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Versatile Palladium-Catalyzed C-H Arylation of Fluoroarenes with 2-Chloropyridine Derivatives

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Direct C—H arylation of fluoroarenes with 2-halopyridines remains underexplored, due to the low reactivity of both partners and the reliance on harsh conditions or toxic solvents. Herein, we report a general and sustainable method for the C—H arylation of fluoroarenes with 2-chloropyridines using Pd/SPhos as a simple catalytic system in isopropyl acetate. The protocol employs inexpensive starting materials, shows broad functional group tolerance, and delivers a wide range of 2-(fluorinated aryl)pyridines in up to 90% yield. Substrate scope studies uncovered key substituent effects on both coupling partners, while Density Functional Theory (DFT)-supported mechanistic analysis rationalized the observed reactivity and chemoselectivity. This research advances sustainable and practical methodologies for the synthesis of complex fluorinated aromatic compounds with potential applications in materials science, agrochemistry, and medicinal chemistry.

1. Introduction

The pyridine motif is one of the most prevalent nitrogen heterocycles[1–3] in a wide range of compounds with applications in various fields such as catalysis,[4–7] functional materials,[8,9] agrochemistry[10] and medicinal chemistry.[11–13] Across these fields, pyridine-containing compounds can be found in numerous small-molecule drugs on the market or under development. A relevant and well-known functionalization of the pyridine core is at the C-2 position, where usually metal-catalyzed cross-coupling is performed for the synthesis of diverse heterobiaryl motifs.[14–21] An important category contains derivatives of 2-(fluorinated aryl)pyridines, among which functional materials (e.g., betaine dye),[22–24] ligands such as metal-based photocatalysts,[25–27] agrochemicals such as halauxifen-methyl or florpyrauxifen-benzyl[28,29] and drugs,[30–34] such as KRas inhibitor sotorasib for lung cancer treatment, were developed (Figure 1).[35–39]

These motifs can be synthesized by classic cross-coupling reactions like Hiyama, Kumada, Stille, Negishi couplings[14,40,41] or by the classic and well-established Suzuki reaction from fluorinated phenylboronic acids and 2-halopyridines (Scheme 1a).[42–49] Although these are considered as robust reactions, several limitations or difficulties might be encountered. First, the general use of electron-deficient heteroaryl and fluoroaryl nucleophiles usually undergoes a transmetallation process at a relatively slower rate.[50,51] Second, the preparation of highly electron-deficient nucleophiles is not straightforward. As well, electron-deficient arylboronic acids are moderately stable since they usually decompose via rapid protodeboronation, which often happens with 2-pyridyl boronic acids (or boronates). A solution for that might lie in recently developed types of boronates, such

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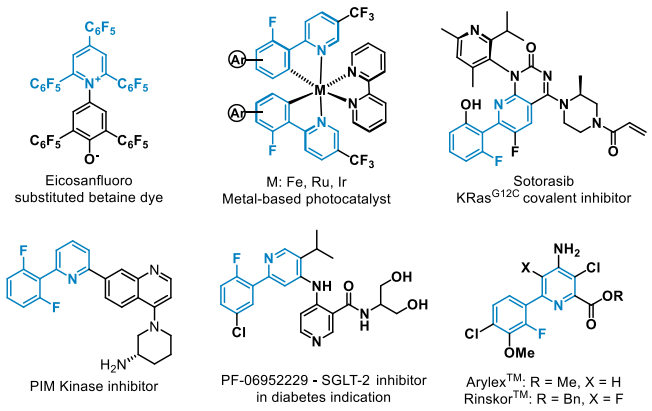


Figure 1. Selected examples of 2-(fluorinated aryl)pyridines used in diverse fields of chemistry.

as *N*-methyliminodiacetic acid (MIDA) boronates.[52,53] However, few have become commercially available, and their synthesis is generally laborious.[14,50,51,54]

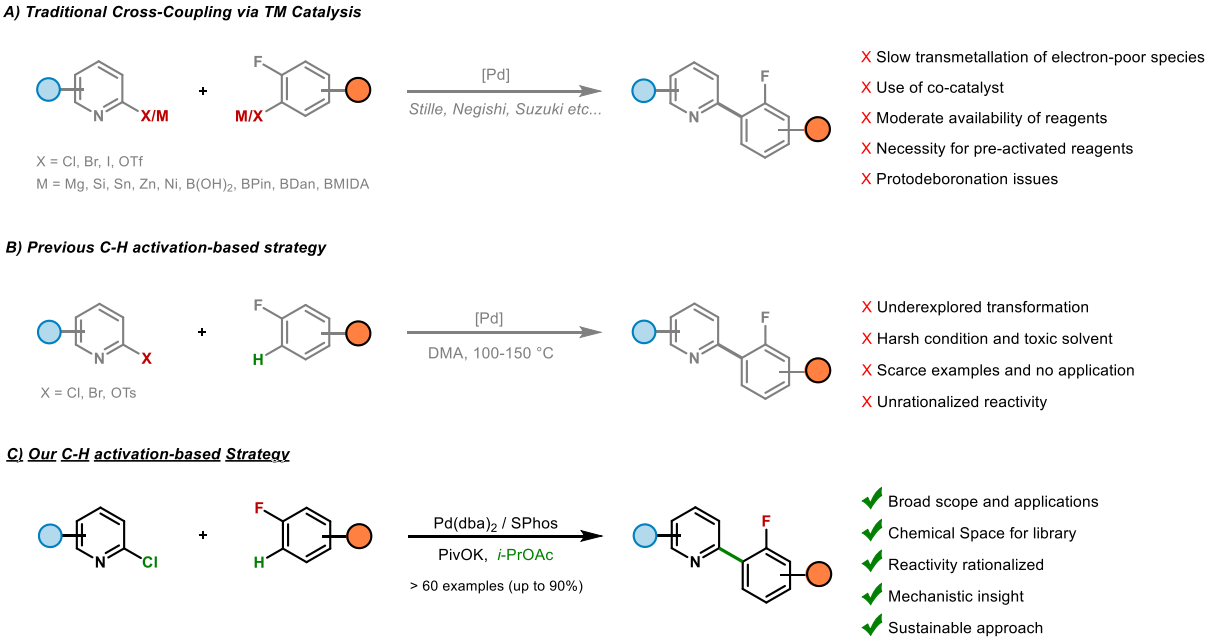
Recently, C—H activation has gained prominence as a powerful tool for increasing molecular complexity directly from simple, readily available starting materials. This transformation eliminates the need for pre-functionalization, offering more streamlined chemical processes. In the context of 2-(fluorinated aryl)pyridine synthesis, direct C—H arylation of fluoroarene substrates presents a promising and efficient approach, reducing synthetic steps and broadening access to these valuable compounds.[54–61] However, despite its advantages, C—H activation still faces practical limitations. It often requires high catalyst loadings of precious metals, stoichiometric oxidants, and elevated temperatures, which restrict its industrial applicability[62] Addressing these challenges is crucial for expanding the practical utility of C—H activation. While direct C—H arylation represents an attractive route to 2-(fluorinated aryl)pyridines, only a limited number of studies have pursued this strategy (Scheme 1b). Although isolated examples of C—H arylation between fluoroarenes and heteroaryl partners exist, they remain scarce, mechanistically unexplored, and restricted in substrate scope, mainly involving pentafluorobenzene or selected pyridine derivatives[63].

Previously reported methodologies operate under demanding conditions and rely on toxic solvents such as DMA, which has come under increasing regulatory restrictions in recent years.[55–64] In addition, they exhibit a scarce substrate scope, lack mechanistic insight, and offer no demonstration of synthetic applicability. In this work, we present an efficient and sustainable method for the direct C—H arylation of fluoroarenes with substituted 2-chloropyridines under milder conditions using isopropyl acetate as a green solvent. This protocol enables a systematic investigation of substituent effects on both coupling partners, rationalizes reactivity trends through a combination of experimental and computational studies, and employs low-cost, readily available starting materials. Moreover, it provides streamlined access to a structurally diverse library of 2-(fluorinated aryl)pyridines (Scheme 1c), addressing key limitations of previous approaches.

2. Results and Discussion

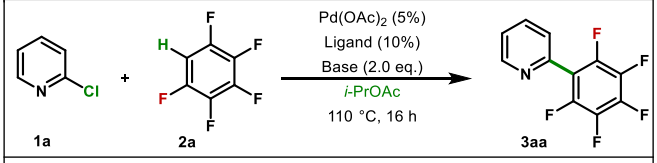
2.1. Optimization of the Model Reaction

Optimization efforts were guided by the dual objective of avoiding toxic solvents and employing inexpensive, readily available reagents. Drawing from established precedent and the demonstrated efficacy of Buchwald-type ligands in cross-coupling chemistry, SPhos in combination with palladium acetate was selected as a simple catalytic system. Isopropyl acetate was



Scheme 1. Strategies for synthesizing 2-(fluorinated aryl)pyridines via TM-catalyzed cross-coupling.

Table 1. Initial screening for the palladium-catalyzed arylation of pentafluorobenzene with different bases and ligands.

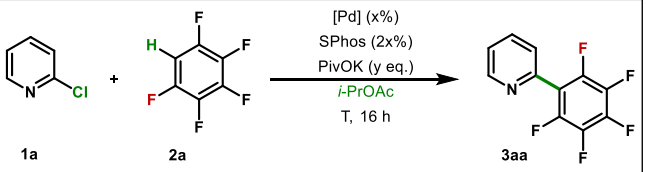


1a 2a 3aa

Entry[a]	Base	Ligand	Yield %*
1	KOAc	SPhos	11
2	K_2CO_3	SPhos	35
3	Cs_2CO_3	SPhos	48
4	K_3PO_4	SPhos	70
5	PivOK	SPhos	80
6	PivOK	$P(Cy)_3$	Traces
7	PivOK	XPhos	41
8	PivOK	CyJohnPhos	74
9	PivOK	JohnPhos	5
10	PivOK	CataCXium A	79

Reaction conditions:
[a] 0.3 mmol 2-chloropyridine, 5 equiv. pentafluorobenzene, 0.4 mL of solvent, argon atmosphere, 16 hours.
* Yield of the formed product quantified by GC-MS with internal standard.

Table 2. Optimization of the cross-coupling reaction between 2-chloropyridine and pentafluorobenzene.



1a 2a 3aa

Entry[a]	[Pd] [%]	Temp.	Yield %*
1	$Pd(OAc)_2$ (5%)	110 °C	80
2	$Pd(TFA)_2$ (5%)	110 °C	33
3	$PdCl_2$ (5%)	110 °C	70
4	$Pd(NO_3)_2{\cdot}2H_2O$ (5%)	110 °C	76
5	$Pd(dba)_2$ (5%)	110 °C	55
6	$Pd(dba)_2$ (2,5%)	110 °C	85
7[b]	$Pd(dba)_2$ (2,5%)	110 °C	80
8[b,c]	$Pd(dba)_2$ (2,5%)	110 °C	78
9[b,c]	$Pd(dba)_2$ (2,5%)	125 °C	90**(88)
10[b,c,d]	$Pd(dba)_2$ (2,5%)	125 °C	5
11[b,c,e]	$Pd(dba)_2$ (2,5%)	125 °C	8
12[b,c,f]	$Pd(dba)_2$ (2,5%)	125 °C	20

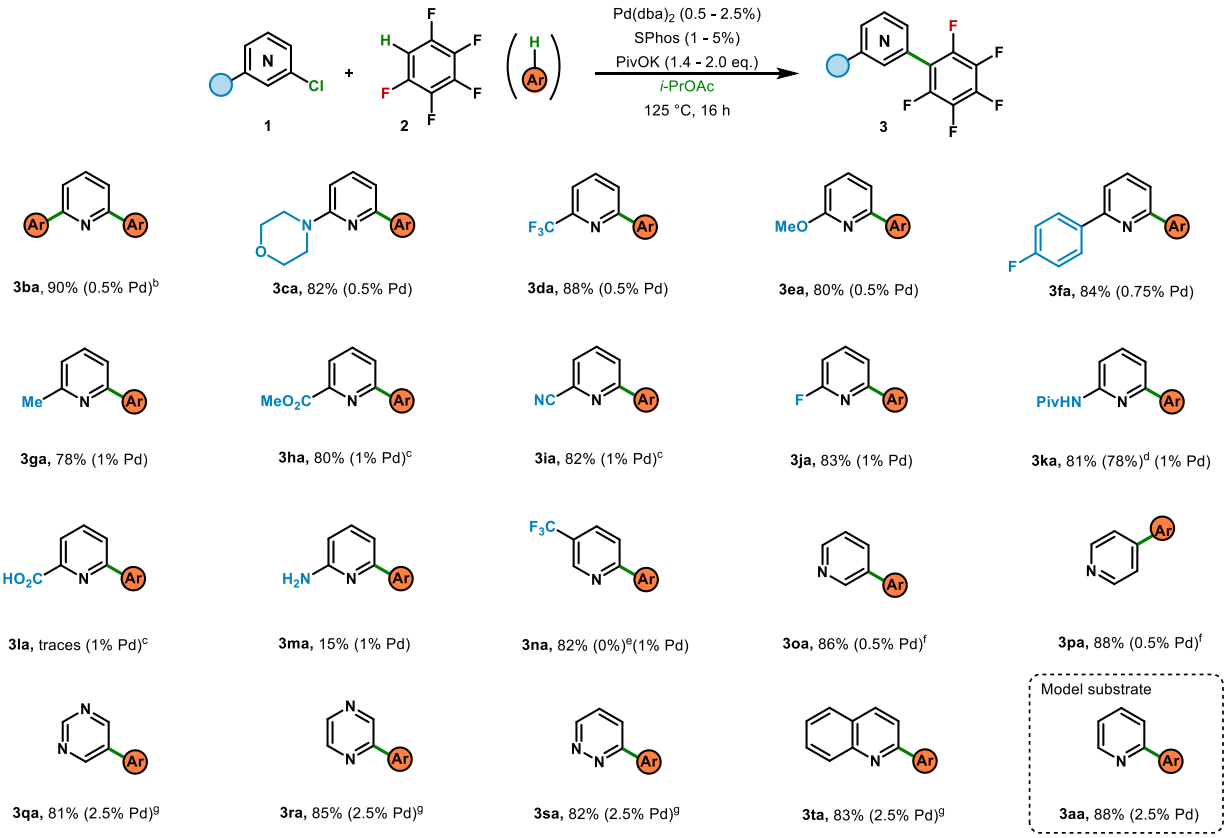
Reaction conditions:
[a] 0.3 mmol 2-chloropyridine, 5 equiv. pentafluorobenzene, 2 equiv. PivOK, 0.4 mL solvent, argon atmosphere, 16 hours. The amount of the ligand is always two times than the Pd-source.
[b] With 1.4 equiv PivOK.
[c] With 2.5 equiv. pentafluorobenzene and 1.4 equiv PivOK.
[d] with DMA instead of *i*-PrOAc.
[e] with THF instead of *i*-PrOAc.
[f] with toluene instead of *i*-PrOAc
* Yield of the formed product quantified by GC-MS with internal standard.
** Average of 3 trials. In brackets the isolated yield.

chosen as a green alternative to conventionally used, but more hazardous, polar aprotic solvents such as DMA or DMF.[65–69] The arylation of pentafluorobenzene with 2-chloropyridine was selected as the model reaction to evaluate initial conditions, and a systematic screening of ligands and bases was carried out to identify an optimal protocol (Table 1). From the results regarding the bases, KOAc (11%, Table 1, entry 1) works worse than K_2CO_3 (35%, Table 1, entry 2), and a more lipophilic carbonate base enhances the yield (Cs_2CO_3, 48%, Table 1, entry 3). A relevant improvement came out with K_3PO_4 (70%, Table 1, entry 4), and the best output is obtained using PivOK (Table 1, entry 5) with a yield of 80%. Other bases have been tested (see Table S1), but worse results have been obtained.

Next, the ligand screening emphasized how crucial it is to have a Buchwald–type ligand to make the catalytic system active. The complete lack of reactivity with PCy_3 (Table 1, entry 6) highlights how the introduction of a biphenyl unit enhances reactivity, with additional influence from substituents on the biphenyl framework (Table 1, entries 7,8). However, replacing the cyclohexyl group with a *tert*-butyl group resulted in a poorly active catalytic system (Table 1, entry 9). An alternative ligand, CataCXium A, exhibited activity comparable to SPhos (79%, Table 1, entry 10); however, its significantly higher cost made it less practical, and SPhos was therefore selected for further studies. Also, other ligands have been tested (see Table S2), but worse results have been obtained.

Having in hand the best combination of base and ligand, more variables, particularly the Pd source and its amount and the temperature, have been taken into consideration to enhance the performance of the reaction (Table 2 and Table S3). A large decrease was visible when the $Pd(TFA)_2$ (33%, Table 2, entry 2) was used as a catalyst, while similar results to palladium acetate have been obtained with $PdCl_2$ (70%, Table 2, entry 3) or $Pd(NO_3)_2{\cdot}2H_2O$ (76%, Table 2, entry 4). Pd(0) sources like $Pd(PPh_3)_4$ (see Table S3) and $Pd(dba)_2$ also provided lower yields (55%, Table 2, entry 5).

However, with Pd(0) sources we observed the formation of a large amount of palladium black, which might indicate that side reactions or decomposition processes are predominant. Therefore, we thought that decreasing the amount of catalyst loading might help to increase the yield. As expected, the reduction of the loading by 50% improved the yield to 85% (Table 2, entry 6) relative to $Pd(OAc)_2$ (58%, see Supplementary Table S3) or other Pd(II) pre-catalyst. Further fine-tuning allowed for a reduction in reagent amounts, leading to a decrease in process mass intensity (PMI) (Table 2, entries 7, 8),[70,71] but at the cost of operating at a higher temperature (Table 2, entry 9). The protocol using $Pd(dba)_2$ was repeated with Buchwald ligands, yielding either similar or worse results compared to SPhos. Both CyJohnPhos and JohnPhos were tested with $Pd(dba)_2$, but the same trend was observed as with $Pd(OAc)_2$, with only minor differences in yield (Table S3). Next, other solvents like DMA, THF, and toluene have been tested (Table 2, entries 10, 11, and 12, respectively), showing a dramatic decrease in the yield. Other acetate solvents did not improve the outcome but still afforded good results



Scheme 2. Reactivity exploration for the Pd-catalyzed cross-coupling reaction between 2-chloropyridines and related *aza*-heterocycles with pentafluorobenzene[a]. Reaction conditions: a) 0.75 mmol of Ar-X, 2.5 equiv. pentafluoroarene, 1.0 mL of solvent, argon atmosphere, 16 hours. b) With 2.4 equiv of PivOK. c) With 2.0 equiv. of PivOK. d) Product obtained using *tert*-butyl *N*-(6-chloro-2-pyridinyl) carbamate as a starting material. e) no product from the same transformation done by *Doucet* et al.[63e] f) Yield of the product quantified by GC-MS with internal standard. g) Catalyst loading not optimized. All the examples show full conversion, and the yield indicated is referred to the isolated one.

(Table S3). At last, 2-bromopyridine (**1 u**) and 2-iodopyridine (**1v**) have been tested, but they showed limited reactivity, giving 39% and 19% yields, respectively (Table S3). This enhances the positive aspects of using 2-chloropyridines for the large number of available and cheap substrates and the formation of KCl as a harmless byproduct.

2.2. Investigation of Reaction Scope

With the optimal conditions established, we next turned our attention to exploring the reaction scope with various pyridines and fluoroarenes. The initial focus was on examining how substitution at the 6-position of the pyridine core influences reactivity, along with the functional group tolerance of the system (Scheme 2). A brief preliminary screening—varying the catalyst loading for the synthesis of **3ba**, **3ca**, and **3 da**, revealed that full conversion could be achieved with as little as 0.5 mol% Pd. This finding underscored the notable impact of a substituent at the 6-position, a trend further examined in the mechanistic studies.

The first interesting result came from the double pentafluoroarylation of the pyridine core (3ba), starting from 2,6-dichloropyridine, in which an excess of PivOK was required for the full conversion, but not a higher palladium catalyst loading or a larger excess of pentafluorobenzene was necessary. This might suggest that there is an exchange between the Cl^- and $PivO^-$ (and so, formation of KCl) during the evolution of the catalytic cycle (for more details, see Figure 2a). Morpholine (3ca), trifluoromethyl (3 da), methoxy (3ea), 4-fluorophenyl (3fa), methyl (3ga, 75%), and fluorine (3ja) substituents were well tolerated and showed very good yields (≥80%). Furthermore, very good yields (≥80%) were obtained with esters (3 ha), nitrile (3ia), and protected amine (3ka). Notably, the compound 3ka could be obtained from the NH-Boc-protected 1k. Also, 2-chloropyridine bearing a substituent at position 5 performed well (3na, 82%), with a slightly higher amount of catalyst (1%) needed rather than having the same substituent at the 6-position. Furthermore, to gain a deeper understanding of the specific reactivity of 2-chloropyridine, its behavior was compared with 3-chloropyridine (1o) and 4-chloropyridine (1p). In both cases excellent yields were obtained (3-chloropyridine (3oa, 86%), 4-chloropyridine (3pa, 88%)) with five times less Pd catalyst (0.5%) than in the reaction with 2-chloropyridine (3aa). This outcome reflects the lower reactivity of the pyridine 2-position and highlights the reaction's efficiency, proceeding with a minimal catalyst loading even in the absence of a substituent at the 6-position. This finding opens prospects for further exploration toward a more efficient and sustainable synthesis of 3- and 4-pyridyl derivatives, suggests possible expansion toward myriads of new biaryls, and supports the general applicability of the approach.

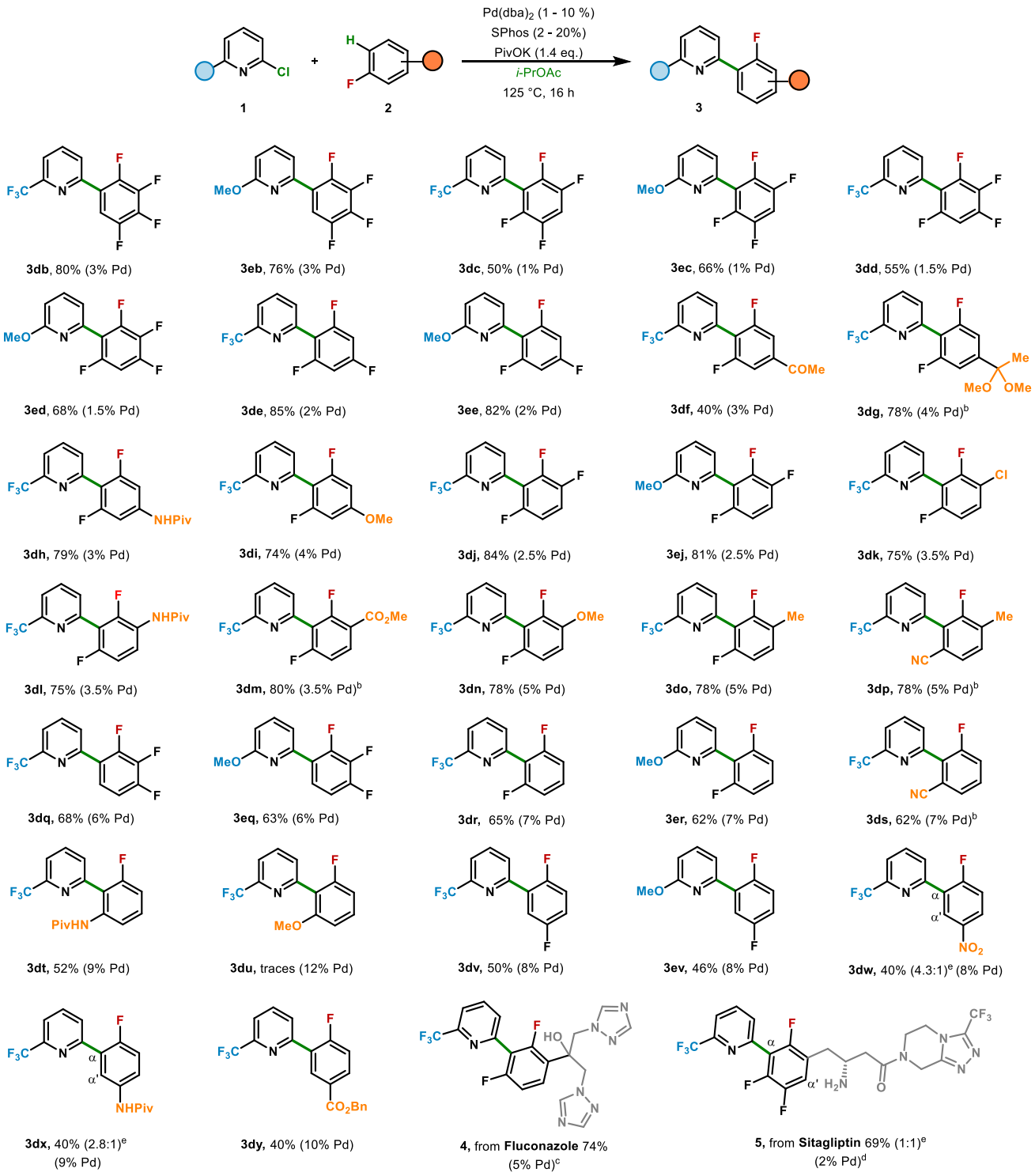
Additionally, the developed protocol was tested on similar *aza*-heterocycles to assess the broader applicability of the catalytic system. The reaction conditions of the model reaction were applied but not optimized for these substrates. Pyrimidine (**3qa**, 81%), pyrazine (**3ra**, 85%), pyridazine (**3sa**, 82%), and quinoline (**3ta**, 83%) showed very good reactivity (yields $\geq$ 80%), enabling access to a larger library on demand.

After systematically investigating the reactivity of the pyridine core, we next focused on the fluoroarene partner to assess how its reactivity is influenced by stepwise defluorination and functional group substitution. This approach aimed not only to broaden the accessible chemical space but also to rationalize how changes within the fluoroarene motif impact the overall reactivity. Whenever possible, nonvolatile fluorinated arenes, used in stoichiometric excess (see reaction conditions), were recovered, enhancing the sustainability of the protocol (see Supporting Information). As reported in the literature, the reactivity of the C—H bond in fluorinated arenes correlates with both the number and position of fluorine atoms, which influence the acidity of the reactive site.[72–74] With these considerations in mind, we examined representative fluoroarenes ranging from tetrafluorobenzene to (mono)fluorobenzene and extended the scope by introducing substituents in place of fluorine when three or fewer were present (Scheme 3). The arylation with 1,2,3,4-tetrafluorobenzene (**2b**) affords the product with very good yields either with an EWG (**3db**, 80%) or an EDG (**3eb**, 76%) substituent on the pyridine core, but an increase of the palladium catalyst (3%) is required to reach full conversion. The arylation with 1,2,4,5-tetrafluorobenzene (**2c**) required only 1% catalyst loading to achieve full conversion, but lower yields were obtained (**3dc** 50% and **3ec** 66%) due to the formation of the bis-pyridylated side product, detected by GC-MS and LC-MS. Thus, the first arylation produces a compound with reactivity similar to pentafluorobenzene, making the mono-pyridylated product the new, more reactive C-H substrate. A slight increase in the yield, of **3ec** (66%), might be caused by the methoxy group, which increases the electron density of the pyridine core, making it more similar to 1,2,4,5-tetrafluorobenzene in terms of reactivity (the bis-pyridylated product was also detected in GC-MS and LC-MS). The same behavior was encountered when 1,2,3,5-tetrafluorobenzene (**2d**) was used for the cross-coupling but with slightly higher selectivity toward the mono-pyridylated product (**3dd** and **3de** with yields of 55% and 68%, respectively).

1,3,5-Trifluorobenzene and related derivatives were the next to be explored, and so, very good yields ($\geq$80%) by low catalyst loading (2%) have been obtained (entries **3de** and **3ee**). When replacing the fluorine at position 3 with an EWG or EDG, a slight decrease in reactivity has been observed. It is supposed that the primary reason is related to the acidity of the reactive C-H bond, while other effects might play a secondary role.[73–76] As a result, it is necessary to increase the catalyst loading up to 3% for EWG and up to 4% for EDG to reach full conversion. Next, 3,5-difluoroacetophenone (**2f**) has been tested to afford product **3df** in only 40% yield. Investigating the product profile after purification, it is revealed that the main product came from the α-arylation of the acetophenone (see Supporting Information). This is explained by the easy formation of the enolate species due to the presence of acidic methyl hydrogen.[77–80]

One solution to this limitation was to protect the ketone as a dimethyl ketal, resulting in **3dg** in very good yield (78%) without any decomposition of the ketal. Amide (**3dh**) and methoxy (**3di**) substituents also afforded the related products with very good yield (79–80%).Next, 1,2,4-trifluorobenzene has been tested, showing very good results in terms of product formation (**3dj** 84% and **3ej** 81%), but higher catalyst loading (2.5%) was required compared to 1,3,5-trifluorobenzene to reach full conversion. Moreover, further exploration was conducted with different derivatives, such as 1-chloro-2,4-difluorobenzene (**2k**), where only the chlorine on the pyridine motif reacts selectively, affording **3dk** in 75% yield. Amide (**3dl**), methyl ester (**3dm**), methoxy (**3dn**), and methyl (**3do**) derivatives also showed good reactivity under the reaction conditions (78–80% yields). The product **3do** differs from product **3dp** by the presence of a cyano substituent instead of a fluorine atom at position 4. Although fluorine and the cyano groups exhibit different effects on the acidity for the C-H bond at the *ortho* position,[72] the respective starting materials (2,4-difluorotoluene **2o** and 3-fluoro-4-methylbenzonitrile **2p**) exhibit similar reactivity in terms of catalyst loading. Both compounds achieved full conversion and the same yield (78%). This suggested that in addition to the acidity, other possible interactions with the metal catalyst might play a significant role, particularly in the reactivity of 1,2,4-trifluoroarenes and their derivatives.[73] Without further exploration, 1,2,3-trifluorobenzene (**2q**) was tested and appeared to be the least reactive among the tri-fluorobenzene family, affording the products **3dq** and **3eq** with good yields (68% and 63%, respectively) but requiring 6% catalyst loading to achieve full conversion.

As the number of fluorine atoms decreased, higher catalyst loadings were generally required to reach full conversion. For instance, 1,3-difluorobenzene (**2r**) afforded **3dr** and **3er** in yields $\geq$ 62%. Attempts to improve conversion by increasing temperature instead led to by-product formation. Substrates such as 3-fluorobenzonitrile (**2 s**) also delivered the desired product (**3ds**) in 62% yield, showing reactivity comparable to 1,3-difluorobenzene and suggesting that C—H bond acidity alone does not govern the outcome. A meta-pivalamide-substituted arene gave moderate yield (**3dt**, 52%) under slightly increased catalyst loading. The reactivity turned upside down when an electron-donating substituent (OMe, **2 u**) was present instead of the fluorine. To reach full conversion, catalyst loading up to 12% afforded around 7% of product (**3du**) with impurities, and further purification attempts were unsuccessful, leading to significant product loss. The low reactivity might be correlated to the effect of the methoxy substituent on the Hammet constant in *ortho* position,[74] and so, most probably, the energetic barrier for the C-H activation might become quite high. Higher temperature (150 °C) led only to major formation of by-products. When the 1-chloro-3-fluorobenzene (**2ad**) was used as a coupling partner, it afforded a mixture of the starting material, desired



Scheme 3. Palladium-catalyzed cross-coupling reaction between 2-chloropyridines and fluoroarenes[a].
Reaction conditions: a) 0.75 mmol of Ar-X, 2.5 equiv. of fluoroarene, 1.0 mL of solvent, argon atmosphere, 24 hours. b) with 2 equiv. of PivOK. c) In this case, 2.5 equiv. of the drug was used and 42% was recovered after purification. d) In this case, 2.5 equiv. of the drug was used, and 49% was recovered after purification. e) Ratio α:α'. All the examples show full conversion, and the yield indicated refers to the isolated one.

product, isomers, and dechlorinated by-products (see Supplementary Information, chapter 3.5).

We assume that dehalogenation side reactions are favored under our reaction conditions when the chlorine substituent is in the *ortho* position to the C-H bond. Next, 1,4-difluorobenezene (**2x**) showed lower reactivity than the other fluorinated motifs, affording the related products **3dv** and **3ev** in discrete yields. Switching from 1,4-difluorobenzene to 1,4-disubtitued aryl

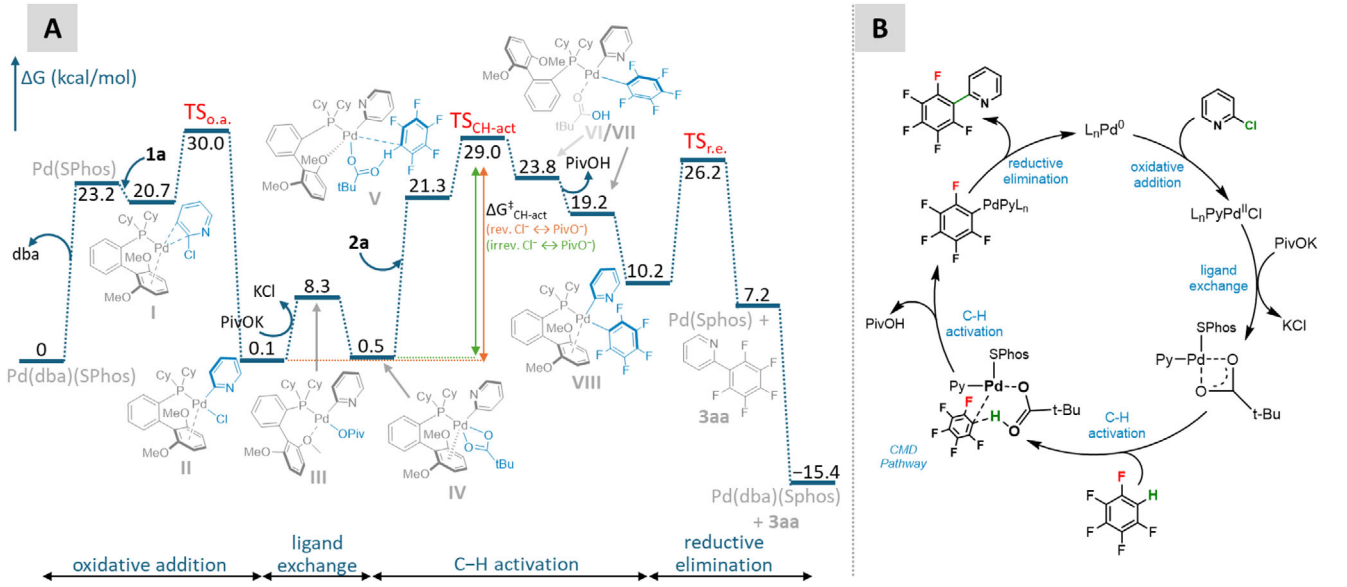


Figure 2. A) The detailed reaction free energy profile of the Pd-catalyzed cross-coupling reaction between 2-chloropyridine and pentafluorobenzene. B) Schematic representation of the proposed catalytic cycle.

substrate, in general, even lower reactivity has been encountered. Nitro substituent was tolerated, yielding a mixture of the product **3dw** (α) and its isomers (α') in 40% total yield with 4.3:1 selectivity toward α. Starting from the *N*-(4-fluorophenyl)pivalamide (**2x**), it has obtained a mixture of the product **3dx** (α) and its isomers (α') in 40% total yield with 2.8:1 selectivity toward α. Within the use of benzyl 4-fluorobenzoate (**2y**), it was possible to achieve fair yields (~40%) by affording **3dy**. 4-Fluoroacetophenone (**2z**) led to complex mixtures, though no α-arylation side product was detected. Ketal protection (**2aa**) failed to improve reactivity, yielding only trace amounts of product (**3daa**). Similarly, strongly electron-donating substrates like 4-fluoroanisole (**2ab**) and fluorobenzene (**2ac**) proved unreactive, with only traces of **3dab** observed—likely due to suppressed C—H acidity under these conditions. (see Supplementary Information, chapter 3.5).

To demonstrate the potential of the method in medicinal chemistry, the protocol was applied to the late-stage C—H arylation of drug molecules.[81–84] Fluconazole, a widely used antifungal,[85,86] underwent selective C—H arylation to give product **4** in 74% yield using 5% catalyst loading, with the free alcohol group left untouched. Sitagliptin, used for the type 2 diabetes treatment,[87] was successful, and it achieved **5** in good yield (70%) using 2.5% catalyst, loading showing no issue with the free alkyl-amino group in contrast with the previous issue noticed by the aryl-amino group. The unexpected formation of both isomers here ($\alpha + \alpha'$) might derive from the free -NH_2 acting as a directing group.[88,89]

2.3. Investigating the Mechanism of the Reaction by DFT Computations

Density Functional Theory (DFT) studies were performed to explore the mechanism of the reaction (Figure 2A). The [Pd(dba)$_2$] complex was considered as the Pd source, and the reaction Gibbs free energies for the formation of different complexes with the synthetically most successful SPhos ligand were calculated. The exchange of one or both dba ligands leads to the almost isoenergetic [Pd(dba)(SPhos)] and [Pd(SPhos)$_2$] complexes, which are 19.8 and 19.6 kcal mol^{-1} more stable than [Pd(dba)$_2$], respectively. This indicates that both complexes can be present in the reaction mixture, but only the slightly more stable [Pd(dba)(SPhos)] is considered the active catalyst.[90] Also, dialkylbiaryl phosphine ligands like SPhos have been shown to feature arene interaction between the metal and the lower ring of the biaryl that promotes ligand dissociation before C-X bond cleavage.[90–93]

The reaction proceeds via a Pd^0/Pd^{II} catalytic cycle that typically starts with the oxidative addition into the heteroaryl-halide reactant. Therefore, the calculated reaction free energy profile in Figure 2A starts with the replacement of a dba ligand in [Pd(dba)(SPhos)] by 2-chloropyridine (**1a**), which then undergoes oxidative addition via a 3-centered concerted mechanism.[94–96] The oxidative addition yields the [Pd(SPhos)(Py)(Cl)] (**II**) complex through an overall barrier ($\Delta G^{‡}_{o.a.}$) of 30.0 kcal mol^{-1}. This intermediate is also expected to feature the metal-arene bond that fills the fourth coordination site around Pd^{II} and provides stabilization.[97] The halide in **II** is then exchanged with a pivalate via PivOK addition and KCl salt formation (**III**, **IV**) (note that although the calculated energies suggest an endergonic process, this step is assumed to be irreversible based on the insolubility of KCl in *i*-PrOAc). The coordinated pivalate facilitates the next main step of the reaction, which is the C-H activation of pentafluorobenzene (**2a**) in **V** via concerted metalation-deprotonation (CMD), leading to a barrier ($\Delta G^{‡}_{CH-act}$) of 28.5 kcal mol^{-1}. The pivalic acid formed in this step then leaves **VI** (to yield **VII**), and reductive elimination takes place in the rearranged **VIII** with the participation of the pyridine and the fluoroaryl ligands through a barrier ($\Delta G^{‡}_{r.e.}$) of 25.7 kcal mol^{-1}. In the final steps, the

Table 3. Barriers (in kcal mol^{-1}) calculated for different substrate and ligand combinations.

Entry	Substrate	Ligand	$\Delta G^{\ddagger}_{o.a.}$	Ligand exchange	$\Delta G^{\ddagger}_{CH\text{-}act}$	$\Delta G^{\ddagger}_{r.e.}$
1	1a	SPhos	30.0	0.1 » 0.5	28.5	26.1
2	1a	JohnPhos	24.0	−2.5 » −0.4	28.7	22.8
3	1a	CyJohnPhos	31.4	1.4 » 1.1	23.2	25.8
4	1d	SPhos	28.8	−2.9 » −1.6	28.2	25.8
5	1v	SPhos	23.2	−6.6 » -6.7	28.6	25.6

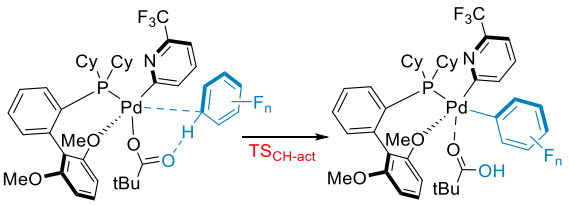
product **3aa** leaves, and [Pd(dba)(SPhos)] is recovered after dba coordination. Overall, the rate-determining step is predicted to be the oxidative addition, although the C-H activation is also close. The computed 26–30 kcal mol^{-1} barriers support the observation that elevated temperatures are required for the reaction. The simplified catalytic cycle is shown in Figure 2B. Key catalytic steps were computed for the SPhos, JohnPhos, and CyJohnPhos ligands. Entries 5, 8, and 9 in Table 1 show that SPhos and CyJohnPhos are very similar, while JohnPhos is considerably less efficient as a ligand. In contrast, the DFT results in Table 3 indicate that the overall barriers for all three ligands are very similar. The main difference is the progression of the energy profiles (Figure S1 and Table 3 entries 1, 2, and 3), which reveals a similarity between SPhos and CyJohnPhos with the possibility that JohnPhos follows a distinct pathway. This is indicated by the energies of the Pd(JohnPhos)$_2$] and [Pd(JohnPhos)(Py)(Cl/OPiv)] complexes, which are significantly less stabilized than their analogues with the other phosphines. As a result, the TS of the C-H activation for JohnPhos is higher in energy, but surprisingly, it does not affect the TS of the oxidative addition that leads to an unexpectedly low oxidative addition barrier of 24.0 kcal mol^{-1}. Therefore, based on comparison with the experimental results, it can be assumed that the mechanism in Figure 2A does not apply for JohnPhos.

The experiments have also revealed that 6-substitution of 2-chloropyridine improves catalytic efficiency (i.e., 0.5% of catalyst loading is enough instead of 2.5% to reach full conversion, Scheme 2). To confirm this computationally, the main reaction steps were calculated for the trifluoromethyl substituent, mainly used for the scope (substrate **1d**, product **3 da**, Figure S2, Table 3 entry 4). All three barriers are lower than those for **3aa** (Table 3 entry 1) in line with the experimental findings, but the barriers of 28.8 kcal mol^{-1} for oxidative addition and 28.2 kcal mol^{-1} for C-H activation are very close to each other, making the assignment of the rate-determining step less accurate.

The C-H activation step was also calculated for different fluorobenzenes and **1d**. The results in Table 4 indicate good agreement with the experiments, as the calculated barriers increase in parallel (28.2 » 36.2 kcal mol^{-1}) with the increased catalyst loadings (0.5% » 12%) required for full conversion as the number of fluorine atoms is reduced. Note that the comparison of Tables 3 and 4 also indicates that C-H activation becomes rate-determining for fluoroarenes with less than five fluorine substituents.

In Table 4 we show that although there seem to be small changes in $\Delta G^{\ddagger}_{CH\text{-}act}$, yet there is a significant difference in yields and catalyst loadings that suggests the

Table 4. C-H activation barriers (in kcal mol^{-1}) calculated for various fluorobenzenes.



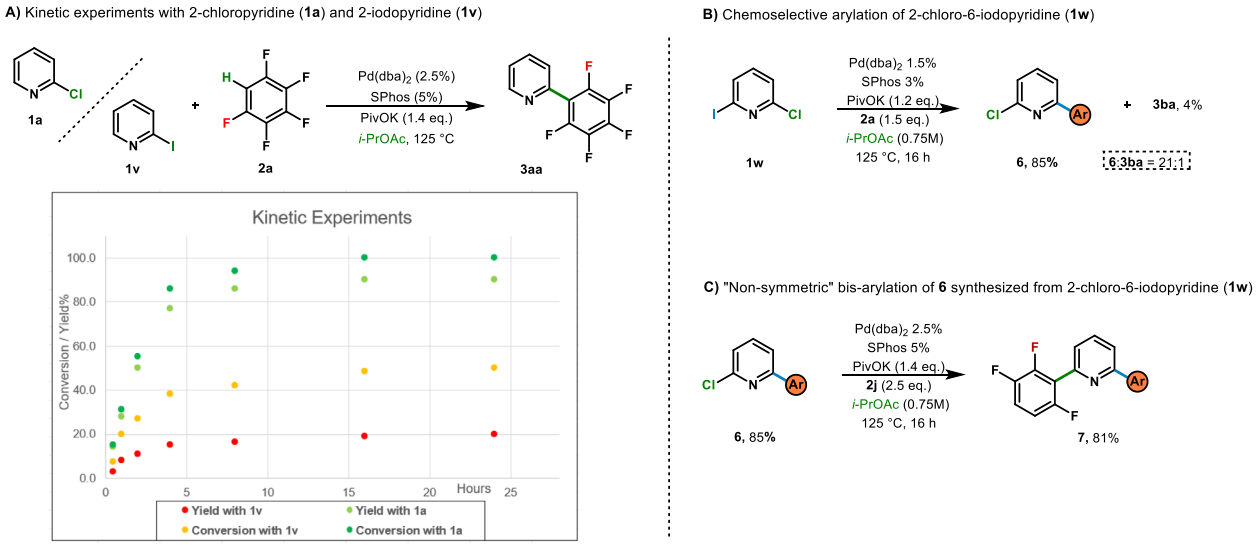
Entry	F-position	$\Delta G^{\ddagger}_{CH\text{-}act}$	Expt. yield	Pd loading
1	1,2,3,4,5	28.2	88%	0.5%
2	1,2,3,4	30.3	80%	3.0%
3	1,3,5	30.6	82%	2.0%
4	1,2,4	31.0	84%	2.5%
5	1,2,3	33.0	65%	6.5%
6	1,3	32.8	62%	7.0%
7	1,4	35.1	50%	8.0%
8	1	36.2	traces	12.0%

presence of secondary effects as well.[73,74] As already highlighted from the optimization of the model reaction, using 2-iodopyridine instead of 2-chloropyridine as reactant offers only 19% yield.

GC-MS-based kinetic measurements were also conducted to examine the variation in yield and conversion over time, providing additional data that could assist in formulating a hypothesis. In Scheme 4A the conversion and the yield of the reaction using 2-chloropyridine and 2-iodopyridine were compared. The kinetic experiment with 2-chloropyridine not only confirmed the findings from the optimization phase, which showed high selectivity for product formation and full conversion after 16 hours, but also revealed that the reaction achieves 86% conversion in just 4 hours.

The kinetic profile of 2-iodopyridine confirmed that product formation is very slow, with poor yield and low selectivity. Extending the reaction beyond 16 hours did not lead to significant improvements. The discrepancy between conversion and yield suggests that approximately 30% of the starting material undergoes a different transformation (50% conversion vs. 20% yield after 16 hours). In fact, one of the main by-products detected might be 2,2′-bipyridine, although the exact quantity formed, along with any other potential side products, remains unclear.

DFT analysis of 2-iodopyridine (**1v**) (Figure S3, Table 3 entry 5) revealed an oxidative addition barrier of 23.2 kcal mol^{-1}, forming



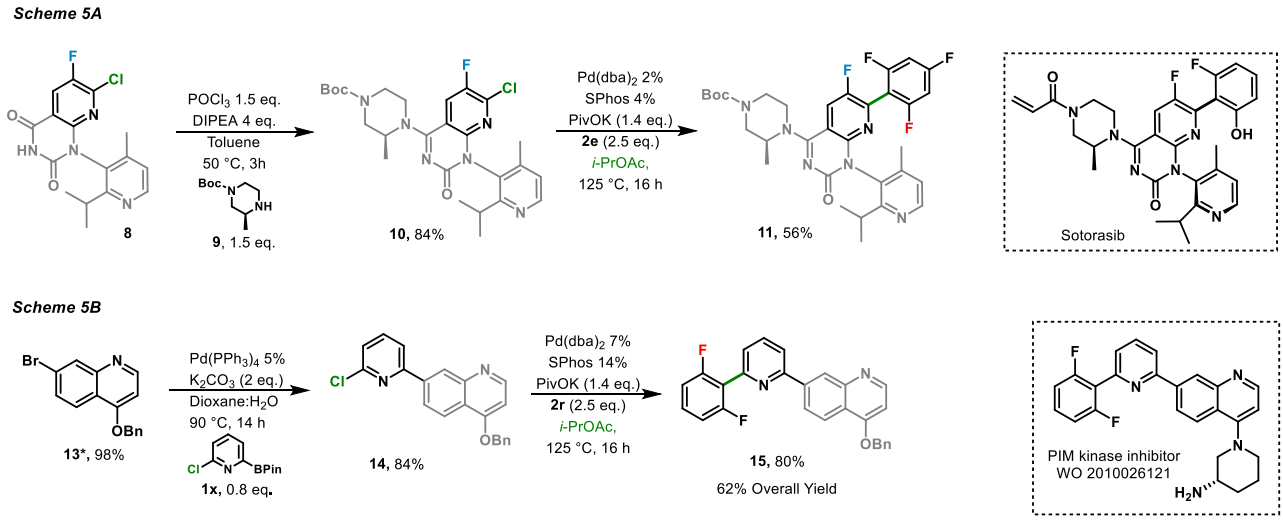
Scheme 4. A). Kinetic comparison of the yield and conversion reacting 2-chloropyridine and 2-iodopyridine with 2a. B). Palladium catalyzed one-step arylation of 2-chloro-6-iodopyridine (**1 w**). The yield for 6 and the ratio for 6 and 3ba were determined by NMR. C). Palladium catalyzed "nonsymmetric" two-step arylation of 2-chloro-6-iodopyridine (**1 w**).

a stable [Pd(SPhos)(Py)(I)] complex. Although oxidative addition is typically more favorable for Ar—I than Ar—Cl,[98–100] in our case the difference of 8.5 kcal mol^{-1} between energy levels of $TS_{ox\text{-}add}$ for Ar-I (21.5 kcal mol^{-1}) and Ar-Cl (30.0 kcal mol^{-1}) also means that the 23.2 kcal mol^{-1} energy required to replace the dba ligand in [Pd(dba)(SPhos)] becomes the real barrier for the oxidative addition of 2-iodopyridine instead of the C-I bond cleavage. Note that dba replacement constitutes most of the oxidative addition barrier for 2-chloropyridine as well; see Figure 2A. The iodide complex is also more stable by 6.7 kcal mol^{-1}, but subsequent steps—halide exchange and C—H activation proceed with similar barriers as in the 2-chloropyridine pathway. Based on these data, we assume that the desired transformation rapidly terminates after the oxidative addition of 2-iodopyridine. It has been hypothesized that the influencing factors might be the formation of a more stable complex (leading to off-cycle inactive species as well as triggering side reactions) or the generation of side products that might interfere negatively with the catalytic cycle.[101] The significant difference in reactivity between **1a** and 2-iodopyridine (**1v**) suggested the possibility of selectively arylating only one C—X bond. This finding led us to investigate 2-chloro-6-iodopyridine (**1 w**) as a potential substrate for chemoselective mono-arylation, with the goal of accessing either a nonsymmetric bis-arylated pyridine or selectively targeting a single C—X bond (Scheme 4B). To optimize selectivity and prevent over-arylation, lower amounts of PivOK and pentafluorobenzene (**2a**) were used. However, slightly higher catalyst loading was required to achieve full conversion. Two surprising findings emerged from this test. First, a complete reversal of the reactivity of the C—X bond was observed, with iodine becoming the primary reactive site (no mono-arylation at the C—Cl bond was detected), leading to **6** with excellent selectivity and high yield (85%). Next, we successfully performed an exemplary tandem cross-coupling to nonsymmetric bis-arylated pyridine **7** with high efficacy, offering potential for novel moieties (Scheme 4C).[102–107]

Next, DFT computations have been performed to compare the reactivity of the two halogenated centers in **1 u** and explain the selectivity and reactivity observed (Figure S3). The trend observed for the oxidative addition into the C—Cl bond and the C—I bond aligns with the same observation made before, indicating a more favorable pathway for oxidative addition into the C—I bond. This pathway has an energy barrier of 21.3 kcal mol^{-1}, which is 8.2 kcal mol^{-1} lower than that for the C—Cl bond (a similar energy difference is observed for the oxidative addition into 2-chloropyridine (**1a**) and 2-iodopyridine (**1v**)). For **1a**, however, KCl formation is exergonic while KI formation is endergonic, bringing the I and Cl pathways closer in energy before C-H activation. Comparing the C—H activation barriers of 28.9 kcal mol^{-1} for 2-chloropyridine and 28.5 kcal mol^{-1} for 2-iodopyridine with those of 2-chloro-6-iodopyridine, which are 27.5 kcal mol^{-1} for the chlorine pathway and 27.4 kcal mol^{-1} for the iodine pathway, reveals the well-established trend that 6-substituted halo pyridines react more quickly. These results also indicate that the C-H activation barriers are very similar for both halogen substituents. Therefore, the selectivity observed in Scheme 4 can be explained by the more facile oxidative addition of 2-chloro-6-iodopyridine at its I-site and the reduced likelihood for the back reaction (or side reaction/degradation) from the oxidative addition product due to its stability, in contrast to the observation for 2-iodopyridine. Also, for the reaction at the Cl-site, the respective oxidative addition is rate-determining instead of the C-H activation.

2.4. Synthesis of a Sotorasib Analogue and a PIM Kinase Inhibitor Intermediate

Building upon the perspective of C-H activation,[59–62] it would be intriguing to investigate how the developed methodology could serve as a promising alternative for synthesizing drugs and other relevant compounds. For our case study, two substrates



Scheme 5. Palladium-catalyzed synthesis of sotorasib analogue and an intermediate of PIM kinase inhibitor. *Synthesized from 7-bromoquinolin-4-ol (see Supporting information).

have been chosen for this type of exploration: an analogue of sotorasib,[108] a $KRas^{G12C}$ inhibitor, and an analogue of a patented PIM kinase inhibitor.[32]

The synthesis of the sotorasib analogue was done starting from the commercially available **8** that was transformed to **10** following the literature procedure.[109,110] Key intermediate **10** was subjected to fluoroarylation using 1,3,5-trifluorobenzene (**2e**) using the methodology developed that affords product **11** in a yield of 56%, representing a valuable starting point for future development (Scheme 5A).

The synthesis of the PIM kinase inhibitor intermediate was done starting from the commercially available substrate **12,** which was benzylated, affording **13**. The 2-chloropyridine motif was inserted by Suzuki cross-coupling to the main molecule, affording **14** in very good yield. At this point, **14** was subjected to fluoroarylation with 1,3-difluorobenzene (**2r**) using the methodology developed by affording the product **15** in 80% yield, better than the model reaction (Scheme 5B). This positive outcome offers a valuable alternative for API synthesis and beyond, potentially streamlining processes for easy, on-demand access to a broader library of complex molecules.

3. Conclusions

We have developed a sustainable and efficient method for the direct C—H arylation of fluorobenzenes with 2-chloropyridines, enabling access to a broad library of mostly novel 2-(fluorinated aryl)pyridines in yields up to 90% and showing options for further expansion to new biaryls by the effective transformation of a set of *N*-heterocycles substituted at various positions. The protocol uses low-cost starting materials, isopropyl acetate as a green solvent, and generates KCl as the sole by-product. The methodology shows broad functional group tolerance on both coupling partners, providing a platform for further diversification.

Mechanistic insights supported by DFT calculations clarified key features of the reaction. These include the full energy profile of the model transformation, the impact of 6-substitution on the pyridine ring, and the influence of Buchwald-type ligands on intermediate and transition state stability. The unexpected low reactivity of 2-iodopyridine was attributed to post-oxidative addition inhibition, while the selective monoarylation of 2-chloro-6-iodopyridine demonstrated the potential for chemoselective functionalization of bis-halogenated substrates. Additionally, computed C—H activation barriers for fluoroarenes confirmed that lower fluorine content correlates with decreased acidity and higher activation energy.

The method was successfully applied to the late-stage functionalization of drug molecules, including analogues of sotorasib and PIM kinase inhibitors, highlighting its relevance for pharmaceutical synthesis. Despite minor limitations with certain difluorinated substrates, this study offers a practical and mechanistically guided approach to C—H arylation of challenging heterocycles, with strong potential for further development.

Supporting Information

Supporting Information contains experimental details including: materials and methods, compound characterization, computational details, xyz coordinates. Supporting tables and figures of reaction optimization and mechanism computation. The authors have cited additional references within the Supporting Information.[111–130]

Author Contributions

F.B. conceived the work, designed the experiments, optimized the reaction conditions, participated in the DFT exploration, performed the scope and wrote the paper. P.F. performed the DFT calculations and co-wrote the paper. T.H. contributed to project

management, A.S. participated and supervised the theoretical study. Cs. G. N. and P. Á.-B. participated in the experiments and analytics. G. M.K. and P. Á.-B. supervised the project and co-wrote the paper.

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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 from the corresponding author upon reasonable request.

Keywords: C-H arylation · cross-coupling · DFT · fluorinated arenes · mechanism · pyridine · sustainability

[1] A. O Plunkett, *Nat. Prod. Rep.* **1994**, *11*, 581.
[2] J. P. Q. Michael, *Nat. Prod. Rep.* **2005**, *22*, 627.
[3] M. C. Bagley, C. Glover, E. A. Merritt, *Synlett* **2007**, *16*, 2459.
[4] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322.
[5] M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898.
[6] R. Gujjarappa, N. Vodnala, C. C. Malakar, *ChemistrySelect* **2020**, *5*, 8745.
[7] S. Zhang, Y. Ouyang, Y. Gao, P. Li, *Acc. Chem. Res.* **2024**, *57*, 957.
[8] B. Tang, F. Yu, P. Li, L. Tong, X. Duan, T. Xie, X. Wang, *J. Am. Chem. Soc.* **2009**, *131*, 3016.
[9] A. Wild, A. Winter, F. Schlütter, U. S. Schubert, *Chem. Soc. Rev.* **2011**, *40*, 1459.
[10] A. Y. Guan, C. L. Liu, X. F. Sun, Y. Xie, M. A. Wang, *Bioorg. Med. Chem.* **2016**, *24*, 342.
[11] R. Álvarez, L. Aramburu, P. Puebla, E. Caballero, M. González, A. Vicente, M. Medarde, R. Peláez, *Curr. Med. Chem.* **2016**, *23*, 1100.
[12] R. Sahu, R. Mishra, R. Kumar, M. Salahuddin, C. Majee, A. Mazumder, A. Kumar, *Mini-Rev. Med. Chem.* **2021**, *22*, 248.
[13] Y. Ling, Z. Y. Hao, D. Liang, C. L. Zhang, Y. F. Liu, Y. Wang, *Drug Devel Ther* **2021**, *15*, 4289.
[14] X. A. F. Cook, A. de Gombert, J. McKnight, L. R. E. Pantaine, M. C. Willis, *Angew. Chem. Int. Ed.* **2021**, *60*, 11068.
[15] L. Yet, *Prog. Heterocycl. Chem.* **2020**, *31*, 431.
[16] T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitti, M. C. Willis, *Chem. Sci.* **2017**, *8*, 4437.
[17] M. Baloch, D. Roy, S. Bensaid, V. Guerchais, H. Doucet, *Eur. J. Inorg. Chem.* **2012**, *2012*, 4454.
[18] Y. Hu, Y. Gao, J. Ye, Z. Ma, J. Feng, X. Liu, P. Lei, M. S.-M. Szostak, *Org. Lett.* **2023**, *25*, 2975.
[19] R. R. Surgenor, H. Lee, *Chem.–Eur. J.* **2024**, *30*, e202401552.
[20] Z. J. Quan, F. Q. Jing, Z. Zhang, Y. X. Da, X. C. Wang, *Eur. J Org Chem* **2013**, *2013*, 7175.
[21] H. Andersson, F. Almqvist, R. Olsson, *Org. Lett.* **2007**, *9*, 1335.
[22] A. A. Stefopoulos, S. N. Kourkouli, S. Economopoulos, F. Ravani, A. Andreopoulou, K. Papagelis, A. Siokou, J. K. Kallitsis, *Macromolecules* **2010**, *43*, 4827.
[23] P. Giannopoulos, A. Nikolakopoulou, A. K. Andreopoulou, L. Sygellou, J. K. Kallitsis, P. Lianos, *J. Mater. Chem. A* **2014**, *2*, 20748.
[24] C. Reichardt, *Pure Appl. Chem.* **2008**, *80*, 1415.
[25] R. Boyaala, M. Peng, W. S. Tai, R. Touzani, T. Roisnel, V. Dorcet, Y. Chi, V. Guerchais, H. Doucet, J. F. Soulé, *Inorg. Chem.* **2020**, *59*, 13898.
[26] L. H. M. de Groot, A. Ilic, J. Schwarz, K. Wärnmark, *J. Am. Chem. Soc.* **2023**, *145*, 9369.
[27] R. Bevernaegie, S. A. M. Wehlin, B. Elias, L. Troian-Gautier, *ChemPhotoChem* **2021**, *5*, 217.
[28] J. B. Epp, A. L. Alexander, T. W. Balko, A. M. Buysse, W. K. Brewster, K. Bryan, J. F. Daeuble, S. C. Fields, R. E. Gast, R. A. Green, N. M. Irvine, W. C. Lo, C. T. Lowe, J. M. Renga, J. S. Richburg, J. M. Ruiz, N. M. Satchivi, P. R. Schmitzer, T. L. Siddall, J. D. Webster, M. R. Weimer, G. T. Whiteker, C. N. Yerkes, *Bioorg. Med. Chem.* **2016**, *24*, 362.
[29] A. Manabe, H. Ikegami, H. Morishita, Y. Matsuzaki, *Bioorg. Med. Chem.* **2023**, *88–89*, 117332.
[30] A. F. Abdel-Magid, S. Herrera Unda , F. J. Pernasetti , F. M. Rollins , *ACS Med. Chem. Lett.* **2022**, *13*, 1405.
[31] S. Brooks, R. G. J. A. Zuiker, C. Bleys, D. Ziagkos, J. A. Moyer, L. van Nueten, P. Bonaventure, W. C. Drevets, J. M. A. van Gerven, G. Salvadore, G. E. Jacobs, *J. Psychopharmacol.* **2023**, *37*, 577.
[32] WO2010026121A1 – Bicyclic kinase inhibitors – Google Patents. https://patents.google.com/patent/WO2010026121A1/en (accessed 2025-02-11).
[33] C. M. V. Rudin, *Clin. Cancer Res.* **2012**, *18*, 3218.
[34] J. Emmerich, C. J. van Koppen, J. L. Burkhart, R. T. Engeli, Q. Hu, A. Odermatt, R. W. Hartmann, *Eur. J. Med. Chem.* **2018**, *143*, 591.
[35] D. Brazel, M. Nagasaka, *Target Oncol* **2024**, *19*, 297.
[36] A. Lee, *Target Oncol* **2022**, *17*, 727.
[37] Z. Li, Z. Song, Y. Zhao, P. Wang, L. Jiang, Y. Gong, J. Zhou, H. Jian, X. Dong, W. Zhuang, S. Cang, N. Yang, J. Fang, J. Shi, J. Lu, R. Ma, P. Wu, Y. Zhang, M. Song, C. W. Xu, Z. Shi, L. Zhang, Y. Wang, X. Wang, Y. Zhang, S. Lu, *J.Thorac. Oncol.* **2023**, *18*, 940.
[38] I. A. Lugowska, C. Rojas, A. Stathis, S. Weindler, A. Pal, E. Castanon Alvarez, J. Mackiewicz, M. Garrido, M. A. N. Sendur, N. J. Lakhani, S. Frentzas, R. Dziadziuszko, A. G. Sacher, K. Wakuda, T. Kato, R. Perets, O. O. Castillo Fernandez, T. Jemielita, Y. Choi, R. A. Juergens, *J. Clin. Oncol.* **2024**, *42*, TPS232.
[39] D. Wei, L. Wang, X. Zuo, A. Maitra, R. S. Bresalier, *Clin. Cancer Res.* **2024**, *30*, 655.
[40] S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463.
[41] D. Yu, C. S. Wang, C. Yao, Q. Shen, L. Lu, *Org. Lett.* **2014**, *16*, 5544.
[42] Y. You, S. Y. Park, *J. Am. Chem. Soc.* **2005**, *127*, 12438.
[43] L. Chen, P. Ren, B. P. Carrow, *J. Am. Chem. Soc.* **2016**, *138*, 6392.
[44] M. T. Burger, W. Han, J. Lan, G. Nishiguchi, C. Bellamacina, M. Lindval, G. Atallah, Y. Ding, M. Mathur, C. Mcbride, E. L. Beans, K. Muller, V. Tamez, Y. Zhang, K. Huh, P. Feucht, T. Zavorotinskaya, Y. Dai, J. Holash, J. Castillo, J. Langowski, Y. Wang, M. Y. Chen, P. D. Garcia, *ACS Med. Chem. Lett.* **2013**, *4*, 1193.
[45] J. L. Lamola, P. T. Moshapo, C. W. Holzapfel, M. C. Maumela, *RSC Adv.* **2021**, *11*, 26883.
[46] W. Ren, J. Li, D. Zou, Y. Wu, Y. Wu, *Tetrahedron* **2012**, *68*, 1351.
[47] T. Sato, H. Awano, H. Katagiri, Y. J. Pu, T. Takahashi, K. Yonetake, *Eur. J. Inorg. Chem.* **2013**, *2013*, 2212.
[48] W. Lumeras, F. Caturla, L. Vidal, C. Esteve, C. Balagué, A. Orellana, M. Domínguez, R. Roca, J. M. Huerta, N. Godessart, B. Vidal, *J. Med. Chem.* **2009**, *52*, 5531.
[49] K. Tomota, J. Li, H. Tanaka, M. Nakamoto, T. Tsushima, H. Yoshida, *JACS Au* **2024**. *4*, 3931.
[50] P. A. Cox, A. G. Leach, A. D. Campbell, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2016**, *138*, 9145.
[51] P. A. Cox, M. Reid, A. G. Leach, A. D. Campbell, E. J. King, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2017**, *139*, 13156.

[52] A. M. Kelly, P. J. Chen, J. Klubnick, D. J. Blair, M. D. Burke, *Org. Lett.* **2020**, *22*, 9408.
[53] Y. Mutoh, K. Yamamoto, S. Saito, *ACS Catal.* **2020**, *10*, 352.
[54] Y. P. Budiman, S. A. Westcott, U. Radius, T. B. Marder, *Adv. Synth. Catal.* **2021**, *363*, 2224.
[55] Y. P. Budiman, R. N. Perutz, P. G. Steel, U. Radius, T. B. Marder, (2024). *Chem. Rev.* **2024**, *124*, 4822.
[56] L.-Y. Liu, J. X. Qiao, K.-S. Yeung, W. R. Ewing, J.-Q. Yu, *Angew. Chem.* **2020**, *132*, 13935.
[57] R. de Jesus, K. Hiesinger, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2023**, *62*, e202306659.
[58] P. Wedi, M. Farizyan, K. Bergander, C. Mück-Lichtenfeld, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2021**, *60*, 15641.
[59] Y.-Y. Che, Y. Yue, L.-Z. Lin, B. Pei, X. Deng, C. Feng, *Angew. Chem. Int. Ed.* **2020**, *59*, 16414.
[60] H. Cao, Q. Cheng, A. Studer, *Angew. Chem. Int. Ed.* **2023**, *62*, e20230294.
[61] H. Wang, M. F. Greaney, *Angew. Chem. Int. Ed.* **2024**, *63*, e202315418.
[62] a) T. Dalton, T. Faber, F. Glorius, *ACS Cent. Sci.* **2021**, *7*, 245. b) A. Mondal, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2022**, *61*, e202210825. c) L. Monsigny, F. Doche, T. Besset, *Beilstein J. Org. Chem.* **2023**, 19:35 *19*, 448.
[63] a) H. Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 1128. b) H. Q. Do, R. M. K. Khan, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 15185. c) S. Fan, J. Yang, X. Zhang, *Org. Lett.* **2011**, *13*, 4374. d) O. Y. Yuen, M. Charoensak, C. M. So, C. Kuhakarn, F. Y. Kwong, *Chem Asian J* **2015**, *10*, 857. e) W. Hagui, N. Besbes, E. Srasra, J. F. Soulé, H. Doucet, *RSC Adv.* **2016**, *6*, 17110.
[64] Regulation –895/2014 – EN – EUR-Lex. https://eur-lex.europa.eu/eli/reg/2014/895/oj/eng (accessed 2025-04-01).
[65] J. Yang, S. Liu, J. F. Zheng, J. Zhou, *Eur. J Org Chem* **2012**, *2012*, 6248.
[66] K. Billingsley, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3358.
[67] S. Bhaskaran, M. S. A. Padusha, A. M. Sajith, *ChemistrySelect* **2020**, *5*, 9005.
[68] O. Eisenstein, J. Milani, R. N. Perutz, *Chem. Rev.* **2017**, *117*, 8710.
[69] M. M. Heravi, Z. Kheilkordi, V. Zadsirjan, M. Heydari, M. Malmir, *J. Organomet. Chem.* **2018**, *861*, 17.
[70] C. H. Benison, P. R. Payne, *Curr. Res. Green Sustain. Chem.* **2022**, *5*, 100229.
[71] J. Becker, C. Manske, S. Randl, *Curr Opin Green Sustain Chem* **2022**, *33*, 100562.
[72] T. Yan, L. Zhao, M. He, J. F. Soulé, C. Bruneau, H. Doucet, *Adv. Synth. Catal.* **2014**, *356*, 1586.
[73] S. I. Gorelsky, *Organometallics* **2012**, *31*, 4631.
[74] S. I. Gorelsky, *Coord. Chem. Rev.* **2013**, *257*, 153.
[75] M. He, J. F. Soulé, H. Doucet, *ChemCatChem* **2015**, *7*, 2130.
[76] A. Hfaiedh, H. Ben Ammar, J. F. Soulé, H. Doucet, *Org. Biomol. Chem.* **2017**, *15*, 7447.
[77] M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108.
[78] C. Cao, L. Wang, Z. Cai, L. Zhang, J. Guo, G. Pang, Y. Shi, *Eur. J Org Chem* **2011**, *2011*, 1570.
[79] P. M. Macqueen, A. J. Chisholm, B. K. V. Hargreaves, M. Stradiotto, *Chem.–Eur. J.* **2015**, *21*, 11006.
[80] S. M. Crawford, P. G. Alsabeh, M. Stradiotto, *Eur. J Org Chem* **2012**, *2012*, 6042.
[81] N. J. Castellino, A. P. Montgomery, J. J. Danon, M. Kassiou, *Chem. Rev.* **2023**, *123*, 8127.
[82] L. Guillemard, N. Kaplarenis, L. Ackermann, M. J. Johansson, *Nat. Rev. Chem.* **2021**, *5*, 522.
[83] S. Y. Shim, *Chem.–Eur. J.* **2023**, *29*, e202302620.
[84] J. Börgel, T. Ritter, *Chem* **2020**, *6*, 1877.
[85] M. Janowski, O. M. Demchuk, M. Wujec, *Molecules* **2024**, *29*, 2855.
[86] K. Richardson, K. Cooper, M. S. Marriott, M. H. Tarbit, F. Troke, P. J. Whittle, *Rev Infect Dis* **1990**, *12*, S267.
[87] M. Lee, M. K. Rhee, *Expert Rev. Cardiovasc. Ther.* **2015**, *13*, 597.
[88] Y. Liu, H. Ge, *Nat. Chem.* **2017**, *9*, 26.
[89] M. Kapoor, A. Singh, K. Sharma, M. H. Hsu, *Adv. Synth. Catal.* **2020**, *362*, 4513.
[90] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685.
[91] J. P. Norman, N. G. Larson, S. R. Neufeldt, *ACS Catal.* **2022**, *12*, 8822.
[92] X. Chen, K. M. Engle, D. H. Wang, Y. Jin-Quan, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.
[93] D. S. Surry, S. L. Buchwald, S. L. Buchwald, D. S. Surry, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338.
[94] B. U. W. Maes, S. Verbeeck, T. Verhelst, A. Ekomié, N. V. Wolff, G. Lefèvre, E. A. Mitchell, A. Jutand, *Chem.–Eur. J.* **2015**, *21*, 7858.
[95] J. Lu, H. Celuszak, I. Paci, D. C. Leitch, *Chem.–Eur. J.* **2024**, *30*, e202402282.
[96] J. Lu, N. D. Schley, I. Paci, D. C. Leitch, *Organometallics* **2024**, *43*, 3192.
[97] R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.
[98] C. Amatore, A. Jutand, *Coord. Chem. Rev.* **1998**, *178–180* (PART), 511.
[99] D. J. Jones, M. Lautens, G. P. McGlacken, *Nat. Catal.* **2019**, 2019 2:10 *2*, 843.
[100] A. S. Galushko, D. O. Prima, J. V. Burykina, V. P. Ananikov, *Inorg. Chem. Front.* **2021**, *8*, 620.
[101] a) Y. Cho, Y. H. Chang, K. P. Quirion, Z. H. Strong, Z. J. Dubey, N. Nguyen, S. Lee, N. S. Taylor, J. M. Hoover, N. A. White, P. Liu, M. J. Krische, *Nat. Chem.* **2025**, *17*, 710. b) M. Zeng, Y. Du, L. Shao, C. Qi, X.-M. Zhang, *J. Org. Chem.* **2010**, *75*, 2556.
[102] B. Mondal, P. Ghosh, M. Kundu, T. K. Das, S. Das, *Org. Biomol. Chem.* **2021**, *19*, 360.
[103] M. Akram, M. Adeel, M. Khalid, M. N. Tahir, H. A. R. Aliabad, M. A. Ullah, J. Iqbal, A. A. C. Braga, *J. Mol. Struct.* **2020**, *1213*, 128131.
[104] B. Heinz, D. Djukanovic, P. Filipponi, B. Martin, K. Karaghiosoff, P. Knochel, *Chem. Sci.* **2021**, *12*, 6143.
[105] S. Cardoza, M. K. Shrivash, P. Das, V. Tandon, *J. Org. Chem.* **2021**, *86*, 1330.
[106] I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12774.
[107] M. Yang, J. Chen, C. He, X. Hu, Y. Ding, Y. Kuang, J. Liu, Q. Huang, *J. Org. Chem.* **2020**, *85*, 6498.
[108] A. Lee *Target Oncol* **2022**, *17*, 727.
[109] L. Zhang, D. J. Griffin, M. G. Beaver, L. E. Blue, C. J. Borths, D. B. Brown, S. Caille, Y. Chen, A. H. Cherney, B. M. Cochran, J. T. Colyer, M. T. Corbett, T. L. Correll, R. D. Crockett, X.-J. Dai, P. K. Dornan, R. P. Farrell, S. J. Hedley, H.-W. Hsieh, A. T. Parsons, *Org. Process Res. Dev.* **2022**, *26*, 3115.
[110] WO2021051034A1 – Ras protein degraders, pharmaceutical compositions thereof, and their therapeutic applications – Google Patents. https://patents.google.com/patent/WO2021051034A1/en (accessed 2025-05-19).
[111] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, et al., Gaussian 16, Revision A.03, Gaussian, Inc., Wallingford CT, **2016**.
[112] J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615.
[113] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.
[114] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378.
[115] F. Neese, *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2022**, *12*, e1606.
[116] C. Bannwarth, S. Ehlert, S. Grimme, *J. Chem. Theory Comput.* **2019**, *15*, 1652.
[117] S. Ehlert, M. Stahn, S. Spicher, S. Grimme, *J. Chem. Theory Comput.* **2021**, *17*, 4250.
[118] R. Gerber, C. M. Frech, *Chem.–Eur. J.* **2011**, *17*, 11893.
[119] a) Novartis – WO2022/34529, 2022, A1 Page: 120. b) Z. Peng, G. Hu, H. Qiao, P. Xu, Y. Gao, Y. Zhao, *J. Org. Chem.* **2014**, *79*, 2733.
[120] a) B. Thomas, – *WO2011/50245*, **2011**, A1 Page: 118. b) J. Magano, A. Acciacca, A. Akin, B. M. Collman, B. Conway, M. Waldo, M. H. Chen, K. E. Mennen, *Org. Process Res. Dev.* **2009**, *13*, 555.
[121] a) Boehringer Ingelheim International – WO2019/158572, 2019, A1 Page: 44, 67, 68. b) K. Paridala, S.-M. Lu, M.-M. Wang, C. Li, *Chem. Commun.* **2018**, *54*, 11574.
[122] T. Rossolini, B. Ferko, D. J. Dixon, *Org. Lett.* **2019**, *21*, 6668.
[123] M. Berger, M. S. Lenhard, S. R. Waldvogel, *Chem.–Eur. J.* **2022**, *28*.
[124] C. Abercrombie, C. P. Ashcroft, M. Badland, A. Baldwin, L. T. Baldwin, S. Brisley, W. Callar, P. Daddario, E. Hilou, C. James, R. Li, Y. Liu, S. Monfette, J. L. Piper, G. Reyes, H. Risley, F. H. Salingue, K. Saunyama, M. G. Vetelino, *Org. Process Res. Dev.* **2023**, *27*, 866.

[125] Y. Pang, M. Leutzsch, N. Nöthling, F. Katzenburg, J. Cornella, *J. Am. Chem. Soc.* **2021**, *143*, 12487.
[126] O. Y. Yuen, M. Charoensak, C. M. So, C. Kuhakarn, F. Y. Kwong, *Chem.–Asian J.* **2015**, *10*, 857.
[127] S. Fan, J. Yang, X. Zhang, *Org. Lett.* **2011**, *13*, 4374.
[128] BIOTHERYX – WO2021/51034, 2021, A1: Paragraph 0195, 0333, 0338.
[129] R. De Vreese, K. Muylaert, C. Maton, L. Dereu, F. Taillieu, T. Harth, R. van Deun, H. Vrielinck, C. v. Stevens, M. D'hooghe, *Tetrahedron Lett.* **2017**, *58*, 3803.
[130] RIGEL PHARMACEUTICALS – WO2016/133838, 2016, A1: Paragraph 0164, 0165, 0166.

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