BCSJ

Selected Paper

The Nickel(II)-Catalyzed Direct Benzylation, Allylation, Alkylation, and Methylation of C–H Bonds in Aromatic Amides Containing an 8-Aminoquinoline Moiety as the Directing Group

Yoshinori Aihara, Jendrik Wuelbern, and Naoto Chatani*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871

E-mail: chatani@chem.eng.osaka-u.ac.jp
Received: December 13, 2014; Accepted: January 5, 2015; Web Released: January 16, 2015

Direct alkylation via the cleavage of the *ortho* C–H bonds by a nickel-catalyzed reaction of aromatic amides containing an 8-aminoquinoline moiety as the directing group with alkyl halides is reported. Various alkyl halides, including benzyl, allyl, alkyl, and methyl halides (or pseudo halides) participate as electrophilic coupling partners. The reaction shows a high functional group compatibility. The reaction proceeds in a highly regioselective manner at the less hindered C–H bonds in the reaction of meta-substituted aromatic amides, irrespective of the electronic nature of the substituent. The mechanism responsible for the C–H alkylation reaction is discussed based on the results obtained in a variety of mechanistic experiments.

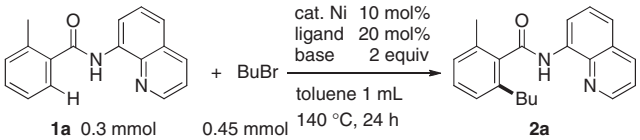
Transition-metal-catalyzed direct C–H bond functionalization has emerged as a powerful method for the construction of organic molecules, and numerous reports on the formation of C–C bonds via C–H bond cleavage have been appeared, especially direct arylation with aryl halides or aryl metal reagents.[1] Compared to arylation reactions, examples of the direct alkylation of C–H bonds to afford alkylated arenes remain limited, because of the resistance of alkyl halides toward oxidative addition and the fact that the resulting alkyl metal complexes are susceptible to β-hydride elimination.[2] Conventional approaches to the synthesis of alkylated arenes rely on Friedel–Crafts-type reactions or S_EAr type reactions, both of which have some limitations including i) a low functional group tolerance, ii) low regioselectivities, and iii) the formation of a mixture of normal and branched products.[3] Numerous efforts have been made to address these limitations, and transition-metal-catalyzed direct alkylation with alkyl halides has emerged as an alternative method for the synthesis alkylated arenes. Due to those efforts, direct alkylations using alkyl halides as the alkylating reagent with Pd,[4] Ru,[5] Fe,[6] and Co[7] catalysts have been developed over the past few years. In 2013, our group also reported the first example of the nickel(II)-catalyzed direct alkylation of ortho C–H bonds in aromatic amides with primary alkyl halides,[8] by taking advantage of a bidentate directing group.[1m] After this paper appeared, other groups have expanded the substrate scope and limitations, such as the direct alkylation of C(sp^3)–H bonds,[9a] alkylation with secondary alkyl halides,[9b] and phosphates[9c] as alkylating reagents by utilizing the same chelation system. In this manuscript, we report the full details of the nickel(II)-catalyzed direct benzylation, allylation, alkylation, and methylation of C–H bonds in aromatic amides, and we also discuss the mechanism for this reaction, based on competition reactions, deuterium labeling experiments, detailed product distributions, and radical clock experiments.

Results and Discussion

Our group has focused on the use of bidentate directing groups, such as 2-pyridylmethylamine[10] and 8-aminoquinoline[8,11] in a catalytic functionalization of C–H bonds. To expand the utility of the present chelation system, we examined the reaction of **1a** with butyl bromide. Fortunately, the alkylation of C–H bonds with alkyl halides was successful, when an 8-aminoquinoline chelation system was used. When the amide **1a** was reacted with butyl bromide under optimal conditions for arylation reactions with phenyl iodide,[11h] no reaction took place (Entry 1 in Table 1). However, the addition of PPh_3 dramatically improved the product yield to 41% NMR yield, along with 54% of unreacted **1a** being recovered (Entry 3). The product yield was significantly affected by the nature of the base used (Entries 3–8). The use of PCy_3 gave **2a** in 26% NMR yield (Entry 9). The use of 2 equivalents of butyl bromide improved the product yield to an isolated yield of 88% (Entry 12). Some Ni(II) complexes could also be used as catalysts (Entries 13–15). Similar to the arylation of C–H bonds,[11h] the Ni(0) complex was also found to show catalytic activity. In all cases, the starting amide **1a** was recovered when the product yield of **2a** was low. No by-products were detected in the reactions.

With the optimized reaction conditions in hand, we examined the scope of the substrate in the reaction. Table 2 shows the results for reactions of various aromatic amides with butyl bromide under the standard reaction conditions. A variety of functional groups were found to be tolerated and, even the

Table 1. The Nickel-Catalyzed Butylation of **1a** with Butyl Bromide



1a 0.3 mmol 0.45 mmol **2a**

Entry	Catalyst	Ligand	Base	Yields (**2a**/**1a**)[a]
1	$Ni(OTf)_2$	none	$NaHCO_3$	0%/101%
2	$Ni(OTf)_2$	none	Na_2CO_3	0%/92%
3	$Ni(OTf)_2$	PPh_3	$NaHCO_3$	41%/54%
4	$Ni(OTf)_2$	PPh_3	Na_2CO_3	79%/15%
5	$Ni(OTf)_2$	PPh_3	Li_2CO_3	3%/109%
6	$Ni(OTf)_2$	PPh_3	K_2CO_3	0%/90%
7	$Ni(OTf)_2$	PPh_3	NaOAc	5%/101%
8	$Ni(OTf)_2$	PPh_3	2,6-lutidine	0%/105%
9	$Ni(OTf)_2$	PCy_3	Na_2CO_3	26%/63%
10	$Ni(OTf)_2$	DMF 1.5 mmol	Na_2CO_3	0%/95%
11	$Ni(OTf)_2$	DMSO 1.5 mmol	Na_2CO_3	0%/97%
12[b]	**$Ni(OTf)_2$**	**PPh_3**	**Na_2CO_3**	**91% (88%)/0%**
13	$Ni(OAc)_2$	PPh_3	Na_2CO_3	70%/19%
14	$NiCl_2$	PPh_3	Na_2CO_3	66%/31%
15	$[NiBr_2(dme)]$	PPh_3	Na_2CO_3	76%/10%
16	$[Ni(cod)_2]$	PPh_3	Na_2CO_3	51%/35%

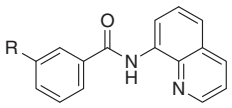
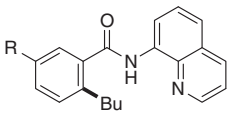
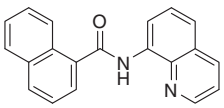
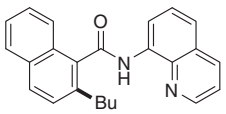
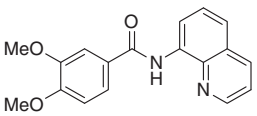
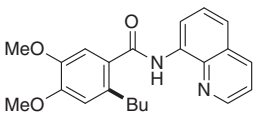
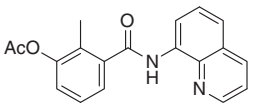
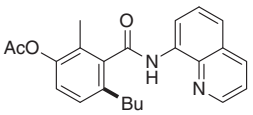
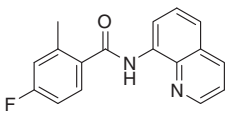
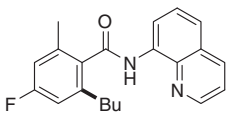
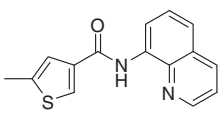
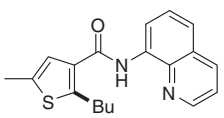
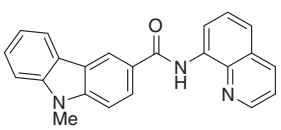
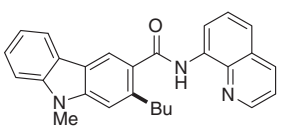
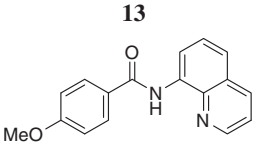
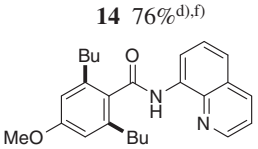
a) NMR yields. The number in parenthesis is the isolated yield of **2a**. b) BuBr (0.6 mmol) was used.

iodide remained intact, as in **2h**. The reaction of meta-substituted substrates resulted in alkylation to proceed exclusively at the less hindered C–H bonds, irrespective of the electronic nature of the substituent. In general, electron-withdrawing groups tended to give butylation products in higher yields. The addition of NaI was found to improve the product yields in some cases.

This C–H bond alkylation reaction was also found to be applicable to α,β-unsaturated amides, as shown in Table 3. The cyclic amides, **17**, **19**, and **21** gave the corresponding butylation products in good yields. However, in the case of the acyclic amide **23**, a mixture of stereoisomers **24**, was produced, with the *E*-isomer being favored. The reaction was limited to trisubstituted α,β-unsaturated amides, suggesting that the presence of the substituent at the α-carbon is an important factor in terms of the reactivity of the substrates. In fact, reactions of **25** and **27** failed to give the corresponding butylation products.

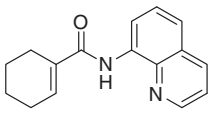
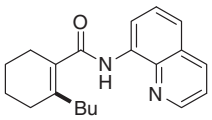
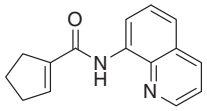
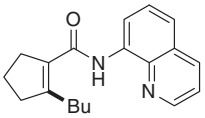
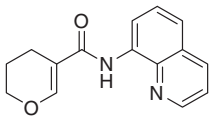
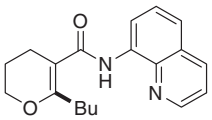
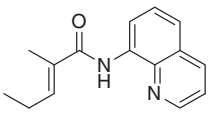
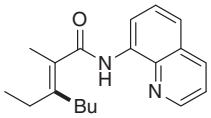
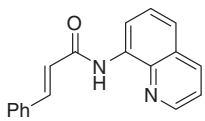
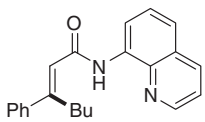
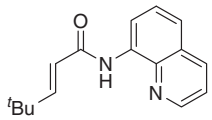
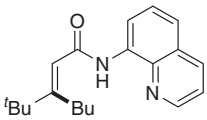
A variety of alkyl halides were also found to be applicable to this reaction, as shown in Table 4. Octyl iodide as well as octyl bromide gave the octylation product **29** in high yield. While no reaction took place in the case of octyl chloride, it is noteworthy that the addition of NaI (2 equivalents) dramatically improved the product yield to 88% isolated yield. This effect of NaI was also observed in the case of other sterically demanding alkyl halides or some functionalized alkyl halides. When phenethyl bromide was used as the coupling partner, the corresponding product **34** was obtained in 57% yield, however the yield was improved to 88% isolated yield when 2 equivalents of NaI was added.[12] The use of 3-methylbutyl bromide and

Table 2. The Ni-Catalyzed Butylation of C–H Bonds in Aromatic Amides[a]

Amide	Product[b]
	
R = OMe (**1b**)	**2b** 74% (89%)[c]
OCH_2Ph (**1c**)	**2c** 72% (85%)[c]
$OSiMe_2Bu^t$ (**1d**)	**2d** 75%
Me (**1e**)	**2e** 92%[d]
Ph (**1f**)	**2f** 81%[d]
Cl (**1g**)	**2g** 92%[e]
I (**1h**)	**2h** 68%[e]
$C(O)CH_3$ (**1i**)	**2i** 75%[d]
CF_3 (**1j**)	**2j** 95%[d]
	
3	**4** 79%[d]
	
5	**6** 92%
	
7	**8** 52%
	
9	**10** 87%
	
11	**12** 50%
	
13	**14** 76%[d,f]
	
15	**16** 88%[d,f]

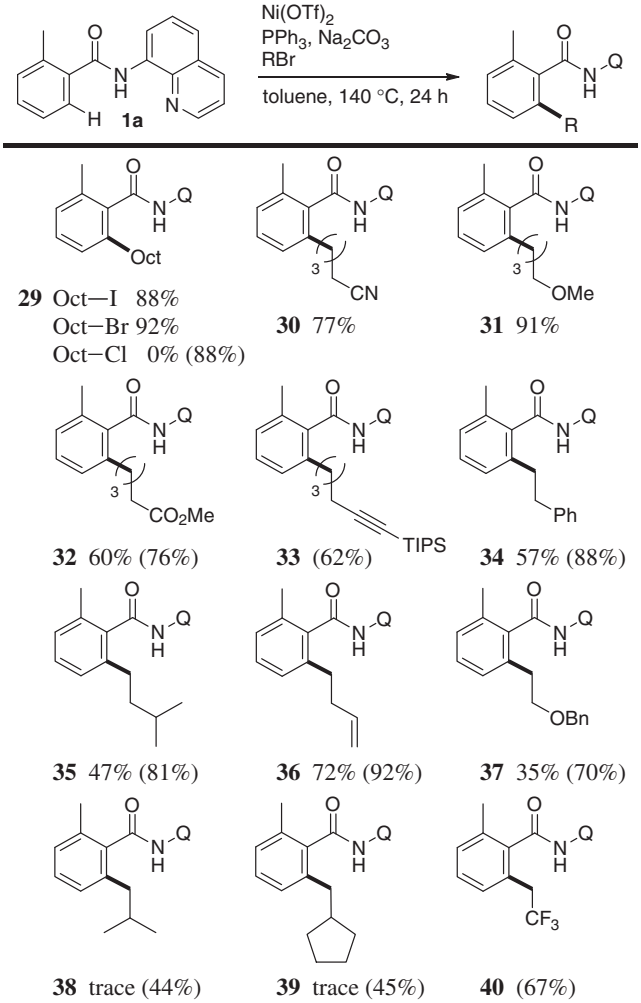
a) Reaction conditions: amide (0.3 mmol), BuBr (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), PPh_3 (0.06 mmol), and Na_2CO_3 (0.6 mmol) in toluene (1 mL) at 140 °C for 24 h. b) Isolated yields. c) NaI (0.6 mmol) was used as an additive. d) Run at 160 °C. e) BuI (0.6 mmol) was used instead of BuBr. f) BuBr (1.2 mmol) was used.

Table 3. The Ni-Catalyzed Butylation of C–H Bonds in α,β-Unsaturated Amides[a)]

Amide	Product[b)]
 **17**	 **18** 81%
 **19**	 **20** 67%
 **21**	 **22** 72%
 **23**	 **24** 54% (*E*:*Z* = 85:15)
 **25**	 **26** 0%
 **27**	 **28** 0%

a) Reaction conditions: amide (0.3 mmol), BuBr (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), PPh_3 (0.06 mmol), and Na_2CO_3 (0.6 mmol) in toluene (1 mL) at 140 °C for 24 h. b) Isolated yields.

Table 4. The Ni-Catalyzed Alkylation of C–H Bonds in Aromatic Amides with Functionalized Alkyl Halides[a),b)]



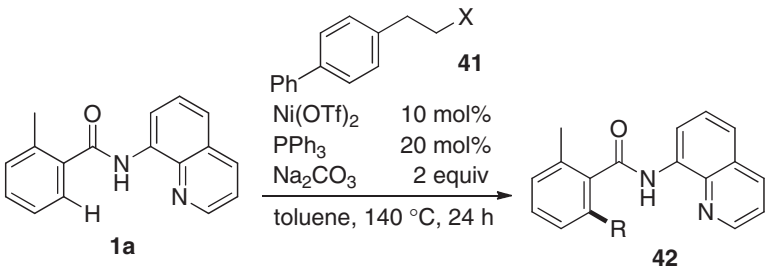
a) Reaction conditions: amide **1a** (0.3 mmol), RBr (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), PPh_3 (0.06 mmol), and Na_2CO_3 (0.6 mmol) in toluene (1 mL) at 140 °C for 24 h. b) Isolated yields. The number in the parenthesis is the yield using NaI (0.6 mmol).

cyclopentylmethyl bromide in the absence of NaI resulted in essentially no reaction, but the yields of **38** and **39** were improved to 44% and 45% yields, respectively, when NaI was added.

To examine the effect of NaI in more detail, the reaction of **1a** with 4-phenylphenethyl bromide (**41-Br**) was carried out in the absence of NaI (Scheme 1). The corresponding alkylation product **42** was formed in 43% yield, along with 33% of **1a** and 53% of **41-Br** being recovered, and only a 3% NMR yield of 4-phenylstyrene (based on the bromide **41-Br**) was formed. However, when **1a** was reacted with **41-Br** in the presence of NaI, **42** was produced in 88% isolated yield, with a 10% yield of 4-phenylstyrene. These results suggest that β-hydride elimination leading to the formation of 4-phenylstyrene is not the cause of the low conversion in the reaction without NaI. Rather, the low yield of **42** in the reaction of **1a** with **41-Br** can be attributed to the low reactivity of the C–Br bond in **41-Br**. In support of this, essentially the same results were obtained in the reaction of **1a** with **41-I**, the corresponding iodide **41-I** is generated by a Finkelstein reaction under the conditions in the reaction with NaI.

The reaction of **1a** with a secondary halide, such as cyclopentyl bromide under reaction conditions suitable for primary halides gave only a trace amount of the alkylation product **43**. After optimization of the reaction conditions, and using $IMes^{Me}$ and PPh_3 as the ligand, the product yield was improved to 51% (Scheme 2).[13]

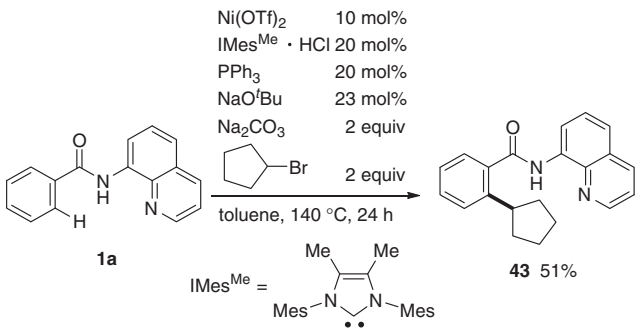
Several studies were carried out, in an attempt to obtain information regarding the mechanism for the reaction. We hypothesized that the alkylation products are formed via the addition of C–H bonds to alkenes which may involve the generation of an alkyl halide via dehydrobromination under the reaction conditions employed. However, when **1a** was reacted with 1-octene, the expected alkylation product **29** was not detected (Scheme 3). Because the PPh_3 is essential for the alkylation reaction to proceed, a quaternary phosphonium



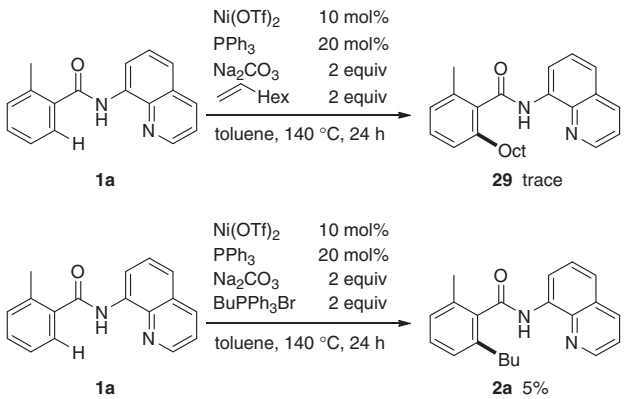
	42	recovery of 41	Ph
X = Br (**41-Br**)	43% (33%)[a]	53% (based on **41**)	3% (based on **41**)
X = Br with NaI	88% (9%)[a]	15%[b] (based on **41**)	10% (based on **41**)
X = I (**41-I**)	86% (9%)[a]	trace	5% (based on **41**)

[a]The number in parenthesis is the recovery of **1a**.
[b]The corresponding iodide **41-I** was obtained.

Scheme 1. The effect of NaI.

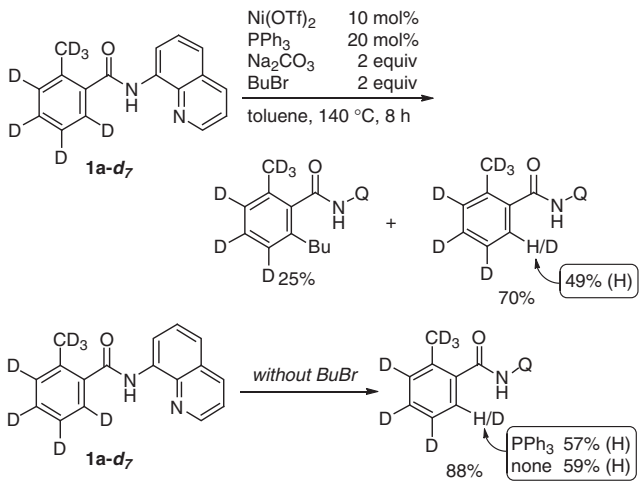


Scheme 2. The Ni-catalyzed alkylation with secondary alkyl halide.



Scheme 3. Alkylation sources.

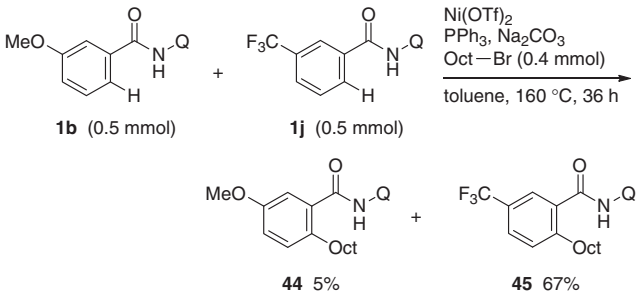
bromide is also another candidate for the use of an alkylation reagent. However, the corresponding butylation product **2a** was formed in only 5% yield. These results indicate that neither the olefin nor the quaternary phosphonium bromide is involved in this alkylation and that the alkyl halides themselves function as the coupling partner.



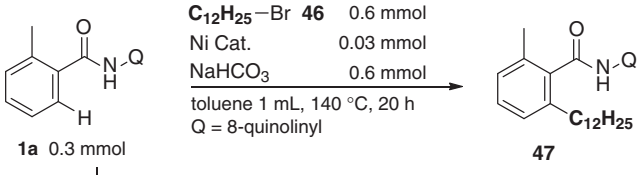
Scheme 4. Deuterium labeling experiments.

The deuterated amide **1a-*d*$_7$** was reacted with BuBr for 8 h under otherwise standard reaction conditions (Scheme 4). As observed in the case of arylation,[11h] a significant amount of H/D exchange at the ortho position (the d-content decreased from >98% to 51% (49%H)) and on the amide nitrogen in the recovered amide was observed. A significant amount of H/D exchange occurred, even in the absence of BuBr, indicating that the cleavage of C–H bonds is reversible. These results indicate that the cleavage of C–H bonds is not likely the rate determining step in the reaction. It was also found that the presence of PPh_3 had no effect on the H/D exchange reaction.

We next performed a competition experiment using an excess amount of a 1:1 mixture of **1b** and **1j** in a reaction with octyl bromide (Scheme 5). The findings indicate that **1j** reacted to give **45** as the major product. This result again indicates that the presence of an electronic-withdrawing group on aromatic amides facilitates the reaction.[14]



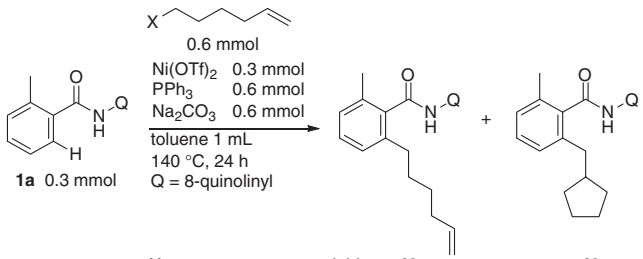
Scheme 5. Competition experiment.



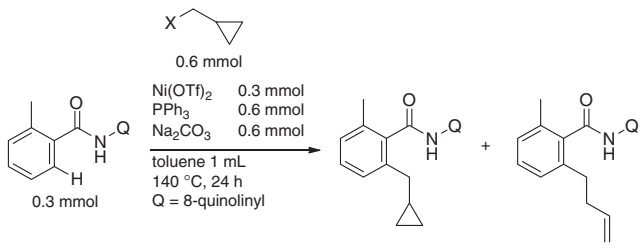
	47	recovery of 46	$C_{12}H_{25}$—H	$C_{10}H_{21}$
$Ni(OTf)_2$	76% (19%)	53%/**46**	3%/**46**	trace
$[Ni(cod)_2]$	94% (trace)	16%/**46**	14%/**46**	6%/**46**

[a]The numer in parenthesis is the recovery of **1a**.

Scheme 6. Product distribution.



X	yield	**48**	:	**49**
Br	88%	18	:	1
I	94%	11	:	1



X	yield	**50**	:	**51**
Br	81%	2.9	:	1
I	88%	2.0	:	1

Scheme 7. Radical clock experiments.

As shown in Table 1, both Ni(0) and Ni(II) complexes showed a high catalytic activity. The product distribution was examined in considerable detail in order to develop a better understanding of the difference between the Ni(II)- and Ni(0)-catalyzed reactions (Scheme 6). When $Ni(OTf)_2$ was used as the catalyst, the alkylation product **47** was produced in 76% yield, along with 19% of **1a** and 53% of the bromide **46** being recovered. No evidence for β-hydride elimination leading to the formation of dodecene was found. In contrast, the halide **46** was recovered only in 16%, and 14% yield of dodecane and 6% of dodecene were produced when the $Ni(cod)_2$ catalyst was used. In both cases, no dimerization of **46** leading to the formation of tetracosane ($C_{24}H_{50}$) was observed.[15]

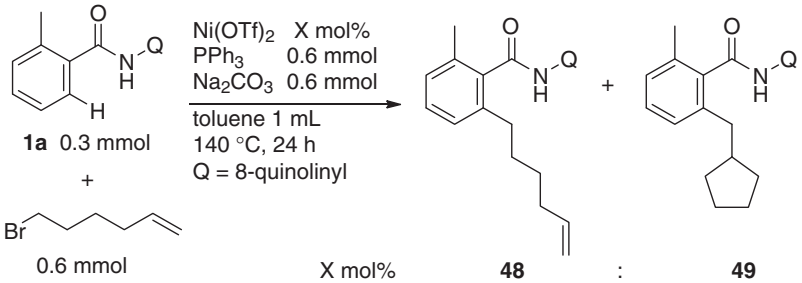
These results exclude the possibility of a Ni(0)/Ni(II) catalytic cycle. However, a Ni(I)/Ni(III) catalytic cycle, which involves a radical path cannot be excluded, based on the findings reported herein. In fact, a Ni(I)/Ni(III) catalytic cycle was proposed in the Ni-catalyzed alkylation of C(sp^3)–H bonds.[9a] In order to obtain mechanistic information regarding this, reactions were run in the presence of radical scavengers. The addition of TEMPO (2 equivalents) resulted in no detectable products being formed. The alkylation product was not formed and **1a** was recovered in 79% NMR yield. We next used GALVINOXYL (2 equivalents) in place of TEMPO. Again, a reaction did not take place and **1a** was recovered in 52% yield.

To gain more insights into the mechanism, radical clock experiments were next carried out. The reaction of **1a** with 6-bromohex-1-ene gave the unrearranged product **48** selectively (Scheme 7). Although the use of 6-iodohex-1-ene resulted in a slight decrease in the ratio of **48**/**49**, the unrearranged alkylation product **48** was still the major product. We next used cyclopropylmethyl halides, since the cyclopropylmethyl radical is known to undergo ring-opening faster than the cyclization of the 5-hexenyl radical.[16] The reaction with cyclopropylmethyl bromide gave a mixture of the unrearranged product **50** and the rearranged product **51** in a total isolated yield of 81% in favor of the unrearranged product **50**.

We next examined the effect of catalyst concentration on the products formed in the reaction of **1a** with 6-bromohex-1-ene. If a radical chain mechanism were operative, then the **48**/**49** ratio would be expected to increase at higher catalyst concentrations because the radical would have less time to rearrange before reacting with another nickel.[17] In contrast, if a radical chain were not involved, the **48**/**49** ratio would be expected to be unchanged as a function of catalyst concentration. However, the ratio was found to be constant, irrespective of the catalyst concentration used (Scheme 8), suggesting that the radical chain mechanism is not operative.

Although some mechanistic studies were performed, it remains difficult to reach a firm conclusion regarding the mechanism for this reaction, i.e., whether or not the reaction proceeds via a radical mechanism, because of the inconclusive results obtained. The results shown in Scheme 8 suggest that free radical species are not involved in the reaction. The possibility that the key intermediate has a radical character, but that a radical species is not free, but instead remains in the coordination sphere in a nickel center cannot be excluded.

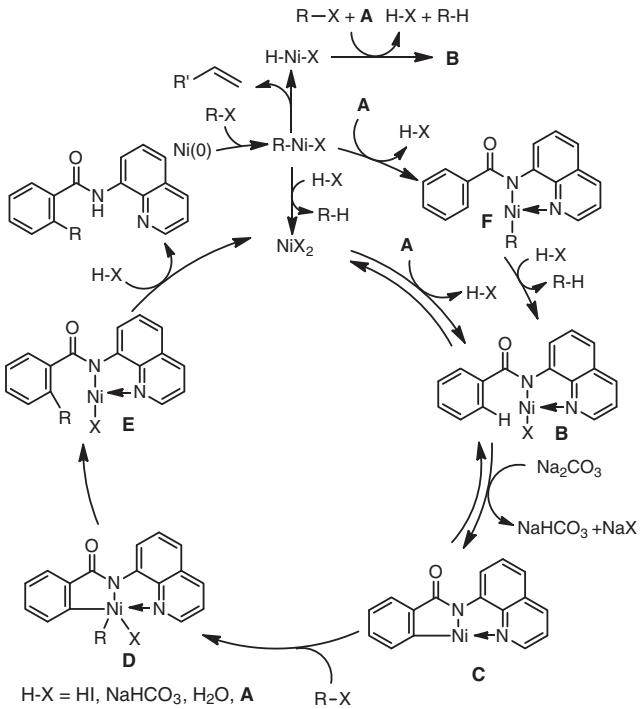
The alkylation of C–H bonds essentially proceeds through a mechanism similar to that proposed in the arylation of C–H bonds (Scheme 9).[11h,18] Amide **A** coordinates to NiX_2 followed by a ligand exchange with the generation of HX, which is accelerated by Na_2CO_3, to give the nickel complex **B**. Complex **B** then undergoes a reversible cyclometalation to give complex **C** via a concerted metalation deprotonation (CMD) mechanism,



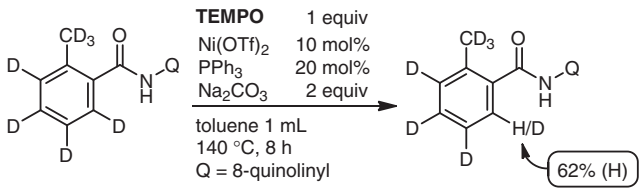
X mol%	48	:	49
5 mol%	20	:	1
10 mol%	18	:	1
15 mol%	19	:	1

The ratio of product was determined by NMR.

Scheme 8. Dependence of the ratio of **48** and **49** on the concentration of nickel catalyst.



Scheme 9. Proposed reaction mechanism.



Scheme 10. Effect of TEMPO on the H/D exchange.

which is also accelerated by the presence of Na_2CO_3. The oxidative addition of an alkyl halide to the complex **C** gives the nickel(IV) species **D**. Complex **D** undergoes a reductive elimination to give **E**, which is then protonated to afford the alkylation product with the regeneration of the nickel(II) catalyst. As shown in Scheme 4, C–H bond cleavage appears to be reversible and does not appear to be the rate-determining step in this reaction. As shown in Table 1, both Ni(II) and Ni(0) complexes have high catalytic activities. Based on the results shown in Scheme 6, even when Ni(0) is used as the catalyst precursor, the nickel complexes are converted into Ni(II) species and participate in the main catalytic cycle as the complex **B**.

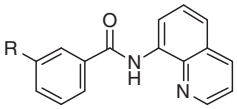
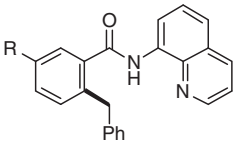
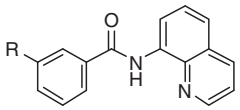
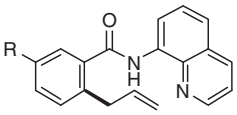
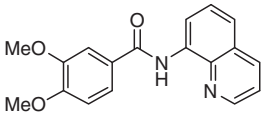
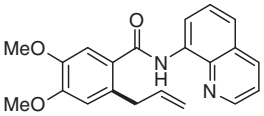
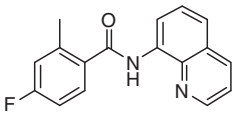
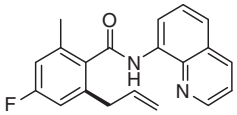
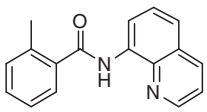
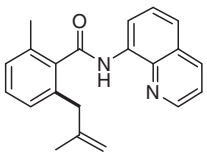
The findings clearly show that the presence of TEMPO had no effect on the cleavage of C–H bonds. Thus, even in the presence of TEMPO, an H/D exchange reaction of **1b** took place to the same extent as that for the reaction in the absence of TEMPO (Scheme 10). As shown in Scheme 4, the presence of PPh_3 also had no effect on the cleavage of C–H bonds, indicating that the presence of PPh_3 is essential for the oxidative addition of an alkyl halide with a nickel center and but that it is not involved in the cleavage of C–H bonds.

Benzylation and Allylation. Benzyl and allyl bromides were also found to participate as electrophilic counter partners in the reaction (Table 5). Crotyl bromide was not a viable reactant, but the reaction with 3-bromo-2-methylprop-1-ene gave the corresponding allylation product **56** in good yield. The regioselectivity was again controlled by steric factors. In all cases, the less hindered C–H bonds reacted exclusively.

Methylation. It is important to note that the regioselective methylation of C–H bonds is a research topic of considerable interest in the area of pharmaceutical chemistry, because of the well-known "magic methyl effect" which, in many cases, greatly improves the biological activity of a drug.[19] However, examples of the methylation of C(sp^2)–H bonds with methyl halides (or pseudohalide) are very rare. Tremont reported that acetanilides react with MeI in the presence of a stoichiometric amount of $Pd(OAc)_2$ resulting in methylation at the ortho position.[4a,20] A catalytic version was recently reported using MeI as the methylation reagent.[4c–4e,4i,4k,21] While organometallic reagents,[22] such as Me_4Sn, $MeB(OH)_2$, peroxides[23] and others[24] can also be used in the methylation of C(sp^2)–H bonds, the methylation of C–H bonds continues to be a significant challenge.

When **1a** was reacted with methyl iodide under the standard reaction conditions, which involve the use of 4 equivalents of methyl iodide, the corresponding methylation product **57** was obtained in 56% NMR yield, along with the *N*-methylation product in 47% yield (Scheme 11). When MeOTs was used,

Table 5. The Ni-Catalyzed Benzylation and Allylation of C–H Bonds in Aromatic Amides[a)]

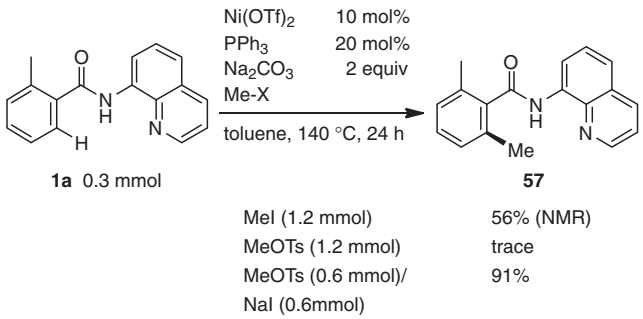
Amide	Product[b)]
	
R = OMe (**1b**)	**52b** 66%
Me (**1e**)	**52e** 60%
Cl (**1g**)	**52g** 55%
CF_3 (**1j**)	**52j** 65%
	
R = OMe (**1b**)	**53b** 71%
Cl (**1g**)	**53g** 63%
CF_3 (**1j**)	**53j** 71%
	
5	**54** 70%
	
9	**55** 49%
	
1a	**56** 88%

a) Reaction conditions: amide **1a** (0.3 mmol), bromides (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), PPh_3 (0.06 mmol), and Na_2CO_3 (0.6 mmol) in toluene (1 mL) at 140 °C for 24 h. b) Isolated yields.

only a trace amount of **57** was obtained. However, the use of a combination of methyl iodide/NaI dramatically increased the product yield to 91% isolated yield.

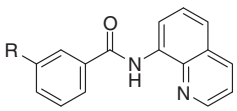
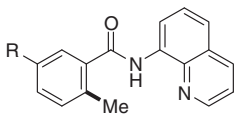
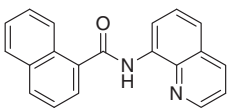
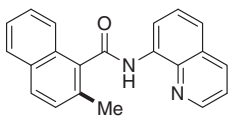
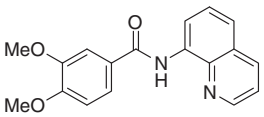
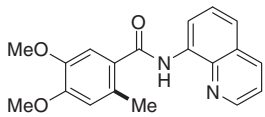
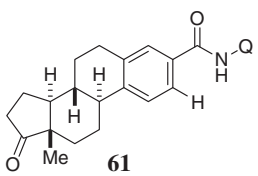
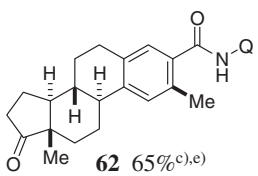
Results for the methylation of various aromatic amides are shown in Table 6. In the reaction of meta-substituted aromatic amides, the less hindered C–H bonds were exclusively monomethylated, even though the methyl group is sterically less bulky.

All reactions, including arylation, alkylation, benzylation, allylation, and even methylation took place at the less hindered C–H bonds in the reaction of meta-substituted aromatic amides. To gain more insights into the mechanism, a deuterium labeling experiment using **1e-d_7** was conducted (Scheme 12). The findings showed that the hindered C–H bonds also undergo H/D exchange to some extent, suggesting that the cleavage of C–H bonds takes place, but that the oxidative addition of halides or reductive elimination does not occur at the hindered



Scheme 11. Ni-catalyzed methylation.

Table 6. The Ni-Catalyzed Methylation of C–H Bonds in Aromatic Amides[a)]

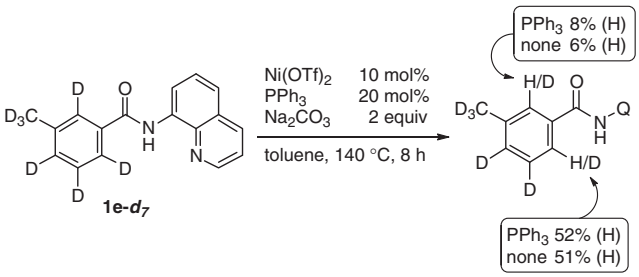
Amide	Product[b)]
	
R = OMe (**1b**)	**58b** 91%
Ph (**1f**)	**58f** 95%[c),d)]
Cl (**1g**)	**58g** 91%[c),d)]
$C(O)CH_3$ (**1i**)	**58i** 93%
CF_3 (**1j**)	**58j** 71%[c),d)]
	
3	**59** 86%
	
5	**60** 74%
	
61	**62** 65%[c),e)]

a) Reaction conditions: amide (0.3 mmol), MeOTs (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), PPh_3 (0.06 mmol), Na_2CO_3 (0.6 mmol), and NaI (0.6 mmol) in toluene (2 mL). b) Isolated yields. c) At 160 °C. d) PPh_3 (10 mol %) was used. e) Reaction conditions: amide (0.15 mmol), MeOTs (0.3 mmol), $Ni(OTf)_2$ (0.015 mmol), PPh_3 (0.03 mmol), Na_2CO_3 (0.3 mmol), and NaI (0.3 mmol) in toluene (2 mL).

C–H bonds because of steric hindrance. Similar to the case shown in Scheme 4, the presence of PPh_3 also had no effect, either on the efficiency of C–H bond cleavage or on the regioselectivity of the cleavage of C–H bonds.

Conclusion

Regioselective alkylation at the ortho-position of aromatic amides with alkyl halides (or pseudo halides) was achieved



Scheme 12. Deuterium labeling experiment using a meta-substituted aromatic amide (**1e-d_7**).

using Ni catalysts in conjunction with an 8-aminoquinoline directing group. Various groups, such as benzyl, allyl, alkyl, and methyl groups can be introduced at the ortho position. A variety of functional groups are tolerated in the reaction. The reaction proceeds in a highly selective manner at the less hindered C–H bonds in the reaction of meta-substituted aromatic amides, irrespective of the electronic nature of the substituents. Both Ni(II) and Ni(0) shows a high catalytic activity, but, based on various mechanistic experiments, it appears that that Ni(II) is the key catalytic species and Ni(0) is converted to Ni(II) under the reaction conditions employed. The proposed mechanism involves a Ni(II)/Ni(IV) catalytic cycle. The key intermediate appears to have a radical character, but the reaction probably does not proceed via a radical chain mechanism. To reach a firm conclusion regarding the mechanism for this reaction, further experiments and theoretical studies will be required. A DFT calculation study is currently in progress.

This work was supported, in part, by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from The Ministry of Education, Culture, Sports, Science and Technology, and by JST Strategic Basic Research Programs "Advanced Catalytic Transformation Program for Carbon Utilization (ACT-C)" from Japan Science and Technology Agency. This work was supported by the JSPS Japanese-German Graduate Externship from Japan Science and Technology Agency and the Deutsche Forschungsgemeinschaft through the International Research Training Group "Selectivity in Chemo- and Biocatalysis" (or "Seleca") Y.A. expresses his special thanks for a JSPS Research Fellowship for Young Scientists.

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available electronically on J-STAGE.

References

1 a) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013. b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624. c) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074. d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147. e) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev.* **2010**, *110*, 824. f) M. Wasa, K. M. Engle, J.-Q. Yu, *Isr. J. Chem.* **2010**, *50*, 605. g) L.-M. Xu, B.-J. Li, Z. Yang, Z.-J. Shi, *Chem. Soc. Rev.* **2010**, *39*, 712. h) D. Y.-K. Chen, S. W. Youn, *Chem.—Eur. J.* **2012**, *18*, 9452. i) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. j) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. k) B. Li, P. H. Dixneuf, *Chem. Soc. Rev.* **2013**, *42*, 5744. l) M. Corbet, F. De Campo, *Angew. Chem., Int. Ed.* **2013**, *52*, 9896. m) G. Rouquet, N. Chatani, *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. n) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369. o) K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208. p) Z. Huang, G. Dong, *Tetrahedron Lett.* **2014**, *55*, 5869. q) L. C. Misal Castro, N. Chatani, *Chem. Lett.* **2015**, in press. doi:10.1246/cl.150024.

2 a) S. Messaoudi, J.-D. Brion, M. Alami, *Eur. J. Org. Chem.* **2010**, 6495. b) L. Ackermann, *Chem. Commun.* **2010**, *46*, 4866. c) L. Ackermann, *J. Org. Chem.* **2014**, *79*, 8948.

3 M. B. Smith, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, John Wiley & Sons, **2013**.

4 a) S. J. Tremont, R. U. Hayat, *J. Am. Chem. Soc.* **1984**, *106*, 5759. b) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *Angew. Chem., Int. Ed.* **2009**, *48*, 6097. c) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965. d) M.-J. Jang, S.-W. Youn, *Bull. Korean Chem. Soc.* **2011**, *32*, 2865. e) Y. Zhao, G. Chen, *Org. Lett.* **2011**, *13*, 4850. f) L. D. Tran, O. Daugulis, *Angew. Chem., Int. Ed.* **2012**, *51*, 5188. g) K. Chen, F. Hu, S.-Q. Zhang, B.-F. Shi, *Chem. Sci.* **2013**, *4*, 3906. h) S.-Y. Zhang, G. He, W. A. Nack, Y. Zhao, Q. Li, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 2124. i) S.-Y. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 12135. j) B. Xiao, Z.-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 616. k) R.-Y. Zhu, J. He, X.-C. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 13194. l) K. Chen, B.-F. Shi, *Angew. Chem., Int. Ed.* **2014**, *53*, 11950. m) S.-Y. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2015**, *137*, 531.

5 L. Ackermann, P. Novák, R. Vicente, N. Hofmann, *Angew. Chem., Int. Ed.* **2009**, *48*, 6045.

6 a) E. R. Fruchey, B. M. Monks, S. P. Cook, *J. Am. Chem. Soc.* **2014**, *136*, 13130. b) L. Ilies, T. Matsubara, S. Ichikawa, S. Asako, E. Nakamura, *J. Am. Chem. Soc.* **2014**, *136*, 13126. c) B. M. Monks, E. R. Fruchey, S. P. Cook, *Angew. Chem., Int. Ed.* **2014**, *53*, 11065.

7 a) Q. Chen, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 428. b) K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2013**, *135*, 9279. c) B. Punji, W. Song, G. A. Shevchenko, L. Ackermann, *Chem.—Eur. J.* **2013**, *19*, 10605. d) K. Gao, T. Yamakawa, N. Yoshikai, *Synthesis* **2014**, *46*, 2024.

8 Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2013**, *135*, 5308.

9 a) X. Wu, Y. Zhao, H. Ge, *J. Am. Chem. Soc.* **2014**, *136*, 1789. b) W. Song, S. Lackner, L. Ackermann, *Angew. Chem., Int. Ed.* **2014**, *53*, 2477. c) X. Cong, Y. Li, Y. Wei, X. Zeng, *Org. Lett.* **2014**, *16*, 3926.

10 a) S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 6898. b) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 8070. c) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 14952. d) N. Hasegawa, K. Shibata, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *Tetrahedron* **2013**, *69*, 4466.

11 a) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984. b) Y. Aihara, N. Chatani, *Chem. Sci.* **2013**, *4*, 664. c) G. Rouquet, N. Chatani, *Chem. Sci.* **2013**, *4*, 2201. d) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2014**, *136*, 898. e) K. Shibata, N. Chatani, *Org. Lett.* **2014**, *16*, 5148. f) Y. Aihara, M. Tobisu, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2014**, *136*, 15509. g) M.

Al-Amin, M. Arisawa, S. Shuto, Y. Ano, M. Tobisu, N. Chatani, *Adv. Synth. Catal.* **2014**, *356*, 1631. h) A. Yokota, Y. Aihara, N. Chatani, *J. Org. Chem.* **2014**, *79*, 11922. i) M. Iyanaga, Y. Aihara, N. Chatani, *J. Org. Chem.* **2014**, *79*, 11933. j) T. Uemura, T. Igarashi, M. Noguchi, K. Shibata, N. Chatani, *Chem. Lett.* **2015**, in press. doi:10.1246/cl.150041.

12 Our preliminary paper (ref 8) reported that only traces of **34** are produced, but the yield was improved to 61% when NaI was added to the reaction mixture. However, this is an error and the data shown in Table 4 show the correct values.

13 Recently, Ackermann successfully found the optimized reaction conditions for C–H alkylation with secondary alkyl halides. See ref 9b.

14 A similar electronic effects were also observed in C–H arylation. See ref 11h.

15 It was known that Ni complex reacts with RX gives a coupling product with the generation of Ni(II). M. F. Semmelhack, P. M. Helquist, L. D. Jones, *J. Am. Chem. Soc.* **1971**, *93*, 5908.

16 D. Griller, K. U. Ingold, *Acc. Chem. Res.* **1980**, *13*, 317.

17 a) R. J. Kinney, W. D. Jones, R. G. Bergman, *J. Am. Chem. Soc.* **1978**, *100*, 7902. b) C. E. Ash, P. W. Hurd, M. Y. Darensbourg, M. Newcomb, *J. Am. Chem. Soc.* **1987**, *109*, 3313. c) S. Biswas, D. J. Weix, *J. Am. Chem. Soc.* **2013**, *135*, 16192. d) J. Breitenfeld, J. Ruiz, M. D. Wodrich, X. Hu, *J. Am. Chem. Soc.* **2013**, *135*, 12004. e) J. Choi, P. Martín-Gago, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 12161. f) C. Zhao, X. Jia, X. Wang, H. Gong, *J. Am. Chem. Soc.* **2014**, *136*, 17645.

18 a) Kambe proposed a Ni(II)/Ni(IV) catalytic cycle in the Ni-catalyzed Grignard cross-coupling. J. Terao, N. Kambe, *Acc. Chem. Res.* **2008**, *41*, 1545. b) Sanford suggested the intermediacy of Ni(IV) species in halogenation of cyclometallated nickel complex(II). A. T. Higgs, P. J. Zinn, M. S. Sanford, *Organometallics* **2010**, *29*, 5446. c) Recently, Mirica reported on the first isolated organometallic Ni(III) complexes that can undergo reductive elimination reactions to form new C–C or C–heteroatom bonds. B. Zheng, F. Tang, J. Luo, J. W. Schultz, N. P. Rath, L. M. Mirica, *J. Am. Chem. Soc.* **2014**, *136*, 6499.

19 H. Schönherr, T. Cernak, *Angew. Chem., Int. Ed.* **2013**, *52*, 12256.

20 J. S. McCallum, J. R. Gasdaska, L. S. Liebeskind, S. J. Tremont, *Tetrahedron Lett.* **1989**, *30*, 4085.

21 a) C. Verrier, C. Hoarau, F. Marsais, *Org. Biomol. Chem.* **2009**, *7*, 647. b) S.-Y. Zhang, G. He, W. A. Nack, Y. Zhao, Q. Li, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 2124. c) L. C. Misal Castro, N. Chatani, *Chem.—Eur. J.* **2014**, *20*, 4548.

22 a) X. Chen, J.-J. Li, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 78. b) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510. c) H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7222. d) S. R. Neufeldt, C. K. Seigerman, M. S. Sanford, *Org. Lett.* **2013**, *15*, 2302. e) B. R. Rosen, L. R. Simke, P. S. Thuy-Boun, D. D. Dixon, J.-Q. Yu, P. S. Baran, *Angew. Chem., Int. Ed.* **2013**, *52*, 7317.

23 Y. Zhang, J. Feng, C.-J. Li, *J. Am. Chem. Soc.* **2008**, *130*, 2900.

24 a) Q. Chen, L. Ilies, N. Yoshikai, E. Nakamura, *Org. Lett.* **2011**, *13*, 3232. b) B. Yao, R.-J. Song, Y. Liu, Y.-X. Xie, J.-H. Li, M.-K. Wang, R.-Y. Tang, X.-G. Zhang, C.-L. Deng, *Adv. Synth. Catal.* **2012**, *354*, 1890. c) F. Pan, Z.-Q. Lei, H. Wang, H. Li, J. Sun, Z.-J. Shi, *Angew. Chem., Int. Ed.* **2013**, *52*, 2063. d) J. Gui, Q. Zhou, C.-M. Pan, Y. Yabe, A. C. Burns, M. R. Collins, M. A. Ornelas, Y. Ishihara, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 4853.