Switching to the non-PFAS-containing fluorosulfate leaving group, together with a Pd oxidative addition complex: rapid aminations of functionalized aromatics *in water*

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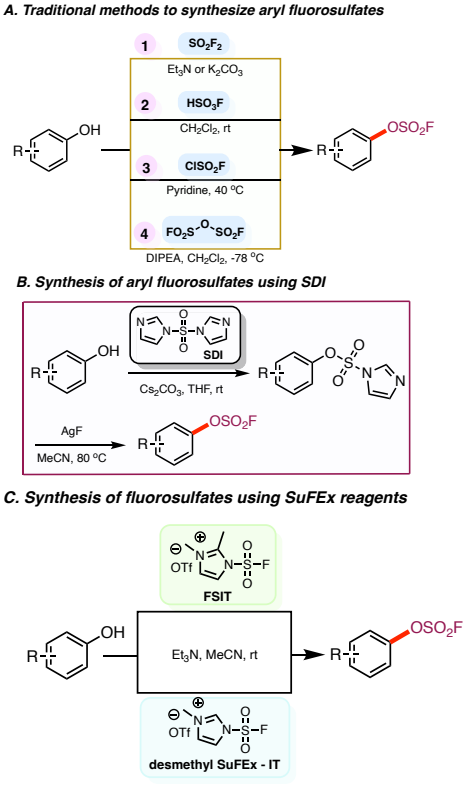
ABSTRACT: Aryl fluorosulfates of varying complexities have been used in amination reactions in water using a new Pd oxidative addition complex (OAC) developed specifically to match the needs of the fine chemicals industry, not only in terms of functional group tolerance, but also reflecting time considerations associated with these important C–N couplings. Also especially noteworthy is that they replace both PFAS-related triflates and nonaflates, which are today out of favor due to recent government regulations. The new complex based on the BippyPhos ligand is used at low loadings and under aqueous micellar conditions. Moreover, it is easily prepared and stable to long term storage. DFT calculations on the OAC precatalyst compare well with the X-ray structure of the crystals with π-complexation to the aromatic system of the ligand and also confirm the NMR data showing a mixture of conformers in solution that differ from the X-ray structure in rotation of the phenyl and *t*-butyl ligand substituents. An extensive variety of coupling partners, including pharmaceutically relevant APIs, readily participate under mild and environmentally responsible reaction conditions.

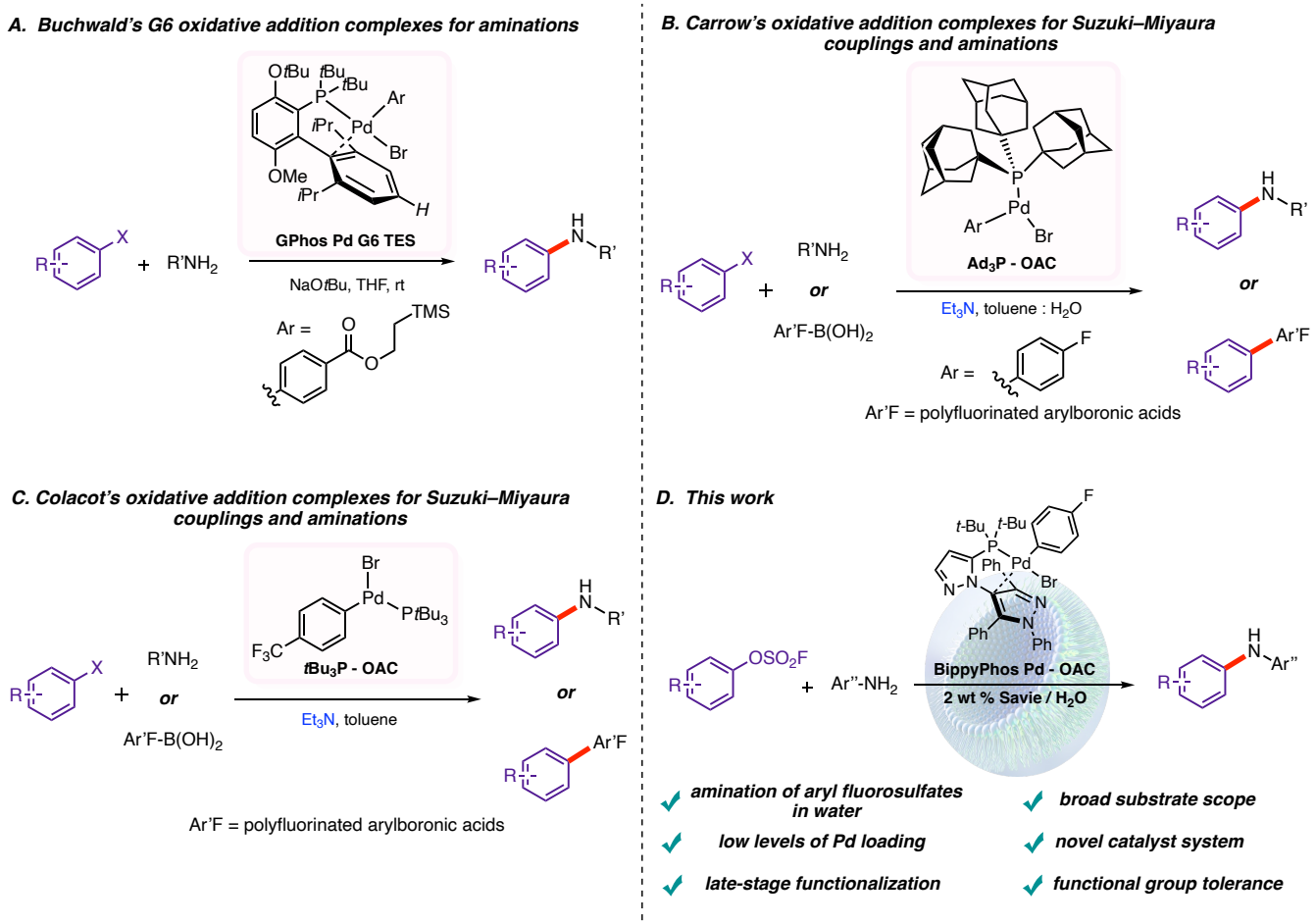
INTRODUCTION

Over the past 29 years, Group 10-metal-catalyzed aminations of aryl pseudohalides mainly focusing on triflates and more recently, Knochel's nonaflates, have become fundamental processes in organic synthesis for the formation of C(sp^2)–N bonds. Given the ubiquitous nature of the *N*-aryl and *N*-heteroaryl-amine motif in natural products,[1-4] pharmaceuticals,[1,5-7] and fine chemicals,[8-10] should the status of one or more components of a reaction be altered, a need for the development of new technologies arises, preferably those that are not only environmentally responsible but are also efficient, mild, and general. Couplings with aryl triflates and nonaflates are especially common, notwithstanding the alternative, albeit less reactive, mesylates and tosylates.[11-15] And while they have some inherent disadvantages (such as instability, environmental toxicity, cost of preparation, and poor atom economy in the making of triflates),[16] they are taken for granted as the two main options available for use in synthetic organic chemistry.[17] Unfortunately, as both contain C(sp^3)–F bonds, they are technically polyfluorinated alkyl substances (PFASs),[18] reagents that only recently have been flagged for their environmental impact. On the other hand, aryl fluorosulfates, first described more than four decades ago,[19] have thus become increasingly popular as coupling partners, all the more so given the range of processes that now exist for their generation from phenolic starting materials (Scheme 1). Hence, a new process that fulfills all of these criteria may represent a breakthrough in the common utilization of phenol-based electrophiles in cross-coupling research in modern synthetic chemistry.[20-26]

Scheme 1. Approaches to aryl fluorosulfates from phenols.



Scheme 2. Previously developed Pd-Oxidative addition complexes for cross coupling reactions.



The evolution of new generations of ligands is a recent trend in modern transition metal-catalyzed cross coupling reactions.[27] As examples in this regard, several biaryl phosphines,[28] QPhos-based ligands,[29] as well as CataCXium-based ligands[30] have been developed to tackle challenging reactions involving pseudohalides. Additionally, significant advancements have been made with the discovery of ferrocene-based ligands by the Colacot group,[31] and *N*–heterocyclic carbene (NHC)-based ligands by Hermann, Nolan, and Organ.[32-34] Nonetheless, the search for alternative monodentate phosphine-based pre-catalysts is still very much ongoing, especially given the differences between their anticipated usage in traditional organic solvents *versus* use in more environmentally responsible processes, including in water under micellar catalysis conditions. One area that remains underexplored, especially from the green chemistry perspective, is development of metal-containing Oxidative Addition Complexes (OACs). A number of groups[35-37] have previously prepared palladium-containing OACs, albeit for mechanistic studies. More recently, OACs using biarylphosphines (*e.g.,* Buchwald's Pd-G6 complexes) have been found useful for various applications (Scheme 2A). [38, 39] Carrow has reported studies describing the Pd–OAC formed using Ad_3P as a unique ligand to carry out both Suzuki-Miyaura couplings of challenging polyfluoroarylboronic acids, as well as otherwise difficult C–N couplings of aryl halides under mild conditions (Scheme 2B).[40,41] Especially noteworthy is the work by Colacot *et al.* who have developed a general Pd–OAC using relatively inexpensive tBu$_3$P as ligand enabling various C–C and C–N cross couplings of aryl halides (Scheme 2C).[42]

Prior seminal studies[43-46] have already established that aryl fluorosulfates function as effective cross-coupling partners using traditional Pd (or Ni) catalysis in aminations[43b] and other C–C cross coupling reactions.[44–46] Nonetheless, catalyst loadings are not only costly but unsustainable (typically run in organic solvents with >2 mol % Pd) when considered for use at scale. Moreover, the very limited substrate scope in each renders these protocols even more worthy of further exploration. Importantly, other factors such as solvent and/or catalyst recycling, and metrics relating to the environmental friendliness of these processes (such as E Factors,[47] PMI,[48] etc.) have rarely been considered. These parameters, yet again, highlight the pressing need for an alternative, far more environmentally attractive and sustainable process for aminations. In addition, significant reaction rate enhancements associated with what are otherwise typically time-consuming processes would also represent a significant advance.

This report, therefore, is the outcome of a lengthy investigation into the development and use of a new oxidative addition complex (**1**) based on the commercially available bipyrazole ligand, BippyPhos (Scheme 2D).[49] This previously unknown OAC leads to rapid aminations of fluorosul-

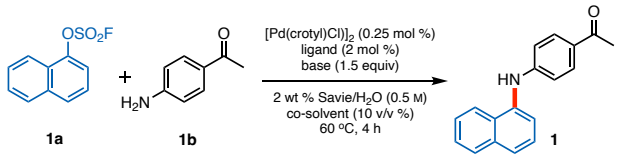
fates, matched to its use in water[50] containing our recently introduced biodegradable amphiphile, Savie.[51] As a newly fashioned pre-catalyst, **OAC-1** offers several attractive features, including (1) it is considerably less expensive[49b] and yet, easier to synthesize (see SI) as compared to other previously developed OACs;[39–42] (2) **OAC–1** catalyzes aminations between educts that display broad functional group tolerance; (3) reactions occur at relatively low Pd loadings in the presence of Et_3N, an inexpensive and mild base; (4) **OAC–1** outperforms traditional Pd-phosphine complexes in terms of catalyst loading and substrate scope, including a variety of sensitive functional groups; and (5) it leads to faster reactions relative to other aminations using OAC complexes; (6) it allows the use of fluorosulfates as non-PFAS-containing pseudohalides, leading to an overall attractive option for aminations in both academic and industrial settings.

RESULTS AND DISCUSSION

Optimization. In efforts to find a ligand for chelation to Pd that leads to an effective catalyst under aqueous micellar coinditions, naphthalen-1-yl sulfurofluoridate (**1a**) and 4-aminoacetophenone (**1b**), as model substrates, were selected for initial amination studies (Table 1). Based on our prior aminations of aryl *halides*,[50a, b] reactions were run starting with catalytic amounts of Colacot's readily available and bench stable dimeric species $[Pd(crotyl)Cl]_2$ as the source of Pd(II) in 2 wt % Savie as the aqueous reaction medium. Potassium *t*–butoxide (KO*t*Bu) was selected since aryl amination protocols tend to utilize alkoxide bases.[52] An initial investment of 0.25 mol % of Pd dimer (hence, 0.5 mol % [Pd]; administered as a stock solution in THF; see SI, section 3) was made. The key to success, and to eventually focus on **OAC-1**, was the eventual finding that the ligand BippyPhos complexed with Pd efficiently mediated C–N bond construction (entry 3; see SI, section 3.1 for the complete list of ligands screened). Among other ligands[28-30] evaluated, none led to productive C–N couplings (entries 1–2 and 5–7). Screening bases (see SI, section 3.2) indicated that milder conditions would be necessary, as aryl fluorosulfates are known to undergo sulfamation in the presence of amines under strongly basic conditions.[53] Ultimately, Et_3N (entry 11) proved to be the most effective base, affording biarylamine **1** in 98% yield (as determined by ^1H NMR; 92% isolated). Other weak bases such as Cs_2CO_3 and Proton Sponge proved equally effective; however, considering cost, Et_3N turned out to be the base of choice. Screening co-solvents led to use of 10 v/v % cyclopentyl methyl ether (CPME), a greener alternative to THF and 2-MeTHF (entry 15).[54] Of note is that these aminations also work efficiently using no co-solvent (entry 16), which may be of considerable value if used at industrial scales. Also worth pointing out as foreshadowing, full conversion was observed within a 2 h period under these reaction conditions (*i.e.,* a global concentration of 0.5 M).

Another variable was the choice of surfactant, which leads to variations in the nature of the nanomicelles (i.e., the nanoreactors) formed in the aqueous micellar medium in which the couplings take place.[55] Thus, a series of amphiphiles was evaluated in terms of effectiveness at enabling aminations (Table 2). Under otherwise identical conditions (2 wt % of each surfactant in water), yields of **1** ranged from 27 to 99%. The recently introduced, more polar and biodegradable Savie[51] gave the best result for this model coupling (entry 6; 99%) as compared to other ionic and nonionic amphiphiles (entries 1–3, 5, 7–11). The corresponding background reaction "on water"[56] (entry 4), likewise, afforded the desired product, albeit in a modest 51% yield.

Table 1. Screening of reaction conditions.



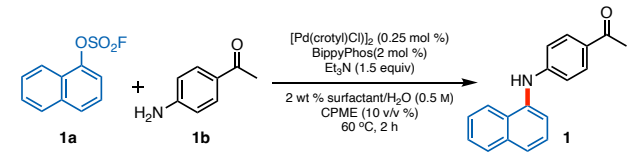
1a 1b 1

entry[a]	ligand	base	co-solvent	yield (%)[b]
1	*t*BuXPhos	KO*t*Bu	THF	48
2	*t*BuBrettPhos	KO*t*Bu	THF	trace
3	**BippyPhos**	**KO*t*Bu**	**THF**	**63**
4	AdBippyPhos	KO*t*Bu	THF	59
5	CataCXium A	KO*t*Bu	THF	N/D
6	CataCXium ABn	KO*t*Bu	THF	N/D[c]
7	AdBrettPhos	KO*t*Bu	THF	38
8	BippyPhos	KOH	THF	37
9	BippyPhos	K-2-ethyl hexanoate	THF	49
10	BippyPhos	K_3PO_4	THF	85
11	**BippyPhos**	**Et_3N**	**THF**	**98 (92);[d] 97[e]**
12	BippyPhos	Cs_2CO_3	THF	91
13	BippyPhos	Et_3N	2-MeTHF	90
14	BippyPhos	Et_3N	*i*PrOAc	24
15	**BippyPhos**	**Et_3N**	**CPME**	**99**
16	BippyPhos	Et_3N	no co-solvent	93

[a] Reactions were carried out at 0.25 mmol scale; [b] NMR yields using 1,3,5-trimethoxybenzene as internal standard. [c] N/D = not detected; [d] isolated yield; [e] Reaction was run at 60 °C for 2 h.

Synthesis and characterization of OAC-1. Once BippyPhos had been identified as the ligand within a new Pd complex for catalyzing C–N couplings in water, the focus shifted to the corresponding OAC. While preparation of the G6 oxidative addition complex uses $(cod)Pd(CH_2TMS)_2$,[39,57] as the Pd precursor, its high cost and extreme air and temperature sensitivity led us to search for an alternative approach. Ultimately, starting with commercially available allyl palladium chloride (Scheme 3A),[58] **OAC-1** could be smoothly prepared using a slightly modified protocol reported from Pfizer (see SI, section 4).[59] Thus, treatment of $(Pd(allyl)Cl)_2$ with BippyPhos in degassed, anhydrous THF, and sodium triflate led to coordination of the metal to the ligand, the targeted species being formed *in situ*.[60] Without its isolation, subsequent nucleophilic attack by the sodium salt of diethyl malonate (generated *in situ*; see SI, section 4) afforded the Pd(0) species that underwent subsequent

Table 2. Surfactant screening.

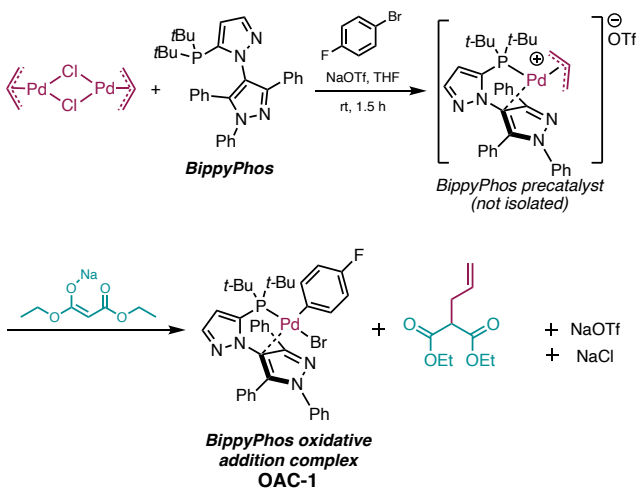


entry[a]	surfactant	yield (%)[b]
1	MC-1	78
2	**TPGS-750-M**	**97**
3	Coolade	78
4	pure H_2O	51
5	SDS[c]	79
6	**Savie**	**99**
7	**Brij 30**	**91**
8	Brij 35	58
9	TTAB[d]	27
10	HPMC[e]	82
11	Kolliphor EL	50

[a] Reactions were carried out at 0.25 mmol scale; [b] NMR yields using 1,3,5-trimethoxybenzene as internal standard; [c] SDS = sodium dodecyl sulfate; [d] TTAB = tetradecyl trimethylammonium bromide; [e] HPMC = hydroxypropylmethyl cellulose.

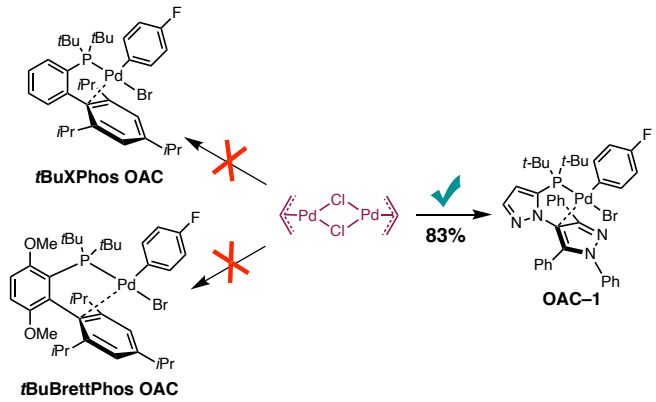
oxidative addition with *p*-fluorobromobenzene. The choice of this aromatic halide, once again, was influenced by the recent state-of-affairs suggesting avoidance of a precursor containing a Csp^3-F bond (*e.g.,* a CF_3-substituted aromatic ring). This led to selection of 4-bromofluorobenzene (bp 150 °C), ultimately affording **OAC-1** isolated in 83% yield. This method is attractive in that it is accomplished in a 1-pot operation and avoids use of a glovebox, producing a bench-, air-, and moisture-stable complex that can easily be purified on silica gel.

Scheme 3. Route to the oxidative addition complex OAC-1.



Upon screening, the amount of Pd needed to form **1** in the model reaction using **OAC-1** (see SI, section 6.2) was 0.5 mol % for complete reaction in 10 min, *versus* 2 h when run without the oxidative addition complex (*vide supra*).

Scheme 4. Attempts towards other biarylphosphine-containing OACs.



The Pd loading was then lowered to 0.25 mol %, thereby affording an almost quantitative yield of **1** in only 30 min. Attempts to make OACs from biaryl phosphines,[28] using *t*BuXPhos and *t*BuBrettPhos as representative examples and applying the identical successful protocol that led to **OAC-1**, were unsuccessful due to their instability to both air and silica gel (Scheme 4). The fast rate of reaction can presumably be attributed to **OAC–1** being a pre-catalyst[40–42] (*i.e.,* bypassing an initial oxidative addition for catalyst activation; Scheme 5). Scheme 5 has the usually postulated catalytic mechanism for arylbromides,[39] modified to show fluorosulfate salt intermediates. It also shows one possible way that the precatalyst **OAC-1** could form the **LPd⁰** catalyst by amine coordination, followed by deprotonation and reductive elimination to produce **P1**, initially. Ultimately, this could form **LPd⁰**, which then could undergo oxidative addition to the aryl fluorosulfate, thereby starting the actual the catalytic cycle leading to the desired product.

Scheme 5. Postulated Mechanism of aminations using an OAC.

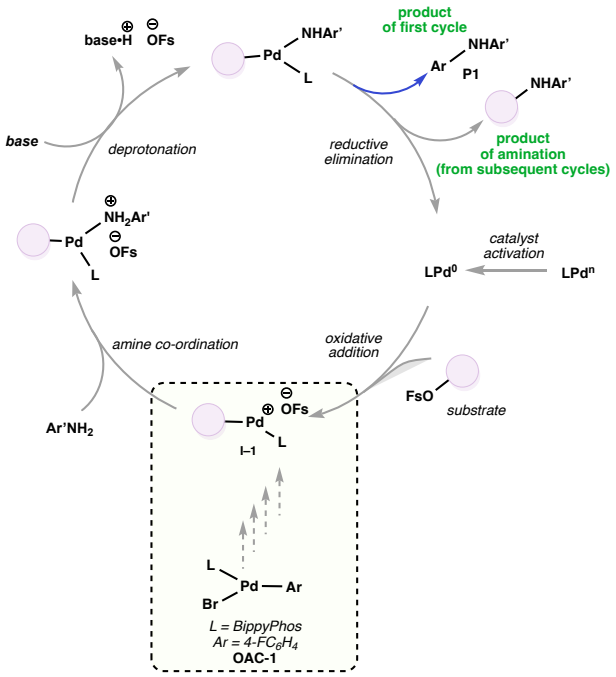
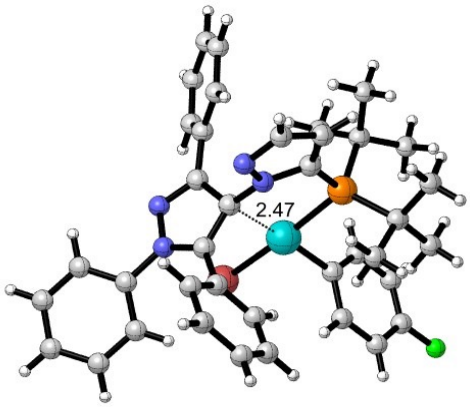
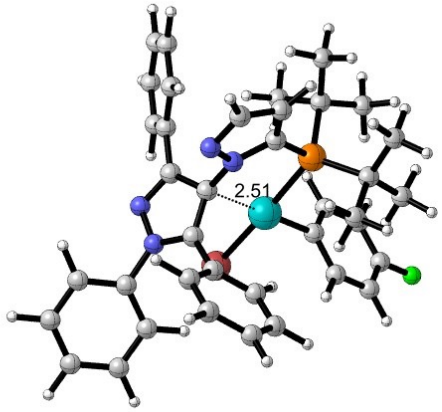


Figure 1. X–ray structures for OAC–1, conformer D.

a. OAC-1 X-ray crystal structure as conformer D.



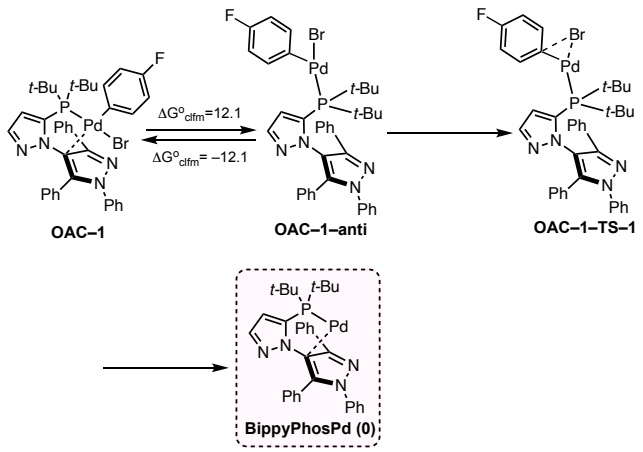
b. OAC-1 Conformer D structure calculated at the M06/6-31+G(d,p)/SDD(Pd,Br) level of theory.



To gain insight into the structure of **OAC-1**, a single crystal X-ray structure was determined (see Figure 1a). A structure for **OAC-1** was also calculated at the M06/6-31+G(d,p)/SDD(Pd,Br) level of theory, giving a geometry for a conformer, **D**, that very closely matches the X-ray crystal structure, except for a minor difference of 15° in dihedral angle for one phenyl group (Figure 1b), consistent with other comparisons we have made between X-ray crystal structures and calculated gas-phase structures.[61] Surprisingly, the ^{1}H and ^{13}C NMR spectra for chloroform solutions of **OAC-1** show evidence of three low-energy conformers with a ratio of 9.0:6.5:1.3. Relative free energies [M06/6-31+G(d,p)/SDD(Pd,Br)/SMD($CHCl_3$)] for the four lowest energy conformers **A**, **B**, **C** and **D** were 0.00, 0.13, 0.29, and 2.17 kcal/mol, respectively, with low barriers for rotation of the phenyl and *t*-butyl groups as observed in the NMR spectra (see SI–2 for details). This accounts nicely for the experimental NMR ratios but is unusual in that the highest energy conformer **D** corresponds to the observed geometry in the crystal structure. This could be the result of crystal packing forces that have a large enough effect that all three of the lowest energy conformers become less stable than conformer **D**.[61]

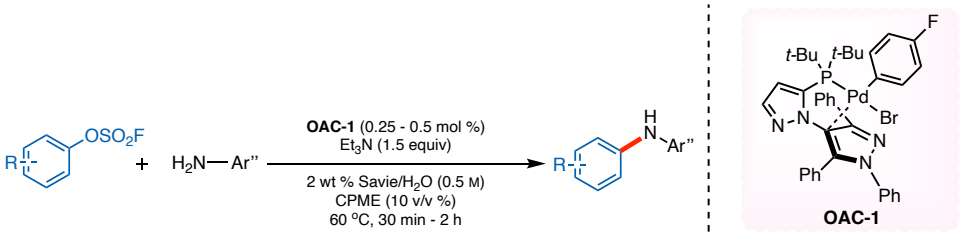
An interesting feature of the calculated structure for **OAC-1** was the bonding between Pd and a pyrazole ring in BippyPhos, which was later confirmed in the X-ray crystal structure (*vide supra*). This appears to be a sort of π-complexation to the heterocycle ring carbon and has some precedent in an X-ray structure of an aryl group bound to Pd in a G6 OAC pre-catalyst, (see Scheme 2A**)**.[39a,62] We find evidence of the energetic consequences of this π-complexation to Pd by comparing the free energy at 298K of conformer **A** of **OAC-1** with that of conformer **OAC-1-anti** in which the Pd is rotated *anti* to the heterocycle rings of the ligand, as shown in Scheme 6. Species **OAC-1-anti** is uphill by 12.1 kcal/mol in chloroform when this π-complexation is ruptured. The reductive elimination transition state **OAC-1-TS–1** would be on one of several pathways by which **OAC-1** could conceivably return to a Pd(0) catalytic intermediate for the coupling reaction.[39b]

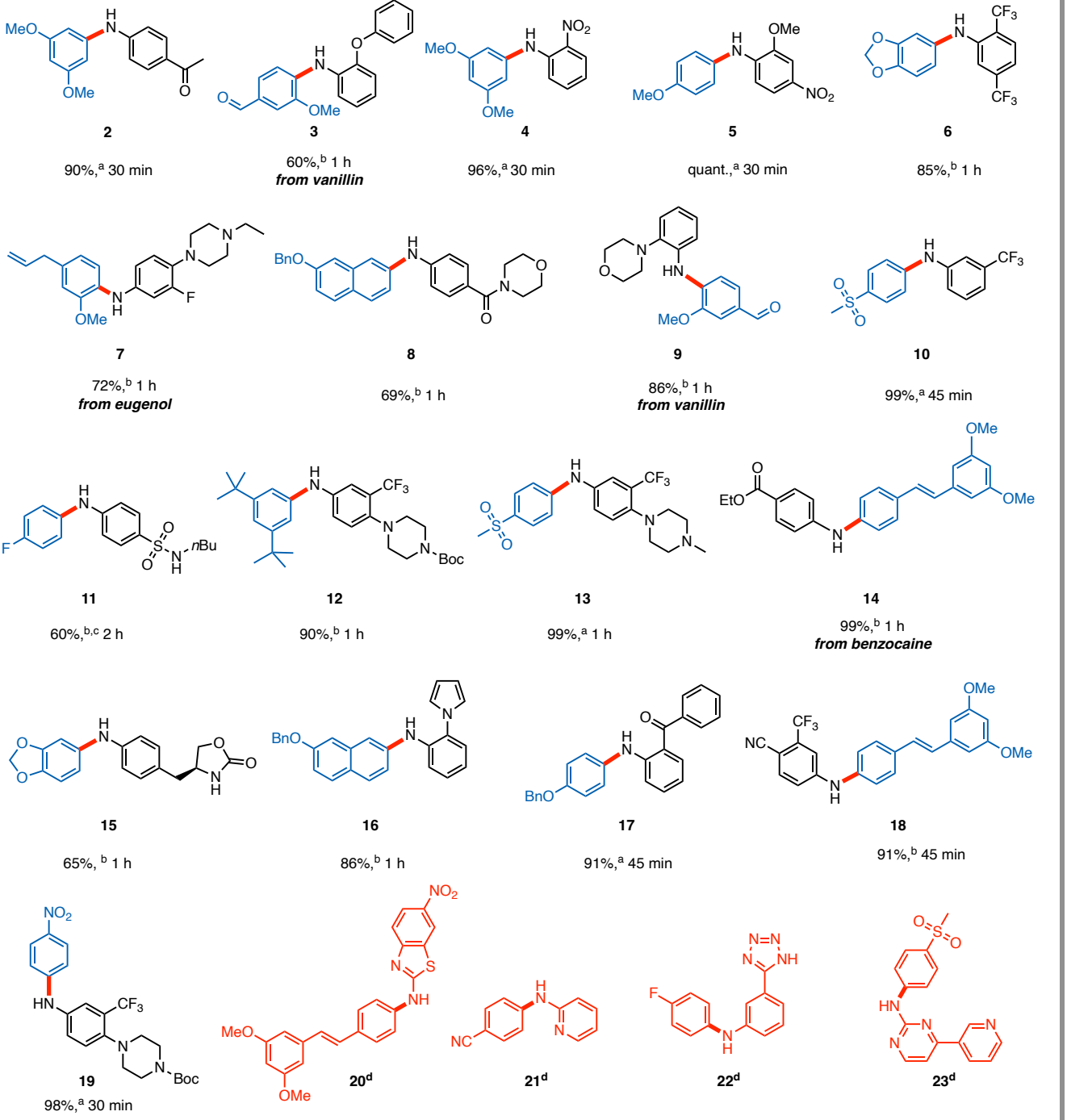
Scheme 6. Some reaction pathways associated with OAC–1. Free energies (in kcal/mol) of reaction in chloroform(clfm) at 298K are from M06/6-31+G(d,p)/SDD(Pd,Br)/SMD($CHCl_3$) calculations.



Scope of C–N cross couplings. A wide variety of couplings between aryl fluorosulfates and substituted anilines catalyzed by **OAC-1** is illustrated in Scheme 7. Catalyst loadings were 0.25–0.5 mol % while reaction temperatures of 60 °C for typically 30 min to 2 h led to moderate-to-high isolated yields of functionalized amina ted products. Reaction partners containing electron-donating or electron-withdrawing groups, or both, readily participated in the coupling independent of their placement in either the fluorosulfate or amine. Base-sensitive functionality (*e.g.,* ester, aldehyde, oxazolidinone) was well-tolerated (products **3, 9, 14, 15**). Aryl fluorosulfates or anilines containing acidic protons (*e.g.,* product **2**) demonstrated excellent selectivity towards amination, rather than competitive α–arylation or imine formation (product **3**).

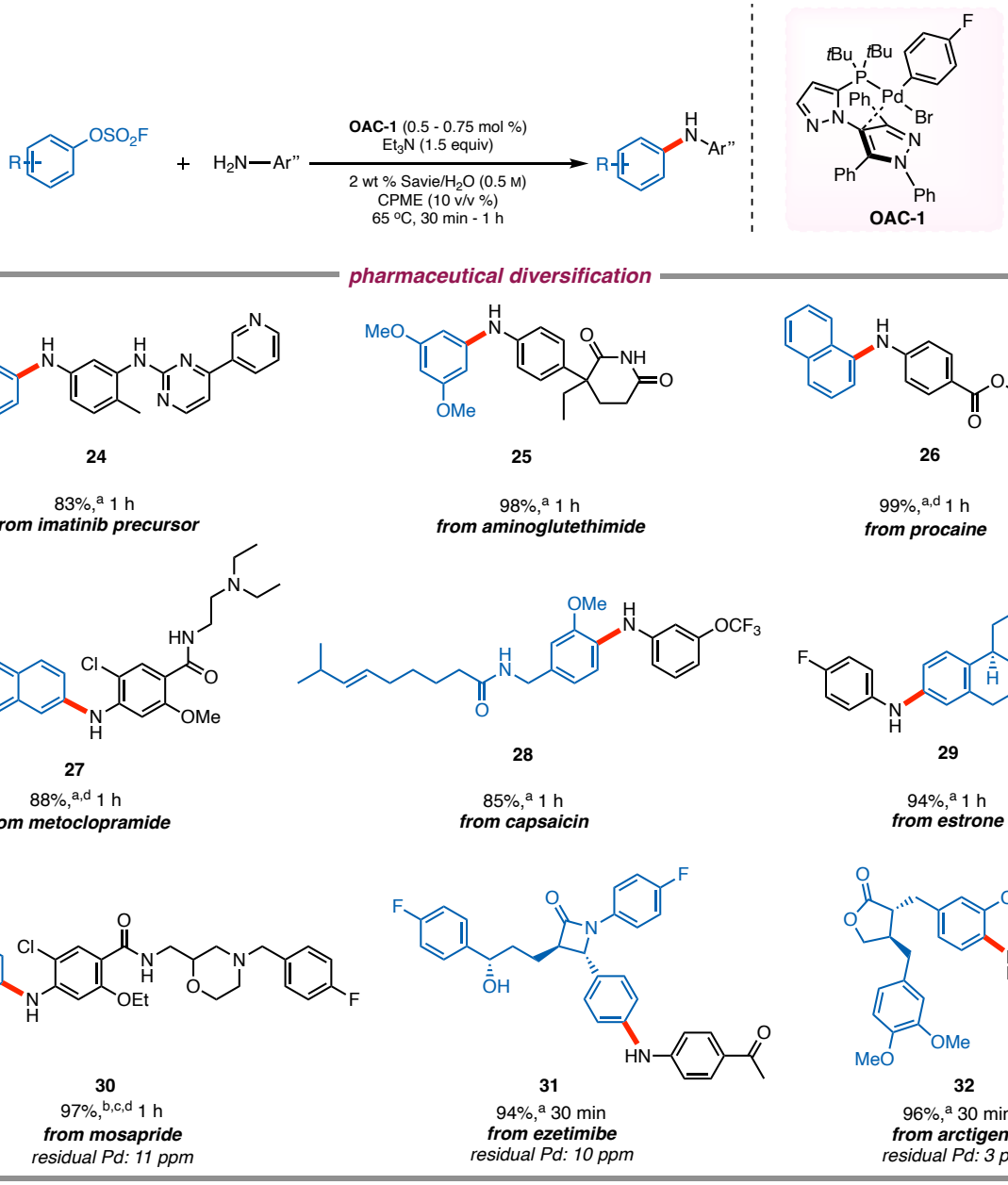
Scheme 7. Scope of aminations: representative examples.





[a] Unless otherwise mentioned: $ArOSO_2F$ (1 equiv), $Ar''NH_2$ (1.5 equiv), **OAC-1** (0.25 mol %), Et_3N (1.5 equiv), 2 wt % Savie/H_2O (0.5 M), 10 v/v % CPME, 60 °C; [b] **OAC-1** (0.5 mol %); [c] Reaction was run at 65 °C; [d] attempted couplings that were unsuccessful; Yields mentioned are of isolated compounds.

Scheme 8. Representative examples of late-stage C–N bond formation.



[a] Unless otherwise mentioned: $ArOSO_2F$ (1 equiv), $Ar''NH_2$ (1.5 equiv), **OAC-1** (0.5 mol %), Et_3N (1.5 equiv), 2 wt % Savie/H_2O (0.5 M), 10 v/v % CPME, 60 °C; [b] **OAC-1** (0.75 mol %); [c] Reaction was run at 80 °C; [d] $ArOSO_2F$ (1.5 equiv), $Ar''NH_2$ (1 equiv); Yields mentioned are of isolated compounds.

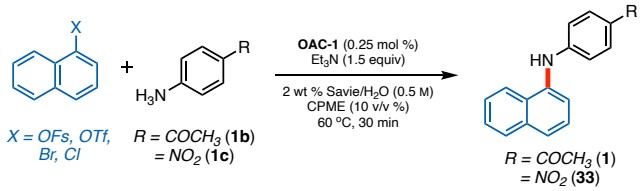
As the extent of functionality in each partner increased, the loading of catalyst increased to 0.50 mol %. This was the case with several *N*-heterocycle–containing anilines, presumably due to their known propensity to coordinate with the catalyst[63] (see products **7–9, 12, 13, 16,** and **19**). It is also worthy of note that *ortho*–substituted fluorosulfates and amines couple without incident (*e.g.,* see products **9, 16** and **17**). On the other hand, amines with low nucleophilicity at the NH_2, including 2-aminobenzothiazoles, 2-aminopyridine, 2-aminopyrimidine, and substrates containing pyrazoles or tetrazoles (that would have led to products **20–23**, respectively) were poor coupling partners.

Late–stage C–N cross couplings with complex, pharmaceutically relevant substrates. C–N Bond formation involving late–stage pharmaceutical derivatives bearing multiple functional groups can exhibit a high rate of failure.[64] Nevertheless, given the large number of nitrogen-containing biologically active compounds, both discovery and process chemists place significant value in Pd–catalyzed C–N couplings.[65] In order to extend the generality of this methodology, several pharmaceutically relevant compounds were made using **OAC-1**. Thus, with only 0.50–0.75 mol % of **OAC-1**, complex pharmaceuticals bearing multiple functional groups could be aminated to products **24**-**32** with a variety of aryl fluorosulfates (Scheme 8).

Arylation of a pyrimidine containing polycyclic aniline, a reaction partner *en route* to the anti-cancer drug imatinib (Gleevec™, affording product **24)** was realized in excellent yield. Furthermore, arylation of aminoglutethimide (Elipten™), which is used in the treatment of seizures, Cushing's syndrome, breast, and prostate cancer proceeded very smoothly to product **25** in close to quantitative isolated yield. It is noteworthy that under these mild reaction conditions, the glutarimide moiety does not fragment. Likewise, arylation of (i) Procaine (affording product **26**; Novocain™), a local anesthetic; (ii) Metoclopramide (affording product **27**; Reglan™); an anti-emetic and gut motility stimulator; and (iii) Mosapride (affording product **28**; Gasmotin™); a prokinetic 5-HT4 receptor agonist used to stimulate gastric motility, all proceeded very efficiently to afford excellent yields of the corresponding coupled products. Moreover, aryl fluorosulfates derived from pharmaceutically relevant phenols, such as: (i) Capsaicin, used in the treatment of neuralgia and rheumatoid arthritis (affording product **28**); (ii) Estrone (Estragyn™; affording product **29**), used in hormone therapy; (iii) Ezetimibe (Zetia™; affording product **31**), used in the treatment of high cholesterol, and (iv) Arctigenin, a plant lignan with antioxidant, anti-inflammatory, and antiviral properties (affording product **32**), all proceeded smoothly. Collectively, C–N couplings of this nature involving complex pharmaceuticals and materials used under environmentally responsible conditions further establishes the generality of these technologies as important tools in the growing toolbox that are based on chemistry in water. Noteworthy is the finding that levels of residual Pd in products from ICP-MS analyses are relatively quite low (see **30**-**32** in Scheme 8). This is reflective of the levels needed for these otherwise challenging aminations which, as part of any sequence, should eventually lead to products well below FDA limits.[66]

Reactivity comparisons with other electrophiles (OFs *vs.* OTf *vs.* Br *vs.* Cl). An interesting comparison was made of the rates of amination of aryl fluorosulfates with other common aryl electrophiles under these relatively mild reaction conditions. Arylation involving two different anilines (**1b** and **1c**) with a variety of aryl electrophiles originating from 1-naphthol were investigated (Table 3). Notably, the fluorosulfate was the most reactive electrophile, affording products **1** and **33**, respectively, in almost quantitative yield in just after 30 min. Amination of the aryl bromide was slightly slower, giving **1** and **33** in 78 and 68% yields, respectively. Surprisingly, the aryl triflate and aryl chloride only formed trace amounts of these products. It is known that aryl triflates have rates similar to bromides towards oxidative addition to palladium;[67, 68] however, under these reaction conditions, ligand exchange (after the first cycle; *vide supra)* may be the rate-determining step. These data suggest that the nature of the leaving group X in the resultant species $L_nPd(1\text{-naphthyl})X$ formed after oxidative addition (*vide supra)* greatly affects the rates of these aminations in water. The aryl fluorosulfate, therefore appear to offer the optimal combination of activity toward oxidative addition and the ability to promote facile nucleophilic attack by the amine substrate in the presence of a weak base like Et_3N.

Table 3. Aminations of various aryl electrophiles under mild conditions.



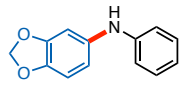
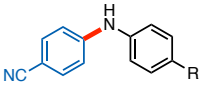
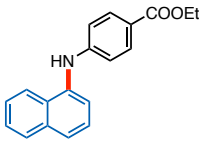
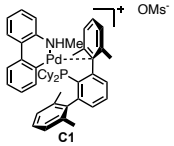
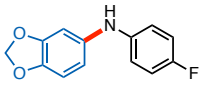
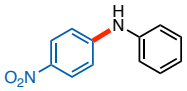
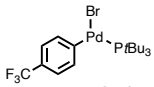
entry[a]	X	yield (%) **1**[b]	yield (%) **33**[b]
1	OFs	99 (95)[c]	99 (97)[c]
2	OTf	11	6
3	Br	78	68
4	Cl	3	—

[a] Reactions were carried out on a 0.25 mmol scale; [b] NMR yields using 1,3,5 - trimethoxybenzene as internal standard; [c] isolated yield.

Direct comparisons with recent literature. Direct comparisons with the current, state-of-the-art procedures for the aminations of phenol-derived electrophiles were also made.[42,43a,69-71] Aminations arriving at products **34–38** indicate that the catalytic system described here based on the oxidative addition complex **OAC-1**, in general, appears to be more effective than the other systems (Scheme 9). That is aminations occur at lower catalyst loadings, take place in predominantly aqueous micellar media, and lead to typically far faster couplings than the corresponding reactions in organic solvents. The same is the case even when using an alternative OAC (see entry 5). Moreover, yields tend to be comparable, if not higher, than those reported previously. The commercial availability of the Pd dimer precursor[58] and BippyPhos,[49b] along with the sheer simplicity of the synthesis of **OAC-1** suggest that this system offers many advantages that were previously unavailable.

Recycling studies. One of the most employed benchmarks for promptly evaluating a reaction's environmental viability is Sheldon's time-honored E Factor.[47] However, alternative metrics including process mass intensity (PMI),[48] notably, life cycle assessment (LCA)[72] are increasingly gaining prominence. Recycling of aqueous reaction mixtures can have a significant impact on each of these parameters. Thus, following an initial reaction between naphthalen-1-yl sulfurofluoridate (**1a**) and 4-aminoacetophenone (**1b**) (Scheme 10), the desired product **1** can be readily isolated using an in-flask extraction with minimal amounts of recyclable EtOAc (see SI, section 7). Subsequently, re–use of the aqueous phase remaining in the original reaction vessel for two additional cycles led to excellent yields of aminated product **1**. Only additional catalyst, ligand, base, and starting materials need to be added, preferably under inert atmosphere, after each coup-

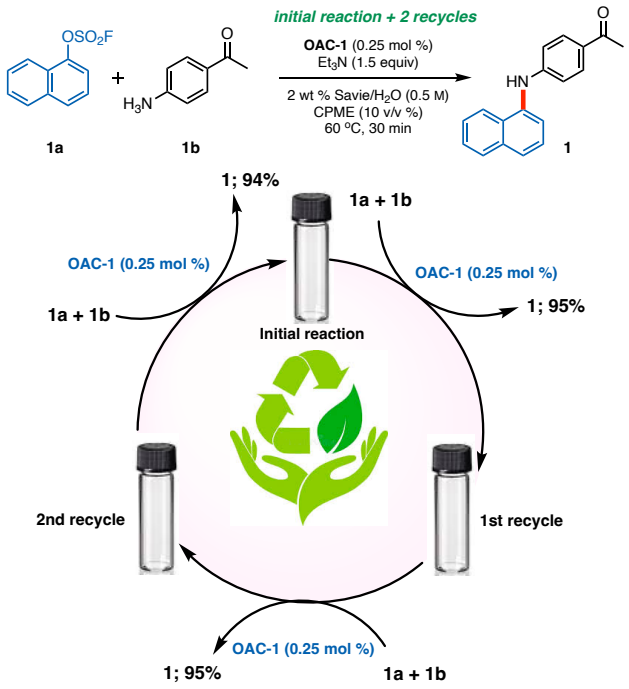
Scheme 9. Direct comparisons with recent literature.

entry	product	lit. conditions	lit. yield (%)	this work	lit. ref.
1	 **34**	from ArOFs CpPd(cinnamyl) (1 mol %) XantPhos (1.2 mol %) K_2CO_3 , **1,4-dioxane** 80°C, 18 h	**92%**	**OAC-1** (0.25 mol %) Et_3N (1.5 equiv) 2 wt % Savie/H_2O 10 v/v % CPME 60 °C, 45 min **94%**	*ACS Catal.* **2016**, *6*, 3515–3519.[43b]
2	 *R = F* (**35**), *OMe* (**36**)	from ArOFs $Pd(PPh_3)_4$ (**5 mol %**) Cs_2CO_3, toluene 4 Å MS, **110 °C**, 12 h	**70% (35)** **70% (36)**	**OAC-1** (0.25 mol %) Et_3N (1.5 equiv) 2 wt % Savie/H_2O 10 v/v % CPME 60 °C, 45 min **91% (35); 89% (36)**	*Asian J. Org. Chem.* **2017**, *6*, 1222-1225.[69]
3	 **37**	 **C1** from $ArOSO_2NMe_2$ C1 (**2.5 mol %**) NaO*t*Bu *t*BuOH : H_2O (1:1) **110 °C**, 18 h	**78%**	**OAC-1** (0.25 mol %) Et_3N (1.5 equiv) 2 wt % Savie/H_2O 10 v/v % CPME 60 °C, 45 min **85%**	*ACS Catal.* **2023**, *13*, 10945–10952.[70]
4	 **38**	from ArX + $Ph_2PO\text{-}ONH_2$ + $Ar'B(OH)_2$ *t*BuBrettPhos Pd G3 (**1 — 3 mol %**) *t*BuBrettPhos (1 mol %) KOH, MeCN 80 °C, 24 h	**62%**	**OAC-1** (0.25 mol %) Et_3N (1.5 equiv) 2 wt % Savie/H_2O 10 v/v % CPME 60 °C, 1 h **74%**	*Science* **2024**, *383*, 1019-1024.[71]
5	 **39**	 ***t*Bu$_3$P - OAC** NaO*t*Bu toluene, **100 °C**, 24 h	**84%**	**OAC-1** (0.25 mol %) Et_3N (1.5 equiv) 2 wt % Savie/H_2O 10 v/v % CPME 60 °C, 45 min **82%**	*ACS Catal.* **2023**, *13*, 8106-8118.[42]

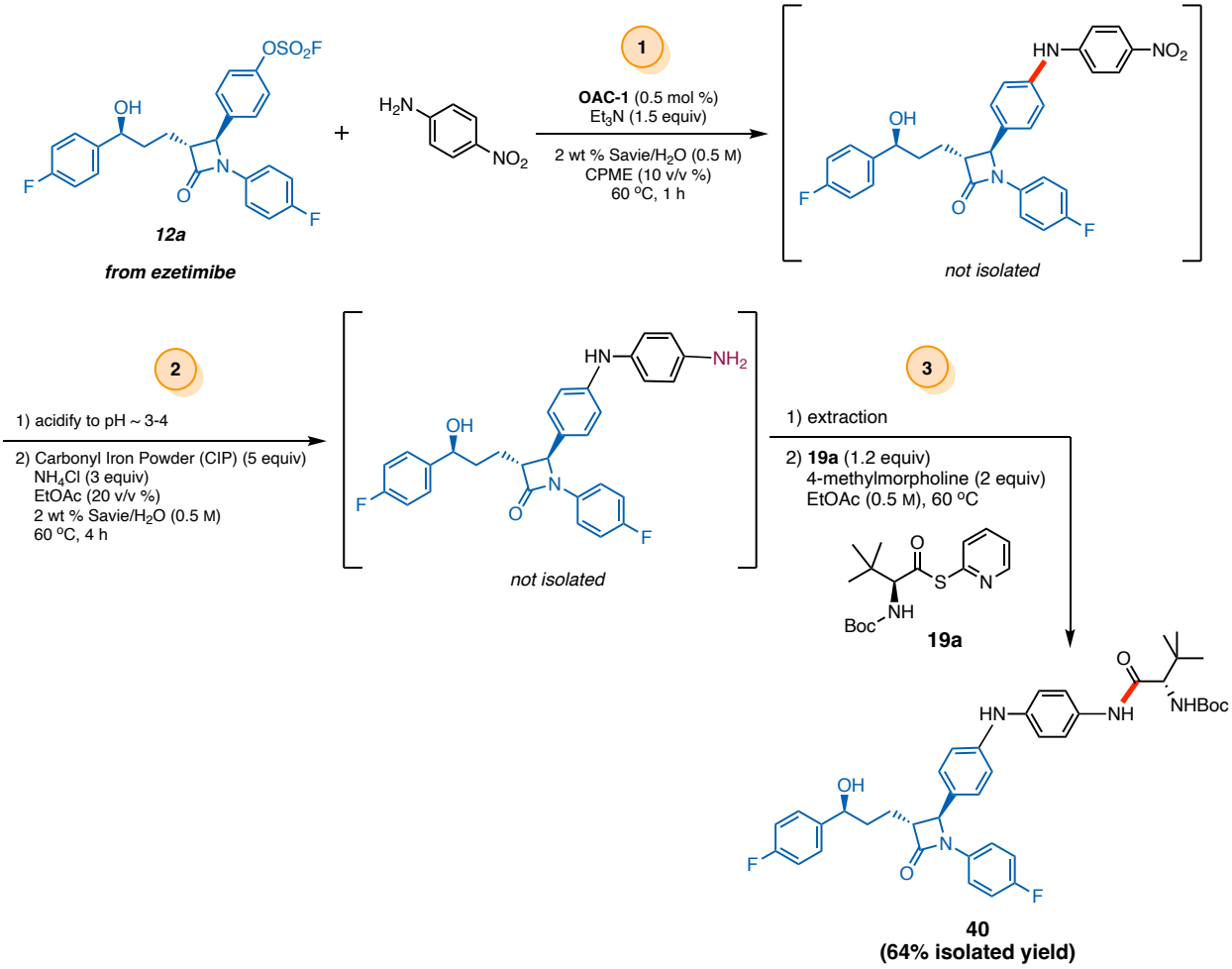
ling. Overall, these three reactions required a total investment of only 0.25 mol % Pd per amination. After the 3rd reaction (2nd recycle), salt buildup increased viscosity to the point where additional usage of the aqueous reaction mixture was precluded. E Factors associated with this recycling were 2.5 (when recyclable EtOAc is not considered waste; see SI section 7) and 17 (when EtOAc is not recycled). These values compare very favorably with typical E Factors associated with the pharmaceutical industry that vary, according to Sheldon,[47] between 25 and 100, *without inclusion of water in the calculation.*

Representative 3-step, tandem sequence. As the scope of reactions feasible under aqueous micellar conditions continues to broaden,[73] so too do the benefits of telescoping, yielding significant efficiencies in both "time"[74] and "pot"[75] economies. These advantages, alongside organic waste reduction, have become focal points in recent scholarly reports and analyses highlighting the imperative of optimizing reaction methodologies for both sustainability and productivity. In Scheme 11, a 3-step tandem sequence is illustrated that employs some of the more commonly used reactions in the pharmaceutical industry.[76] Hence, an initial Pd–catalyzed amination between 4-nitroaniline and a highly functionalized aryl fluorosulfate

Scheme 10. Recycling studies



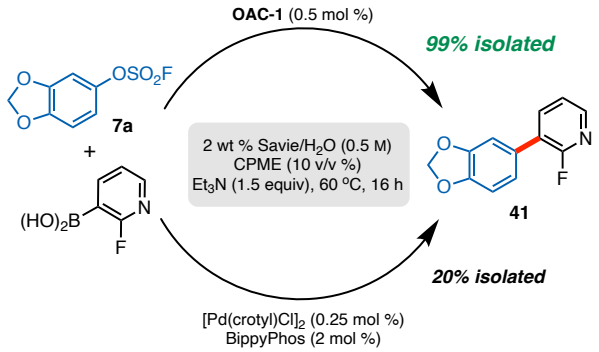
Scheme 11. A representative 3-step tandem sequence showing pharmaceutically relevant reactions.



derived from ezetimibe (**12a**) was carried out to afford the corresponding secondary amine. The resulting crude mixture was acidified using conc. HCl to pH 3-4, after which the mixture was subjected to nitro group reduction using carbonyl iron powder (CIP)[77] in the same pot. The resulting aniline, used crude after filtration away from the CIP, was subjected to amide bond formation upon treatment with the thioester[78] of *N*–Boc *t*-leucine (used previously *en route* to nirmatrelvir),[79] to afford product **40** in 64% isolated yield over 3 steps.

Finally, the applicability of **OAC-1** to C-C bond-forming reactions was initially tested using fluorosulfate **7a** and a pyridyl-3-boronic acid shown in Scheme 12. The resulting biaryl product **41** was isolated in close to quantitative yield, while the coupling using BippyPhos, but not in its OAC form, led to only a 20% yield under the same conditions of reaction concentration, temperature, and time. These results suggest that **OAC-1** may provide, with fine-tuning, similar enhancements in other types of highly valued cross couplings.

Scheme 12. Representative rates of Suzuki-Miyaura couplings with and without OAC-1.



CONCLUSIONS

In summary, a novel Pd-containing oxidative addition complex (**OAC-1**) has been developed and applied to aminations of aryl fluorosulfates in water using aqueous micellar media derived from a biodegradable surfactant, Savie. DFT calculations on **OAC-1** match the X-ray structure, with π-complexation of the Pd to one of the heterocycle rings in the ligand. The calculations also show that three conformations of the phenyl and *t*-butyl ligand substituents are

more stable than the conformation of the X-ray structure in the solid state, consistent with the NMR spectra.

This homogeneous catalysis technology relies on low loadings of precious metal, and offers several advances in sustainability, including:

- the first use of an oxidative addition complex for Pd-catalyzed aminations in an aqueous medium;
- reliance on commercially available catalyst precursors;
- use of a recyclable aqueous medium;
- aminations of structurally diverse, non-PFAS aryl fluorosulfates as pseudohalides and amines, which can also be highly functionalized, complex pharmaceuticals and related species;
- The option of applying this technology to multi-step sequences, all performed in an aqueous surfactant medium.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, optimization details, and analytical data of isolated materials (NMR, HRMS); and quantum computational details.

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Author Contributions

All authors have given approval to the final version of the manuscript. K. S. I. conceived the project, drafted the manuscript, and mentored K. B. D. R., R. M. L. and J. R. Y. K. B. D. R. performed optimization and helped in preparation of starting materials. R. M. L. helped in optimization and assisted in the synthesis of **OAC–1**. J. R. Y. assisted in experimental work and preparation of starting materials. J. M. S. was involved in the initial brainstorming. R. D. K. assisted in preparation of starting materials. D H. A. did all the quantum calculations and participated in drafting the final manuscript. B. H. L. oversaw the work and aided in drafting the final manuscript. ‡K. D. R. and R. M. L. contributed equally.

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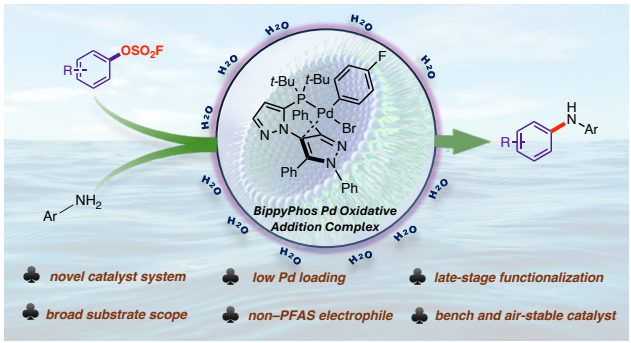

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