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ARTICLE

Product Inhibition in Nucleophilic Aromatic Substitution through DPPPent-Supported π-Arene Catalysis

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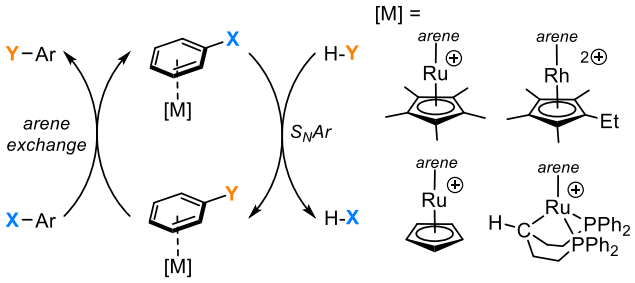
Nucleophilic aromatic substitution (S_NAr) of fluorobenzene by morpholine at a bis(diphenylphosphino)pentane-supported ruthenim complex is investigated as a model system for π-arene catalysis through the synthesis and full characterization of proposed intermediates. The S_NAr step proceeds quickly at room temperature, however the product N-phenylmorpholine binds tightly to the ruthenium ion. In the case examined, the thermodynamics of arene binding favor product N-phenylmorpholine over fluorobenzene binding by a factor of 2,000, corresponding to significant product inhibition. Observations of the catalyst resting state support this hypothesis and demonstrate an additive-controlled role for a previously-proposed ligand cyclometalation.

Introduction

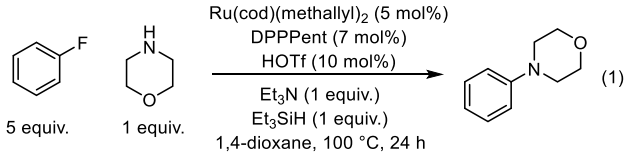
Nucleophilic aromatic substitution (S_NAr) of haloarenes is a powerful synthetic tool that finds wide use in organic chemistry. A major limitation of this reaction, however, is the requirement for electron deficient arene electrophiles. One strategy for the activation of otherwise unactivated arenes is through η^6 binding to a metal center, which gives π arene complexes with significantly enhanced electrophilicity.[1-6] S_NAr reactions of η^6 haloarenes often proceed at room temperature even for substrates like chlorobenzene[7-9] which is largely inert absent metal-ion activation. In principle, catalytic turnover can be achieved by product arene exchange for the starting material haloarene as depicted in Scheme 1. However in most cases the strong binding of the arene to the metal requires photolytic or oxidative conditions for liberation the product,[10] which has largely precluded catalytic applications with rare exceptions.

All existing examples of catalytic S_NAr reactions involving η^6-arene coordination are limited to 2nd row transition metal catalysts. A rhodium(III) example[11] and a limited number of ruthenium(II) complexes - two containing cyclopentadienyl derivatives and three containing phosphine ligands, have been shown to serve as catalysts for S_NAr of haloarenes by fluoride[12] and amines[13-16] at temperatures ranging from 100 °C to 180 °C. Among these, the phosphine-supported ruthenium(II) catalysts have been more successful for the S_NAr of fluoroarenes by amines.[13-15] In all cases, the reaction is speculated to follow a general mechanism proposed by Semmelhack et. al.[17] (Scheme 1) wherein arene exchange allows for catalytic turnover after S_NAr. Electron-deficient arenes have poorer arene binding thermodynamics while electron-rich arenes have poor arene exchange kinetics.[18] This ensures that product inhibition is an intrinsic challenge in all cases where the product arene is more electron rich than the haloarene starting material, though to our knowledge this has never been quantified in a catalytic system.



Scheme 1. Reported catalysts for π-arene S_NAr.

The potential complementarity of catalytic S_NAr to better-developed cross-coupling methods has encouraged our research group to examine this class of transformations in more detail. We chose to begin with a mechanistic study of a 1,5-bis(diphenylphosphino)pentane (DPPPent)-supported Ru catalyst for S_NAr reported by the Shibata group (eqn. 1).[15] This catalytic system is closely related to one applied in the catalytic anti-Markovnikov hydroamination of styrene by the Hartwig group.[19] In that study Hartwig was able to show that DPPPent undergoes cyclometalation to give a facial, tridentate ligand-supported ruthenium complex that binds η^6 arenes.[19]



(1)

When applied to S_NAr catalysis, DPPPent gave a complex (generated *in situ*) that displayed the highest turnover numbers and mildest reaction conditions of any intermolecular π-arene S_NAr reaction at the time.[15] Their preliminary mass spectrometry and $^{31}P\{^1H\}$ NMR experiments suggest that ruthenium arene complexes analogous to those characterized

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by Hartwig may be formed *in situ*, which represented an ideal starting point for further study.

Results and Discussion

On the basis of mass spectrometric data, Shibata proposed π-arene intermediates[15] supported by a cyclometalated κ^3 DPPPent ligand analogous to the one observed by Hartwig.[19] We undertook the synthesis of two arene derivatives bearing a κ^3 DPPPent ligand in an effort to study their properties in π-arene S_NAr catalysis. Complexes **1** and **2** were synthesized in a single step from Ru(cod)(methallyl)$_2$ using variations on a reported procedure (eqn. 2 and 3).[19] Both complexes were characterized by ^{1}H and ^{31}P{^{1}H} NMR and combustion analysis, and their structures were confirmed by single crystal X-ray diffraction (Figure 1).

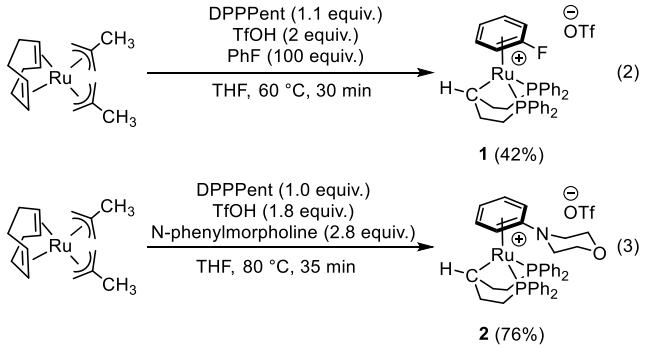


Figure 1. ORTEP diagrams of complexes **1** (left) and **2** (right). Ellipsoids are shown at 50% probability.

Catalyst Resting State and the Role of Additives

Under the previously reported catalytic conditions, both **1** and **2** catalyze the reaction between fluorobenzene and morpholine in similar yields to the catalyst generated *in situ* from Ru(cod)(methallyl)$_2$ (Table 1). The optimized conditions reported by Shibata include triethylamine and triethylsilane additives in stoichiometric amounts which they show are required for high yields. This observation is born out in our own studies; in the absence of additives the product is still formed but in reduced yield (46% vs 93% with additives). To address the possibility that reaction additives might influence catalyst speciation, the identity of the catalyst resting state was investigated by ^{31}P{^{1}H} NMR both in the presence and absence of silane and amine additives.

Based on the proposed mechanism put forth by Semmelhack[17] and our own arene binding measurements (*vide supra*), the bound phenylmorpholine compound (**2**) would be the expected resting state. Indeed, **2** is observed as the catalyst resting state by ^{31}P{^{1}H} NMR in the *absence* of triethylsilane and triethylamine, confirming that it represents a relevant system for mechanistic experiments (*vide infra*). However, in the presence of these additives (the reported *optimized* catalytic conditions), **2** is observed only at very short reaction times. Instead a second, previously unknown species **3** is observed as the major species during productive catalysis. Initial attempts to characterize **3** revealed that triethylsilane is necessary for its formation and that **3** possesses a metal hydride which resonates upfield at −9.5 ppm. Analysis of a single-crystal of **3** obtained by careful isolation from a variation of a catalytic reaction (eqn. 4) revealed that **3** is a bis(phosphine)ruthenium hydride lacking the alkyl ligand resulting from backbone cyclometalation in **2** (Figure 2). In separate experiments we found that **3** can be formed by treatment of **2** with 20 equiv. of triethylsilane, suggesting a route for the conversion of κ^3 cyclometalated complexes to the κ^2 form observed in **3**.

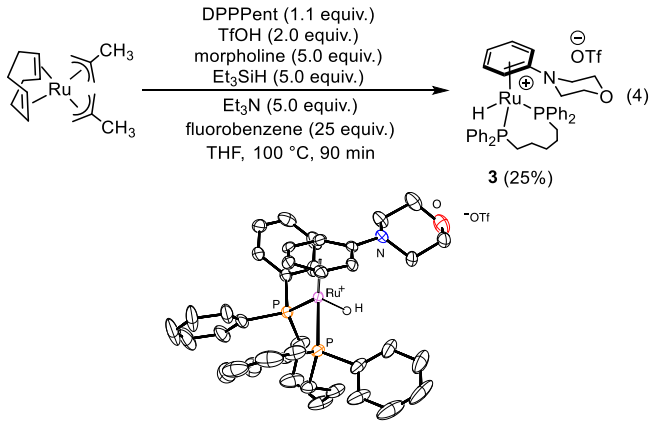


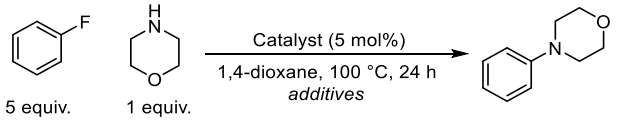
Figure 2. ORTEP diagram of complex **3**. Ellipsoids are shown at 50% probability.

When complex **3** is used as a precatalyst under Shibata's optimized conditions, the N-phenylmorpholine product is obtained in quantitative yield. (Table 1, Entry 4) This observation argues that ligand cyclometalation observed in **1** and **2** is not necessary for reactivity. Unlike in the case of complex **2**, the performance of complex **3** does not suffer in the absence of Et_3SiH and Et_3N additives. (Table 1, Entry 8) The Shibata group has previously hypothesized that the inclusion of triethylsilane and triethylamine is necessary to sequester hydrofluoric acid generated as a byproduct of fluoroarene S_NAr. The observation that silane is not required when **3** is used as a precatalyst argues against this hypothesis for the primary function of silane in the productive catalytic reaction. Instead its most-significant function appears to be the switch in ligand binding mode and thus the catalyst resting state from **2** to **3**.

Catalytic reactions conducted without additives (Table 1 entries 5-7, Table 2 entries 4-6) tended to give lower yields and were observed to deposit a yellow precipitate within the first several hours of the reaction except when **3** was used as a catalyst. Filtration and analysis of this precipitate after reaction completion showed that complex **2** precipitates in 85% yield with respect to the ruthenium precursor. Precipitation was not observed in the presence of additives, a result which argues that

the change in catalyst resting state from **2** to **3** is accompanied by increased catalyst solubility.

Table 1. Effect of precatalyst and additives on reaction yield.



5 equiv. 1 equiv.

Entry	Catalyst	Additives[a]	% Yield[b]
1	*in situ*[c]	Et_3N, Et_3SiH	93
2	**1**	Et_3N, Et_3SiH	98
3	**2**	Et_3N, Et_3SiH	92[d]
4	**3**	Et_3N, Et_3SiH	> 99[d]
5	*in situ*[c]	None	46
6	**1**	None	57
7	**2**	None	47[d]
8	**3**	None	> 99[d]

[a] 1 equiv. of each additive. [b] Yield by GC-FID [c] 5 mol% $Ru(cod)(methallyl)_2$, 7 mol% DPPPent, 10 mol% TfOH. [d] **2** and **3** contribute 5% to total yield, see SI.

Having determined that the presence of triethylsilane and triethylamine additives results in a switch in catalyst resting state from **2** to **3**, we attempted to investigate the corresponding fluorobenzene adduct. Unfortunately, efforts to prepare a fluoroarene complex analogous to **3** by treatment of **1** with triethylsilane gave complex mixtures of products without evidence for fluoroarene binding by NMR spectroscopy.

S_NAr Kinetics and Arene Binding Thermodynamics

Despite our inability to prepare the fluoroarene partner to complex **3**, the observation that **2** serves as the catalyst resting state in the absence of additives and leads to a productive catalytic reaction led us to pursue mechanistic studies on the **1**/**2** pair. In particular, the isolation of complex **1** affords us a unique opportunity to directly measure the rate of S_NAr on a π-arene in a system with catalytic relevance. Under pseudo-first order conditions, **1** reacts rapidly with morpholine to give **2** within 10 minutes at 23 °C, corresponding to a k_{obs} of 3.8 x 10^{-3} s^{-1} (Figure 3). The reactivity of complex **1** with morpholine at room temperature stands in contrast to the metal-free reaction of morpholine with even very highly-activated nitrofluorobenzenes. 2-nitrofluorobenzene has been reported to undergo amination by morpholine at 40 °C,[20] while 3-nitrofluorobenzene requires heating to 100 °C for 60 hours.[21]

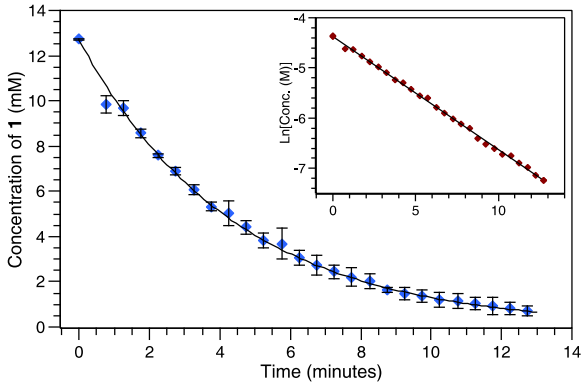


Figure 3. Stoichiometric S_NAr reaction of complex **1** with morpholine at 23 °C under pseudo-first order conditions. Inset: Ln[**1**] vs time. Conditions: 0.0127 M **1**, 0.127 M morpholine in 4:1 dioxane/DMF. See the SI for additional details.

The high rate of conversion of **1** to **2** observed at 23 °C suggests that this step is unlikely to be the primary determinant of the overall reaction rate under the reported catalytic conditions (5 mol% Ru, 24 hrs, 100 °C). Thus we next examined the arene exchange step in Scheme 1. Efficient displacement of product from the metal center is believed to be the most challenging aspect in the development of catalytic S_NAr reactions of π-arenes. Hartwig has previously examined the rate of displacement of N-phenethylmorpholine by styrene on the same ruthenium system.[19]

When complex **1** is treated with free N-phenylmorpholine (2 equiv.) in neat fluorobenzene at 23 °C, no arene exchange is observed. On heating to 100 °C, a stable equilibrium between **1** and **2** is obtained that allows for the determination of an equilibrium constant K_{eq} = 2 x 10^3 at 100 °C. Using this experimental equilibrium constant we can predict the ratio of complexes **2** and **1** during catalysis. After a single turnover, the ratio of **2** to **1** is predicted to be 4:1, a value that rises rapidly to > 200:1 after 10 turnovers (50% conversion). The predicted fraction of complex **1** as a function of turnover number is shown in Figure 4, and demonstrates the dramatic influence of strong product binding on the predicted catalyst resting state. Thus, even under idealized conditions, the proportion of catalyst in the fluoroarene form is predicted to fall by two orders of magnitude by the time the reaction yield has reached 25%.

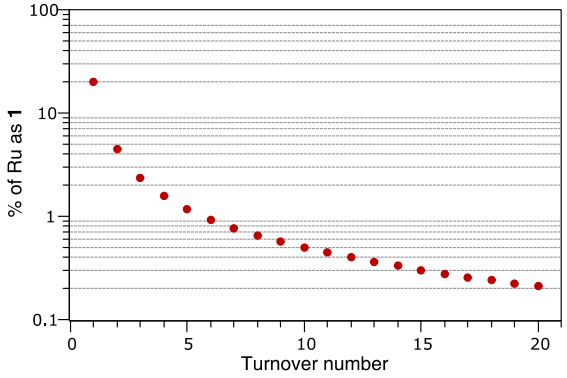
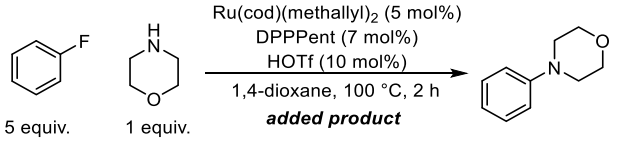


Figure 4. Predicted fraction of fluoroarene complex **1** as a function of turnover number; estimated from K_{eq}.

Indeed, product added at the beginning of the reaction has a strong inhibitory effect on catalytic turnover both in the presence and absence of additives (**3** and **2** as resting state respectively). The addition of 0.5 equiv. of N-phenylmorpholine leads to poor catalyst performance over 2 hours, while addition of a full equivalent of product inhibits catalysis even more dramatically (Table 2). The additive-free case appears to be affected to a larger extent, which may stem from the low apparent solubility of **2** (*vide supra*).

Table 2. Effect of added product on reaction yield after 2 hours.

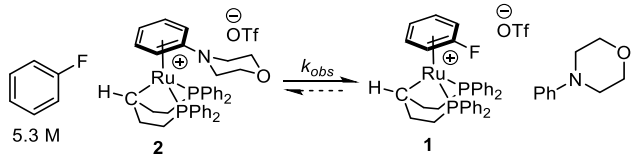


Entry	Additives[a]	Time	N-phenylmorpholine	% Yield[b]
1	Et_3N, Et_3SiH	2 hr	0 equiv.	32
2	Et_3N, Et_3SiH	2 hr	0.5 equiv.	10
3	Et_3N, Et_3SiH	2 hr	1.0 equiv.	2
4	None	2 hr	0 equiv.	15
5	None	2 hr	0.5 equiv.	1
6	None	2 hr	1.0 equiv.	2

[a] 1 equiv. Et_3N, 1 equiv. Et_3SiH. [b] Yield by GC-FID.

While the thermodynamics of product binding can be expected to decrease the fraction in the active form at equilibrium, the rate of arene exchange should determine whether equilibrium concentrations are achieved under catalytic conditions. To that end, we examined the rate of displacement of N-phenylmorpholine by a large excess of fluorobenzene (conversion of **2** to **1**). Initial rate constants for the conversion of **2** to **1** via arene exchange are shown as a function of temperature in Table 3. Under these conditions, product displacement at 65 °C is found to be two orders of magnitude slower than S_NAr measured at 23 °C. From these data the activation energy of arene exchange is calculated to be 34 kcal·mol^{-1}. The precise mechanism of arene exchange can be complex and conditions-dependent,[18, 22-26] but these values provide some insight into the lability of the product arene in **2**.

Table 3. Rate of product arene exchange in **2**.

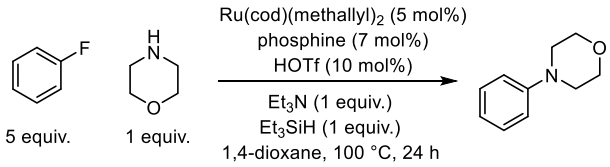


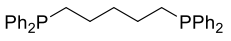
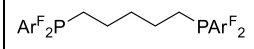
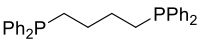
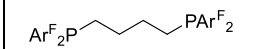
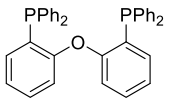
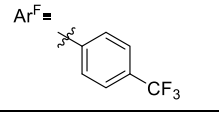
Entry	Temperature	Rate constant **2**→**1** (k_{obs})
1	65 °C	5.6 x 10^{-5} s^{-1}
2	70 °C	1.3 x 10^{-4} s^{-1}
3	75 °C	2.4 x 10^{-4} s^{-1}
4	80 °C	4.8 x 10^{-4} s^{-1}
5	85 °C	1.1 x 10^{-3} s^{-1}

Together our rate and equilibrium measurements on this system demonstrate two important features of this reaction: 1) the N-phenylmorpholine product arene binds with roughly 2000 times greater affinity than fluorobenzene, leading to strong product inhibition and 2) that the requirement for elevated reaction temperatures is likely dictated largely by the kinetics of arene exchange and the requirement for S_NAr on the minute fraction of catalyst present as **1**.[27] While comparable studies have not been performed on related catalysts, all catalytic π-arene alkoxylation and amination systems appear to achieve no more than *ca.* 20 TON under reported conditions.[11, 13-14]

Role of Phosphine Ligands. Further evidence for the suggestion that cyclometalation is not necessary for the reactivity of the DPPPent system can be obtained through the substitution of other phosphine ligands. A number of bidentate phosphines are found to give modest catalytic activity (Table 4). For instance while 2,2'-bis(diphenylphosphino)diphenyl ether (DPEPhos) can coordinate through the biarylether moiety, it cannot cyclometalate to give an anionic alkyl donor, but still gives comparable yields to DPPPent (Table 4, Entry 7).[28] Other phosphines give reduced but still appreciable yields (Entries 2-7). The results of our phosphine comparison when taken together with evidence showing a silane-controlled resting state of the catalytic reaction suggest that ligand cyclometalation is not a defining feature of S_NAr catalysis by the DPPPent system.

Table 4. Effect of phosphine ligand on reaction yield.



Phosphine	Yield[a]	Phosphine	Yield[a]
PPh_3	49%[b]	PAr^F_3	19%[b]
	93%		23%
	50%		66%
	81%		

[a]Yield by GC-FID [b]14 mol% phosphine used.

Both the bis(phosphine) monohydride ligand set in **3** and the κ^3-phosphine in **2** provide monoanionic 5-electron donor environments, a motif that is conserved in pentamethylcyclopentadienyl and cyclopentadienyl catalysts reported by Grushin[12] and Williams[16] respectively. Among published systems for π-arene catalyzed S_NAr, only a recent report from Shi diverges from this pattern by employing a *dicationic* ruthenium bis(phosphine) complex.[13] This observation inspired the preparation of complex **4-OTf** (eqn. 5 and Figure 5), which conserves the hydrido bis-phosphino motif found in **3**. Like **3**, **4-OTf** catalyzes the amination of fluorobenzene by morpholine in good, albeit not quantitative yield in the absence of additives (Table 5, entry 1). **4-OTf** does outperform *in situ*-generated conditions for PPh_3 (Table 5 Entry

1 versus Table 4). Thus **4-OTf** offers a convenient, single-component precatalyst that can be prepared in a single step from a commercially-available ruthenium source.

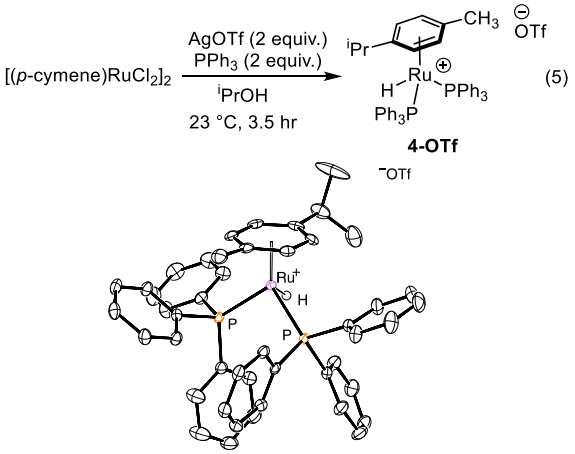
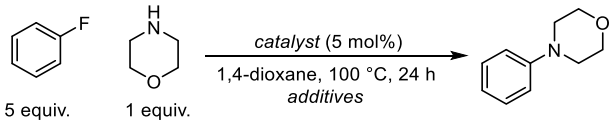


Figure 5: ORTEP diagram of complex **4-OTf**. Ellipsoids are shown at 50% probability.

Role of Acid Additives. Having identified that **4-OTf** is an accessible, single-component catalyst with some room for improvement versus **3**, we examined the role of added Brønsted acid and/or metal triflates with both **4-OTf** and the triflate-free **4-PF$_6$** complex. In theory, protonation of the aniline product could decrease product inhibition, though any potential improvement would be counterbalanced by competing protonation of the more-basic morpholine nucleophile. In practice, addition of triflic acid with or without added triethylamine leads to reductions in yield (Table 5). Small amounts of triflate ion appear to be beneficial[22] (entries 1 vs 5 and 5 vs 6), though larger quantities of lithium triflate led to poorer results. Thus it would appear that alternative approaches are still necessary to address product inhibition if higher TONs are desired.

Table 5. Effect of acid and base additives on reaction yield.



Entry	Cat.	Additives	% Yield[a]
1	**4-OTf**	None	72
2	**4-OTf**	1 equiv. TfOH	3
3	**4-OTf**	1 equiv. TfOH, 1 equiv. Et_3N	41
4	**4-OTf**	0.1 equiv. TfOH, 1 equiv. Et_3N	71
5	**4-PF$_6$**	None	51
6	**4-PF$_6$**	0.1 equiv LiOTf	60
7	**4-PF$_6$**	0.2 equiv LiOTf	53
8	**4-PF$_6$**	1.0 equiv LiOTf	30

[a] Yield by GC-FID

Arene binding in 2 vs 3. Owing to our inability to isolate the fluorobenzene analogue of **3**, the reactivity of this putative intermediate can only be inferred by comparison to complex **1**. We undertook a computational comparison of arene binding thermodynamics using our experimentally-determined energies for the complex **1**/**2** pair as a benchmark. DFT calculations (M06L/def2-SVP/TZVP) indicate that N-phenylmorpholine binding by **1** is exergonic by -8.3 kcal·mol^{-1} at 100 °C, which is in good agreement with our experimentally determined value of -5.3 kcal·mol^{-1} derived from the equilibrium constant at 100 °C. N-phenylmorpholine displacement of fluorobenzene in the ruthenium hydride version of the catalyst to give **3** is computed to be exergonic by -9.6 kcal·mol^{-1}. Thus the small difference in affinity for the N-phenylmorpholine and fluorobenzene arene pair, computed for **2** and **3**, ($\Delta\Delta G_{calc}$ = 1.3 kcal·mol^{-1}) predicts that the decyclometalated and cyclometalated forms of the catalyst are subject to comparably strong product arene binding.

Conclusions

In summary, our examination of the Ru-catalyzed S_NAr of fluoroarenes has revealed new details that shed light on a very rare example of catalytic nucleophilic aromatic substitution at a π-arene. We have demonstrated an additive-dependent switch in the identity of the resting state of the catalyst resulting from the ligand's ability to bind in either a κ^2 or cyclometalated κ^3 forms. Isolation of both catalytic intermediates in the cyclometalated form has allowed us to estimate the difference in the free energy of product N-phenylmorpholine binding vs fluorobenzene binding – a key consideration in the arene exchange step necessary for catalytic turnover. These experimental results are contextualized with DFT calculations showing comparable binding affinities for the κ^2 form of the catalyst observed in the presence of silane additives. Experimental measurements and predictions of binding enthalpies quantify the severity of product inhibition encountered in this example of π-arene S_NAr amination. We show that ligand cyclometalation is not a determining factor in the ability of this class of cationic ruthenium complexes to serve as catalysts for S_NAr. The silane additive previously hypothesized to function to sequester fluoride ion appears to contribute to productive catalysis primarily through its ability to modulate ligand cyclometalation, an observation which has allowed us to employ a simple, single-component precatalyst for fluorobenzene amination. Attempts are currently underway to translate these findings into the design of more-robust and efficient catalysts for π-arene catalyzed S_NAr.

Conflicts of interest

There are no conflicts to declare.

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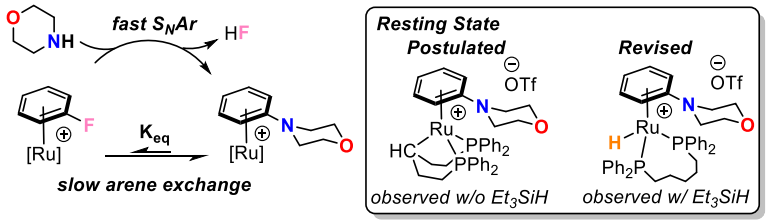
ARTICLE

Graphical Abstract



Investigation of a DPPPent-supported Ru catalyst for S_NAr through π-arene activation provides details of catalyst structure and product inhibition.