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Communication

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Ru(II)-Catalyzed Amination of Aryl Fluorides *via* η^6-Coordination

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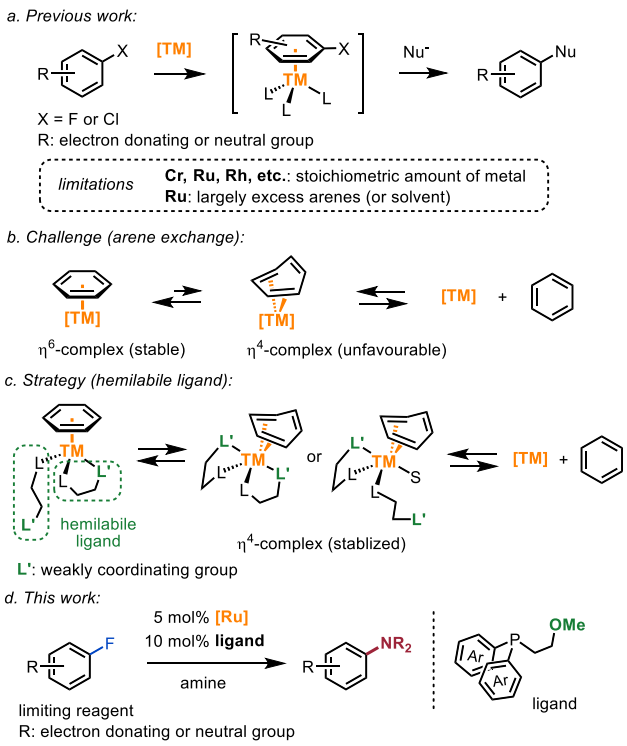
Supporting Information Placeholder

ABSTRACT: We developed a Ru/hemilabile-ligand catalyzed nucleophilic aromatic substitution (S_NAr) of aryl fluorides as the limiting reagents. Significant ligand enhancement was demonstrated by the engagement of both electron-rich and neutral arenes in the S_NAr amination without using excess arenes. Preliminary mechanistic studies revealed that the nucleophilic substitution proceeds on a η^6-complex of the Ru-catalyst and the substrate, and the hemilabile ligand facilitates dissociation of products from the metal center.

Nucleophilic aromatic substitution reactions of aryl halides with external nucleophiles are among the most reliable transformations for arene functionalization. In 2016, Brown analyzed reactions used in medicinal chemistry research, and revealed that S_NAr is the most frequently transformation after amide bond formation.[1] Although various applications have been demonstrated, the classical stepwise S_NAr reaction, in general, is limited to the highly electron-deficient arenes.[2] In comparison, concerted protocols in part overcome the above disadvantage by employing a stoichiometric amount of activating reagents and/or strong bases.[3] In addition, the stepwise S_NAr promoted by transition-metals (*umpolung* aromatic substitution) is compatible with an array of unreactive aryl halides by using the corresponding η^6-arene-complexes as substrates (Scheme 1a).[4] In contrast to numerous stoichiometric reactions reported to date, only a few catalytic examples that require large excess of aryl halides have been addressed.[5] TM-catalyzed S_NAr reaction of electron-rich or neutral aryl fluorides as limiting reagents remains to be demonstrated.

In general, *umpolung* aromatic substitution involves arene association, nucleophilic aromatic substitution of the resulting η^6-complex, and product dissociation.[4] In a catalytic process, substrate association and product dissociation merge as arene exchange, which markedly affects the catalytic efficiency.[5] A typical obstacle in arene exchange is the detachment of one double bond from a relatively stable η^6-complex, which generates the corresponding η^4-intermediate (Scheme 1b).[6] Following an observation that donor molecules such as THF and cyclohexanone benefit arene exchange, chemists introduced a coordinating group as a side chain on the ligands to accelerate the exchange rate.[5g,7] However, examples for the ligand promoted S_NAr by the strategy outlined above are absent. To overcome the obstacle, we envisioned to utilize hemilabile, bidentate ligands, which could benefit catalytic S_NAr reactions in two ways (Scheme 1c): 1) a side chain group L' that coordinates to TM temporarily may promote product dissociation through steric repulsion; 2) the ligand's hemilabile nature may provide flexibility to stabilize reaction intermediates, as well as reduce steric effect in the coordination of substrates to the catalyst. Herein, we present a bisphosphine-Ru catalyzed S_NAr amination that converts the inert aryl C–F bond without the remnant of excessive arenes (Scheme 1d).[8]

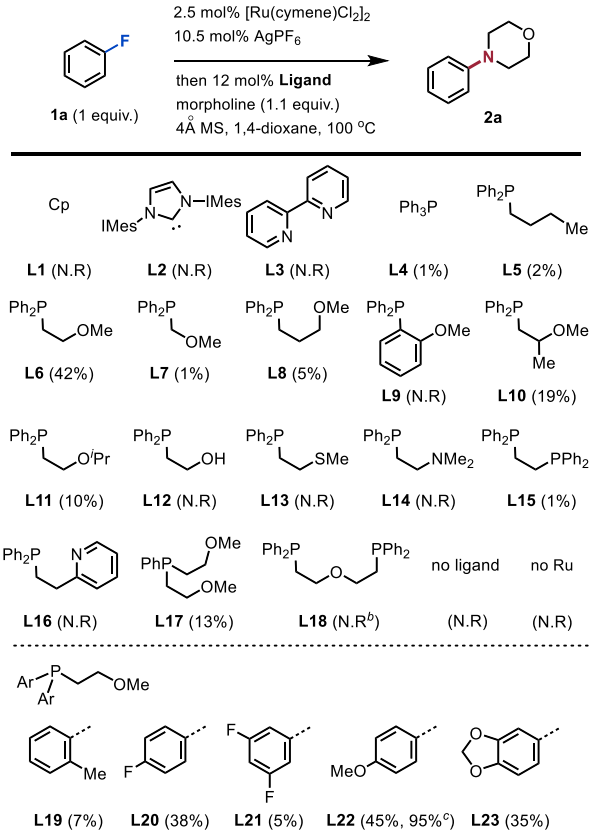
Scheme 1. S_NAr reaction *via* η^6-coordination



To execute this strategy, we selected fluorobenzene **1a** as a limiting reagent to explore the feasibility of S_NAr amintion (Table 1). Dichloro(cymene)ruthenium dimer was used as a precursor of the real catalyst, cationic Ru(II)-ligand complex, which was formed through a Ag-promoted dechlorination and subsequent ligand coordination. We firstly investigated the reaction conditions with several representative ligands such as cyclopentadienyl anion (Cp, **L1**), *N*-heterocyclic carbene (NHC, **L2**), and bipyridine (**L3**). However, none of them gave any observable amination product **2a**. We then

turned to test phosphine ligands, and detected a trace amount of **2a** by utilizing monodentate triphenylphosphine (**L4**) or diphenylbutylphosphine (**L5**). Notably, following our design, when a hemilabile phosphine ligand (**L6**) bearing a methoxyl side chain was used, a dramatic improvement of the yield (42%) was obtained. Changing either the flexibility of the side chain (**L7**, **L8**, **L9**) or the steric environment around the chelating atom oxygen (**L10**, **L11**, **L12**) reduced the yield or even inhibited the reaction. An array of stronger donating groups, thioether (**L13**), amine (**L14**), phosphine (**L15**), and pyridine (**L16**), were examined and proved ineffective, demonstrating the importance of matching the two chelating groups on the hemilabile ligand. Tridentate ligand **L17** bearing two methoxyl groups reduced the yield of **2a** to 13%, while **L18** did not afford any desired product, which is consistent with the above observation that using a strongly coordinating group instead of the OMe suppressed the reaction. We then evaluated aryl groups of phosphines: 1) both the steric hindrance of an *ortho* substituent (**L19**) and electron-deficient arenes (**L20**, **L21**) decreased the yield; 2) introducing an electron-donating group (**L22**) slightly improved the yield to 45%, but further increasing the electron-density of the arene (**L23**) only resulted in 35% yield. Further optimization of the conditions, including solvent and temperature, enhanced the yield to 95% with **L22** as the ligand (for more details of optimization, see Supporting Information).

Table 1. Catalyst Development for S_NAr Amination[a]



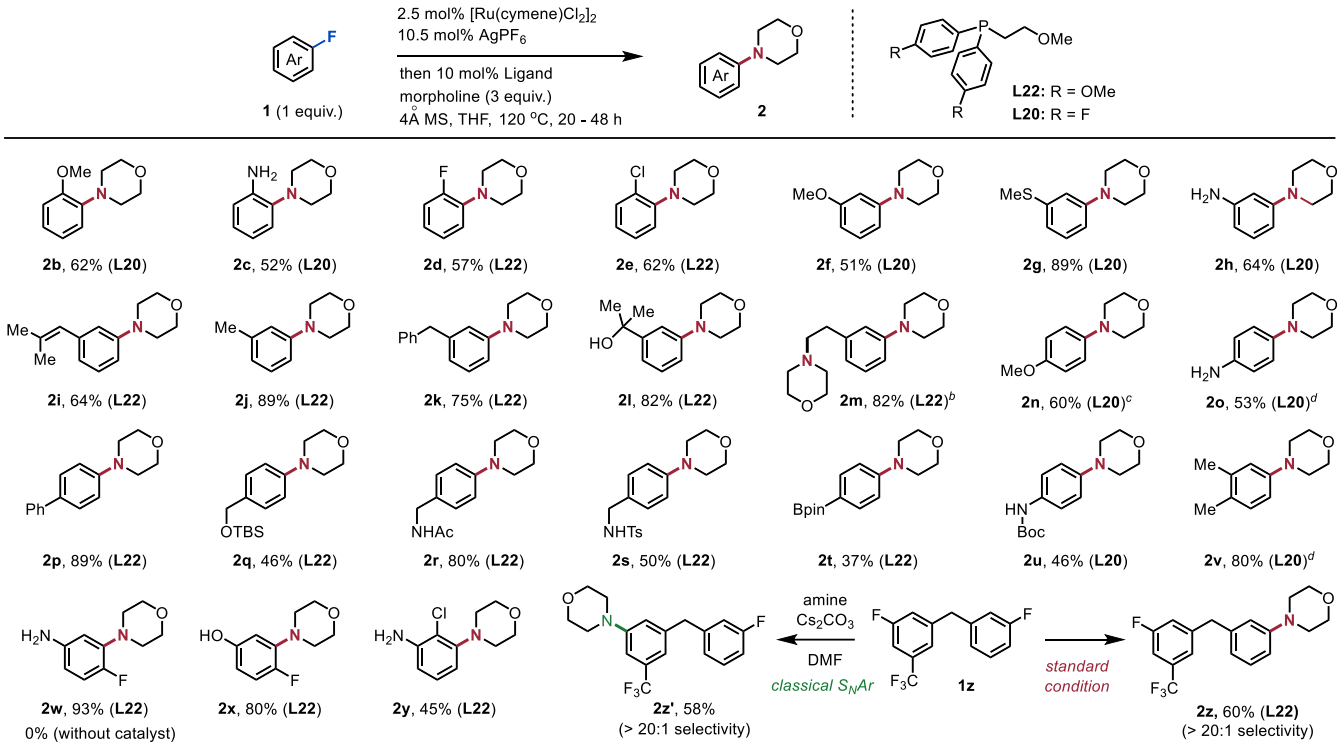
[a]Conditions: **1a** (0.40 mmol), morpholine (0.44 mmol), [Ru(cymene)Cl_2]$_2$ (0.010 mmol), $AgPF_6$ (0.042 mmol), Ligand (0.048 mmol), 4Å MS (20 mg), 1,4-dioxane (0.10 mL), N_2, 100 °C. Yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [b]Ligand (0.024 mmol). [c]Ligand (0.040 mmol), morpholine (1.2 mmol), THF (0.10 mL), 120 °C.

The optimized amination conditions proved effective for introduction of the morpholine motif on a wide range of aromatics. (Table 2). Both electron-rich (**2b**, **2c**) and deficient (**2d**, **2e**) *ortho*-substituted aryl fluorides were compatible, giving more than 50% yields. Notably, the C–Cl bond (**2e**), which is more reactive than a C–F bond in both Hartwig-Buchwald[9] and Ullmann aminations[10], survived under the conditions. A broad range of substituents at the *meta*-position, including strongly electron-donating groups such as -OMe (**2f**), -SMe (**2g**), -NH_2 (**2h**) and alkene (**2i**), as well as electron-neutral methyl (**2j**) and benzyl (**2k**) groups, were all tolerated, providing desired products in good yields. The free hydroxyl group did not inhibit the reaction (**2l**, **2m**), while the primary alcohol was converted to the amine **2m** under the conditions. *Para*-substituted aryl fluorides bearing various functional groups (**2n-2u**) showed good reactivity in the reactions. An array of active motifs were tolerated, for example: amine (**2o**), amide (**2r**), sulfamide (**2s**), borate (**2t**), and carboamide (**2u**). Multi-substituted aryl fluorides also gave desired products in good yields (**2v-2y**). Notably, exclusive regio-selectivity was observed in the aminations of difluoroaniline (**2w**) and difluorophenol (**2x**). For substrate **1z**, which bears two aromatic fluoride motifs, the nucleophilic substitution predominantly happened on the more electron-rich arene (**2z**), giving complete opposite selectivity with classical S_NAr reactions (**2z'**).

We next examined the scope of amines by using 3,4-difluoroaniline as the limiting reagent (Table 3). Piperidine (**3a**) and its analogues (**3b** to **3e**), including hydroisoquinoline and *N*-methylpiperazine, turned out to be suitable nucleophiles, giving the yield up to 98%. The 4-membered amine, azetidine, was not stable under the conditions, and only a trace amount of product was observed. In comparison, both 5- and 7-membered amines gave the desired products in good yields, respectively (**3g**, **3h**). Other than cyclic amines, linear secondary and primary amines were all compatible, affording products in moderate yields (**3i-3l**). Notably, a high *meta*-selectivity was observed in each of the above case.

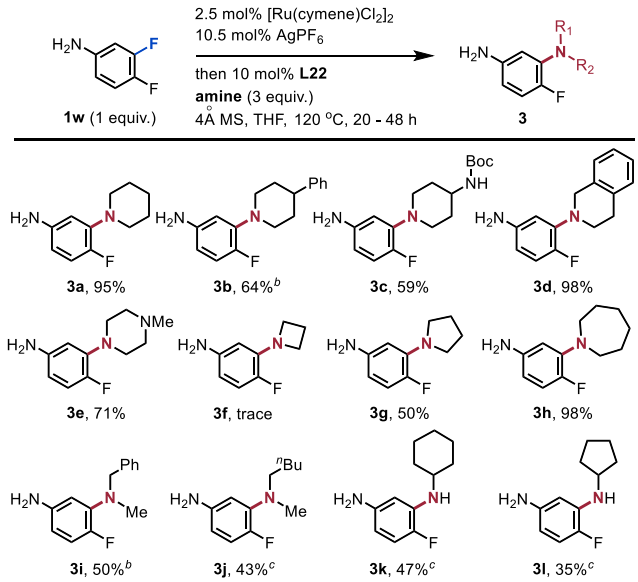
Given the limited knowledge on phosphine-supported Ru-fluoroarene complex,[5d,5e,11] we synthesized a Ru-fluoroarene η^6-complex **4** to gain insights into the reaction process (Scheme 2a). The proposed S_NAr amination precursor **5**, bisphosphine-Ru arene η^6-complex, was synthesized from complex **4** and characterized by NMR spectroscopy. According to the ^{1}H and ^{31}P NMR spectra, we propose that the two hemilabile ligands on intermediate **5** are asymmetric: one chelates the Ru by the phosphine and oxygen simultaneously, while the other is mono-coordinated. Unexpectedly, the fluorine peak disappeared instantly after adding morpholine, which suggests the amination proceeds fast even at room temperature. Finally, heating the reaction mixture released the free aniline product in 65% yield based on the starting complex **4**. During the above investigations, no signal of free fluoroarene was detected by ^{19}F NMR. The experiments support that the amination proceeds on a η^6-complex of the Ru-catalyst and fluoroarene. Furthermore, we compared diphenylbutylphosphine **L5** that possesses a non-coordinating, linear group with the hemilabile ligand **L6** in the arene dissociation (Scheme 2b). The hemilabile ligand coordinated Ru complex **8** released the aniline completely in a half hour under heating conditions. In comparison, only a trace amount of the free aniline was detected by using ligand **L5**, which revealed that the weakly coordinating group facilitates dissociation of product arenes from the Ru center.

Table 2. Scope of Aryl Fluorides[a]



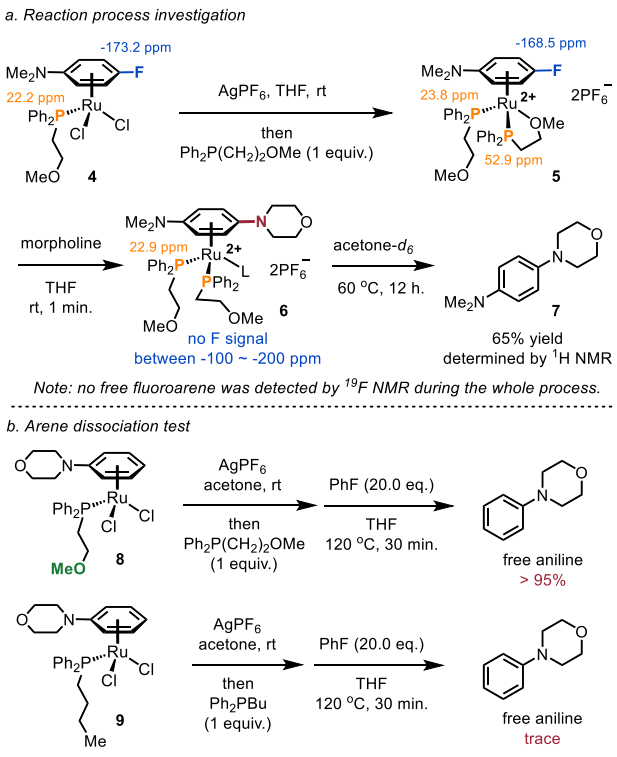
[a]Conditions: **1** (0.40 mmol), $[Ru(cymene)Cl_2]_2$ (0.010 mmol), $AgPF_6$ (0.042 mmol), Ligand (0.040 mmol), morpholine (1.2 mmol), 4Å MS (20 mg), THF (0.10 mL), N_2, 120 °C. [b]2-(4-Fluorophenyl)ethanol was used as the substrate. [c]$[Ru(cymene)Cl_2]_2$ (0.040 mmol), $AgPF_6$ (0.168 mmol), Ligand (0.16 mmol). [d]$[Ru(cymene)Cl_2]_2$ (0.020 mmol), $AgPF_6$ (0.084 mmol), Ligand (0.080 mmol). Data are reported as isolated yield of purified compound.

Table 3. Scope of Amines[a]



[a]Conditions: **1w** (0.40 mmol), amine (1.20 mmol), $[Ru(cymene)Cl_2]_2$ (0.010 mmol), $AgPF_6$ (0.042 mmol), **L22** (0.040 mmol), 4Å MS (20 mg), THF (0.10 mL), 120 °C. [b]**L6** (0.040 mmol). [c]$[Ru(cymene)Cl_2]_2$ (0.020 mmol), $AgPF_6$ (0.084 mmol), **L22** (0.080 mmol). Data are reported as isolated yield of purified compound.

Scheme 2. Mechanistic Studies



In conclusion, a Ru-catalyzed S_NAr amination of aryl fluorides as the limiting reagents by utilizing a hemilabile, bidentate ligand has been developed. The mild reaction conditions, as well as broad substrate scope, make this protocol attractive for synthesis and functionalization of bioactive compounds. Preliminary mechanistic studies reveal that the substitution proceeds *via* η^6-coordination, and the weakly coordinating group on the hemilabile ligand promotes the arene exchange step. Further studies into the mechanism, and the extension to related transformations are currently ongoing.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, characterization of new compounds and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interests.

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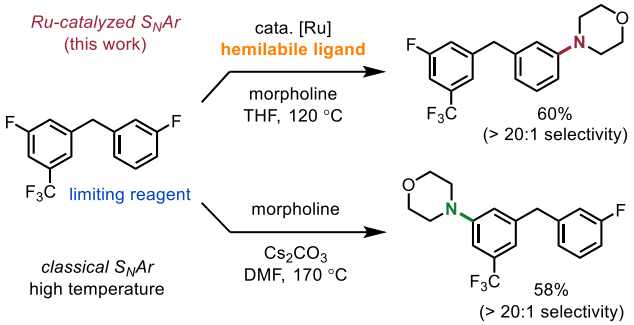
Ru-catalyzed SNAr
(this work)
cata. [Ru]
hemilabile ligand
morpholine
THF, 120 °C
F
F3C
limiting reagent
F
N
O
60%
(> 20:1 selectivity)
morpholine
Cs2CO3
DMF, 170 °C
classical SNAr
high temperature
O
N
F
F3C
58%
(> 20:1 selectivity)