Catalytic S_NAr reaction of non-activated fluoroarenes with amines *via* Ru η^6-arene complexes†

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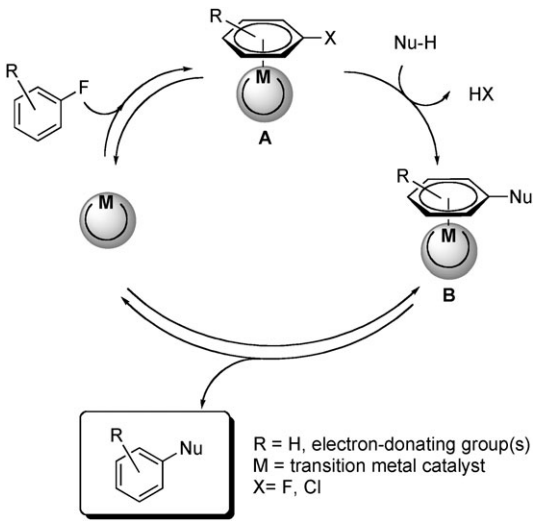
Ru-catalyzed S_NAr reaction of non-activated fluoroarenes with secondary amines proceeded through η^6-arene complexes to give aminated products in up to 79% yield.

The nucleophilic aromatic substitution (S_NAr) reaction of haloarenes is a widely used transformation in organic syntheses; multi-substituted arenes, including several pharmaceutical products and natural products, have been synthesized using this method. However, the S_NAr reaction generally requires "electron-poor" aromatic compounds with strong electron-withdrawing group(s), such as nitro and cyano groups, because the aromatic ring is intrinsically electron-rich, and haloarenes without electron-withdrawing group(s), namely non-activated haloarenes, are not suitable as electrophiles in the S_NAr reaction.[1] The conversion into a transition metal η^6-arene complex is a commonly used protocol for making haloarenes more electron-poor, and even non-activated haloarenes undergo S_NAr reaction by complexation.[2] However, the main drawback of this procedure is that it requires the use of stoichiometric amounts of transition metals that are attached to and detached from the benzene ring. In this regard, there has been no practical catalytic S_NAr reaction using relatively electron-rich haloarenes.[3] The purpose of our study is to develop the first catalytic S_NAr reaction of non-activated fluoroarenes with amines.[4]

We hypothesized that the desired catalytic S_NAr reaction could be realized according to the following mechanism (Scheme 1). First, a catalyst **M** associates with a haloarene to yield a transition metal η^6-arene complex **A**. Second, it undergoes nucleophilic attack and is converted into metal η^6-arene complex **B**. Third, the complex dissociates a substituted arene as a product, and the catalyst is regenerated. The most difficult problem in this catalysis would be the arene-exchange step from catalyst-product complex **B** to catalyst-substrate complex **A**.

We chose *p*-fluorotoluene as a model haloarene with an electron-donating group, because fluoroarene is the most reactive among haloarenes in the S_NAr reaction. The reaction of *p*-fluorotoluene with morpholine was examined in the presence of catalytic amounts of transition metal complexes, which are known to form metal η^6-arene complexes. For example, $[RhCp^*Cl_2]_2$ with $AgPF_6$,[5] $[Ru(p\text{-cymene})OTf_2]_n$,[6] and $[Rh(cod)_2]BF_4$[7] were submitted, and finally, we were pleased to find that a Ru catalyst, prepared from Ru(cod)-(2-methylallyl)$_2$, 1,5-bis(diphenylphosphino)pentane (DPPPent), and trifluoromethanesulfonic acid (TfOH)[8] showed high activity. Actually, morpholine (1 equiv.) and *p*-fluorotoluene (5 equiv.) were added in refluxed 1,4-dioxane to the above-mentioned Ru complex (5 mol%), and the reaction proceeded to furnish aminated product **1** in 48% isolated yield.[9] Under the same reaction conditions, only a trace amount of aminated product **1** was obtained in the reaction of *p*-chlorotoluene, moreover, no product was detected in the reaction of *p*-bromotoluene or *p*-iodotoluene. These results imply that the present transformation proceeds by S_NAr reaction (Scheme 2).

In order to improve the yield, we screened several phosphine ligands (Table 1, entries 1–4). When 1,5-bis(di-*tert*-butylphosphino)pentane (D*t*PPent) was used as a more electron-rich and bulky analogue of DPPPent, product **1** was obtained in low yield (entry 1). BINAP also realized a catalytic reaction but the yield was also low (entry 2). In contrast, 1,1′-bis-(diphenylphosphino)ferrocene (DPPF) and triphenylphosphine, a monodentate ligand, achieve comparable yields with DPPPent (entries 3 and 4). The yields of these reactions were still moderate because morpholine was not completely consumed after 24 h. Then we assumed that *in situ* generated HF would inhibit the catalytic activity, and further investigated the additives that could capture HF. The addition of triethylamine as a base did not improve the yield of product **1**



Scheme 1 Proposed reaction mechanism of catalytic S_NAr reaction *via* Ru η^6-arene complexes.

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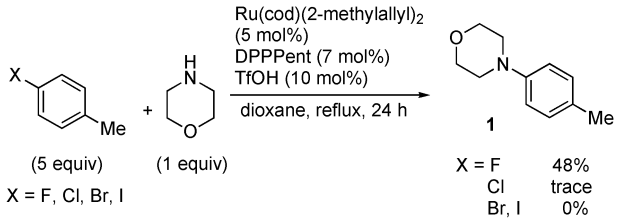
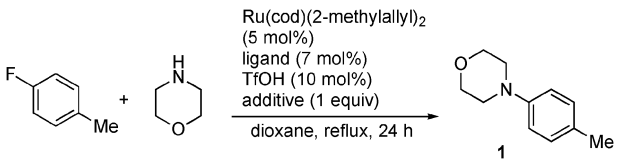


Scheme 2 Ru-catalyzed reaction of morpholine with *p*-halotoluenes.

(entry 5). In the presence of K_2CO_3 or 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), the reaction did not proceed at all. We next used silane as a good scavenger of the fluoride anion (entries 6–8): triethylsilane certainly furnished better results (64% yield). When triethylamine was added, the yield exceeded 70% (entry 9).[10] The use of both triethylsilane and triethylamine was also effective in the case of triphenylphosphine; the yield improved significantly (entry 10).

Under the optimal conditions, we first examined the substrate scope of non-activated fluoroarenes (Table 2). The reaction of fluorobenzene with morpholine furnished product **2** in good yield (entry 1). Moreover, in the case of *m*-fluorotoluene, the best yield of 79% was achieved (entry 2). The reaction of 4-fluoro-*o*-xylene, possessing two electron-donating groups, also proceeded to yield product **4** in moderate yield (entry 3). The methoxy group was tolerable as a substituent of fluoroarene, and the catalytic reaction of *o*-, *m*- and *p*-fluoroanisoles also proceeded. In these cases, the reaction was conducted without triethylsilane, because the corresponding products **5–7** readily react with silane (entries 4–6). It is noteworthy that a fluoroarene with an amino group, which is a strong electron-donating group, underwent the catalytic S_NAr reaction, albeit in low yield (entry 7). In the case of fluorostyrene, the S_NAr reaction proceeded in moderate yield, but the product was reduced partially at the olefinic moiety (entry 8).

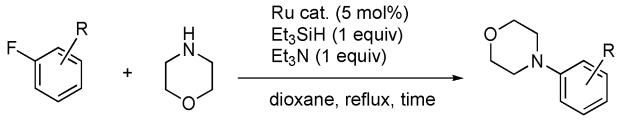
Table 1 Screening of ligands and additives in Ru-catalyzed S_NAr reaction[a]

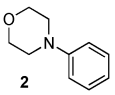
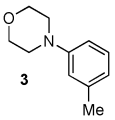
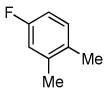
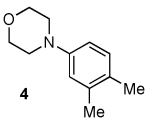
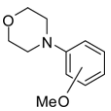
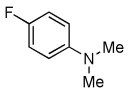
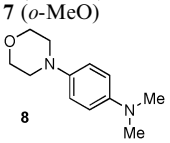
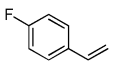
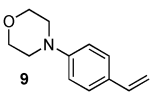


Entry	Ligand	Additive	Yield (%)
1	D*t*PPent	—	20
2	BINAP	—	20
3	DPPF	—	44
4	2 PPh_3	—	50
5	DPPPent	Et_3N	45
6	DPPPent	Et_3SiH	64
7	DPPPent	$(EtO)_3SiH$	53
8	DPPPent	Ph_3SiH	40
9	DPPPent	Et_3N, Et_3SiH	72
10	2 PPh_3	Et_3N, Et_3SiH	68

[a] Reaction conditions: fluoroarene/morpholine/Ru/DPPPent/TfOH = 5 : 1 : 0.05 : 0.07 : 0.10 (0.4 mmol of morpholine) in dioxane.

Table 2 Screening of fluoroarenes in Ru-catalyzed S_NAr reaction[a]



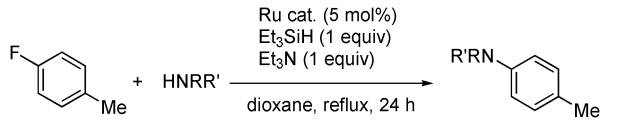
Entry	Substrate	Product	Time/h	Yield (%)
1		 **2**	24	72
2		 **3**	24	79
3		 **4**	24	54
				
4	*p*-MeO	**5** (*p*-MeO)	36	30[b]
5	*m*-MeO	**6** (*m*-MeO)	36	58[b]
6	*o*-MeO	**7** (*o*-MeO)	36	38[b]
7		 **8**	24	25
8		 **9**	36	57[c]

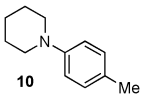
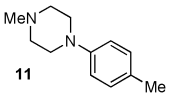
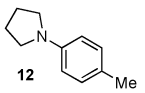
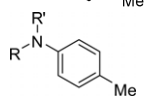
[a] Reaction conditions: fluoroarene/morpholine/Ru cat. = 5 : 1 : 0.05 (0.4 mmol of morpholine) in dioxane. Ru cat. was prepared from Ru(cod)(2-methylallyl)$_2$ (5 mol%), DPPPent (7 mol%), and TfOH (10 mol%). [b] Et_3N (1.5 equiv.) was added without Et_3SiH. [c] 4-Ethyl-1-morpholinobenzene was included (30% of the product).

We next examined the scope of amines as nucleophiles in the reaction with *p*-fluorotoluene (Table 3). Cyclic amines, such as piperidine, *N*-methylpiperazine, and pyrrolidine, furnished aminated products in moderate to good yield (entries 1–3). The catalytic S_NAr reaction proceeded for acyclic amines as well, albeit lower yields (entries 4–6). In contrast, the reaction did not proceed with *N*-methyl aniline. These results show that high nucleophilicity is crucial to achieve a high yield.

We investigated evidence for the formation of Ru η^6-arene complexes as intermediates, and attempted to characterize intermediates **17** and **18** in Scheme 3, which correspond to **A** and **B**, respectively in Scheme 1, by NMR and mass analyses. First, an excess amount of fluorobenzene-d_5 was added to a mixture of Ru(cod)(2-methylallyl)$_2$, DPPPent, and TfOH in THF-d_8; the mixture was then heated at 80 °C for 10 min. ^{31}P NMR analysis of the resulting solution at room temperature showed a single peak at 65.7 ppm, which was almost in agreement with the ^{31}P NMR spectrum of the pincer-type Ru η^6-arene complex prepared from styrene or *p*-cymene with the Ru catalyst in THF.[8] The ESI-MS analysis showed an

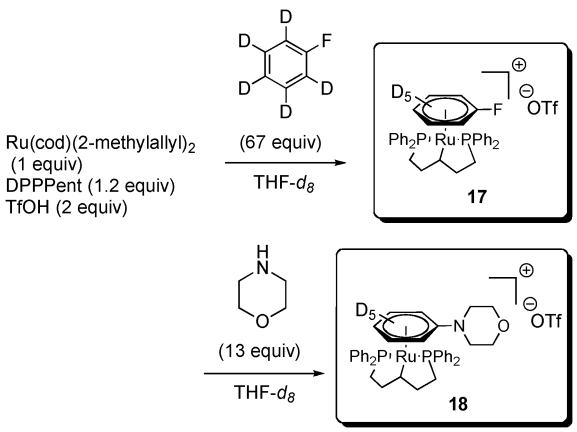
Table 3 Screening of amines in Ru-catalyzed S_NAr reaction[a]



Entry	Substrate	Product	Yield (%)
1		 **10**	75
2		 **11**	75
3		 **12**	55
			
4	*n*-Hex, Me	**13** (R,R' = *n*-Hex, Me)	44
5	Bn, Me	**14** (R,R' = Bn Me)	20
6	*c*-Hex, H	**15** (R,R' = *c*-Hex, H)	22

[a] Reaction conditions: fluoroarene/morpholine/Ru cat. = 5 : 1 : 0.05 (0.4 mmol of morpholine) in dioxane. Ru cat. was prepared from Ru(cod)(2-methylallyl)$_2$ (5 mol%), DPPPent (7 mol%), and TfOH (10 mol%).

expected peak for [Ru(dpppent)(η^6-fluorobenzene-d_5)]$^+$ (m/z = 642.1, 19%), moreover, the detected isotope pattern matches with the theoretical isotope pattern (see ESI†). Next, an excess amount of morpholine was added to the reaction mixture containing complex **17**, and the generation of Ru η^6-arene complex **18** was also ascertained by the ^{31}P NMR analysis (68.1 ppm) and ESI-MS analysis [Ru(dpppent)-(η^6-morpholinobenzene-d_5)]$^+$ (m/z = 709.2, 27%) (see ESI†).



Scheme 3 Characterization of Ru η^6-arene complexes **17** and **18**.

The above results strongly suggest that the catalytic S_NAr reaction proceeds *via* Ru η^6-arene complexes.[11]

In conclusion, we achieved S_NAr reactions of non-activated fluoroarenes with amines using Ru-η^6 arene complex as a catalytic template. To the best of out knowledge, the present reaction is the first example of a catalytic conversion of the C–F bond of fluoroarenes into a C–N bond. We are carrying out further studies on the elucidation of the reaction mechanism and the modification of catalysts.

This work was supported by a Waseda University Grant for Special Research Projects. We are also grateful to the Japan Society for the Promotion of Science for the fellowship support to M. Otsuka.

Notes and references

1 Nucleophilic substitution reaction of non-activated haloarenes proceeded only when strong anionic nucleophiles, such as lithium amides and alkoxides, were used: (*a*) R. Huisgen and J. Sauer, *Chem. Ber.*, 1958, **91**, 1453; (*b*) G. Wittig, H. J. Schmidt and H. Renner, *Chem. Ber.*, 1962, **95**, 2377; (*c*) J. R. Rodriguez, J. Agejas and A. B. Bueno, *Tetrahedron Lett.*, 2006, **47**, 5661.

2 (*a*) M. F. Semmelhack and A. Chlenov, in *Transition Metal Arene π-Complexes in Organic Synthesis and Catalysts*, ed. E. P. Kündig, Springer-Verlag, Heidelberg, Germany, 2004, p. 43; (*b*) M. F. Semmelhack, in *Comprehensive Organometallic Chemistry II*, ed. A. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon, New York, vol. 12, 1995, p. 979.

3 Only limited catalytic system using modified cyclopentadienyl Rh complexes was reported in S_NAr reaction using oxygen nucleophiles: (*a*) R. P. Houghton and M. Voyle, *J. Chem. Soc., Perkin Trans. 1*, 1984, 925; (*b*) L. I. Goryunov, V. V. Litvak and V. D. Shteingarts, *Zhurn. Org. Khim.*, 1987, **23**, 1230.

4 For selected examples of S_NAr reactions of non-activated fluoroarene with amines using a stoichiometric amount of transition metals, see: (*a*) W. Braun, B. Calmuschi-Cula, U. Englert, K. Höfener, E. Alberico and A. Salzer, *Eur. J. Org. Chem.*, 2008, 2065; (*b*) K. Kamikawa, S. Kinoshita, M. Furusyo, S. Takemoto, H. Matsuzaka and M. Uemura, *J. Org. Chem.*, 2007, **72**, 3394; (*c*) C. Baldoli, S. Maiorana, E. Licandro, L. Casiraghi, G. Zinzalla, P. Seneci, E. D. Magistris, A. Paio and C. Marchioro, *J. Comb. Chem.*, 2003, **5**, 809; (*d*) F.-E. Hong, S.-C. Lo, M.-W. Liou, L.-F. Chou and C.-C. Lin, *J. Organomet. Chem.*, 1996, **516**, 123; (*e*) J. P. Gilday and D. A. Widdowson, *Tetrahedron Lett.*, 1986, **27**, 5525.

5 [RhCp*Cl$_2$]^2 was used as an analogue of modified cyclopentadienyl Rh complex; see ref. 3.

6 For selected examples, see: (*a*) E. L. Velarde, R. A. Stephen, R. N. Mansour, L. T. Hoang and D. J. Burkey, *J. Am. Chem. Soc.*, 2003, **125**, 1188; (*b*) A. Schluter, K. Bieber and W. S. Sheldrick, *Inorg. Chim. Acta*, 2002, **340**, 35; (*c*) S. Chen, V. Carperos, B. Noll, R. J. Swope and M. R. DuBois, *Organometallics*, 1995, **14**, 1221.

7 (*a*) H. Matsuzawa, Y. Tanabe, Y. Miyake and Y. Nishibayashi, *Organometallics*, 2008, **27**, 4021; (*b*) M. Maekawa, N. Hashimoto, K. Sugimoto, T. Kuroda-Sowa, Y. Suenaga and M. Munakata, *Inorg. Chim. Acta*, 2003, **344**, 143.

8 J. Takaya and J. F. Hartwig, *J. Am. Chem. Soc.*, 2005, **127**, 5756.

9 This reaction did not proceed at all without the Ru catalyst in refluxed dioxane.

10 The present catalytic reaction proceeded even with 1–4 equiv. of fluorotoluene, but the yield was lower (22–60%) (see ESI†).

11 The same experiment was conducted with bromobenzene, and the Ru η^6-bromobenzene complex was detected by ^{31}P NMR and ESI-MS analyses, but S_NAr reaction did not proceed by the addition of an excess amount of morpholine (see ESI†).

