Sonogashira Cross-Coupling of Aryl Ammonium Salts by Selective C–N Activation Catalyzed by Air- and Moisture-Stable, Highly Active [Pd(NHC)(3-CF$_3$-An)Cl$_2$] (An = Aniline) Precatalysts

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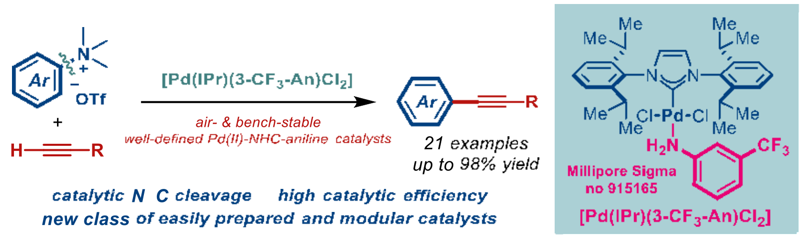
Supporting Information



ABSTRACT: We report the Sonogashira cross-coupling of aryl ammonium salts catalyzed by air- and moisture-stable [Pd(NHC)(3-CF$_3$-An)Cl$_2$] (An = aniline). This highly active Pd(II)–NHC complex features broad scope and excellent C–N activation selectivity in the challenging alkynylative cross-coupling of aryl ammonium salts. Full structural characterization and computational studies demonstrate the effect of pyridine to aniline replacement as highly effective stabilizing ancillary ligand in well-defined Pd(II)–NHCs. Considering the high reactivity and the recent commercialization of [Pd(NHC)(3-CF$_3$-An)Cl$_2$] (Millipore Sigma, no 915165), this catalyst represents an attractive approach to the activation of C–N bonds of broad synthetic interest.

Activation of N–C bonds has recently emerged as an attractive approach in transition metal catalysis.[1] In this context, over the years, a plethora of electrophilic coupling partners have been developed, predominantly focused on halides and phenolic electrophiles,[2,3] while more recent studies have begun to address the cross-coupling of aryl sulfur and aryl phosphorous bonds.[4,5] With respect to aromatic carbon–nitrogen bonds, this mode of oxidative addition is severely underdeveloped despite the prominent role of aromatic carbon–nitrogen bonds in organic synthesis and drug discovery.[6] Out of several classes of C–N electrophiles, including the recent surge of interest in amide bond C–N activation,[7] the use of trialkyl ammonium salts as readily available, safe and benign C–N electrophiles is highly desirable.[8,9] Following the pioneering studies by Wenkert and MacMillan on Ni-catalyzed Kumada and Suzuki cross-coupling of aryltrimethyl ammonium salts[10], recent advances have been made by using specifically designed ligands and substrate classes for activation of C–N bonds in aryl ammonium salts.[9,11]

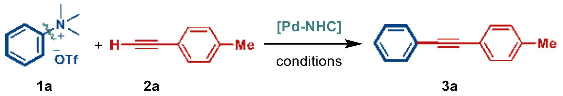
The use of well-defined Pd(II)–NHC complexes has led to major developments in advancing cross-coupling reactions in academia and industry owing to high nucleophilicity of strongly σ-donating NHC ligands, superb bench-stability and facile activation to mono-ligated Pd(0)–NHCs.[12,13] These collective features of Pd–NHCs enable facile oxidative addition of less reactive bonds, while the mild activation allows for user-friendly handling and operational-simplicity in using Pd(II)–NHC complexes.[14,15] The key aspect of developing new Pd(II)–NHCs is the stabilizing ancillary ligand, with several classes reported to date, such as [Pd(NHC)(allyl)Cl] complexes,[16]

chloro dimers [Pd(NHC)($\propto$-Cl)Cl]$_2$,[17] heterocyclic Pd-PEPPSI systems[18] or palladacycle-supported SingaCycle catalysts.[19] Recently, we have introduced [(NHC)PdCl$_2$(An)] complexes, which take advantage of anilines as an unexplored class of ancillary ligands for Pd–NHCs.[20] These catalysts are based on the mechanistic hypothesis that activation of aniline-ligated Pd(II)–NHCs is facile compared with related heterocyclic Pd–PEPPSI complexes.[14,15]

The [(NHC)PdCl$_2$(aniline)] complexes have been commercialized in collaboration with Millipore Sigma to enable broad access for researchers for reaction screening and optimization (no 916161; no 915165). In our initial study we reported the reactivity of the parent [Pd(IPr)(An)Cl$_2$] (An = Aniline) complex.[20] Now, we report that a meta-substituted analogue, [Pd(NHC)(3-CF$_3$-An)Cl$_2$] (An = aniline), is a highly active Pd(II)–NHC complex for the Sonogashira cross-coupling of aryl ammonium salts by selective C–N bond activation. This catalyst offers substantial improvement over other Pd(II)–NHC complexes in the challenging alkynylative cross-coupling of aryl ammonium salts.[9a] Considering the high reactivity and commercial availability of [Pd(NHC)(3-CF$_3$-An)Cl$_2$] (An = aniline), the complex represents an attractive approach to the activation of C–N bonds of broad synthetic interest.

Based on our previous work on C–N activation,[14,15] our study commenced with evaluating the reaction conditions for the cross-coupling of phenyltrimethylammonium (**1a**) with 4-methylphenylacetylene (**2a**) according to Cao (Table 1).[9a] Under optimized conditions (entry 1), the cross-coupling proceeded in excellent 92% yield ([Pd(NHC)(3-CF$_3$-An)Cl$_2$], 10 mol%; *t*-BuONa, 2 equiv; THF, 45 °C). As expected, the choice of base was critical to the reaction efficiency, with *t*-BuONa providing the optimal results (entries 1-6). Interestingly, the addition of water proved detrimental (entry 7). The reaction temperature was also a key variable, with the efficient conversion observed at 45 °C, while lower or elevated temperatures resulted in diminished yields due to incomplete conversions or alkyne dimerization (entries 8-9). Finally, out of various solvents screened, THF was identified as the most suitable solvent (entries 10-17). Reactions without additional base indicated that base is required in this coupling (entries 18-20).

Table 1. Optimization of the Reaction Conditions[a,b]

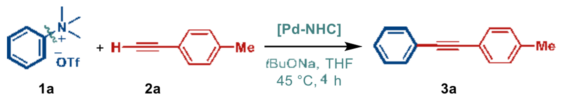


entry	base	solvent	*T* (°C)	yield (%)
1	*t*-BuONa	THF	45	92
2	NaOH	THF	45	<5
3	K$_2$CO$_3$	THF	45	<5
4	K$_3$PO$_4$	THF	45	7
5	LiHMDS	THF	45	6
6	*t*-BuOK	THF	45	15
7[c]	*t*-BuONa	THF	45	7
8	*t*-BuONa	THF	30	32
9	*t*-BuONa	THF	60	58
10	*t*-BuONa	2-MeTHF	45	50
11	*t*-BuONa	CPME	45	25
12	*t*-BuONa	*i*-PrOAc	45	43
13	*t*-BuONa	*p*-cymene	45	19
14	*t*-BuONa	DEC	45	5
15	*t*-BuONa	MTBE	45	28
16	*t*-BuONa	EA	45	32
17	*t*-BuONa	anisole	45	16
18[d]	*t*-BuONa	THF	45	25
19[e]	*t*-BuONa	THF	45	<2
20	-	THF	45	<2

[a]Conditions: **1** (1.0 equiv), **2** (1.0 equiv), [Pd(IPr)(3-CF$_3$-An)Cl$_2$] (10 mol%), *t*-BuONa (2.0 equiv), THF (0.20 M), 45 °C, 4 h. [b]GC/^{1}H NMR yields. [c]H$_2$O (3.0 equiv). [d]*t*-BuONa (1.0 equiv). [e]*t*-BuONa (0.2 equiv).

Next, we screened Pd(II)-NHC precatalysts with various ancillary ligands (Table 2). Our catalyst selection involved variation of the ancillary ligand in the imidazolyl-2-ylidene IPr and saturated imidazolinyl-2-ylidene SIPr series. As shown in Table 2, [Pd(IPr)(3-CF$_3$-An)Cl$_2$] showed the highest efficiency (entry 1). Furthermore, the aniline supported [Pd(IPr)(An)Cl$_2$] was less effective, consistent with the ease of activation of the [Pd(IPr)(3-CF$_3$-An)Cl$_2$] catalyst to monoligated Pd(0) (entry 2). Furthermore, catalysts based on the SIPr scaffold, [Pd(SIPr)(3-CF$_3$-An)Cl$_2$] and [Pd(SIPr)(An)Cl$_2$], were generally less effective (entries 3-4). Moreover, the heterocyclic PEPPSI-based catalysts, [Pd(IPr)(3-Cl-Py)Cl$_2$] and [Pd(SIPr)(3-Cl-Py)Cl$_2$], were less effective (entries 5-6). Finally, the established allyl-supported and chloro-dimer complexes, [Pd(IPr)(cin)Cl] and [Pd(IPr)(∝-Cl)Cl]$_2$,[16,17] showed significantly lower efficiency in the cross-coupling (entries 7-8).

Table 2. Screening of Pd–NHC Precatalysts[a,b]



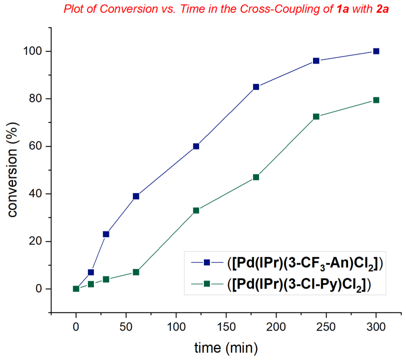
entry	catalyst	yield (%)
1	[Pd(IPr)(3-CF$_3$-An)Cl$_2$]	92
2	[Pd(IPr)(An)Cl$_2$]	64
3	[Pd(SIPr)(3-CF$_3$-An)Cl$_2$]	62
4	[Pd(SIPr)(An)Cl$_2$]	72
5	[Pd(IPr)(3-ClPy)Cl$_2$]	77
6	[Pd(SIPr)(3-ClPy)Cl$_2$]	68
7	[Pd(IPr)(cin)Cl]	27
8	[Pd(IPr)(μ-Cl)Cl]$_2$	29

[a]Conditions: **1** (1.0 equiv), **2** (1.0 equiv), [Pd] (10 mol%), *t*-BuONa (2.0 equiv), THF (0.20 M), 45 °C, 4 h. [b]GC/^{1}H NMR yields.

Kinetic studies were conducted to examine the effect of aniline-based [Pd(IPr)(3-CF$_3$-An)Cl$_2$] vs. [Pd(IPr)(3-Cl-py)Cl$_2$] on the cross-coupling (Scheme 1). As shown, the use of [Pd(IPr)(3-CF$_3$-An)Cl$_2$] results in faster activation, which enables for a faster conversion under the reaction conditions. Overall, [Pd(NHC)(3-CF$_3$-An)Cl$_2$] is a highly active Pd(II)–NHC complex, where the 3-CF$_3$-An ancillary ligand enables high air- and bench-stability, while permitting fast activation under the reaction conditions.

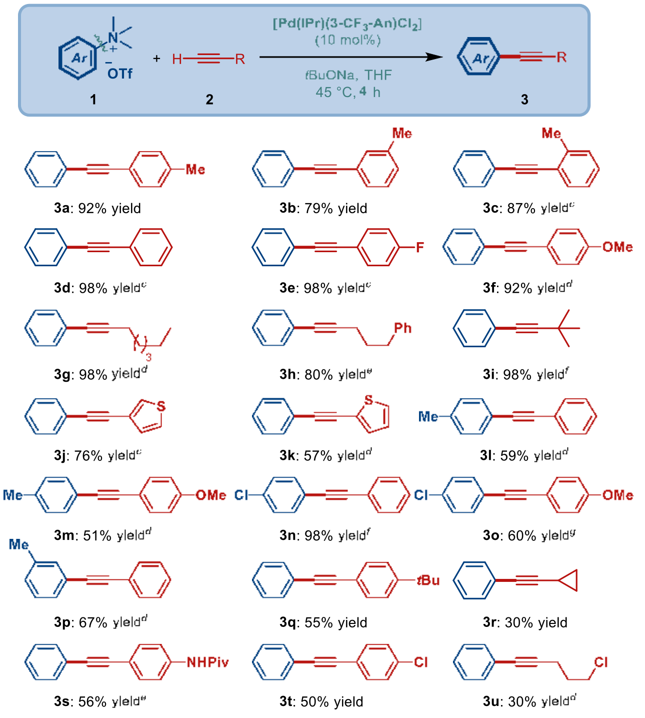
Having identified optimal conditions for the Sonogashira cross-coupling using [Pd(IPr)(3-CF$_3$-An)Cl$_2$], we next sought to define the scope of this N–C activation (Scheme 2). For comparison, the scope was examined using a similar set of substrates cf. Cao.[9a] As shown, a series of differently substituted alkynes and ammonium

Scheme 1. Kinetic Profile in the Sonogashira Cross-Coupling of Aryl Trimethylammonium Salts[a]



[a] Conditions: $PhNMe_3OTf$ (**1a**) (1.0 equiv), 4-methylphenylacetylene (**2a**) (1.0 equiv), [Pd] (10 mol%), *t*-BuONa (2.0 equiv), THF (0.20 M), 45 °C, 0-300 min. [Pd] = [Pd(IPr)(3-CF_3-An)Cl_2], [Pd(IPr)(3-Cl-Py)Cl_2].

Scheme 2. Scope of the Sonogashira Cross-Coupling of Aryl Trimethylammonium Salts Catalyzed by [Pd(IPr)(3-CF_3-An)Cl_2][a,b]

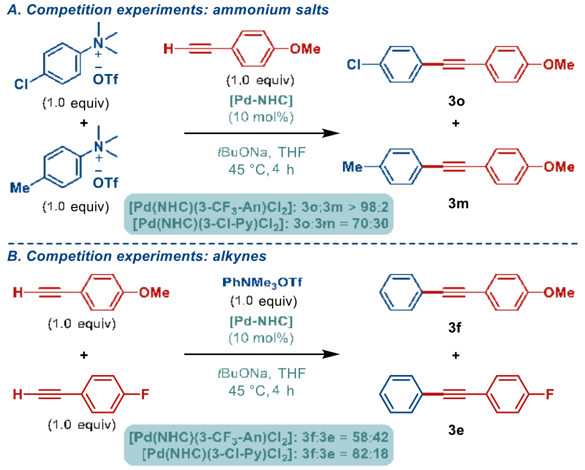


[a] Conditions: **1** (1.0 equiv), **2** (1.0 equiv), [Pd(IPr)(3-CF_3-An)Cl_2] (10 mol%), *t*-BuONa (2.0 equiv), THF (0.20 M), 45 °C, 4 h. [b] Isolated yields. [c] **2** (2.0 equiv). [d] **2** (2.0 equiv), 80 °C, 15 h. [e] **2** (2.0 equiv), *t*-BuONa (5.0 equiv), 15 h. [f] **2** (2.0 equiv), 80 °C. [g] **2** (2.0 equiv), 15 h

salts readily underwent cross-coupling using [Pd(IPr)(3-CF_3-An)Cl_2]. Electron-neutral tolyl-acetylenes with systematic variation of the substitution at the para- (**3a**), meta- (**3b**) and ortho- (**3c**) positions gave high yields of the cross-coupled products. Furthermore, electronically-neutral phenylacetylene (**3d**) as well as both electron-deficient (**3e**) and electron-rich (**3f**) arylacetylenes served as viable cross-coupling partners. Moreover, aliphatic alkynes are also productive cross-coupling partners, including simple aliphatic (**3g**), phenyl substituted (**3h**) and *tert*-butyl-acetylene (**3i**). Likewise, heterocyclic alkynes are well-accommodated, as represented by 3-thienyl (**3j**) and 2-theinyl (**3k**) substitution, affording the products in good yields. Furthermore, the present protocol allows to use electronically-unactivated arylacetylenes, such as **3l**. This protocol is also advantageous in providing good reaction efficiency with electron-rich phenylacetylenes (**3m**). Pleasingly, halide substitution on the aryl ammonium component were also tolerated (**3n-3o**), providing handles for further functionalization. Several additional substrates were tested, including meta-tolylammonium (**3p**), branched *tert*-butyl substitution on the arylalkyne component (**3q**) and the challenging cyclopropyl acetylene that is prone to ring opening/isomerization (**3r**). A final survey established that functionalized acetylenes with amide (**3s**), aryl halide (**3t**) and alkyl halide (**3u**) functional groups that have propensity to undergo side-reactions serve as suitable coupling partners. Preliminary studies with 4-iodo- and 4-bromophenylammonium salts indicated that these substrates are not compatible with the coupling. Overall, it is noteworthy that the 3-CF_3-An catalyst outperforms other catalyst systems as the preferred Pd-catalyst for this cross-coupling.[9] A feature of this protocol is high reaction efficiency using electronically-unbiased substrates in the challenging C–N bond activation of aryl ammonium salts.

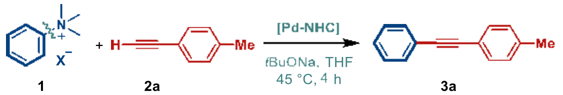
Studies were conducted to gain insight into the reaction mechanism using [Pd(IPr)(3-CF_3-An)Cl_2] (Scheme 3). (1) Intermolecular competitions with differently substituted aryl ammonium salts showed that electron-deficient arenes are significantly more reactive (4-Cl:4-Me >98:2); (2) Further competitions with differently substituted phenylacetylenes showed that electron-donating alkynes are more reactive (4-MeO:4-F = 58:42). These results are consistent with oxidative addition as the kinetically important step in the cross-coupling. The same experiments were conducted using [Pd(IPr)(3-Cl-Py)Cl_2], and revealed (4-Cl:4-Me = 70:30) and (4-MeO:4-F = 82:18), consistent with the fast activation of [Pd(IPr)(3-CF_3-An)Cl_2].

Scheme 3. Mechanistic Studies



Moreover, the counterion effect of the aryl ammonium salt was examined (Table 3). We found that triflate is the preferred counterion, while I, BF_4, OMs and OTs gave lower yields. This trend is similar to other cross-couplings of aryl ammoniums and benefit from the facile methylation of dialkyl anilines with MeOTf.[9a]

Table 3. Effect of the Counterion of Ammonium Salts[a,b]

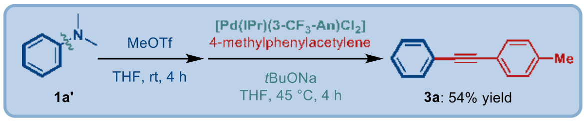


entry	X	yield (%)
1	OTf	92
2[c]	I	30
3[d]	BF$_4$	54
4[e]	OMs	34
5[d]	OTs	50

[a]Conditions: **1** (1.0 equiv), **2** (1.0 equiv), [Pd(IPr)(3-CF$_3$-An)Cl$_2$] (10 mol%), *t*-BuONa (2.0 equiv), THF (0.20 M), 45 °C, 4 h. [b]GC/^{1}H NMR yields. [c]**2** (2.0 equiv), 80 °C, 15 h. [d]**2** (2.0 equiv), 80 °C. [e]**2** (2.0 equiv).

Furthermore, one-pot telescoped N–C activation of dialkyl anilines by in situ quaternization and cross-coupling is feasible, showing compatibility of [Pd(IPr)(3-CF$_3$-An)Cl$_2$] with this tandem process (Scheme 4).

Scheme 4. One-Pot Alkylation/C–N Cross-Coupling



To gain insight into the structure of this new [Pd(IPr)(3-CF$_3$-An)Cl$_2$] catalyst, crystal suitable for X-ray diffraction was obtained by slow diffusion of hexane into a saturated dichloromethane solution of the complex (Figure 1A). The Pd–C$_{(carbene)}$ and Pd–N bond lengths of 1.969 Å and 2.123 Å can be compared with the analogous bond lengths of 1.973 Å and 2.110 Å for the [Pd(IPr)(An)Cl$_2$] catalyst. Furthermore, HOMO and LUMO as well as NBO distribution of [Pd(IPr)(3-CF$_3$-An)Cl$_2$] were determined (Figure 1B). HOMO (-6.23 eV) and LUMO (-1.95 eV) of [Pd(IPr)(3-CF$_3$-An)Cl$_2$] can be compared with [Pd(IPr)(An)Cl$_2$] (-6.08 eV, -1.76 eV) and [Pd(IPr)(3-Cl-py)Cl$_2$] (-6.07 eV, -1.75 eV). The Wiberg bond orders for the Pd–C$_{(carbene)}$ and Pd–N bonds in [Pd(IPr)(3-CF$_3$-An)Cl$_2$] are 0.6838 and 0.3031 (Pd–Cl$_1$, 0.6341: Pd–Cl$_2$, 0.6312); cf. [Pd(IPr)(An)Cl$_2$] of 0.6776 and 0.3142 and [Pd(IPr)(3-Cl-py)Cl$_2$] of 0.6871 and 0.3267. Overall, the data show a strong Pd–C$_{(carbene)}$ and less coordinating Pd–N bond in [Pd(IPr)(3-CF$_3$-An)Cl$_2$], with the net effect of stabilizing the metal center and facilitating activation to Pd(0).

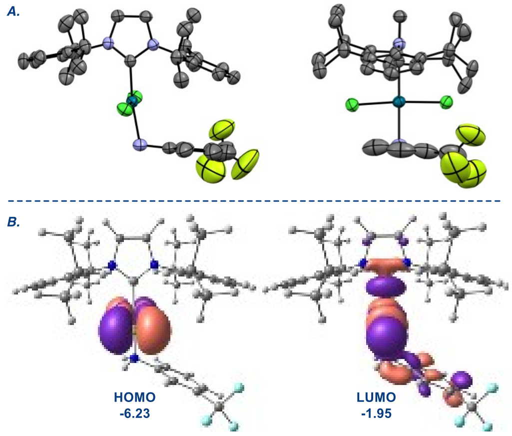


Figure 1. (A) X-ray crystal structure of [Pd(IPr)(3-CF3-An)Cl$_2$]. Two views: front (left); side (right). Hydrogen atoms have been omitted for clarity. Crystallographic data have been deposited with the CCDC (2191722). (B) HOMO and LUMO and energies (eV) of [Pd(IPr)(3-CF3-An)Cl$_2$] calculated at B3LYP 6-311++g(d,p). See SI for details.

In conclusion, we have reported the Sonogashira cross-coupling of aryl ammonium salts catalyzed by air- and moisture-stable [Pd(NHC)(3-CF$_3$-An)Cl$_2$] (An = aniline). This catalyst shows high activity and broad scope in the alkynylative cross-coupling by challenging C–N bond activation. The favorable features of [Pd(NHC)(3-CF$_3$-An)Cl$_2$] combined with its commercial availability (Millipore Sigma, no 915165) offer an attractive approach to activation of C–N bonds.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare the following competing financial interest(s): Rutgers University has filed patent(s) on precatalysts described in this manuscript (US 62/958,583, Jan 8, 2020).

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