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Abstract: Catalytic S_NAr reaction of fluoroarenes possessing no electron-withdrawing group(s) with cyclic amines was achieved using a readily accessible Ru catalyst, which was prepared from [Ru(benzene)Cl₂]₂, AgOTf, and P(*p*-FC₆H₄)₃. The coexistence of molecular sieves MS4A realized high conversion and various substituted aryl amines were obtained in good to high yields.

Key words: catalysis, S_NAr reaction, ruthenium, fluoroarenes, amines

The nucleophilic aromatic substitution (S_NAr) reaction of haloarene is one of the most established and practical reactions to synthesize various substituted arenes. Electrondeficient aromatic compounds with strong electron-withdrawing group(s), such as nitro and cyano groups, can be submitted to this reaction, while nonactivated arenes, which have no electron-withdrawing substituent(s), are generally inappropriate substrates.¹

Recently, we developed the first catalytic S_NAr reaction of nonactivated fluoroarenes with amines using a ruthenium catalyst (Scheme 1).^{2,3} The stoichiometric use of transition metal η^6 -arene complex, such as chromium carbonyl complex, had been a common protocol for the S_NAr reaction of electron-rich arenes,⁴ therefore, our results could eliminate the stepwise process where the transition metal must be attached and detached.⁵



 $\label{eq:Scheme 1} \begin{array}{c} \text{Our previous work on catalytic S_NAr reaction} \end{array}$

In our previous paper, however, we used thermally sensitive ruthenium complex [Ru(cod)(2-methylallyl)₂], DPP-Pent [1,5-bis(diphenylphosphino)pentane], and strong acid (trifluoromethanesulfonic acid) for the preparation of Ru η^6 -fluoroarene complex, which is the key intermediate in the S_NAr reaction (complex **2** shown in Scheme 2).⁶

SYNLETT 2010, No. 17, pp 2601–2606 Advanced online publication: 30.09.2010 DOI: 10.1055/s-0030-1258774; Art ID: U07110ST © Georg Thieme Verlag Stuttgart · New York Moreover, the addition of triethylamine and triethylsilane was needed for high conversion. We next explored a more facile protocol using η^6 -arene ruthenium(II) complex such as 1, which directly provides the key intermediate 2 by arene exchange with fluoroarenes (Scheme 2).



 $\mbox{Scheme 2} \quad \mbox{Exchange of η^6-arene ligand following S_NAr reaction}$

With these facts in mind, we examined η^6 -benzene ruthenium(II)-phosphine complex, using the dichloro(benzene)ruthenium(II) dimer { $[Ru(benzene)Cl_2]_2$ } as a stable precursor. The dichloro(arene)ruthenium(II) dimers are widely used as precursors for various monomeric Ru catalysts. For example, they are mostly used for the preparation of ruthenium-chiral diphosphine catalysts in asymmetric hydrogenation, but their use as arene templates in catalytic reaction has never been reported as far as we know. The reaction of *p*-fluorotoluene with morpholine was chosen as a model reaction (Table 1). When $[Ru(benzene)Cl_2]_2$ was used with PPh₃ in refluxing 1,4-dioxane, the reaction did not proceed at all (entry 1). Next, we examined a few silver salts for the preparation of cationic complexes, which are expected to induce facile arene exchange. As a result, the desired aminated product 3 was obtained and AgOTf gave the best yield among them (entries 2-4).⁷

We then screened phosphine ligands. As for monodentate ligands, electron-rich monodentate phosphines, such as $P(p-MeC_6H_4)_3$ and $P(p-MeOC_6H_4)_3$ gave comparable results with PPh₃. In contrast, electron-deficient monodentate phosphine $P(p-FC_6H_4)_3$ improved the yield up to 55%, but more electron-deficient $P(p-CF_3C_6H_4)_3$ did not give better results (entries 5–8). Bidentate ligands, such as DP-PB, DPPPent and DPPF, also facilitated the reaction but the yields did not exceed that of $P(p-FC_6H_4)_3$ (entries 9–11). For the further optimization, we examined organic bases as HF scavenger and the addition of triethylamine realized the yield of 60% (entries 12–14). Inorganic bases, such as K_2CO_3 and Na_2CO_3 , were ineffective but molecu-

Table 1 Screening of Reaction Conditions



^a Diphosphine ligand (6 mol%) was used.

^b MS4A (40 mg) was used in the 0.4-mmol scale reaction. DPPF: 1,1-bis(diphenylphosphino)ferrocene, DPPB: 1,4-bis(diphenylphosphino)butane, TMEDA: *N,N,N',N'*-tetramethylethylenediamine.

lar sieves 4A (MS4A) promoted this reaction⁸ and the highest yield of 80% was achieved (entry 15).

With the optimized conditions in hand, we then examined the substrate scope in the present catalytic system (Table 2). Fluorobenzene, *m*-fluorotoluene, and fluoroxylene underwent S_NAr reaction and furnished the corresponding products in high yields (entries 1–3). Fluoroarenes bearing ethyl group and allyl group also achieved good yields but double-bond isomerization occurred to give styrene derivative in the latter case (entries 4 and 5).⁹ In the case of sterically hindered *o*-fluorotoluene, the yield was moderate (entry 6). Methoxy-substituted fluoroarenes were also available for this reaction (entries 7–9). Even a fluoroarene bearing two methoxy groups also realized a catalytic reaction (entry 10). Dimethylamino group is more electron-donating than methoxy group, but it could be furnished into the substrate (entry 11).^{10,11}

Table 2 Screening of Fluoroarenes in the Reaction with Morpholine



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[Ru(benzene)Cl₂]₂ (2.5 mol%) AgOTf (10.5 mol%) P(*p*-FC₆H₄)₃ (12 mol%) 4 Å MS, dioxane, reflux, 24 h 5 equiv 1 equiv Yield (%) Entry Substrate Product 2 83 3 81 4 70 5 68^a 44 6 7 50 `OMe OMe 8 57 Me ÓМе 9 55 Me MeC OMe .OMe 10 30 ÓМе ÓMe 11 47 NMe₂ NMe₂

Table 2 Screening of Fluoroarenes in the Reaction with Morpholine (continued)

^a E:Z = 18:1.



Scheme 3 S_NAr reaction of fluorotoluene with piperidine and *N*-methylpiperazine

The results of the reactions of other amines with *p*-fluorotoluene are shown in Scheme 3. Piperidine and *N*-methylpiperazine were also good substrates and gave the corresponding products in good yields (Scheme 3).

We supposed that the reaction proceeds via cationic Ru η^{6} -arene complexes **A**, **B** and **C**, which possess arene, two phosphines and a trifluoromethanesulfonate group as weakly coordinating ligands (Scheme 4). We actually confirmed the reaction intermediates by ESI mass analysis. Ru η^{6} -benzene complex **A** was prepared from [Ru(benzene)Cl₂]₂, AgOTf and P(*p*-FC₆H₄)₃ in 1,4-dioxane.^{12,13} It was treated with excess amounts of *p*-fluorotoluene, and heated at reflux for four hours. Then the resulting mixture was analyzed by ESI mass analysis. As a result, the expected ruthenium η^{6} -fluorotoluene complex **B** was detected (Figure 1).¹³ Addition of morpholine converted the complex **B** into the ruthenium η^{6} -morpholinotoluene complex **C**, which was also detected (Figure 2).¹³



detected by MS ([M-TfOH]+)



Figure 1 Detection of complex B prepared by arene exchange with complex A

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Figure 2 Detection of complex C prepared by S_NAr reaction of complex B with morpholine

In conclusion, we have developed a facile rutheniumcatalyzed S_NAr reaction using dichloro(benzene)ruthenium(II) dimer as a catalyst precursor.¹⁴ The cationic species were generated by the addition of silver salt in the presence of P(*p*-FC₆H₄)₃, and the reaction key intermediates were directly generated in situ by arene exchange with fluoroarenes. The reaction of various fluoroarenes with cyclic amines efficiently proceeded in the coexistence with MS4A and the corresponding aminated products were obtained in good to high yields.

Acknowledgment

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- (9) When 1-allyl-4-fluorobenzene was submitted under the previous conditions (ref. 2), the yield of the styrene derivative was low (21%). Moreover, a hydrogenated byproduct also formed, because silane was used as an additive.
- (10) Excess amounts of fluoroarenes would be needed for efficient arene exchange: when 1-dimethylamino-4fluorobenzene (3 equiv) was used, the yield significantly decreased to 30%.

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- (11) When the reaction was examined at the higher reaction temperature (160 °C), the yield decreased to 25%.
- (12) [Ru(*p*-cymene)(OTf)(dppben)]OTf [DPPBen: 1,2-bis(diphenylphosphino)benzene] was synthesized and characterized by X-ray single crystal structural analysis:
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- (13) The detected isotopic patterns of A, B and C ([M TfOH]⁺) by ESI–MS matched with the theoretical isotope patterns.
- (14) **Typical Procedure** (Entry 15 in Table 1): Under an atmosphere of argon, MS4A (40 mg) was dried up in a

Schlenk tube. To this container, the mixture of $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ (5.0 mg, 0.010 mmol) and AgOTf (10.8 mg, 0.042 mmol) in acetone was transferred with a syringe filter. After acetone was excluded, a 1,4-dioxane solution (0.10 mL) of P(*p*-FC₆H₄)₃ (15.2 mg, 0.048 mmol), *p*-fluorotoluene (220 µL, 2.0 mmol) and morpholine (35 µL, 0.40 mmol) was added. The reaction mixture was stirred under reflux for 24 h, then MS4A was filtered off. After the filtrate was evaporated, the crude products were purified by thin-layer chromatography (hexane–AcOEt = 10:1) to give analytically pure **3** (80%).

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