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Graphical Abstract

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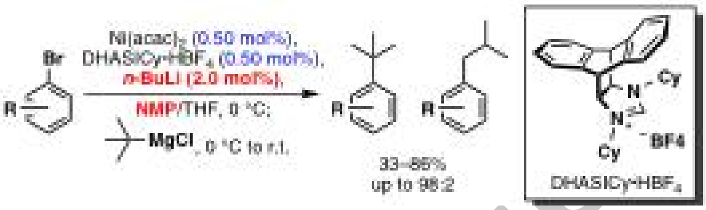

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An N-heterocyclic carbene-based nickel catalyst for the Kumada-Tamao-Corriu coupling of aryl bromides and tertiary alkyl Grignard reagents

Shin Ando,∗ Mai Mawatari, Hirofumi Matsunaga, and Tadao Ishizuka∗

Faculty of Life Sciences, Kumamoto University, 5-1 Oe-honmachi Chuo-ku, Kumamoto 862-0973, Japan

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ABSTRACT

In this study, nickel-catalyzed coupling reactions between arylhalides and *tert*-alkyl Grignard reagents were developed. Our original bicyclic NHC ligands reduced the formation of isomerized products, and we found that NMP as a co-solvent suppressed the reduction process. Under the optimal conditions we developed, the catalyst loading was lowered to 0.5mol%, and catalyst loading using *ortho*-substituted aryl bromides was also applicable at the level of 2.0 mol%.

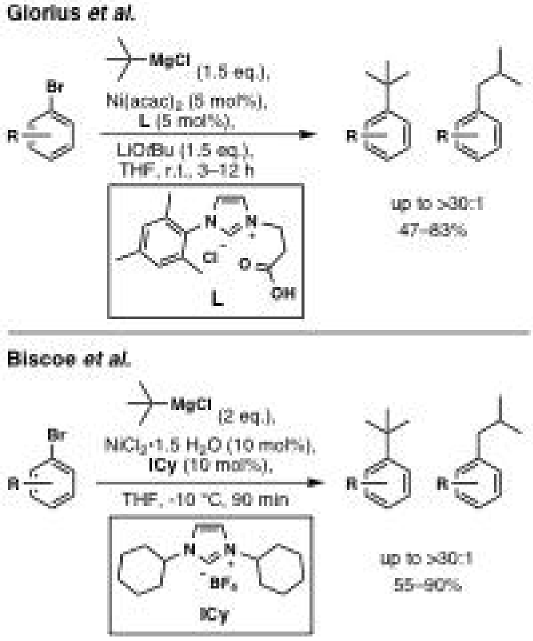
Transition metal-catalyzed coupling reaction for the formation of a C–C bond is now a powerful tool for a wide range of synthetic investigations such as the syntheses of complex natural products and drug discovery. In addition to numerous excellent methodologies for the creation of a C(sp^2)–C(sp^2) bond, C(sp^3)-containing coupling reactions have also been developed, but the reaction systems using secondary or tertiary nucleophiles often suffer from a competing β-hydride elimination leading to a reduction and/or a subsequent isomerization.[1] The use of all-carbon quaternary nucleophiles is particularly challenging because of a low level of nucleophilicity and a high level of steric repulsion.[2]

Over the past decade, the catalysts Co,[3] Cu,[4] and Ni[5] have been useful in the coupling of tertiary Grignard reagents with sufficient control of the isomerization of the tertiary alkyl groups. Among these elegant processes, N-heterocyclic carbene (NHC)-Ni catalysts, which have been independently developed by Glorius[5a] and Biscoe,[5b, c] have shown a broad substrate scope during the Kumada-Tamao-Corriu (KTC) coupling of aryl halides or pseudohalides and tertiary Grignard reagents (Scheme 1). Glorius and co-workers used their original NHC ligand, which has a carboxylic acid on its side chain and an over-stoichiometric amount of LiO*t*Bu as an additive, to accomplish *tert*-butylation. Biscoe and co-workers reported that the H_2O in hydrated $NiCl_2$ salts affected the reaction, and they confirmed that $NiCl_2$•$1.5H_2O$, which was prepared by heating under high vacuum, was the most effective Ni source, generating the coupled products in high yields and selectivities against the isomerized or reduced products.

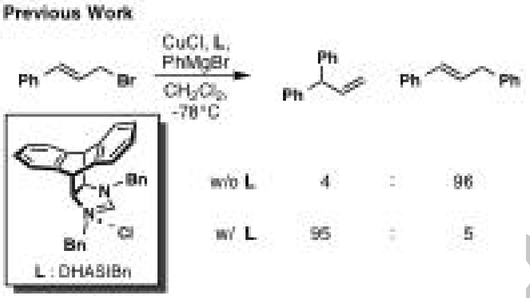
During the course of work with our original bicyclic NHC ligands, we found that the aromatic ring on the bicyclic framework could shield the bound metal, which resulted into an acceleration of the reductive elimination during copper-catalyzed allylic arylations (Scheme 2).[6] We hypothesized that this acceleration effect of our NHC ligand would be preferable in suppressing the β-hydride elimination and/or the subsequent isomerization of *tert*-alkyl groups during the coupling reaction mentioned above. Here, we present the development of an NHC-nickel-catalyzed KTC coupling reaction of aryl bromides and tertiary Grignard reagents, for which our original NHC ligand enabled us to reduce the catalyst loading to 0.5 mol%. Additionally, we discovered that NMP as a co-solvent effectively suppressed the reduction process.

∗ Corresponding author. Tel.: +81-96-371-4579; fax: +81-96-371-4579; e-mail: ando@gpo.kumamoto-u.ac.jp (S.A.)

∗ Corresponding author. Tel.: +81-96-371-4573; fax: +81-96-371-4573; e-mail: tstone@gpo.kumamoto-u.ac.jp (T.I.)



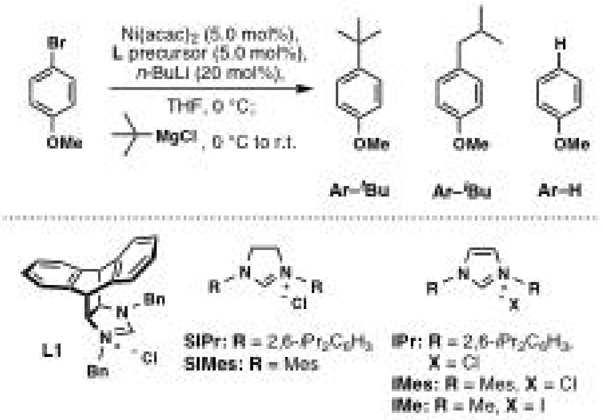
Scheme 1. NHC-Ni-catalyzed KTC coupling between aryl halides and *tert*-alkyl Grignard reagents.



Scheme 2. Regio-selective allylic arylations using our original NHC ligand.

We started our study by comparing NHC ligands in order to probe the properties required for a coupling reaction between aryl bromide and *tert*-BuMgCl (Table 1). Ni(acac)$_2$ was used as a nickel source for our reaction system based on our screening experiment (see Table S1 in the Supporting Information for details), and an NHC-Ni complex was prepared *in situ* using *n*-BuLi as a base at 0 °C. The substrates for the screening included *tert*-BuMgCl and 4-bromoanisole, which were added sequentially to the solution, and the reactions were performed at ambient temperature for 1.5 h. The conversion of aryl bromide was negligible in the absence of an NHC ligand even after 24 h (Entry 1). Theoretically, a Grignard reagent could also serve as a base to deprotonate an NHC precursor; however, it is important to note that the reaction without *n*-BuLi resulted in an 11% conversion. This indicated that the role of *n*-BuLi would be the deprotonation of an NHC precursor as well as the reduction of Ni(II) to an active form.[7] Although the conversion of the substrate was moderate, our original NHC ligand, DHASIBn (Entry 2), suppressed the formation of the isobutylated product more effectively than commercially available *N*-aryl NHCs (entries 3 to 6). This characteristic should be highly preferable for this reaction because isobutylated compounds are difficult to separate from desired tertiary butylated products in most cases. Intriguingly, a 2:1 ratio of NHC ligand : Ni(acac)$_2$, as well as the addition of another ligand such as COD, resulted in no conversion.[8] *N,N'*-dimethyl imidazol-2-ylidene was also available for this transformation, but its conversion was somewhat lower than other NHCs (Entry 7). These results encouraged us to optimize the reaction conditions for the selective formation of a *tert*-butylated product rather than the reduced product.

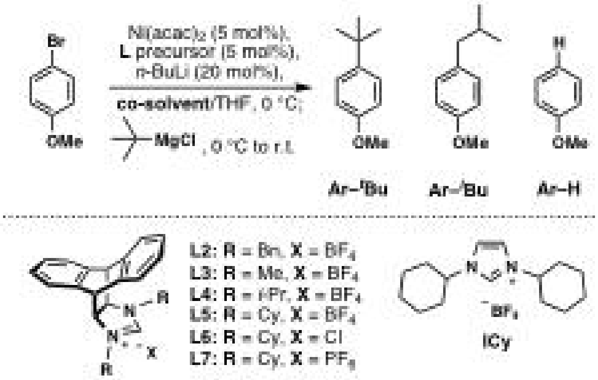
Table 1. The comparison between DHASIBn and commercial NHCs using KTC coupling of *tert*-BuMgCl[a]



Entry	Ligand	Conversion (%)	Ar-^{t}Bu:Ar-^{iso}Bu:Ar-H
1	none[b]	9	67:0:33
2	L1	42	43:17:40
3	SIPr	56	27:23:50
4	SIMes	64	11:70:19
5	IPr	74	10:66:24
6	IMes	60	7:78:15
7	IMe	32	38:9:53

[a] 1.5 eq. of *t*-BuMgCl was used for this screening. The reaction was carried out for 1.5 h at r.t. (see Supporting Information for detail). The conversion and products ratios were calculated using ^{1}H NMR. [b] The reaction was carried out for 24 h.

Table 2. The effects of a co-solvent[a]

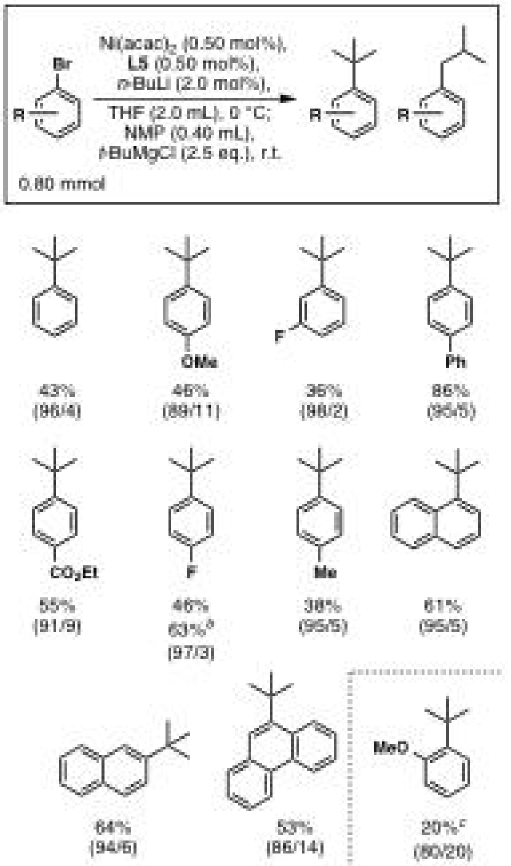


Entry	L	Co-solv.	Conv. (%)	Ar-^{t}Bu:Ar-^{iso}Bu:Ar-H
1	L1	NMP	52	75:4:21
2	L2	NMP	52	73:6:21
3	L3	NMP	40	78:5:17
4	L4	NMP	62	79:6:15
5	L5	NMP	59	80:5:15
6	L6	NMP	57	75:5:20
7	L7	NMP	56	77:3:20
8	L5	DMPU	38	61:8:31
9	L5	DMI	57	84:4:12
10	L5	DMAc	15	73:0:27

11[b]	L5	NMP	100	78:4:18
12[c]	ICy	NMP	100	83:5:12
13[d]	L5	NMP	100	79:6:15

[a] 0.2 mL of a co-solvent was added to 4.0 mL of THF. The reaction was carried out for 1.5 h at r.t. (see Supporting Information for detail). The conversion and product ratios were calculated using ^{1}H NMR. [b] 2.5 eq. of *t*-BuMgCl was used. [c] 2.5 mol% of ICy, Ni(acac)$_2$, and 2.5 eq. of *t*-BuMgCl were used along with 1.0 mL of THF. [d] 0.80 mmol of 4-bromoanisole, 0.5 mol% of L5, Ni(acac)$_2$, and 2.5 eq. of *t*-BuMgCl, NMP (0.4 mL)/THF (2.0 mL) were used.

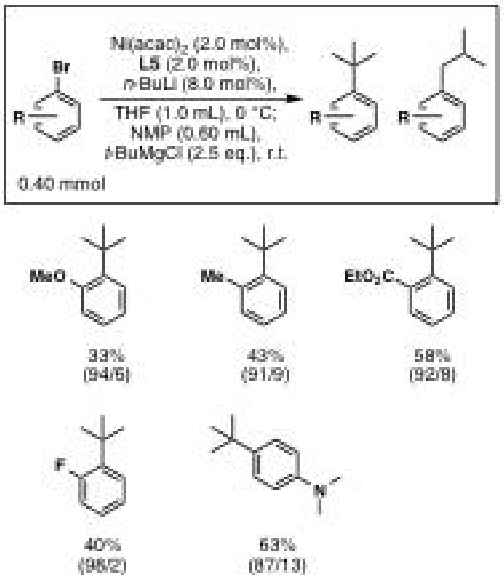
After extensive studies, we found that when an aprotic polar solvent, particularly NMP, was used as a co-solvent, it effectively accelerated the *tert*-butylation (Table 2). Although the influences for the yield of the copper- and iron-catalyzed coupling reactions were clearly described in the report by Cahiez and co-workers,[9] the effects for the β-hydride elimination during the reaction using a tertiary alkyl nucleophile had never been described, as far as we could ascertain.[9-10] Among the aprotic polar solvents we tested, NMP was the most effective (Entries 5, 8–10).[11] The *N*-substituents of DHASI and the counter anion of the NHC precursors showed no significant effect (Entries 1 to 7). Increases in the amount of Grignard reagent resulted in higher conversions. Finally, we found that the 2.5 equivalent of *tert*-Bu-MgCl in the presence of the DHASICy-Ni (L5-Ni) complex and NMP produced the coupled product in a complete conversion with high selectivity (*t*-Bu-Ar:*i*-Bu-Ar = >19:1, Entry 11). We also optimized the amounts of NMP (see Supporting Information for detail). Under the conditions we established, gratifyingly, the catalyst loading was reduced to 0.5 mol%, which is in an order of magnitude smaller than the previous methods (Entry 13; ICy ligand, which was used on the report by Biscoe,[5b] was also compatible under these conditions, but 2.5 mol% loading was required (Entry 12)).



Scheme 3. Substrate scope of a DHASICy-Ni-catalyzed KTC coupling between arybromides and *t*-BuMgCl.[a] [a] The yields of *t*-Bu-Ar after purification via column chromatography are shown. Inseparable *i*-Bu-Ar was obtained as a mixture. A ratio of *t*-Bu-Ar/*i*-Bu-Ar calculated via NMR, and is shown in the parentheses. [b] The reaction was carried out on an 8.0 mmol scale, and the products were purified using a Kugelrohr apparatus. [c] The yield of the crude mixture is shown as calculated via NMR, and the reduced product was obtained in a 33% yield.

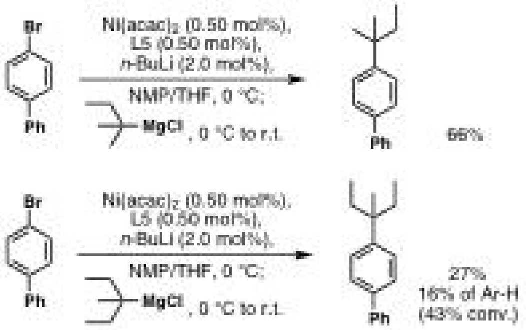
With the optimal reaction conditions in hand, we tested the substrate scope of this reaction system. As a result, a wide range of EWGs and EDGs on the *para*- and *meta*- positions of bromine were well tolerated and gave the coupled product in moderate to good yields with high selectivity (Scheme 3). It should be emphasized that Friedel-Crafts alkylation, which is the most powerful method for *tert*-butylation, is applicable only to the alkylation of electron-rich arenes and heteroarenes. The reaction on a larger scale and for distillation using a Kugelrohr apparatus resulted in a higher yield, suggesting that the volatility of the product might lower the yields in some cases.

Among the substrates we tested, *para*-dimethylamino bromobenzene showed only 18% conversion, and substrates with an *ortho*-substituent resulted in an uncompleted conversion and poor selectivity (the results from 2-bromoanisole are shown in Scheme 3 for example). To convert these tough substrates, we optimized the conditions again, and increases in the loads of the catalyst and NMP proved useful. The reaction using 2.0 mol% of a NHC-Ni complex and a higher amount of NMP (0.6 mL in 1.0 mL of THF) gave us the *tert*-butylated product in the same levels of yield and selectivity as the substrates shown in Scheme 3. By using the re-optimized conditions, the substrates with an EWG or an EDG at the *ortho*-position were coupled with *tert*-Bu-MgCl in an efficient manner (Scheme 4).[12] Unfortunately, the coupling with 2-bromo-*m*-xylene was unsuccessful probably because of larger levels of steric repulsion.



Scheme 4. Substrate scope of DHASICy-Ni catalyzed KTC coupling between *ortho*-substituted arybromides and *t*-BuMgCl.[a] [a] The yields of *t*-Bu-Ar after purification via column chromatography are shown. The inseparable *i*-Bu-Ar was obtained as a mixture. The ratio for *t*-Bu-Ar/*i*-Bu-Ar was calculated via NMR and is shown in parentheses.

We also tested more sterically demanding Grignard reagents. *tert*-Amyl-MgCl reacted smoothly and returned the coupled product in a 66% yield with good selectivity (isomerized product was not observed in NMR). On the other hand, 3-methylpent-3-yl-MgCl was not tolerated (Scheme 5).



Scheme 5. NHC-Ni catalyzed KTC coupling using branched *tert*-alkyl Grignard reagents.

In conclusion, we report the KTC coupling of aryl bromides and *tert*-alkyl Grignard reagents using our original NHC-Ni catalyst. DHASI-type NHC ligands effectively suppressed the pathways leading to the isomerized product. We also discovered that NMP as a co-solvent is useful in suppressing the reduction, and the optimal conditions we established allowed us to reduce the catalyst loading to 0.5 mol%. More challenging *ortho*-substituted aryl bromides were also successfully converted using increased amounts of catalyst and NMP.

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Supplementary Material

Supplementary data (experimental details and the characterization data) associated with this article can be found, in the online version, at

References and notes

1. Reviews; (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525; (b) Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674; (c) Glorius, F. *Angew. Chem. Int. Ed.* **2008**, *47*, 8347; (d) Rudolph, A.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 2656; (e) Hu, X. *Chem. Sci.* **2011**, *2*, 1867.
2. For earlier examples of the coupling reaction using *tert*-alkyl nucleophiles, see (a) Hayashi, T.; Konishi, M.; Yokota, K.-i.; Kumada, M. *Chem. Lett.* **1980**, 767; (b) Bell, T. W.; Hu, L. Y.; Patel, S. V. *J. Org. Chem.* **1987**, *52*, 3847; (c) Daniel Rehm, J. D.; Ziemer, B.; Szeimies, G. *Eur. J. Org. Chem.* **1999**, 2079; (d) Hayashi, T.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, *20*, 1871; (e) Hayashi, T.; Konishi, M.; Kumada, M. *J. Organomet. Chem.* **1980**, *186*, C1.
3. Iwasaki, T.; Takagawa, H.; Singh, S. P.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2013**, *135*, 9604.
4. (a) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 2086; (b) Hintermann, L.; Xiao, L.; Labonne, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8246; (c) Ren, P.; Stern, L.-A.; Hu, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 9110.
5. (a) Lohre, C.; Droge, T.; Wang, C.; Glorius, F. *Chem. Eur. J.* **2011**, *17*, 6052; (b) Joshi-Pangu, A.; Wang, C. Y.; Biscoe, M. R. *J. Am. Chem. Soc.* **2011**, *133*, 8478; (c) Joshi-Pangu, A.; Biscoe, M. R. *Synlett* **2012**, 1103.
6. Ando, S.; Matsunaga, H.; Ishizuka, T. *Tetrahedron* **2013**, *69*, 1687.
7. A Ni(0)–Ni(II) cycle and a Ni(I)–Ni(III) cycle have been proposed for similar reactions, and Biscoe and co-workers discussed about the catalytic cycle for this reaction (see reference 5c). For examples of other discussions about catalytic cycles for similar processes, see; (a) Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 7262; (b) Saito, S.; Sakai, M.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 2993; (c) McGuinness, D. S.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 1596; (d) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 3387; (e) Sato, Y.; Sawaki, R.; Mori, M. *Organometallics* **2001**, *20*, 5510; (f) Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 11113; (g) Dible, B. R.; Sigman, M. S.; Arif, A. M. *Inorg. Chem.* **2005**, *44*, 3774; (h) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175; (i) Phapale, V. B.; Guisan-Ceinos, M.; Bunuel, E.; Cardenas, D. J. *Chem. Eur. J.* **2009**, *15*, 12681; (j) Miyazaki, S.; Koga, Y.; Matsumoto, T.; Matsubara, K. *Chem. Commun.* **2010**, *46*, 1932; (k) Tekavec, T. N.; Zuo, G.; Simon, K.; Louie, J. *J. Org. Chem.* **2006**, *71*, 5834.
8. This observation is simlar to the report by Hermann and co-workers, in which they proposed the NHC-Ni(0) complex is the catalytically active species. See reference 7d.
9. (a) Cahiez, G.; Marquais, S. *Synlett* **1993**, 45; (b) Cahiez, G.; Marquais, S. *Tetrahedron Lett.* **1996**, *37*, 1773; (c) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199; (d) Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* **2000**, *56*, 2733.
10. For examples of reactions using NMP as an effective co-solvent, see; (a) Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem. Int. Ed.* **1996**, *34*, 2723; (b) Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609; (c) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856; (d) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527; (e) Hadei, N.; Kantchev, E. A. B.; O'Brie, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805.
11. These are shown for example. DMI was not effective in the reaction with lowered catalyst loading.
12. It should be noted that the Ni catalyst developed by Lei and co-workers, which worked well for the coupling *sec*-alkyl zinc nucleophile, gave only isobutylated product in the case of the coupling of ethyl 2-iodobenzoate and *tert*-butyl zinc reagent. See; Luo, X.; Zhang, H.; Duan, H.; Liu, Q.; Zhu, L.; Zhang, T.; Lei, A. *Org. Lett.* **2007**, *9*, 4571.

***Highlights**

Our original NHC-Ni complex aptly catalyzes a *tert*-butylation of aryl bromides.

n-BuLi works as a reductant of Ni(II) salts to generate the active species.

NMP is an effective co-solvent to yield the *tert*-butylated products.

Hindered substrates are also applicable to the coupling reaction we established.