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Nickel−NHC-Catalyzed α-Arylation of Acyclic Ketones and Amination of Haloarenes and Unexpected Preferential *N*-Arylation of 4-Aminopropiophenone

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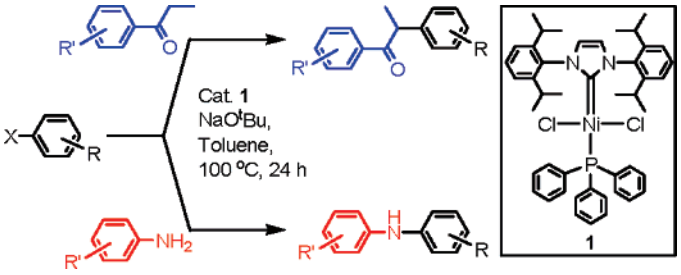

Arylation of both acyclic ketones and primary and secondary amines was achieved using a new, simple, stable, and easy-to-access nickel(II)−halide complex bearing mixed PPh_3/*N*-heterocyclic carbene ligands as a catalyst precursor. Acyclic ketones were first arylated at the α-position with the nickel catalyst. On the other hand, less basic amines, such as diphenylamine and 4-aminobenzophenone, were more favorable in the catalytic amination of haloarenes than basic amines, contrary to previous reports. *N*-Arylation of 4-aminopropiophenone was found to proceed selectively without causing α-arylation of the ketone group.

Introduction

Organonickel-catalyzed organic transformations, which are wide and variable reactions similar to those catalyzed by palladium catalysts, are now increasingly gaining attention as tools using inexpensive metal sources.[1] However, many useful nickel catalysts are not well-known, and there are fewer useful reactions with nickel catalysts in comparison with palladium catalysts,[2] since starting stable nickel(II) precursors are hardly reduced to zerovalent nickel species, which are usually active in the catalytic cycles. Moreover, active nickel(0) compounds are hard to handle because of their toxicity and/or instability in the air.

Although Grignard coupling and Suzuki coupling have proceeded smoothly under mild conditions using various nickel catalysts, α-arylation of carbonyl compounds[3] and amination of haloarenes[4] seem to need more activation energy and are not popular in the nickel-catalyzed coupling reactions. In recent reports, Buchwald et al.[5a] and Chan et al.[5c] showed asymmetric versions of α-arylation of cyclic esters and cyclic ketones, respectively, using chiral ligands in the presence of nickel(0) precursors. However, as Chan commented, the achievement of arylation of acyclic carbonyl compounds requires overcoming some barrier. On the other hand, several efforts to aminate haloarenes have been made using nickel catalysts bearing

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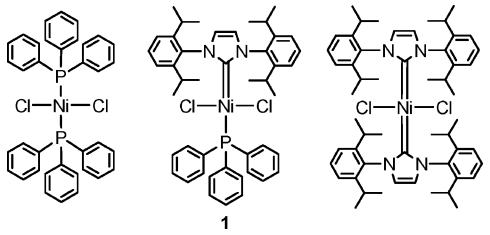
SCHEME 1



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phosphines or carbenes.[6a−c] Recent studies showed that an in situ-generated nickel(0) compound efficiently catalyzed the arylation of amines under mild conditions in the presence of bulky *N*-heterocyclic carbene (NHC) ligands, though neither isolated NHC−nickel complexes nor divalent nickel compounds were directly used.[6b]

Many chemists now use NHC, such as 1,3-dialkyl- or 1,3-diarylimidazol-2-ylidenes, as sterically hindered 2-electron σ-donor ligands in a number of catalytic organic reactions instead of phosphines.[7] Last year, Nolan et al. reported that an easily synthesized, efficient, and versatile palladium(II) pre-catalyst bearing an NHC ligand is useful for catalytic formation of C−N and C−C bonds.[8] In constructing a nickel version of such a new, active, easy-to-prepare, and stable catalyst inducing various catalytic reactions, we also employed NHC ligands and fortunately found a new nickel(II) complex, $NiX_2(PPh_3)$(NHC) (X = Cl or Br, NHC = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-yl), bearing mixed PPh_3/NHC ligands, which was prepared and structurally determined as reported in our latest paper.[9] This nickel complex demonstrated the highest catalytic activity in Grignard cross-coupling of aryl halides among $NiCl_2(PPh_3)_2$, $NiCl_2(NHC)_2$, and the chloride version of the mixed PPh_3/NHC complex, $NiCl_2(PPh_3)$(NHC) (**1**), used as catalysts (Scheme 1). One of the significant factors leading to this high activity in **1** may be the ability to eliminate triphenylphosphine under mild conditions, forming a coordinatively unsaturated site in situ in the nickel center. Thus, we considered that such a property in **1** may be significant in the catalytic α-arylation of carbonyl compounds because, as Hartwig and Buchwald noted, the active species of palladium in α-arylation should have only one monodentate supporting ligand.[10] In addition, our recent study showed that two strongly binding NHC ligands in a palladium complex deactivated the catalyst activity in the α-arylation of ketones, while the reaction proceeded efficiently when one of two NHC ligands was removed.[11]

Thus, in this study, we applied this nickel complex **1** to the catalytic α-arylation of acyclic ketones as a catalyst, which has not been reported to our knowledge, and obtained arylation products efficiently. The arylation of ketones was carried out in the presence of a sufficient amount of strong base which was added for the purpose of enolization of ketones and reduction of nickel(II) species, and further, *N*-arylation of primary and secondary amines took place under the same conditions and is reported in this paper. The amination of haloarenes proceeded efficiently when primary and secondary arylamines, especially sterically hindered amines and/or those substituted with electron-withdrawing groups, were used, whereas a secondary donating alkylamine, which was generally advantageous for the aryl analogues in the previous *N*-arylation with Pd and Ni catalysts, did not react efficiently. Interestingly, preferential arylation of the amine moiety occurred when using 4-aminopropiophenone as a substrate, even though arylation at the α-position of the acyclic ketone moiety seems possible.

Results and Discussion

Nickel-Catalyzed α-Arylation of Acyclic Ketones. The α-arylation of cyclic ketones and esters and highly acidic malononitrile by nickel catalysts was reportedly studied in detail;[5] however, the arylation of standard acyclic ketones, which have already been established in organopalladium chemistry, has never been reported.[12] Thus, we conducted reactions of some acyclic alkyl aryl ketones with haloarenes in the presence of NaO^tBu and a catalytic amount of the nickel complex **1**. We considered that facile reduction of the nickel(II) center may make the reaction more efficient, using an appropriate base as the reducing reagent. Sodium hydride was reported to be able to reduce the nickel atom easily by way of transmetalation and H_2 evolution.[6b] However, employing NaH in our system instead of NaO^tBu caused no reaction. Our first attempt with acetophenone in toluene at 100 °C for 24 h, which is the simplest reagent and easily reacts with haloarenes in the presence of palladium catalysts,[13] provided only aldol adducts by itself on adding any aryl halides. After several attempts, using propiophenone as a substrate, the reaction of 4-bromobenzophenone, an electronegative aryl bromide, afforded an α-arylation product in 11% isolated yield, with the rest of the starting materials being recovered, when using 3 mol % **1**. Methyl 4-bromobenzoate was converted into both the α-arylation product and a Claisen condensation product in a 1:1 ratio. The reactions of simple haloarene derivatives, such as *p*-bromotoluene and *p*-bromoanisole, with propiophenone resulted in complete recovery of the starting materials under this condition.

Under more severe conditions using 10 mol % **1**, we finally achieved the α-arylation of propiophenone with several haloarenes in excellent yields (Table 1). This successfully led to the efficient arylation of chlorobenzene, bromobenzene, 4-bromobiphenyl, *p*-bromoanisole, and *p*-bromotoluene, which did not react under the previous conditions (entries 2−5 and 7). In the case of 4-bromobenzophenone, only 5 mol % **1** was required to complete the coupling reaction (entry 8). These results

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(12) The reason for the low reactivity of acyclic ketones has not been explained.[5c] We considered that the steric demand around the α-position of the carbonyl group might induce such a low reactivity in comparison with that of the cyclic analogues.

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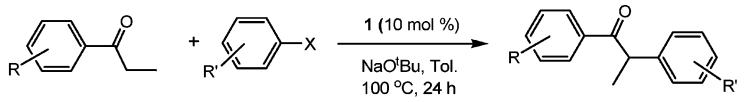
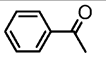
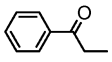
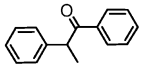
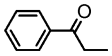
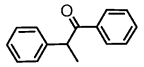
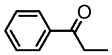
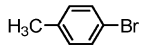
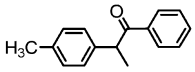
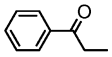
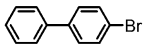
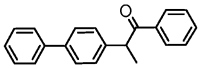
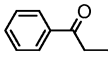
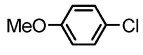
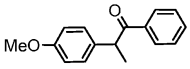
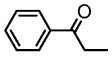
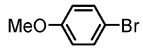
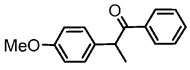
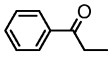
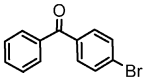
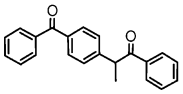
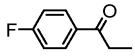
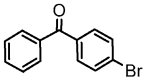
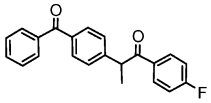
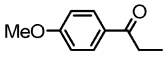
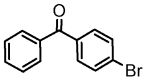
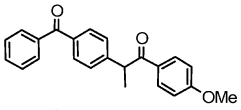
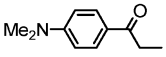
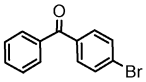
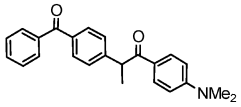
TABLE 1. α-Arylation of Ketones Catalyzed by [$NiCl_2(PPh_3)$(NHC)] (1)[a]



entry	ketones	aryl halides	products	yield (%)[c]
1			-[b]	0
2				54
3				42
4				65
5				87
6				39[d]
7				78
8				91[e]
9				70
10				66
11				48

[a] Conditions: in toluene (0.3 mL), at 100 °C for 24 h, ketones (0.154 mmol), aryl halides (0.128 mmol), NaO^{t}Bu (0.192 mmol), and catalyst **1** (0.0128 mmol, 10 mol %). [b] Only the Aldol condensation product was obtained. [c] Each reaction was carried out more than two times, and the yield was determined by column chromatography (SiO_2). [d] The yield was determined by means of the ^{1}H NMR spectrum of the crude mixture. [e] Catalyst **1** (6 μmol, 5 mol %) was used.

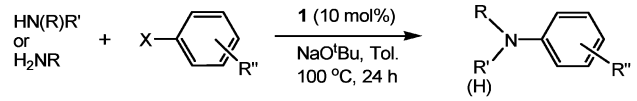
indicated that the coupling reactions of aryl bromides did not depend upon the substituents at the *para* position under these conditions. With *p*-chloroanisole, the product was given in lower yield than the others, the starting material was recovered, and trace amounts of undetermined byproducts were detected in this case (entry 6).[14] Then, as listed in entries 9−11, we conducted arylation of propiophenones having substituents at the *para* position, such as 4-fluoropropiophenone, 4-methoxypropiophenone, and 4-(*N*,*N*-dimethylamino)propiophenone. These substrates also reacted with 4-bromobenzophenone to form corresponding products in good to moderate yields (entries 9−11), indicating that the acidity of propiophenones due to the substituents at the *para* position is low comparable to the reaction rates, except for the propiophenone having the strongly donating dimethylamino group. This was also pointed out in the palladium-catalyzed α-arylation.[3] As shown above, nickel-catalyzed α-arylation of acyclic ketones was first achieved under harder conditions than those with cyclic carbonyl compounds using nickel(0) catalysts.

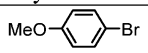
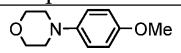
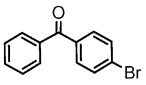
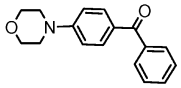
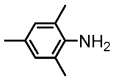
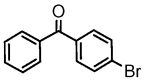
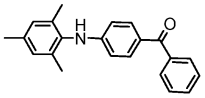
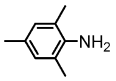
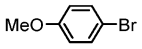
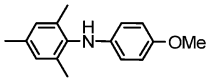
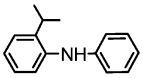
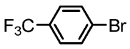
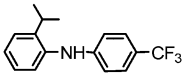
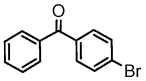
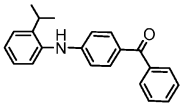
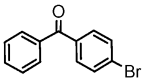
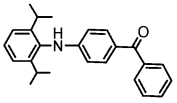
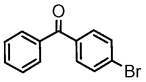
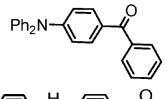
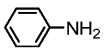
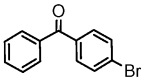
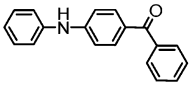
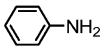
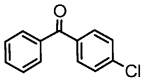
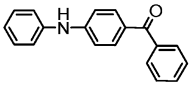
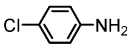
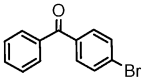
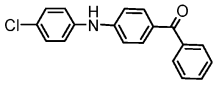
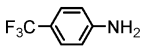
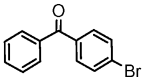
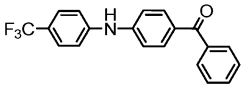
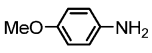
In considering the active catalyst in the reaction media, we suspected that a metathesis reaction of compound **1** took place to form bisphosphine and biscarbene complexes $NiCl_2(PPh_3)_2$ and $NiCl_2(NHC)_2$ (NHC = bis(2,6-diisopropylphenyl)imidazol-2-yl),[9] respectively, which could truly act in the α-arylation of acyclic ketones.[15] To exclude the above potential process, we added a mixture of equal amounts (5 mol % each) of these compounds, $NiCl_2(PPh_3)_2$ and $NiCl_2(NHC)_2$, instead of **1** to the solution of propiophenone and *p*-bromoanisole in the presence of the base. As a result, the reaction gave an arylation product (36% determined by means of ^{1}H NMR) with a remarkable amount of the reduced byproduct, anisole (31%), which was not obtained in the arylation with **1**. Generally, the formation of anisole was attributed to the occurrence of β-elimination of the metal *C*-enolate species due to the unhindered phosphine

(14) The reduced product, anisole, did not form in the reaction. The C−O bond activation of the anisole derivatives was also anticipated and is shown in the following report on nickel-catalyzed Grignard coupling: Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428−2432.

(15) Although such a ligand exchange reaction of **1** was not detected at room temperature,[8] those of mixed NHC/PR_3 palladium complexes were reported; see: Herrmann, W. A.; Böhm, V. P. W.; Gstöttmayr, C. W. K.; Grosche, M.; Reisinger, C. -P.; Weskamp, T. *J. Organomet. Chem.* **2001**, *617*−*618*, 616−628.

TABLE 2. Amination of Aryl Halides Catalyzed by [$NiCl_2(PPh_3)$(NHC)] (1)[a]



entry	amines	aryl halides	products	yield (%)
1				23
2				55
3				98
4				89
5				79
6				0
7				87
8				46
9	Ph_2NH			99
10				79
11				44
12				75
13				0
14				85
15				78

[a] Conditions: in toluene (0.3 mL), at 100 °C for 24 h, amines (0.154 mmol), aryl halides (0.128 mmol), NaO^tBu (0.192 mmol), and catalyst **1** (0.0128 mmol, 10 mol %). Each reaction was carried out more than two times, and the yield was determined by column chromatography (SiO_2).

ligands in the metal complex, such as $MCl_2(PPh_3)_2$, strongly suggesting that such a ligand exchange of **1**, which formed $NiCl_2(PPh_3)_2$ and $NiCl_2(NHC)_2$, did not proceed under these conditions.

Amination of Haloarenes. The coupling reaction of primary and secondary amines with aryl halides was developed mainly employing palladium catalysts,[4] and in 1997, nickel-catalyzed amination was first discovered.[6a] Recently, Fort et al. reported that in situ-generated nickel(0) compounds in the presence of bulky NHC ligands had high activity in regard to the arylation of primary and secondary amines.[6b] Although the nickel center in **1** is divalent, we attempted a reaction of morpholine with aryl halides, such as *p*-chloroanisole and *p*-bromoanisole, under similar conditions. However, the starting materials were completely recovered when the reaction was conducted at 65 °C for 24 h using 5 mol % **1**. At last, using 10 mol % **1** at 100 °C for 24 h afforded amination products from aniline derivatives in high yields without the primary nickel-reduction operation from **1**. As shown in Table 2, the reaction of several aryl halides, including *p*-bromoanisole with secondary and primary amines,

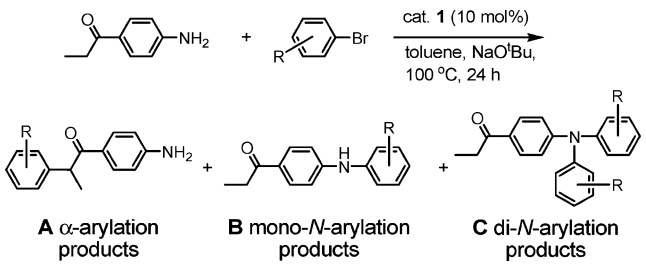
proceeded to form corresponding amination products. Hartwig et al. explained that secondary aliphatic amines, which are sterically hindered and electron-donating, are suitable for catalytic amination of haloarenes using Pd catalysts bearing monodentate phosphorus ligands and that aromatic amines can be coupled facilely by "second-generation" Pd catalysts bearing bidentate phosphine ligands.[4,17] Therefore, it was unexpected that morpholine, which more facilely coupled with haloarenes than anilines according to other reports,[6] did not react efficiently in our case (entries 1 and 2), whereas the arylation of aniline (entry 10) gave a product in even higher yield (79%) than that from morpholine. Moreover, the reaction of diphenylamine with haloarene gave the triphenylamine quantitatively, while, in contrast, it did not react at all using Fort's nickel catalyst,[6b] indicating that less basic arylamines are more favorable to amination than basic alkylamines when using nickel catalyst **1**. We confirmed this by the reaction of less basic 4-aminobenzophenone with *p*-bromoanisole to form the secondary arylamine in high yield (78%) (entry 15) without giving the diarylation product. On the other hand, the arylation of rather bulky anilines, such as 2,4,6-trimethylaniline, also resulted in quantitative formation of the coupling product (entry 3). Higher yields in the arylation of 2,4,6-trimethylaniline than that of nonsubstituted aniline (entry 10) revealed that the hindered amines are preferable, as Hartwig suggested. However, lower yields in the coupling of bulkier 2,6-diisopropylaniline (entry 8) suggested that the appropriate size and/or shape of amines is required for an efficient coupling process. A yield of the amine (44%), lower than that from 4-bromobenzophenone (entry 10), was obtained after 24 h by the reaction of its chloro analogue with aniline (entry 11). Surprisingly, the reaction of reagents bearing the trifluoromethyl moiety, 4-(trifluoromethyl)bromobenzene and 4-(trifluoromethyl)aniline, only gave the starting materials dominantly (entries 6 and 13), while, reportedly, 4-(trifluoromethyl)chlorobenzene efficiently gave amination products by a palladium catalyst.[16] We now attribute this to an unknown catalyst-deactivation process which should occur in the presence of such trifluoromethyl-substituted arenes.

The reason for such preferable arylation of less basic arylamines is unclear now. Tighter primary coordination of arylamines to the nickel center than that of basic alkylamines might make the catalytic reaction favorable. An alternative explanation is that facile amide formation in situ from "acidic" anilines by sodium *tert*-butoxide might increase the reaction rate, while more basic amines were hardly deprotonated by the base. This is discussed later in detail.

Although chemists have reported that the reduction of aryl halides sometimes occurs to form arene derivatives in the amination of aryl halides, as a result of β-elimination of the palladium alkylamide species,[18] our results showed that they were not reduced by nickel catalyst **1** (entries 1 and 2). We also could not detect diarylation products from primary anilines in any reaction, which were sometimes yielded when using electron-negative amines with palladium catalysts.[4]

Bridging phosphine ligands in palladium had provided high activity in the amination of haloarenes,[19] whereas in contrast

TABLE 3. Competing Reactions of 4-Aminopropiophenone[a]



entry	aryl halide	yield[b] (%) A	B	C
1	*p*-bromoanisole	0	38	trace
2	*p*-bromotoluene	0	26	trace
3	4-bromobenzophenone	trace	35	26

[a] Conditions: in toluene (0.5 mL), at 100 °C for 24 h, amines (0.15 mol/L), aryl halides (0.13 mol/L), NaO^{t}Bu (0.19 mol/L), and catalyst (0.013 mol/L). [b] Each reaction was carried out more than two times, and the yield was determined by column chromatography (SiO_2).

Fort et al. reported a nickel(0)-catalyzed efficient system using monodentate NHC ligands.[6b] In our case, without the prior nickel(II)-reduction system, an efficient amination process using the NHC-bound nickel catalyst was successfully achieved.

Competing Reaction of 4-Aminopropiophenone. The above results showed that nickel complex **1** catalyzed the arylation of both acyclic ketones and amines to form coupling products in good to excellent yields, so we were interested in how aryl halides react with a substrate having both acyclic ketone and primary arylamine groups. Arylation of ketones and amines can be conducted under the same conditions; however, no one has compared these reactions using such reagents to our knowledge. In addition, our slow process may clarify the difference in the rates between these couplings. At first, a simple reagent, 4-aminopropiophenone, was coupled with some aryl halides for 24 h. We expected that arylation of each ketone or amine group would proceed in agreement with the above results. However, surprisingly, α-arylation of the ketone moiety did not take place after 24 h, in contrast to the formation of amination products at the amine moiety in moderate yields. The other remaining products were the starting materials recovered. As listed in Table 3, *p*-bromoanisole and *p*-bromotoluene were coupled with 4-aminopropiophenone to form secondary arylamines in 38% and 26% yields (entries 1 and 2), respectively, but the α-arylation products were not obtained at all. Highly reactive 4-bromobenzophenone also reacted mainly with the amine group to give monoarylation and diarylation products in 35% and 26% yields, respectively, while only a trace amount of arylation product at the ketone group was detected in the crude ^{1}H NMR spectrum (entry 3). Diarylation of both the ketone and amine groups in one molecule was not detected in any case.

Consideration of the Mechanism Using the Nickel Catalyst. In the mechanism of these two coupling reactions, α-arylation and amination, at first generation of the nickel(0) species leads to the oxidative addition of the aryl halide, RX, and then transmetalation of the nickel halide with an enolate or amide occurs to form a nickel enolate or a nickel amide intermediate (Scheme 2). The results employing several sub-

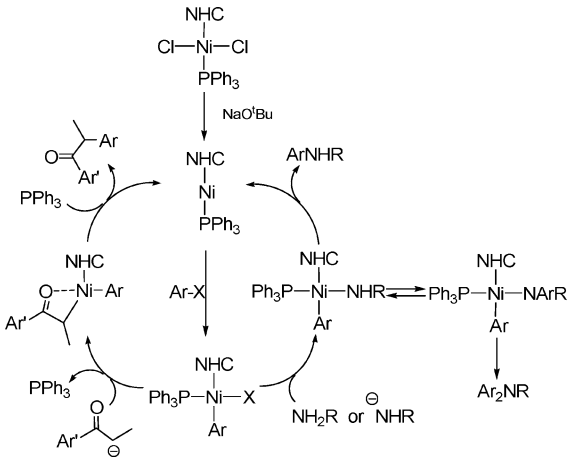
(16) Ackermann, L.; Born, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2444−2447.

(17) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 11695−11696.

(18) Hartwig, J. F.; Richards, S.; Barañano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626−3633.

(19) (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217−7218. (b) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216.

SCHEME 2

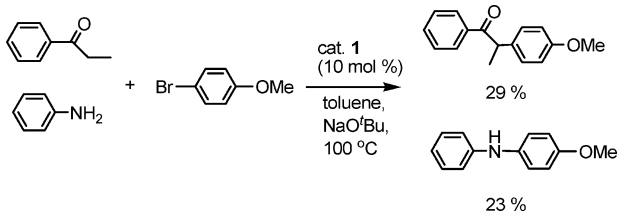


strates, as shown in Tables 1 and 2, suggested the common features of these nickel-catalyzed reactions, as noted above. That is, it can be realized that the substituents in the aryl halides little depended on the yields of the products in either α-arylation or amination, except for inactive chloroarenes. This result suggested that the oxidative addition with the active zerovalent nickel species occurred rapidly and did not affect the overall reaction because, in general, the nickel(0) species are highly active and facilely form the nickel(II) species. In contrast to palladium chemistry,[20,21] some relationship between the acidity of the ketones or amines and the yields of arylation products can be pointed out. In particular, we found that less basic anilines were coupled with haloarenes more favorably than basic alkylamines by **1**, indicating the significance of the transmetalation process in the **1**-catalyzed catalytic cycles.

The diarylation of amines by palladium catalysts has also been studied,[22] though nickel-catalyzed diarylation was not reported; decreased steric hindrance between the ligand and amine and/or the basicity of the generated arylamine frequently induced diarylation. As shown in Table 3, in addition to using less basic ketone-substituted aniline, only the most electron-poor 4-bromobenzophenone among the *para*-substituted aryl halides gave a diarylation product. After reductive elimination of the arylamine in the first arylation process, a generated less basic unhindered amine coordinated the nickel atom strongly, maybe leading to the second arylation, as shown in Scheme 2,[22] suggesting that using both unhindered and electron-negative anilines and haloarenes with **1** only leads to the diarylation of amines.

It is interesting to note that an arylamine having an alkyl ketone moiety was easily arylated preferentially. The experimental results with **1** indicated that the amine moiety may react more easily than the enolate group in the transmetalation process. First, we assumed that prior ligand exchange of phosphine to amine may prevent formation of the nickel enolate species because, in the case of the α-arylation of propiophenone, facile elimination of PPh_3 from the intermediary mixed PPh_3/NHC nickel compound was presumed to enhance the formation

SCHEME 3

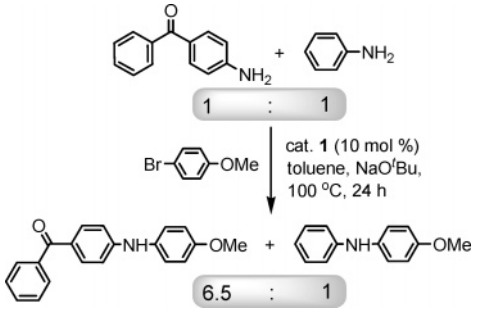


of the C- and O-bound nickel enolate species (Scheme 2). Such a bidentate enolate form may stabilize the nickel enolate species because as reported the formation of the nickel−oxygen bond between the enolate and unsaturated nickel species is significant.[23] However, the assumption does not fit in our case because, interestingly, a competing reaction of *p*-bromoanisole with equal amounts of aniline and propiophenone gave an α-arylation product in 29% yield, higher than that of an amination product (23% yield) (Scheme 3). That is, in sharp contrast to the coupling reactions of 4-aminopropiophenone, the α-arylation product was given dominantly in the competing reaction, suggesting that the existence of contaminating amines does not prevent formation of the nickel enolate species. Thus, we concluded that the result in Table 3 is attributable to the peculiar property of 4-(aminoalkyl)phenones.

Thus, we speculated that the disadvantage to the α-arylation of the ketone group in 4-aminopropiophenone may be due to the powerful electron-donating amino moiety at the *para* position. Indeed, the α-arylation result in Table 1, entry 11, showed that a ketone, 4-(*N*,*N*-dimethylamino)propiophenone, having a similar electron-donating substituent on the aryl moiety, was coupled with 4-bromobenzophenone in moderate yield (48%). It was one of the lowest yields of all arylation products, indicating that the amino substituent at the *para* position is indubitably an important factor for inhibiting the α-arylation of 4-aminopropiophenone.

In addition, we assumed that the acyl-substituted arylamine is acidic enough to compete with the acyl α-hydrogens which have been rendered less acidic by the electron-donating amine moiety for deprotonation by sodium *tert*-butoxide. Contrary to the theory that less basic amines are unfavorable in catalytic *N*-arylation,[4] our *N*-arylation of less basic amines, such as 4-aminobenzophenone and diphenylamine, afforded amination products in higher yields than by using the more basic amines. We also conducted competing reactions of equivalent amounts of 4-aminobenzophenone and aniline with *p*-bromoanisole, resulting in the dominant formation of *N*-arylated aminobenzophenone (product ratio by NMR, 6.5:1.0, respectively) (Scheme 4). Thus, we conclude that both the lower reactivity

SCHEME 4



of the ketone moiety having the electron-donating amino group and the higher reactivity of the acyl-substituted acidic amine

(20) (a) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. (b) Yamashita, M.; Vicario, J. V. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 16347−16360.

(21) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816−5817.

(22) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694−3703.

moiety in 4-aminopropiophenone may be the crucial factors in yielding no α-arylation product.

Conclusion

In summary, we first achieved efficient α-arylation of acyclic ketones using the nickel complex **1**, which, bearing both triphenylphosphine and bulky NHC ligands, is significant as an active, easy-to-access, simple, and air-stable nickel catalyst. Propiophenone was arylated with several haloarenes, whereas the arylation of acetophenone did not proceed. Using the bulky donating NHC ligand and the easy-to-liberate phosphine ligand in nickel(II) complex **1** may have contributed to these successful results. In the presence of the same strong base, the amination of haloarenes also occurred to form secondary or tertiary amines from primary or secondary amines, respectively. Interestingly, in contrast to earlier reports, the amination of less basic arylamines proceeded more efficiently than that of basic alkylamines. The yields of the amination products were high—the same as those of the α-arylation products. The reaction of 4-aminopropiophenone, which is a special reagent leading possibly to both α-arylation and amination, gave only amination products, because of the low acidity of its α-protons and the *low basicity* of the amine moiety. We are now investigating these nickel-catalyzed reaction mechanisms, establishing an efficient reduction process of **1**, modifying **1**, and applying the modified compounds to other various catalytic reactions.

Experimental Section

General Procedures. All catalytic reactions were carried out under an inert gas atmosphere using standard Schlenk techniques and a glovebox, unless otherwise noted. Toluene and chloroform-*d* were distilled from benzophenone ketyl and calcium hydride, respectively, and stored under a nitrogen atmosphere. NaO^{t}Bu was used as purchased. Organic reagents used for the coupling reactions were dried and distilled just before use. Other reagents and solvents were used as received. 4-(*N*,*N*-Dimethylamino)propiophenone, one of the coupling substrates for *N*-arylation, was prepared referring to the synthetic process of 4-(*N*,*N*-dimethylamino)acetophenone in the literature, and the details are described in the Supporting Information.[24] The nickel complexes $NiCl_2(PPh_3)(NHC)$ (**1**) and $NiCl_2(NHC)_2$ were prepared according to the published methods.[8]

A Typical Procedure for α-Arylation of Ketones. To a solution of **1** (5.2 mg, 6.7 μmol), NaO^{t}Bu (20.8 mg, 0.216 mmol), and 4-bromobenzophenone (34.4 mg, 0.132 mmol) in toluene (0.30 mL) was added propiophenone (0.020 mL, 0.154 mmol). The mixture was stirred for 24 h at 100 °C. The reaction was quenched by adding water. Then the mixture was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4. After the solvent was removed in vacuo, the residual mixture was purified by column chromatography by elution with 7−10% ethyl acetate in hexane to give 2-(4-benzoylphenyl)-1-phenyl-1-propanone (25.3 mg, 0.120 mmol, 91%).

Data for 2-(4-Benzoylphenyl)-1-(4-fluorophenyl)-1-propanone. ^{1}H NMR($CDCl_3$, 400 MHz): δ 8.00−7.97 (m, 2H), 7.77−7.74 (m, 4H), 7.57 (t, *J* = 5.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 8.4 Hz, 2H), 4.73 (q, *J* = 6.8 Hz, 1H), 1.57 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 196.1, 166.9, 164.3, 146.0, 137.4, 136.3, 132.5, 132.5, 132.4, 131.4, 131.3, 130.9, 130.0, 128.3, 127.7, 115.9, 115.6, 47.8, 19.3. IR(ν_{CO}, cm^{-1}): 1683 (vs), 1657 (vs), 1598 (vs). EI-MS: *m*/*z* 332 [M$^+$], 333 [M$^+$ + 1], 334 [M$^+$ + 2]. HRMS (*m*/*z*) for $C_{22}H_{17}O_2F$: calcd 332.1213, found 332.1215.

Data for 2-(4-Benzoylphenyl)-1-(4-methoxyphenyl)-1-propanone. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (d, *J* = 8.8 Hz, 2H), 7.77−7.73 (m, 4H), 7.57 (t, *J* = 6.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 4.74 (q, *J* = 6.8 Hz, 1H), 3.83(s, 3H), 1.56 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.1, 196.2, 163.4, 146.6, 137.5, 136.1, 132.3, 131.0, 130.8, 130.0, 129.1, 128.2, 127.7, 113.8, 55.4, 47.3, 19.4. IR($\nu_{CO,}$ cm^{-1}): 1673 (vs), 1657 (vs), 1599 (vs). EI-MS: *m*/*z* 344 [M$^+$], 345 [M$^+$ + 1], 346 [M$^+$ + 2]. HRMS (*m*/*z*) for $C_{23}H_{20}O_3$: calcd 344.1412, found 344.1409

Data for 2-(4-Benzoylphenyl)-1-[4-(dimethylamino)phenyl]-1-propanone. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (d, *J* = 8.8 Hz, 2H), 7.77−7.72 (m, 4H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.47−7.42 (m, 4H), 6.64 (d, *J* = 8.8 Hz, 2H), 4.73 (q, *J* = 6.8 Hz, 1H), 3.03 (s, 6H), 1.55 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.5, 196.3, 153.1, 147.3, 137.6, 135.9, 132.3, 131.0, 130.7, 130.0, 128.2, 127.7, 111.0, 46.8, 40.2, 19.4. IR (ν_{CO}, cm^{-1}): 1654 (s), 1594 (vs). EI-MS: *m*/*z* 357 [M$^+$], 358 [M$^+$ + 1], 359 [M$^+$ + 2]. HRMS (*m*/*z*) for $C_{24}H_{23}NO_2$: calcd 357.1729, found 357.1738.

A Typical Procedure for Amination of Aryl Halides. To a solution of **1** (10.0 mg, 12.8 μmol), NaO^{t}Bu (18.1 mg, 0.192 mmol), and *p*-bromoanisole (16 μL, 0.128 mmol) in toluene (0.30 mL) was added 2,4,6-trimethylaniline (0.021 mL, 0.154 mmol). The mixture was stirred for 24 h at 100 °C. The reaction was quenched by adding water. Then the mixture was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4. After the solvent was removed in vacuo, the residual mixture was purified by column chromatography by elution with 7−10% ethyl acetate in hexane to give an orange solid (27.5 mg, 0.114 mmol, 89%).

Data for *N*-(4-Benzoylphenyl)-*N*-(2,4,6-trimethylphenyl)-aniline. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73−7.71 (m, 4H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 6.96 (s, 2H), 6.48 (d, *J* = 8.4 Hz, 2H), 2.32 (s, 3H), 2.18 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.1, 151.0, 139.0, 136.7, 136.4, 133.7, 133.0, 131.2, 129.5, 129.3, 128.0, 126.8, 111.8, 20.9, 18.2. IR (ν, cm^{-1}): 3328 (NH, sh), 1590 (CO, vs). EI-MS: *m*/*z* 315 [M$^+$], 316 [M$^+$ + 1], 317 [M$^+$ + 2]. HRMS (*m*/*z*) for $C_{22}H_{21}NO$: calcd 315.1623, found 315.1618.

Data for *N*-(4-Benzoylphenyl)-*N*-(2-isopropylphenyl)aniline. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76−7.73 (m, 4H), 7.54 (t, *J* = 6.4 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.39−7.36 (m, 1H), 7.31−7.29 (m, 1H), 7.24−7.21 (m, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 3.18 (sept, *J* = 6.8 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.1, 150.5, 143.7, 138.8, 137.1, 132.8, 131.4, 129.5, 128.0, 127.7, 126.7, 126.5, 126.1, 125.5, 113.2, 27.9, 23.2. IR (ν, cm^{-1}): 3260 (NH, s), 1581 (CO, vs), 1569 (CO, vs). EI-MS: *m*/*z* 315 [M$^+$], 316 [M$^+$ + 1], 317 [M$^+$ + 2]. HRMS (*m*/*z*) for $C_{22}H_{21}NO$: calcd 315.1623, found 315.1618.

Data for *N*-(4-Benzoylphenyl)-*N*-(2,6-diisopropylphenyl)-aniline. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, *J* = 8.0 Hz, 4H), 7.53 (t, *J* = 6.8 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 2H), 6.50 (br, 2H), 5.59 (br, 1H), 3.16 (sept, *J* = 6.8 Hz, 2H), 1.16 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.1, 152.2, 147.7, 139.0, 133.4, 133.0, 131.2, 129.5, 128.2, 128.0, 126.8, 124.1, 111.7, 28.3, 23.8. IR (ν, cm^{-1}): 3323 (NH, sh), 1598 (CO, vs), 1585 (CO, vs). EI-MS: *m*/*z* 357 [M$^+$], 358 [M$^+$ + 1], 359 [M$^+$ + 2]. HRMS (*m*/*z*) for $C_{25}H_{27}NO$: calcd 357.2093, found 357.2088.

Data for *N*-(4-Benzoylphenyl)-*N*-(4-chlorophenyl)aniline. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79−7.74 (m, 4H), 7.56 (t, *J* = 6.0 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.12 (br, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.2, 147.6, 139.3, 138.5, 132.7, 131.7, 129.6, 129.6, 129.1, 128.1, 121.7, 114.5. IR (ν, cm^{-1}): 3310 (NH, vs), 1583 (CO, vs), 1564 (CO, vs). EI-MS: *m*/*z* 307 [M$^+$],

(23) For examples of C- and O-bound nickel enolate complexes, see: (a) Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. *Organometallics* **1990**, *9*, 30−44. (b) Cámpora, J.; Maya, C. M.; Palma, P.; Carmona, E.; Gutiérrez-Puebla, E.; Ruiz, C. *J. Am. Chem. Soc.* **2003**, *125*, 1482−1483.

(24) Gupton, J. T.; Idoux, J. P.; Baker, G.; Colon, C.; Crews, A. D.; Jurss, C. D.; Rampi, R. C. *J. Org. Chem.* **1983**, *48*, 2933−2936.

308 [$M^+ + 1$], 309 [$M^+ + 2$]. HRMS (*m*/*z*) for $C_{19}H_{14}NOCl$: calcd 307.0764, found 307.0767.

A Typical Procedure for the Reaction of 4-Aminopropiophenone. To a solution of **1** (5.0 mg, 6.4 μmol), NaO^{t}Bu (9.5 mg, 0.099 mmol), and 4-bromo-benzophenone (15.9 mg, 0.061 mmol) in toluene (0.20 mL) was added 4-aminopropiophenone (10.9 mg, 0.073 mmol). The mixture was stirred for 24 h at 100 °C. The reaction was quenched by adding water. Then the mixture was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4. After the solvent was removed in vacuo, the residual mixture was purified by column chromatography to give a yellow liquid (1.8 mg, 0.004 mmol, 26%) as a diamination product and a pale yellow solid (7.0 mg, 0.021 mmol, 35%) as a monoamination product by elution with 25−30% and 35−40% ethyl acetate in hexane, respectively. The amount of the α-arylation product was determined by means of the ^{1}H NMR spectrum of the crude mixture (5%).

Data for 4-[*N*-(4-Benzoylphenyl)amino]propiophenone. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.2 Hz, 2H), 7.19 (d, J = 8.8 Hz, 4H), 6.40 (br, 1H), 2.97 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.1, 195.2, 145.6, 145.6, 138.2, 132.5, 131.9, 130.7, 130.6, 130.1, 129.7, 128.2, 117.1, 116.7, 31.4, 8.5. IR (ν, cm^{-1}): 3308 (NH, s), 1587 (CO, s). EI-MS: *m*/*z* 329 [M^+], 330 [$M^+ + 1$], 331 [$M^+ + 2$]. HRMS (*m*/*z*) for $C_{22}H_{19}NO_2$: calcd 329.1416, found 329.1411.

Data for 4-[*N*,*N*-Bis(4-benzoylphenyl)amino]propiophenone. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, J = 8.4 Hz, 2H), 7.82−7.79 (m, 8H), 7.59 (t, J = 7.2 Hz, 2H), 7.50 (t, J = 7.2 Hz, 4H), 7.23−7.20 (m, 6H), 2.98 (q, J = 7.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 199.3, 195.3, 150.2, 150.0, 137.7, 133.0, 132.7, 132.3, 132.0, 129.8, 128.3, 124.1, 123.7, 31.6, 8.3. IR (ν_{CO}, cm^{-1}): 1679 (s), 1651 (s), 1585 (vs). EI-MS: *m*/*z* 509 [M^+], 510 [$M^+ + 1$], 511 [$M^+ + 2$]. HRMS (*m*/*z*) for $C_{35}H_{27}NO_3$: calcd 509.1991, found 509.2002.

Supporting Information Available: Experimental details of the preparation of 4-(*N*,*N*-dimethylamino)propiophenone, ^{1}H and ^{13}C NMR spectra for new organic compounds, and the spectral data of the other products. This material is available free of charge via the Internet at http://pubs.acs.org.

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