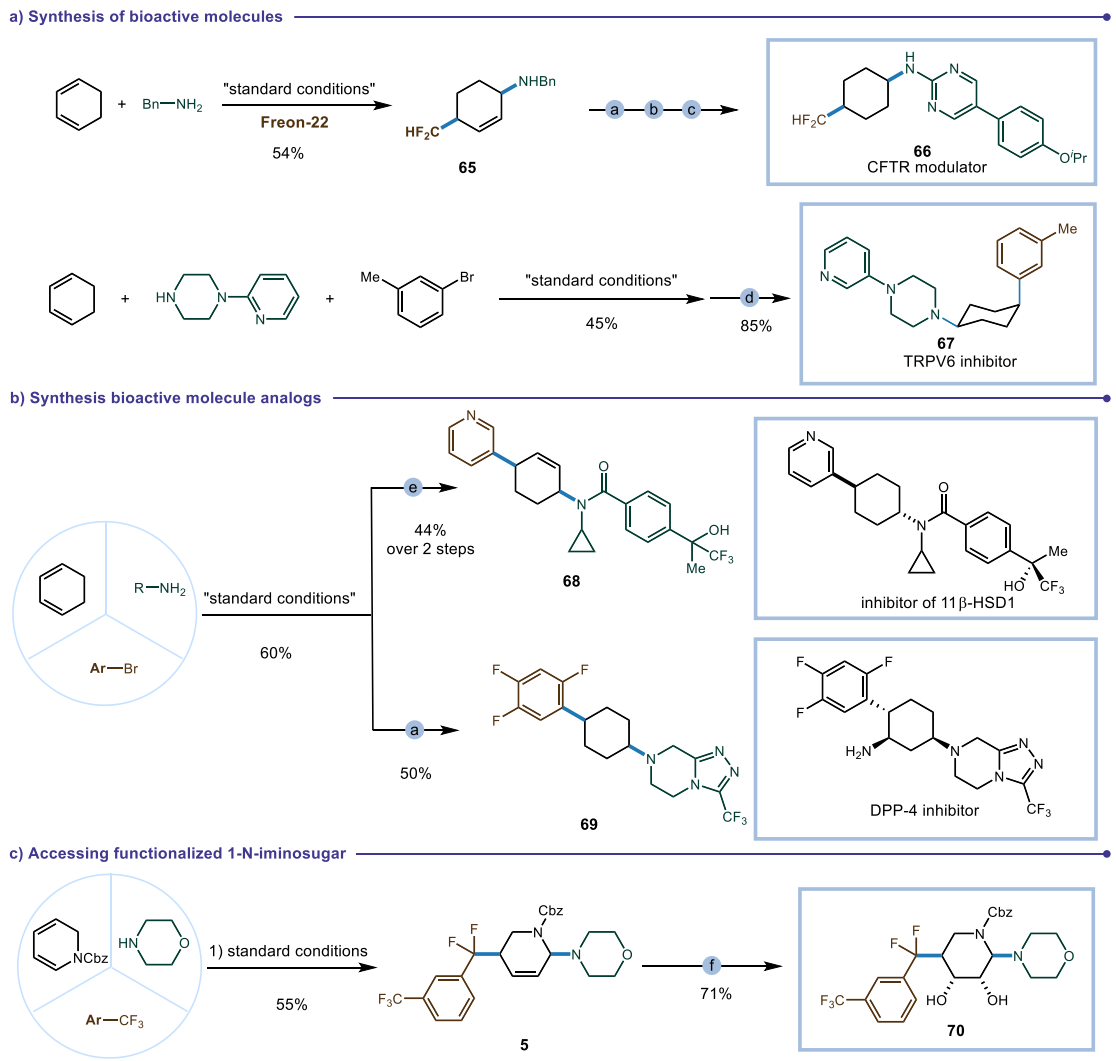



[a]0.15 mmol **S1**, 0.15 mmol **S2**, 0.1 mmol **Nu-H**, 5 mol% $Pd(PPh_3)_4$, 0.15 mmol $K_2HPO_4$, DMSO (2 mL), 460 nm (10 W), 25 °C, 30 h; [b] one additional equivalent of base was added

A diverse range of nitrogen-based nucleophiles was systematically investigated (**Scheme 2**), demonstrating a remarkable versatility of the reaction across various amine substrates. This included both primary and secondary amines, encompassing cyclic counterparts like piperidines (**36**-**39**), and piperazines (**40**-**47**), as well as thiomorpholine (**48**), pyrrolidine (**52**), acyclic secondary amines (**53** and **55**), and primary amines (**56**-**58**). These substrates participated in the three-component coupling, yielding the desired products in moderate to good yields (40% to 92%). More importantly, the medicinally relevant heteroarenes, such as furan (**45**), pyridine (**47**), thiophene (**50**), and ciprofloxacin ethyl ester (**59**) were all compatible with the standard

conditions. Both primary and secondary amine functionalities were accommodated, highlighting the transformation's versatility. Furthermore, the compatibility of free alcohol (**51**) and the NH group within the amide (**54**) underscored the reaction's broad functional group tolerance. Notably, the nucleophilic scope extended to carbon-, oxygen-, and sulfur-based nucleophiles. The incorporation of a carbon-based nucleophile, 2,2-dimethyl-1,3- dioxane-4,6-dione, as a coupling partner resulted in 1,4-difluoromethyl alkylation product (**60**) with a 71% yield. Additionally, simple sodium phenoxide could serve as a nucleophile to furnish the corresponding product (**61**) in an acceptable yield as well. Finally, the utilization of various sodium arylsulfinates (**62-64**) in the reactions yielded the targeted 1,4-difunctionalization products with moderate yields.To further highlight the versatility of this chemical transformation, we successfully synthesized a CFTR modulator (**66**) in just four steps. The key intermediate, cis-4-(difluoromethyl)cyclohex-2-en-1-amine (**65**), was efficiently accessed with exceptional diastereoselectivity from readily available starting materials. Additionally, the *cis*-TRPV6 inhibitor (**67**) which exhibits 10 folds activity than its trans isomer was synthesized via a two-step procedure from commercially available starting materials with excellent diastereoselectivity.

**Figure 2.** Synthetic utilities

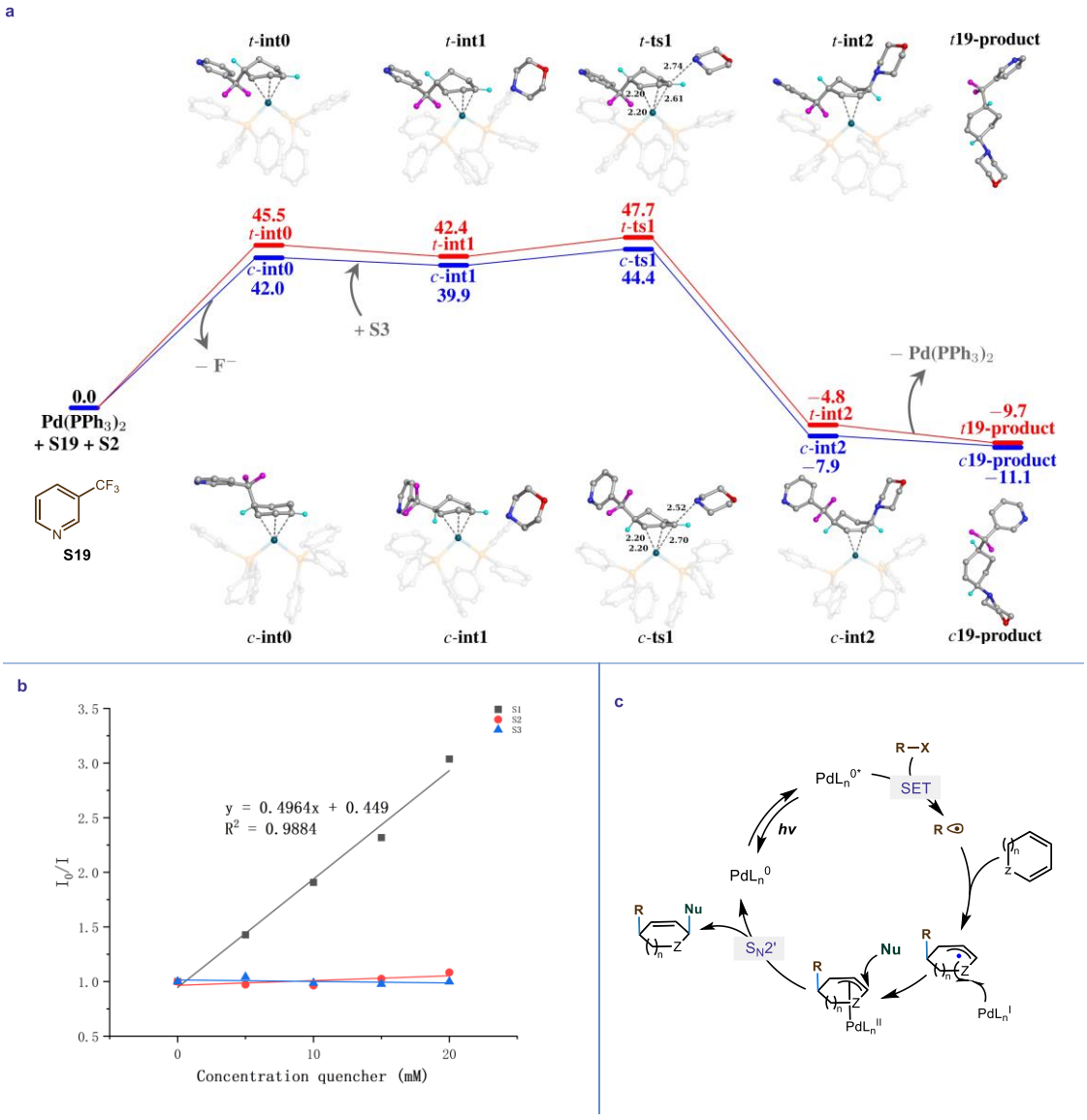



Conditions: a) $HCOONH_4$ (5 equiv), Pd/C (10 mol%), MeOH (5 mL), 65 °C, 18 h; b) TEA (3.2 equiv), 5-bromo-2-chloropyrimidine (1 equiv), 100 °C, 8 h; c) 4-(trifluoromethoxy) phenylboronic acid (2 equiv),

$Na_2CO_3$ (3 equiv), $Pd(PPh_3)_4$ (5 mol%), $CH_3CN/H_2O$ (4:1). d) Pd/C (10 mol%), $H_2$ (1 atm), MeOH (2 mL), r.t., 18 h; e) $NaHCO_3$ (2.0 equiv), 4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid (1.0 equiv), HOAt (1.3 equiv), EDCI (1.3 equiv), DMF (10 mL), 0 - 25 °C, 12 h. e) $HCOONH_4$ (5 equiv), Pd/C (10 mol %), MeOH (5 mL), 65 °C, 18 h; f) NMO (2 equiv), $K_2OsO_4$•$2H_2O$ (10 mol%), t-BuOH/$H_2O$ (1:1), 0 - 25 °C, 12 h.

Moreover, this transformation allowed for the assembly of basic starting materials into biologically relevant compounds. Employing the aryl amination method, the diastereoisomer (**68**) of the inhibitor of 11β-HSD1 featuring a double bond was accessible. Subsequently, by employing palladium-catalyzed hydrogenation of the product, an analog (**69**) of a DPP-4 inhibitor could be synthesized. Furthermore, this procedure offers a straightforward route to functionalized 1-N-iminosugars, with the difluoromethylene-modified 1-N-iminosugar (**5**) being constructed via a straightforward dihydroxylation of the product. The stereochemistry (**68**, **70**) was unambiguously confirmed by single-crystal x-ray crystallography.

**Figure 3**. Mechanistic study



In order to gain a deeper insight into the origin of facial selectivity, the free energy profile of the reaction is computed at the B3LYP-D3/6-31G(d) level of theory (see details in the supplementary materials). The overall energy barrier (45 kcal/mol) associated with the pathway involving $S_N2'$ attack is found to be significantly lower than the pathway where nucleophiles directly interact with palladium, followed by reductive elimination (62 kcal/mol). Therefore, the $S_N2'$ attack pathway depicted in **Figure 3a** is hypothesized to be the primary route. It is worth noting that the free energy of the t- (-9.72 kcal/mol) and c-products (-11.12 kcal/mol) are quite similar. This similarity arises from the rotation of the C-$CF_2$ (θ) and C-N (φ) bonds, rendering the t- and c-products closely resembling each other. The overall higher energy barrier observed in the trans-version of the pathways ($\Delta\Delta G^{\ddagger}$ = 3.5, 2.5, 3.3, and 3.5 kcal/mol for int0, int1, ts1, and int2, respectively) is primarily attributable to the increased steric hindrance exerted by $PPh_3$ in the catalyst towards the allylic carbon radical. According to the Eyring-Polanyi equation, the branching ratio between the cis- and trans-products is predicted to be 285. Therefore, the computation indicates the overwhelming majority of the product should be the kinetically controlled *cis* configuration products, which aligns well with experimental results. Combining the radical scavenger experiments, stern-volmer results (**Figure 3b**) and computational studies, the following mechanism was suggested (Figure 3c). Upon exposure to blue LED irradiation, the Pd(0) catalyst is photoexcited, thus facilitating the donation of an electron to the electrophile. This electron transfer event generates a carbon radical and Pd(I) species. Subsequently, the carbon radical engages in an addition reaction with the 1,3-diene substrate to yield an allylic carbon radical. Notably, owing to steric considerations, the Pd(I) species exhibits a preference for recombination with the allylic radical from the back side. Ultimately, the nucleophile executes a nucleophilic attack on the carbon atom, situated at the back of the palladium, leading to the formation of the syn-addition product.

In summary, a novel strategy has been developed for the construction of 1,4-cis-substituted cyclic frameworks. This approach is enabled by a hybrid palladium catalyzed radical-polar crossover mechanism to achieve reversed facial selectivity. Utilizing common resources such as cyclic 1,3-dienes, amines, and a diverse array of electrophiles (trifluoromethylaromatics, aryl bromides, and alkyl iodides), it realizes the synthesis of various 1,4-cis-substituted cyclic compounds with different ring sizes, spiro structures, and aza-heterocycles, maintaining remarkable diastereoselectivity. Significantly, this method offers a straightforward pathway for synthesizing biologically active compounds, including pharmaceutical molecules and their derivatives.

## ASSOCIATED CONTENT

**Supporting Information**.

Full experimental procedures, spectroscopic data, and detailed X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally.

**Notes**

The authors declare no competing financial interest.

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