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Substituent Effects on Stoichiometric and Catalytic Cleavage of Carbon−Nitrogen Bonds in Aniline Derivatives by Ruthenium−Phosphine Complexes

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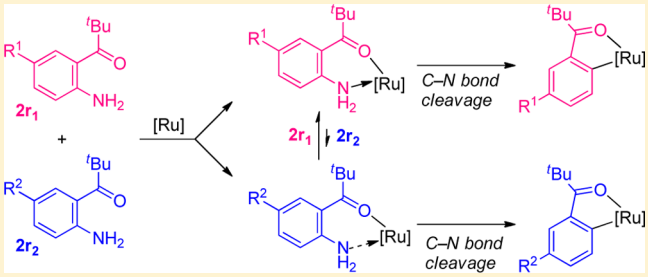
Supporting Information

ABSTRACT: The reactivity of various *o*-acylaniline derivatives with ruthenium complexes was examined. The reaction of *o*-acylanilines with $RuH_2(CO)(PPh_3)_3$ (**1**) or an activated ruthenium species formulated as "$Ru(CO)(PPh_3)_3$" (**4**) gave amido hydrido complexes **3** and aryl amido complexes **6** formed via N−H and C−N bond cleavage, respectively. Addition of olefins, such as vinylsilanes, accelerates the C−N bond cleavage. The aryl amido complexes **6** can provide the C−N arylation product upon treatment with arylboronates. The relative reactivity of *o*-acylanilines bearing various substituents was investigated by competition experiments, and it was found that electron-donating substituents increase the relative facileness of the C−N bond cleavage in both stoichiometric and catalytic reactions. The trend observed here is different from the one observed for the previously reported tantalum-mediated C−N bond cleavage.



INTRODUCTION

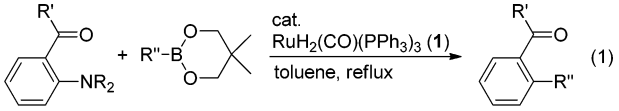
Catalytic bond formation via cleavage of normally unreactive bonds is one of the areas where transition-metal catalysts exhibit significant values in organic synthesis and has been extensively and continuously studied by many researchers.[1] Transition-metal complexes can not only cleave bonds that are inert toward other reactive species but also allow for selective cleavage of the inert bonds without affecting other functional groups. The selectivity of the bond cleavage may depend on the transition-metal complexes, and it is possible to control the order of relative easiness of bond cleavage.[2]

Carbon−nitrogen bonds can be found in numerous organic molecules and are usually regarded as unreactive bonds.[3−12] Aromatic C−N bonds in anilines are particularly inert, and there are not many studies concerning their catalytic[3−7,10] or stoichiometric[8,9,11] cleavage. Therefore, in order to functionalize aromatic C−N bonds, they are often activated by conversion of anilines to arenes bearing better leaving groups, such as diazonium salts,[3] ammonium salts,[4] and triazenes.[5]

In 1980, Fujiwara and co-workers reported that reaction of anilines with olefins in the presence of stoichiometric amounts of palladium salts and carboxylic acids under air gave arylated olefins as products.[7] It was proposed that the reaction proceeds via oxidative addition of the C−N bond of protonated anilines, but it was unclear how the C−N bond was cleaved in the reaction.

The first direct observation of aromatic C−N bonds in anilines was achieved in 1996 by Wolczanski and co-workers using a tantalum(III) siloxide complex.[8] The tantalum complex can cleave either an N−H or a C−N bond, and its propensity to cleave the C−N bond relative to the N−H bond was correlated with Hammett σ-parameters of the substituents. An increase of the electron-withdrawing nature of the substituent enhanced the relative rate of the C−N bond cleavage. Aromatic C−N bond cleavage was also observed for an (*N*-silyl)arylamido molybdenum complex.[9] However, application of the these stoichiometric processes to catalytic functionalization of the aromatic C−N bonds has not been achieved yet.

In 2007, our group reported the first catalytic functionalization via cleavage of an unactivated aromatic C−N bond in anilines (eq 1).[10] A cross-coupling reaction of *o*-acylanilines with various



NR_2 = NH_2, NHMe, NMe_2 etc

organoboronates proceeded using $RuH_2(CO)(PPh_3)_3$ (**1**) as a catalyst. It was proposed that the reaction proceeds via a mechanism similar to cross-coupling reactions as follows: (1) oxidative addition of the C−N bond, (2) transmetalation between the ruthenium amide complex and an organoboronate, and (3) reductive elimination to form the C−C bond. At the time of this report, however, there was no evidence of the direct C−N bond cleavage and the transmetalation between ruthenium amide species and organoboronates.

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Table 1. Selected ^{1}H and ^{31}P{^{1}H} NMR Data of Amido Hydrido Ruthenium Complexes 3

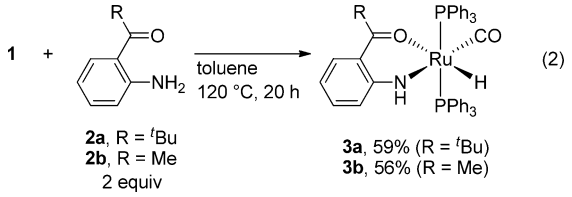
entry	2	R′	R	3	δ (^{31}P) [ppm]	δ (^{1}H) [ppm]	^2J (^{1}H, 31P) [Hz]
1	**2a**	^{t}Bu	H	**3a**	47.0 (s)	−15.08 (t)	21.0
2	**2b**	Me	H	**3b**	47.1 (s)	−14.85 (t)	20.6
3	**2c**	^{t}Bu	Me	**3c**	47.3 (s)	−15.25 (t)	21.2
4	**2d**	^{t}Bu	MeO	**3d**	47.2 (s)	−15.19 (t)	21.6
5	**2e**	^{t}Bu	F	**3e**	46.8 (s)	−15.45 (t)	20.9
6	**2f**	^{t}Bu	CF_3	**3f**	46.2 (s)	−15.44 (t)	20.8

Recently, we also reported a preliminary study of the reactivity of *o*-acylanilines toward catalytically relevant ruthenium complexes and showed that the N−H and C−N bonds can be cleaved on ruthenium centers to give amido hydrido complexes **3** and aryl amido complexes **6**, whose structures were confirmed by single-crystal X-ray diffraction analyses.[11] The aryl amido complex can provide the C−N arylation product upon treatment with an arylboronate and can also function as a catalyst for the C−N arylation reaction.

Here, we describe further details of our mechanistic studies on the catalytic C−N arylations. Particularly, stoichiometiric and catalytic reactions of ruthenium complexes were examined with *o*-acylanilines bearing various substituents on the aromatic rings, and interestingly, it was found that electron-donating substituents increase the relative facileness of the C−N bond cleavage in competition reactions, which is a trend different from the one observed for the previously reported tantalum-mediated C−N bond cleavage.[8]

RESULTS AND DISCUSSION

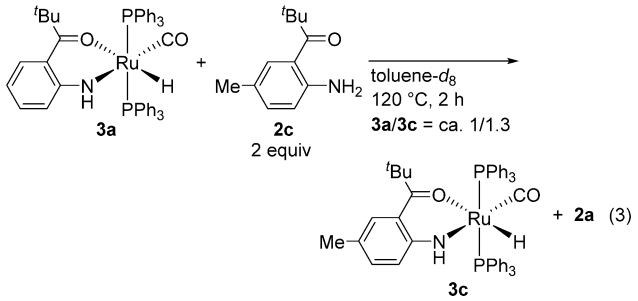
Formation of Amido Hydrido Ruthenium Complexes 3 via N−H Bond Cleavage. The reactivity of ruthenium complex **1** toward various *o*-acylanilines **2** was investigated. When the reaction of complex **1** with 2 equiv of *o*-pivaloylaniline **2a** or *o*-acetylaniline **2b** in toluene-d_8 at 120 °C was monitored periodically by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy, complete consumption of **1** and formation of amido hydrido complex **3** was observed within 20 h (Table 1, entries 1 and 2).[13] Formation of an amido hydrido ruthenium complex from aniline via N−H bond cleavage was reported by Hartwig, Andersen, and Bergman.[14] The chemical shifts of characteristic signals on the ^{1}H and ^{31}P{^{1}H} NMR spectra of amido hydrido complexes were summarized in Table 1. Complexes **3a** and **3b** were isolated by conducting the reaction in toluene (eq 2), and the structure of **3b**



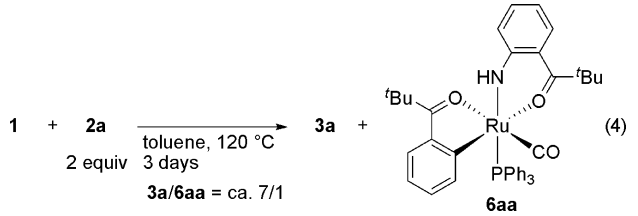
was comfirmed by X-ray diffraction analysis.[11] The reactions of complex **1** with *o*-acylanilines with various substituents (**2c**−**2f**) were also monitored for 20 h by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy, and complete conversion of **1** and formation of the corresponding amido hydrido complexes **3c**−**3f** were observed for each reaction (entries 3−6). While the ^{31}P{^{1}H} NMR spectrum showed a singlet between 46.2 and 47.3 ppm for each case, a triplet with a small coupling constant of ca. 21 Hz appeared on the ^{1}H NMR spectrum. The observation of these signals is consistent with the structural assignment of **3**, which has two phosphines at the trans position to each other.

Our group previously reported that an activated ruthenium complex formulated as "Ru(CO)(PPh$_3$)$_3$" (**4**),[15] which was generated by treatment of **1** with trimethylvinylsilane (**5a**), catalyzed the C−H alkylation of aromatic ketones at room temperature. We examined the reaction of complex **4** with **2a** and found that it proceeds to give amido hydrido complex **3a** at room temperature within 1 h.

The amide ligand of amido hydrido complex **3** was indicated to be exchangeable. Treatment of complex **3a** with 2 equiv of **2c** at 120 °C for 30 min gave a ca. 1:1.3 mixture of **3a** and **3c**, and the ratio remained unchanged even after 1.5 h (eq 3).



Formation of Aryl Amido Ruthenium Complexes 4 via C−N Bond Cleavage. When the reaction of **1** with **2a** at 120 °C was performed for 3 days, a ca. 7:1 mixture of **3a** with aryl amido complex **6aa** was generated. Complex **6aa** was isolated in 6% yield (eq 4), and its structure was confirmed by X-ray diffraction



analysis.[11] The structure of **6aa** clearly shows that the aromatic C−N bond of **2a** was cleaved by ruthenium complex **1**. Complex **6aa** contains pivalophenone backbones of two molecules of **2a**,

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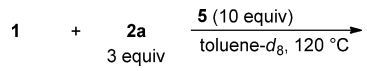
but one of the nitrogens of **2a** was removed from the complex as ammonia possibly by protonation or ligand exchange with **2a**.

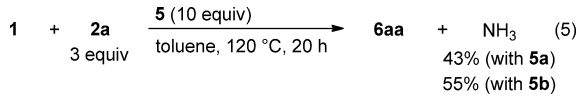
The C−N bond cleavage was considerably accelerated by the addition of olefins (Table 2). The reaction of **1** with **2a** in the presence of vinylsilane **5a** at 120 °C was completed within 2 h to give **6aa** in 96% NMR yield as the only ruthenium species observed (entry 1). The use of *tert*-butylethylene also gave complex **6aa** in 90% NMR yield within 2 h, but no further conversion of **1** to **6aa** was observed after this period (entry 2). The reaction in the presence of triethylvinylsilane (**5c**) was slower than that with **5a**, but after 20 h, complex **6aa** was obtained in 88% yield (entry 3). Electron-deficient olefins, such as methyl acrylate (**5d**) and cyclohex-2-enone (**5e**), were not effective as an additive, and no formation of **6aa** was detected (entries 4 and 5). On the basis of the fact that only electron-rich olefins accelerated the formation of **6aa**, the olefins can be considered to promote the C−N bond cleavage by coordination to donate π electrons to the metal center.

Table 2. Effect of Olefins on the C−N Bond Cleavage

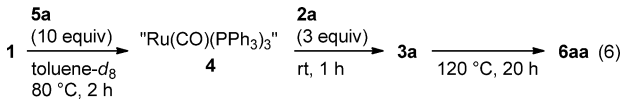


entry	5	time [h]	NMR yield [%]
1	$Me_3SiCH{=}CH_2$ (**5a**)	2	96
2	$Me_3CCH{=}CH_2$ (**5b**)	2	90
3	$Et_3SiCH{=}CH_2$ (**5c**)	20	88
4	$MeOC(O)CH{=}CH_2$ (**5d**)	20	not detected
5	cyclohex-2-enone (**5e**)	20	not detected

Generation of ammonia was confirmed for the reaction of **1** with **2a** in the presence of **5a** or **5b** (eq 5). The amounts of ammonia were quantified by the indophenols-blue method,[16] and 43% and 55% yields of ammonia were detected for the reactions with **5a** and **5b**, respectively.



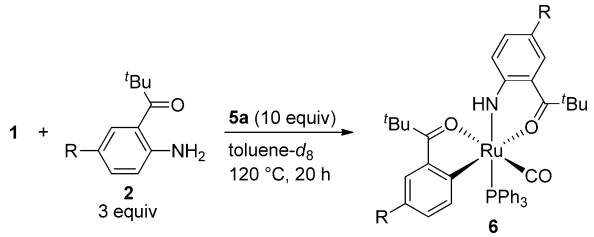
Aryl amido complex **6aa** can also be prepared from **3a** in the presence of **5a** (eq 6). As described above, amido hydrido complex **3a** can be prepared in situ by the reaction of acylaniline **2a** and activated ruthenium complex **4**, generated by treatment of **1** with vinylsilane **5a**. When this mixture of **3a** and an excess amount of **5a** was heated at 120 °C for 20 h, aryl amido complex **6aa** was formed cleanly. This result suggests that vinylsilane **5a** accelerated not only the generation of **4** but also the C−N bond cleavage to give complex **6aa**.



Aryl amido complex **6** can be generated using various acylanilines **2**. Treatment of **1** with 3 equiv of **2** in the presence of 10 equiv of vinylsilane **5a** at 120 °C cleanly gave complex **6** in each case. The chemical shifts of $^{31}P\{^1H\}$ NMR signals are summarized in Table 3.

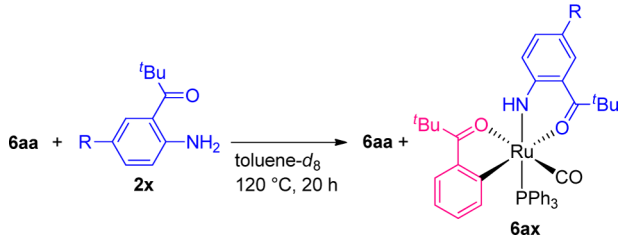
Exchange of an *N,O*-Chelate Ligand of Complex 6. The *N,O*-chelate ligand of **6** can be exchanged with acylaniline **2** without affecting the *C,O*-chelate. The reaction of aryl amido complex **6aa** with 2 equiv of methyl-substituted acylaniline **2c** gave a ca. 1:2 mixture of **6aa** with **6ac**, which contains an *N,O*-chelate derived from **2c** and the same *C,O*-chelate as the one in starting complex **6aa** (Table 4, entry 1). The exchange reaction between **6aa** and **2c** similarly occurred in the presence of vinylsilane **5a**. The *N,O*-chelate exchange was also examined with various acylanilines **2**. While the reaction with methoxy-substituted acylaniline **2d** gave a similar mixture of **6aa** and **6ad** (entry 2), the use of an acylaniline with a trifluoromethyl group (**2f**) gave only **6af** as a product. In the case of the reaction using fluoro-substituted acylaniline **2e**, the $^{31}P\{^1H\}$ NMR signals of **6aa** and **6ae** overlapped, but the formation of **6ae** was suggested by the ^{19}F NMR spectrum.

Table 3. $^{31}P\{^1H\}$ NMR Chemical Shifts of Aryl Amido Ruthenium Complexes 6 Formed by the Reaction of 1 with 2



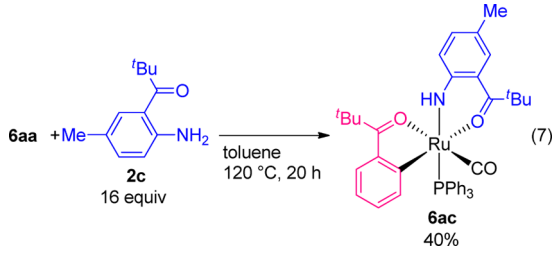
entry	2	R	6	δ (^{31}P) [ppm]
1	**2a**	H	**6aa**	48.35 (s)
2	**2c**	Me	**6cc**	48.44 (s)
3	**2d**	MeO	**6dd**	48.48 (s)
4	**2e**	F	**6ee**	47.49 (s)
5	**2f**	CF_3	**6ff**	46.36 (s)

Table 4. $^{31}P\{^1H\}$ NMR Chemical Shifts of Aryl Amido Ruthenium Complexes 6ax Formed by the Reaction of 6aa with 2



entry	2x	R	6ax	δ (^{31}P) [ppm]
1	**2c**	Me	**6ac**	48.24 (s)
2	**2d**	MeO	**6ad**	48.17 (s)
3	**2f**	CF_3	**6af**	48.66 (s)
4	**2e**	F	**6ae**	48.33 (s)

Using this ligand-exchange process, complex **6ac** was isolated in 40% yield by conducting the reaction with a large excess of **2c**, followed by recrystallization (eq 7). The molecular structure of **6ac** was determined by single-crystal X-ray diffraction analysis.



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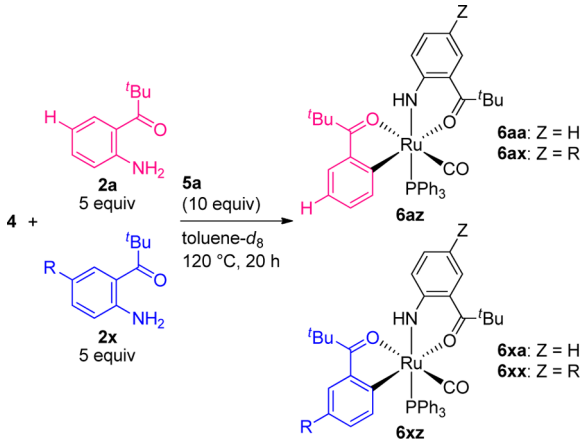
Influence of the Substituents on the Aromatic Ring of *o*-Acylanilines on the C−N Bond Cleavage. The fact that the *C,O*-chelate formed via C−N bond cleavage is stable in the presence of acylanilines and a vinylsilane prompted us to examine the effect of substituents on the aromatic rings of acylanilines on the C−N bond cleavage by competition experiments. The reaction of activated ruthenium complex **4** with two different acylanilines, **2a** and **2x**, would give four possible aryl amido complexes, **6aa**, **6ax**, **6xa**, and **6xx**. Whereas complexes **6aa** and **6ax** are formed by cleavage of the C−N bond of **2a**, generation of complexes **6xa** and **6xx** occurs via C−N bond cleavage of **2x**. Because the *N,O*-chelates are exchangeable under the reaction conditions, the relative reactivity of the C−N bonds in **2a** and **2x** can be estimated by comparison of the total amount of **6aa** and **6ax** with that of **6xa** and **6xx**.

To examine the relative reactivity, the reaction of complex **4** with 5 equiv of **2a** and para-substituted acylaniline **2x** was performed in toluene-d_8 at 120 °C for 20 h in the presence of vinylsilane **5a** and monitored by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy. The ratio of **6az** (**6aa** and **6ax**) to **6xz** (**6xa** and **6xx**) was estimated by intensities of ^{31}P{^{1}H} NMR signals, and the results were summarized in Table 5. The competition

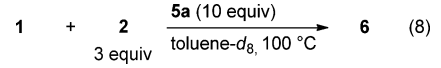
Table 5. Competition Reactions of Two Acylanilines 2 with Activated Complex 4



entry	2x	R	6az/6xz	relative reactivity
1	**2d**	MeO	1/1.7	H < MeO
2	**2c**	Me	1/1.3	H < Me
3	**2e**	F	1/1.2	H < F
4	**2f**	CF_3	1/1.0	H ~ CF_3

experiments using **2a** and methoxy-substituted acylaniline **2c** revealed that the electron-donating methoxy group enhances the relative easiness of the C−N bond cleavage and offered the largest ratio of **6xz** to **6az** (entry 1). On the other hand, the substrate bearing the electron-withdrawing trifluoromethyl group at the para position of the amino group (**2f**) was the least reactive among the para-substituted acylanilines **2c**−**2f**. On the basis of these experiments, the relative reactivity order of **2a**−**2e** is considered to be MeO > Me > F > H ~ CF_3. The substituent effect on the C−N bond cleavage was not cleanly correlated with the Hammett substituent constants,[17] but the electron-donating substituent, such as OMe and Me groups, increased the reactivity of the C−N bonds. Therefore, the subsitutent effect observed here on the C−N bond cleavage is opposite to that of Wolczanski's tantalum-mediated C−N bond cleavage[8] and the general tendency of oxidative addition of polar aromatic C−X bonds.[18,19]

The C−N bond cleavage of individual substrates **2** was then closely monitored by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy. The reaction was performed at 100 °C using complex **1** with 3 equiv of each substrate **2** in the presence of **5a** in toluene-d_8 (eq 8).



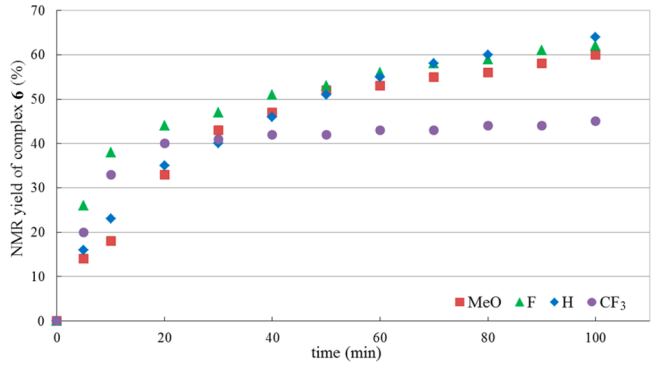


Figure 1. Plots of NMR yields of **6** vs time.

Figure 1 shows the plots of the ^{1}H NMR yields of aryl amido complex **6** versus time. In each reaction, both amido hydrido complex **3** and aryl amido complex **6** were observed. At the early stage of the reactions, formation of aryl amido complex **6** from electron-withdrawing acylanilines **2e** and **2f** was faster than that from **2a** and **2d**, but eventually the rates of the formations of **6** from **2a**, **2d**, and **2e** became all similar. Only in the case of trifluoromethyl-substituted acylaniline **2f**, the formation of **6ff** significantly slowed down after 30 min, probably because amido hydrido complex **3f** is considerably stabilized by the electron-withdrawing trifluoromethyl group and conversion of **3f** to **6ff** is significantly retarded.

The electronic effect of the substituents on *o*-acylaniline **2** can be explained as follows (Figure 2). The N−H bond cleavage to form **3** and the C−N bond cleavage to eventually give **6** can proceed via the same intermediate **7** where *o*-acylaniline **2** coordinates through the oxygen and nitrogen atoms to the ruthenium in a bidentate fashion. The fact that the amido ligand of **3** can be rapidly exchanged with another *o*-acylaniline **2** suggests that, in an competition experiment of *o*-acylanilines $\mathbf{2r_1}$ and $\mathbf{2r_2}$, rapid conversion between amido hydrido complexes $\mathbf{3r_1}$ and $\mathbf{3r_2}$ and *o*-acylaniline-bound intermediates $\mathbf{7r_1}$ and $\mathbf{7r_2}$ takes place. If R_1 is more electron-donating than R_2, $\mathbf{2r_1}$ is expected to bind to the ruthenium more strongly than $\mathbf{2r_2}$. Therefore, the concentration of $\mathbf{7r_1}$ should be higher than that of $\mathbf{7r_2}$. Given that the rate of the C−N bond cleavage itself is not much affected by the substituent on **2**, (based on the result shown in Figure 1), the C−N bond cleavage should occur more often for more electron-rich $\mathbf{2r_1}$ in the competition experiment. Aryl amido complex **6** may be formed via oxidative addition of the C−N bond to a ruthenium(0) center to give *ortho*-ruthenated amido complex **8**, followed by protonolysis or ligand exchange of the Ru−NH_2 bond with another molecule of **2** to generate an ammonia molecule.[11]

C−C Bond Formation by the Reaction of Aryl Amido Complex 6 with Arylboronates. Treatment of aryl amido

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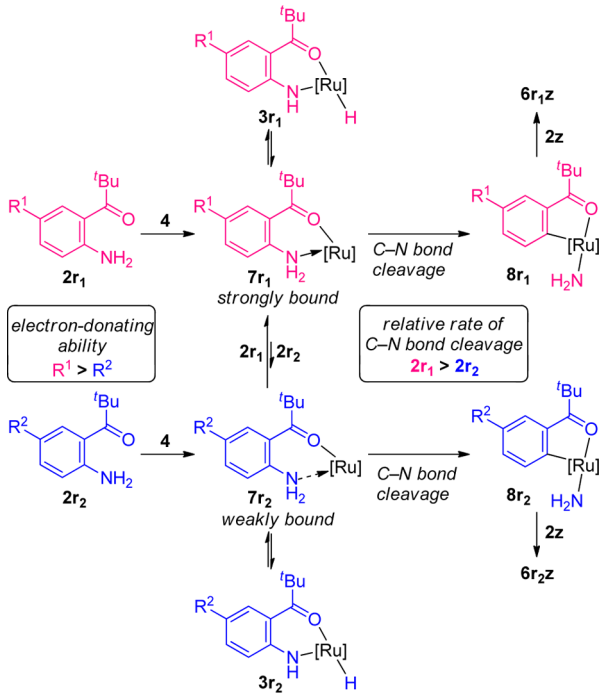
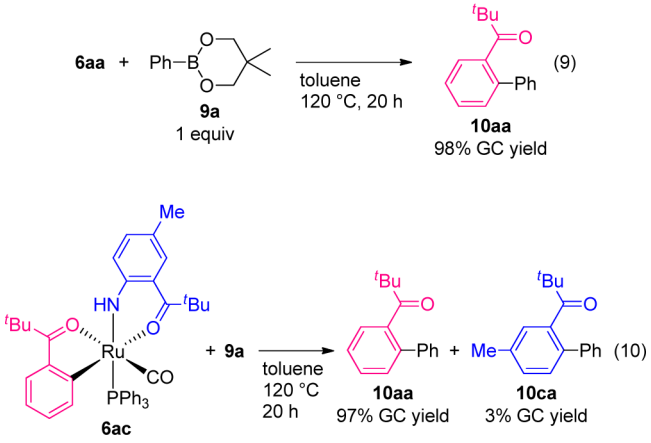


Figure 2. Possible explanation for the effect of substituents on N−H and C−N bond cleavages.

complex **6aa** with an equimolar amount of phenylboronate **9a** at 120 °C provided nearly 1 equiv of phenylation product **10aa** (eq 9). The reaction of aryl amido complex **6ac** with **9a** was also



performed to give **10aa** in 97% yield with a small amount of **10ca** (eq 10), which essentially indicates that the aryl group formed via the C−N bond cleavage, not the amide ligand, was coupled with **9a**. This result also shows that the C−N bond of *o*-acylaniline **2** can be converted to the C−C bond via C−N bond cleavage by ruthenium, followed by coupling with arylboronates.

Catalytic C−C Bond Formation Using Amido Hydrido Complex 3a and Aryl Amido Complex 6aa. To ensure that amido hydrido complex **3** and aryl amido complex **6** are catalytically relevant species, the use of these complexes for catalytic C−N arylation was examined (Table 6). When the reaction of *o*-acylaniline **2a** with phenylboronate **9a** was performed at 120 °C for 20 h using 4 mol % of aryl amido complex **6aa** as a catalyst, phenylation product **10aa** was obtained in 27% yield (entry 1).[20] Addition of triphenylphosphine was then investigated, and the reaction with 1 and 2 equiv

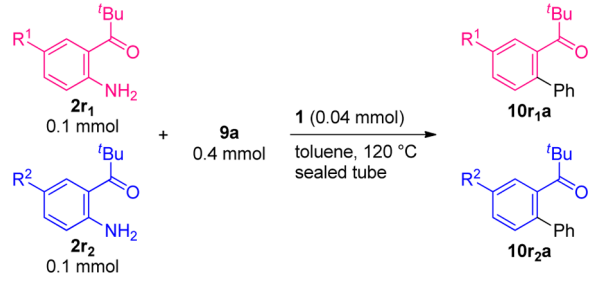
Table 6. C−C Bond Formation via C−N Bond Cleavage Catalyzed by Aryl Amido Complex 6aa and Amido Hydrido Complex 3a

entry	9a [equiv]	catalyst	PPh_3 [equiv]	GC yield [%]
1	1.2	4 mol % **6aa**		27
2	1.2	4 mol % **6aa**	1	49
3	1.2	4 mol % **6aa**	2	66
4	1.2	4 mol % **6aa**	3	65
5	1.2	4 mol % **3a**		29
6	1.2	4 mol % **3a**	1	35
7	2	8 mol % **3a**	1	59

of triphenylphosphine to **6aa** provided **10aa** in 49% and 66% yields, respectively (entries 2 and 3). A further increase of the amount of triphenylphosphine did not improve the yield (entry 4). The reaction using amido hydrido complex **3a** was also performed. The reaction using 4 mol % of **3a** in the absence of additional triphenylphosphine gave product in 29% yield (entry 5). In the case of **3a**, addition of triphenylphosphine did not lead to significant improvement of the yield (entry 6), but using 2 equiv of phenylboronate **9a** with 8 mol % of **3a** and triphenylphosphine, phenylation product **10aa** was obtained in 59% yield (entry 7).

Substituent Effect of *o*-Acylanilines in Competition Experiments of the Catalytic Arylation of the C−N Bonds. The substituent effect of **2** on the catalytic phenylation was also examined by competition experiments using two different *o*-acylanilines (Table 7). The reactions were carried out with 0.1

Table 7. Substituent Effect of *o*-Acylanilines on Catalytic C−C Bond Formation in Competition Experiments



				recovery [%]		GC yields [%]	
entry	R_1	R_2	time [h]	**2r1**	**2r2**	**10r1a**	**10r2a**
1	MeO (**2d**)	H (**2a**)	1	22	52	48	39
2	Me (**2c**)	H (**2a**)	1	28	30	68	43
3	MeO (**2d**)	CF_3 (**2f**)	5	56	77	28	18
4	Me (**2c**)	CF_3 (**2f**)	5	72	62	20	13
5	H (**2a**)	CF_3 (**2f**)	9	60	62	26	22

mmol each of two types of *o*-acylanilines, 0.4 mmol of **9a**, and 0.04 mmol of catalyst **1**, and the results are summarized in Table 7. In general, the phenylation of *o*-acylanilines with relatively more electron-donating substituents is faster than those with less electron-donating or electron-withdrawing ones. When the competition reaction of methoxy- or methyl-substituted substrate, **2d** or **2c**, with unsubstituted *o*-acylaniline **2a** was performed for 1 h, phenylation product **10r$_1$a** from the former

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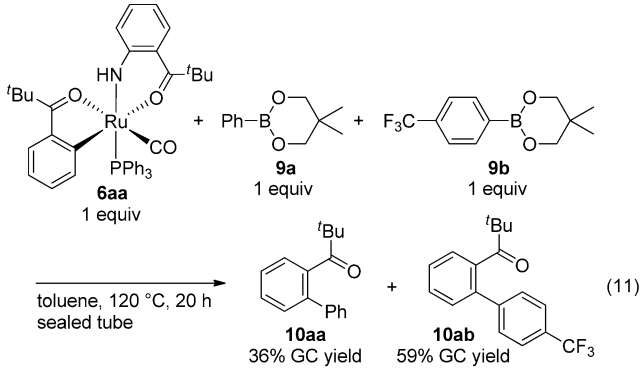
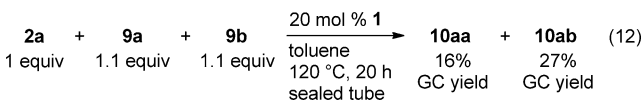
substrate was obtained in higher yield than that from **2a** (entries 1 and 2). The competition reactions using trifluoromethyl-substituted *o*-acylaniline **2f** as one of two substrates was much slower (entries 3−5), but again in these cases, the product from **2f** was formed in lower yields than those from *o*-acylanilines with more electron-donating groups, **2d**, **2c**, and **2a**. Thus, the trend that the C−N bond cleavage of the *o*-acylanilines with electron-donating substituents is faster than those with electron-withdrawing or no substitution in the competition reactions is not only observed in the stoichiometric C−N bond cleavage but also in the catalytic C−N arylation via C−N bond cleavage.

Substituent Effect of Arylboronates on the C−C Bond Formation. The effect of the substituents on the aromatic rings of arylboronates on the C−C bond formation was investigated. The reaction of aryl amido complex **6aa** with two types of **9**, phenyl- and (*p*-trifluoromethyl)phenylboronates, **9a** and **9b**, was conducted to provide phenylation product **10aa** in 36% yield along with 59% yield of product **10ab**, formed from the latter arylboronate (eq 11). The catalytic arylation of *o*-acylaniline **2a**



(11)



(12)

using **9a** and **9b** also gave **10aa** in lower yield than **10ab** (eq 12). Therefore, in both cases, electron-deficient arylboronate **9b** showed higher reactivity than **9a**. Similar electronic effects of organoboron compounds have been observed for the C−N arylation of an *N*,*N*-disubstituted *o*-acylaniline,[10] as well as palladium-catalyzed cross-coupling reaction of propargylic carbonates with arylboron compounds.[21] Enhancement of the Lewis acidity of the boron atom is considered to accelerate transmetalation between an amido ruthenium species and an arylboronate.

CONCLUSION

The reactivity of various *o*-acylanilines **2** with $RuH_2(CO)(PPh_3)_3$ (**1**) and "$Ru(CO)(PPh_3)_3$" (**4**) was investigated. The reaction of **2** with complex **1** at 120 °C for 20 h gave amido hydrido complex **3** via N−H bond cleavage. Complex **3** can also be obtained by treating **2** with activated complex **4** at room temperature. The formation of **3** is considered as a reversible process, and the amido ligand can be easily exchanged by another molecule of **2**.

The C−N bond of **2** can be cleaved by reacting with complex **1** or **4** to form aryl amido complex **6**. The cleavage process is considered to occur via oxidative addition and is accelerated by olefins. The amido ligand of **6** is also easily exchangeable with another molecule of **2**. Aryl amido complex **6** provides biaryl derivative **10** upon treatment with arylboronate **9** by forming a C−C bond between the aryl ligand on the ruthenium of **6** and the aryl group of **9**. Amido hydrido complex **3** and aryl amido complex **6** catalyze the C−N arylation and are considered as catalytically relevant species.

The substituent effect on the C−N bond cleavage was examined by stoichiometric competition reactions, and it was revealed that electron-donating substituents on *o*-acylaniline **2** increase the relative easiness of the C−N bond cleavage. A similar tendency was also observed for the catalytic C−N arylation. The trend observed here is different from the previously reported tantalum-mediated C−N bond cleavage reported by Wolczanski, where lower reactivity was observed for anilines with electron-donating substituents, and many other reactions involving oxidative addition as key steps.

Finally, the substituent effect of arylboronate **9** was investigated, and the aryl group with an electron-withdrawing trifluoromethyl group is more easily reacted with complex **6** than the phenyl group to give arylation product **10**. The electron-deficient arylboronate was also more reactive in the catalytic C−N arylation than the phenylboronate.

Catalytic transformation of sp^2 C−N bonds of anilines is still a difficult process to achieve and has only been attained by our ruthenium-based system using acyl groups as directing groups. The results described here suggest that directing groups may not only assist the cleavage of unreactive bonds but also affect the order of substituents furnishing high reactivity to substrates.

EXPERIMENTAL SECTION

General Information. ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra were recorded using JEOL JNM-EX270, JNM-EX400, JNM-GSX400, JNM-A400, and ECX400 spectrometers. Chemical shifts in ^1H and $^{13}C\{^1H\}$ NMR spectra are expressed in parts per million relative to residual chloroform (δ 7.26 for ^1H, δ 77.0 for ^{13}C) or tetramethylsilane (δ 0.00 for ^1H and ^{13}C). IR spectra were recorded on a JASCO FT/IR-410 infrared spectrometer. Gas chromatography (GC) analyses were performed using a CBP-10 capillary column (25 m × 0.22 mm, film thickness = 0.25 μm). GCMS analyses were performed on a Shimadzu GCMS-QP2010 gas chromatography mass spectrometer. Flash chromatography was carried out with Kanto Chemical silica gel 60N. Unless otherwise noted, all reactions were performed under a nitrogen atmosphere.

Solvents and Materials. Toluene was distilled from Na/benzophenone ketyl. $RuH_2(CO)(PPh_3)_3$ (**1**),[13a] 1-(2-aminophenyl)-2,2-dimethyl-1-propanone (**2a**),[10] 1-(2-amino-4-methylphenyl)-2,2-dimethyl-1-propanone (**2c**),[11] and complexes **3a**,[11] **3b**,[11] **6aa**,[11] and **6ab**[11] were prepared by literature methods.

General Procedure for Observation of 3. To a sealable NMR tube were added in a glovebox complex **1** (0.02 mmol), o-acylaniline **2** (0.04 mmol), and toluene-d_8 (0.6 mL), and the mixture was heated in an oil bath, whose temperature was adjusted to 120 °C. The progress of the reaction was monitored by ^1H and $^{31}P\{^1H\}$ NMR spectroscopy.

General Procedure for Observation of 6. To a sealable NMR tube were added in a glovebox complex **1** (0.02 mmol), *o*-acylaniline **2** (0.06 mmol), olefin (0.6 mmol), and toluene-d_8 (0.6 mL). The mixture was heated in an oil bath, whose temperature was adjusted to 120 °C, and the progress of the reaction was monitored by ^1H and $^{31}P\{^1H\}$ NMR spectroscopy. The NMR yield was measured using 1,3,5-trimethoxybenzene (0.02 mmol) as an internal standard.

Ligand Exchange between the Amido Ligand in 6aa and 2c. To a sealable NMR tube were added in a glovebox complex **6aa** (14.6 mg, 0.02 mmol), *o*-acylaniline **2c** (7.7 mg, 0.04 mmol), trimethylvinylsilane **5a** (30 μL, 0.2 mmol), and toluene-d_8 (0.6 mL), and the

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mixture was heated in an oil bath, whose temperature was adjusted to 120 °C. The progress of the reaction was monitored by ^{1}H and $^{31}P\{^{1}H\}$ NMR spectroscopy.

General Procedure for Stoichiometric Competition Experiment. To a sealable NMR tube were added in a glovebox complex **4** (0.02 mmol), two o-acylanilines **2** (each 0.1 mmol), trimethylvinylsilane **5a** (0.2 mmol), and toluene-d_8 (0.6 mL), and the mixture was heated in an oil bath, whose temperature was adjusted to 120 °C. After 20 h, the ratio of aryl amido complexes **6** was measured by $^{31}P\{^{1}H\}$ NMR spectroscopy.

General Procedure for Catalytic Competition Experiment. To a 10 mL Schlenk tube were added in a glovebox two o-acylanilines **2** (each 0.1 mmol), phenylboronate **9a** (0.4 mmol), complex **1** (0.02 mmol), and toluene (0.1 mmol), and the mixture was heated in an oil bath, whose temperature was adjusted to 120 °C. After the reaction, *n*-eicosane (0.05 mmol) was added to the reaction mixture as an internal standard, and then the resulted mixture was analyzed by GC.

Competition Experiment of 6aa with 9a and 9b. To a sealable tube were added in a glovebox complex **6aa** (14.6 mg, 0.02 mmol), phenyl boronate **9a** (3.8 mg, 0.02 mmol), 4-trifluoromethylphenyl boronate **9b** (5.2 mg, 0.02 mmol), and toluene (0.5 mL), and the mixture was heated in an oil bath, whose temperature was adjusted to 120 °C. After the reaction, *n*-eicosane (5.7 mg, 0.02 mmol) was added to the reaction mixture as an internal standard. GC analysis of the resulted mixture revealed that **10aa** and **10ab** were obtained in 36% and 59% yields, respectively.

Competition Experiment of 2a with 9a and 9b. To a 10 mL Schlenk tube were added in a glovebox o-acylaniline **2a** (88.6 mg, 0.5 mmol), phenyl boronate **9a** (114 mg, 0.6 mmol), 4-trifluoromethylphenyl boronate **9b** (154.8 mg, 0.6 mmol), complex **1** (91.8 mg, 0.1 mmol), and toluene (0.5 mL), and the mixture was heated in an oil bath, whose temperature was adjusted to 120 °C. After 20 h, *n*-eicosane (70.6 mg, 0.25 mmol) was added as an internal standard. GC analysis of the resulted mixture revealed that **10aa** and **10ab** were obtained in 16% and 27% yields, respectively.

Preparation of 1-(6-Amino-3-methoxyphenyl)-2,2-dimethyl-1-propanone (2d). *N*-Boc-2-iodo-4-methoxyaniline (2.86 g, 8.2 mmol) was placed in a 100 mL round-bottom flask and dissolved into 24 mL of MeOH. To this solution was added 30 mL of a 3 M aqueous solution of HCl, and the mixture was stirred at rt for 15 h. The resulting mixture was neutralized with aqueous NaOH solution and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (9:1 hexane/EtOAc) of the crude material afforded 2-iodo-4-methoxyaniline (1.74 g, 85%).

A 100 mL three-neck round-bottom flask equipped with a reflux condenser and a nitrogen inlet was charged with 2-iodo-4-methoxyaniline (1.74 g, 7.0 mmol), cuprous cyanide (0.69 g, 7.7 mmol), and NMP (23 mL), and the mixture was refluxed for 10 h. The reaction mixture was cooled to room temperature, and water was poured into the flask. The resulted mixture was filtered through a pad of Celite, and the filtrate was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (5:1 hexane/EtOAc) of the crude material afforded 2-cyano-4-methoxyaniline as a yellow oil (956 mg, 92%).

A 50 mL two-neck round-bottom flask equipped with a nitrogen inlet was charged with 2-cyano-4-methoxyaniline (889 mg, 6.0 mmol) and THF (6 mL), and the mixture was cooled in an ice bath. Methyllithium (1.07 M in diethyl ether, 5.6 mL, 6.0 mmol) and *tert*-butyllithium (1.70 M in *n*-pentane, 3.5 mL, 6.0 mmol) were added via a syringe. After the addition was completed, the mixture was warmed to room temperature and stirred for 22 h. The resulting mixture was poured into 100 mL of a 1 M aqueous solution of HCl and stirred at rt for 1 h. The organic layer was collected, and the separated aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography of the crude material (10:1 hexane/EtOAc) afforded acylaniline **2d** as a reddish orange oil (643 mg, 52%). IR (NaCl): 3475 s, 3362 m, 2968 m, 2832 w, 1653 s, 1576 s, 1570 s, 1521 m, 1506 m, 1499 m, 1491 m, 1476 m, 1418 m, 1395 m, 1363 m, 1233 m, 1156 m, 1045 m, 976 m, 875 m, 820 m, 668 w, 603 w, 502 w, cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9H, $C(CH_3)_3$), 3.77 (s, 3H, OCH_3), 5.11 (br s, 2H, NH_2), 6.66 (d, J = 8.8 Hz; 1H, Ar*H*), 6.88 (dd, J = 8.3 Hz, 2.9 Hz, 1H, Ar*H*), 7.25 (d, J = 2.4 Hz, 1H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ 28.6, 44.8, 56.0, 114.2, 118.8, 119.7, 120.2, 143.0, 149.8, 209.8. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.25; H, 8.25; N, 6.72.

Preparation of 1-(6-Amino-3-fluorophenyl)-2,2-dimethyl-1-propanone (2e). *N*-Boc-4-fluoroaniline (1.06 g, 5.0 mmol) was placed in a 50 mL two-neck round-bottom flask equipped with a nitrogen inlet and dissolved into 7 mL of Et_2O. The solution was cooled to −40 °C, and *tert*-butyllithium (1.75 M in *n*-pentane, 6.3 mL, 11 mmol) was added dropwise to the solution via a syringe. After stirring the mixture at −40 °C for 30 min, methyl pivalate (0.79 mL, 0.70 g, 6.0 mmol) was introduced and the reaction mixture was gradually warmed to rt and stirred for 24 h. The resulting mixture was poured into water, and the organic layer was separated. The aqueous layer was extracted further with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (20:1 hexane/EtOAc) of the crude material afforded *N*-Boc-2-pivaloyl-4-fluoroaniline as a colorless oil (827 mg, 56%).

N-Boc-2-pivaloyl-4-fluoroaniline (827 mg, 2.8 mmol) was placed in a 100 mL round-bottom flask and dissolved into 8 mL of MeOH. To this solution was added 24 mL of a 3 M aqueous solution of HCl, and the mixture was stirred at rt for 13 h. The resulting mixture was neutralized with aqueous NaOH solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (15:1 hexane/EtOAc) of the crude material afforded acylaniline **2e** as a yellow oil (441 mg, 81%). IR (KBr): 3465 m, 3352 m, 2979 w, 2367 w, 1633 s, 1593 s, 1571 m, 1552 s, 1507 w, 1484 m, 1426 m, 1394 w, 1371 w, 1364 w, 1352 w, 1304 w, 1278 w, 1255 w, 1215 s, 1139 s, 1032 w, 985 m, 936 w, 883 m, 879 m, 814 m, 806 w, 791 w, 780 w, 687 w, 533 w cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9H, $C(CH_3)_3$), 5.40 (br s, 2H, NH_2), 6.64 (dd, J = 8.8, 4.9 Hz, 1H, Ar*H*), 6.97 (m, 1H, Ar*H*), 7.43 (dd, J = 2.9, 10.3 Hz, 1H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ 28.5, 44.8, 115.3 (d, J = 23.2 Hz), 118.7 (d, J = 6.6 Hz), 118.9 (d, J = 5.8 Hz), 120.1 (d, J = 23.2 Hz), 145.6, 153.2 (d, J = 234.9 Hz), 208.9 (d, J = 2.5 Hz). HRMS (ESI) calcd for $[M + Na]^+$ ($C_{11}H_{14}FNNaO$) m/z 218.0957. Found 218.0943.

Preparation of 1-{2-Amino-5-(trifluoromethyl)phenyl}-2,2-dimethyl-1-propanone (2f). *N*-Boc-4-(trifluoromethyl)aniline (2.61 g, 10 mmol) was placed in a 100 mL three-neck round-bottom flask equipped with a nitrogen inlet and dissolved into 15 mL of Et_2O. The solution was cooled to −40 °C, and *tert*-butyllithium (1.50 M in *n*-pentane, 15.0 mL, 23 mmol) was added dropwise to the solution via a syringe. After stirring the mixture at −40 °C for 30 min, methyl pivalate (1.56 mL, 1.37 g, 12 mmol) was introduced and the reaction mixture was gradually warmed to rt and stirred for 20 h. The resulting mixture was poured into water, and the organic layer was separated. The aqueous layer was extracted twice with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (15:1 hexane/EtOAc) of the crude material afforded *N*-Boc-2-pivaloyl-4-(trifluoromethyl)aniline as a yellow oil (1.22 g, 35%).

N-Boc-2-pivaloyl-4-(trifluoromethyl)aniline (1.22 g, 3.5 mmol) was placed in a 100 mL round-bottom flask and dissolved into 10 mL of MeOH. To this solution was added 26 mL of a 3 M aqueous solution of HCl, and the mixture was stirred at rt for 17 h. The resulting mixture was neutralized with aqueous NaOH solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (14:1 hexane/EtOAc) of the crude material afforded acylaniline **2f** as a white powder (3.00 g, 91%). IR (KBr): 3441 s, 3332 s, 2990 w, 2974 w, 2974 w, 1631 s, 1592 m, 1554 m, 1478 w, 1399 w, 1366 m, 1332 m, 1308 m, 1257 m, 1166 s, 1115 s, 1082 m, 1028 w, 967 m, 916 w, 855 w, 836 m, 774 w, 710 m, 633 m, 598 w, 526 w cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9H, $C(CH_3)_3$), 6.09 (br s, 2H, NH_2), 6.72 (d, J = 8.8 Hz, 1H, Ar*H*), 7.40 (dd, J = 8.8, 1.5 Hz, 1H, Ar*H*), 8.08 (s, 1H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ 28.8, 44.8, 116.9, 116.9 (q, J = 33 Hz), 117.8, 124.4 (q, J = 270 Hz), 128.2 (q, J = 4 Hz), 129.1 (q, J = 4 Hz), 152.1, 208.7. HRMS (ESI) calcd for $[M + Na]^+$ ($C_{12}H_{14}F_3NNaO$) m/z 268.0920. Found 268.0945.

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Preparation of 1-(3-Methoxy-6-phenylphenyl)-2,2-dimethyl-1-propanone (10da). Acylaniline **2d** (269 mg, 1.3 mmol), phenylboronate (**9a**) (760 mg, 4.0 mmol), complex **1** (360 mg, 0.39 mmol), and toluene (2 mL) were charged in a 10 mL Schlenk tube, and the mixture was heated at 120 °C for 20 h. The reaction mixture was cooled to room temperature and passed through a basic aluminum oxide column (10:1 hexane/EtOAc). Silica gel column chromatography (30:1 hexane/EtOAc) of the resulting material afforded biaryl **10da** as a brown oil (178 mg, 51%). IR (KBr): 2967 m, 1688 s, 1605 m, 1565 w, 1479 s, 1410 w, 1364 w, 1309 m, 1289 s, 1232 s, 1168 m, 1052 m, 1034 m, 1007 w, 984 m, 856 m, 768 m, 736 w, 704 m, 575 w, 528 w cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.87 (s, 9H, C(CH_3)$_3$), 3.84 (s, 3H, OCH_3), 6.66 (d, J = 2.69 Hz, 1H, ArH), 6.97 (dd, J = 8.52, 2.69 Hz, 1H, ArH), 7.63−7.38 (m, 6H, ArH). ^{13}C NMR ($CDCl_3$): δ 27.2, 44.9, 55.4, 111.3, 114.1, 127.2, 128.4, 129.5, 130.6, 131.0, 140.6, 142.0, 158.3, 216.3. HRMS (ESI) calcd for $[M + Na]^+$ ($C_{18}H_{20}NaO_2$) m/z 291.1361. Found 291.1360.

Preparation of 1-{6-Phenyl-3-(trifluoromethyl)phenyl}-2,2-dimethyl-1-propanone (10fa). Acylaniline **2f** (490 mg, 2.0 mmol), phenylboronate (**9a**) (760 mg, 4.0 mmol), complex **1** (370 mg, 4.0 mmol), and toluene (2 mL) were charged in a 10 mL Schlenk tube, and the mixture was heated at 120 °C for 20 h. The reaction mixture was cooled to room temperature and passed through a basic aluminum oxide column (10:1 hexane/EtOAc). Silica gel column chromatography (200:1 hexane/EtOAc) of the resulting material afforded biaryl **10fa** as a colorless oil (123 mg, 20%). IR (NaCl): 3365w, 3063 w, 3031 w, 2970 m, 2906 m, 2871 m, 1695 s, 1615 m, 1568 w, 1479 m, 1463 m, 1447 m, 1393 m, 1366 m, 1334 s, 1271 s, 1169 s, 1128 s, 1084 s, 1038 w, 1010 w, 982 m, 901 m, 841 m, 801 w, 777 m, 744 m, 726 m, 702 s, 655 m, 642 w, 596 w, 541 w, 517 w, 441 w, 427 w cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.87 (s, 9H, C(C*H*3)3), 7.31−7.42 (m, 6H, ArH), 7.52 (d, J = 8.1 Hz, 1H, ArH), 7.70 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ 27.1, 45.1, 122.8 (q, J = 3.8 Hz), 123.8 (q, J = 272 Hz), 125.5 (q, J = 3.8 Hz), 128.4, 128.9, 129.1 (q, J = 32 Hz), 130.3, 133.8, 139.5, 141.4, 141.6, 215.1. HRMS (ESI) calcd for $[M + Na]^+$ ($C_{18}H_{17}F_3NaO$) m/z 329.1129. Found 329.1132.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and $^{13}C\{^1H\}$ NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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