C–H Functionalization

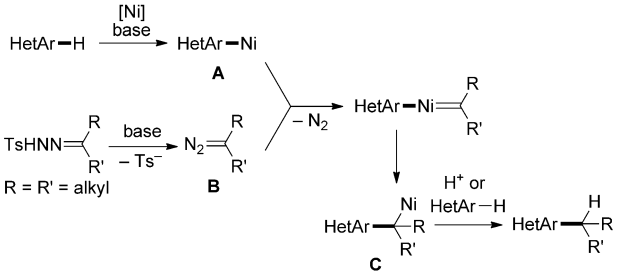
DOI: 10.1002/anie.201106825

Nickel- and Cobalt-Catalyzed Direct Alkylation of Azoles with *N*-Tosylhydrazones Bearing Unactivated Alkyl Groups**

Tomoyuki Yao, Koji Hirano, Tetsuya Satoh, and Masahiro Miura**

The functionalization of heteroaromatic compounds has received much attention from synthetic chemists because heteroaromatic cores are ubiquitously found in pharmaceuticals, biologically active compounds, and functional materials.[1] The transition-metal-catalyzed cross-coupling reaction of heteroaryl halides or organometallic compounds is a powerful and reliable strategy to obtain functionalized heteroaromatic compounds.[2] On the other hand, recent advances in the metal-mediated C–H functionalization provide a complementary and potentially more efficient methodology to heteroaromatic compounds, because additional preactivation steps, such as the halogenation or stoichiometric metalation of the parent heterocycles, to prepare the coupling reagents can be avoided. Direct arylation, alkenylation, and alkynylation have been widely explored.[3] However, the alkylation reaction is relatively challenging,[4,5] despite the fact that alkyl chains attached to aromatic nuclei are known to generally enhance lipophilicity and solubility, and to tune the aromatic π-stacking and π-conjugation of the corresponding oligomers and polymers. In particular, direct introduction of secondary alkyl side chains into heteroarenes remains elusive, probably because of the difficulty in controlling an undesired β-H elimination of an alkyl metal intermediate. A few successful examples with alkyl halides are still restricted in substrate scope to cyclic frameworks, such as cyclohexane and cyclopentane.[4b,g,6] A metal-catalyzed C–H insertion approach with alkenes,[7] and a copper-catalyzed alkylation with *N*-tosylhydrazones, which has very recently been reported by Wang and co-workers (see below),[8] appear to be good alternatives, however, these processes are limited to activated systems, thus only enabling benzylation and allylation. Therefore, further developments for more general alkylation methodologies are strongly desired. Herein, we report nickel- and cobalt-based catalysts for the direct alkylation of azoles with *N*-tosylhydrazones. The catalytic systems are compatible with various unactivated secondary alkyl groups, including cyclic and even more challenging acyclic alkyl groups.

Our working hypothesis is inspired by our previous success in the nickel-catalyzed direct alkylation of azoles with primary alkyl halides[4f] and recent developments in the use of *N*-tosylhydrazones in cross-coupling reactions (Scheme 1).[9] An initial base-assisted direct nickelation of a heteroarene[10] provides a heteroaryl nickel species **A**. On the other hand, the *N*-tosylhydrazone is converted in situ to the corresponding diazo compound **B** with concomitant elimination of the Ts group by the action of a base. Subsequent decomposition of **B** by interaction with **A**[11] and 1,2 migration of the heteroaryl group from Ni to the α carbon center afford an alkyl nickel intermediate **C**. If protonation or ligand exchange with the C–H bond of the starting heteroarene occurred much faster than the conceivable β-H elimination, the desired heterocycles, which bear the secondary alkyl side chain, would be obtained. In accordance with the above-mentioned assumption, our study commenced with benzoxazole (**1a**) and *N*-tosylhydrazone **2a**, which was derived from cyclohexanone as the model substrate (Table 1). In an early experiment, treatment of **1a** with **2a** in the presence of LiO*t*Bu and a $NiCl_2$/1,10-phenanthroline (phen) catalyst in 1,4-dioxane at 100 °C gave 2-cyclohexylbenzoxazole (**3aa**) in 45% yield (determined by GC analysis; Table 1, entry 1). With this intriguing result in hand, we investigated other first transition elements. While the use of $FeCl_3$ instead of $NiCl_2$ was detrimental (Table 1, entry 2), $CoCl_2$ catalyzed the reaction with moderate efficiency (entry 3). In the course of this study, Wang and co-workers reported a relevant CuI-catalyzed coupling of azoles with *N*-tosylhydrazones on the basis of a similar concept.[8] However, they reported only formation of benzylated and allylated products. Indeed, under copper-based conditions, only a trace amount of **3aa** was detected (Table 1, entry 4).[12] After additional evaluations of nickel salts, ligands, and reaction stoichiometry (Table 1, entries 5–12), a combination of $NiBr_2$ and phen, and a 2:1



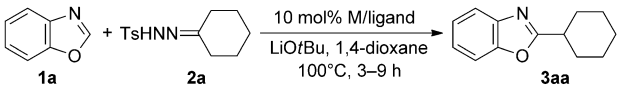
Scheme 1. Working hypothesis. HetAr = heteroaryl, Ts = *p*-toluenesulfonyl.

[*] T. Yao, Dr. K. Hirano, Prof. Dr. T. Satoh, Prof. Dr. M. Miura
Department of Applied Chemistry, Faculty of Engineering
Osaka University, Suita, Osaka 565-0871 (Japan)
E-mail: k_hirano@chem.eng.osaka-u.ac.jp
miura@chem.eng.osaka-u.ac.jp

[**] This work was partly supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology (Japan). K.H. acknowledges the Kansai Research Foundation for the Promotion of Science.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201106825.

Table 1: Optimization studies for direct coupling of benzoxazole (**1a**) with *N*-tosylhydrazone **2a**.[a]



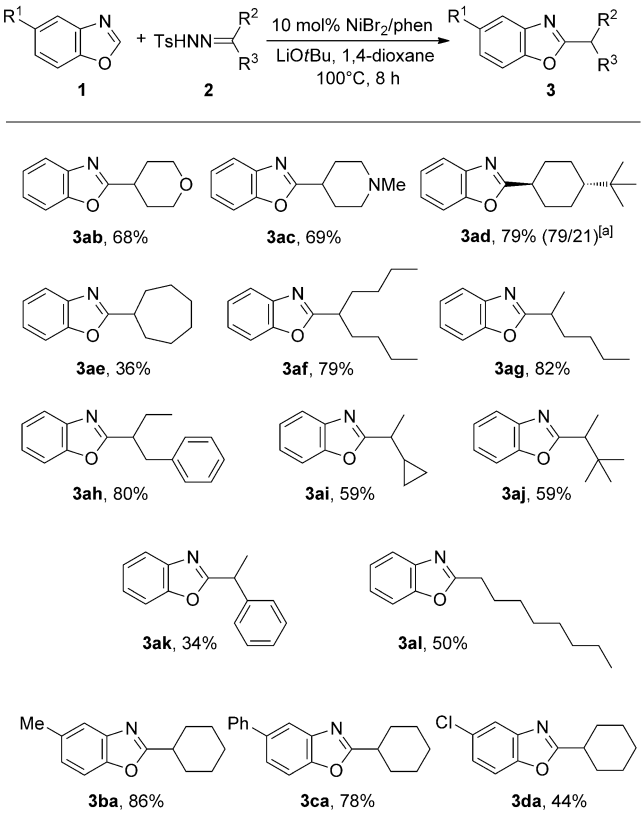
1a **2a** **3aa**

Entry	M	Ligand	Yield [%][b]
1	$NiCl_2$	phen	45
2	$FeCl_3$	phen	1
3	$CoCl_2$	phen	20
4	CuI	phen	trace
5	$NiBr_2$·diglyme	phen	50
6	NiF_2	phen	9
7	$[Ni(acac)_2]$	phen	47
8[c]	$NiBr_2$·diglyme	phen	68
9[c]	$NiBr_2$	phen	85 (84)
10[c]	$[Ni(cod)_2]$	phen	73
11[c]	$NiBr_2$	bpy	63
12[c]	$NiBr_2$	bathophen	64

[a] Reaction conditions: M (0.050 mmol), ligand (0.050 mmol), LiO*t*Bu (1.5 mmol), **1a** (0.50 mmol), **2a** (0.60 mmol), 1,4-dioxane (3.0 mL), 100 °C, N_2. [b] Yield determined by GC analysis. Yield of isolated product given in parenthesis. [c] Reaction performed with **1a** (1.0 mmol) and **2a** (0.50 mmol). acac = acetylacetonate, bpy = 2,2′-bipyridine, bathophen = 4,7-diphenyl-1,10-phenanthroline, phen = 1,10-phenanthroline.

ratio of **1a** and **2a** were found to be optimal, and **3aa** was isolated in 84% yield (entry 9). Although a $[Ni(cod)_2]$/phen catalyst system provided a comparable result (Table 1, entry 10), we employed $NiBr_2$ for the following experiments, owing to it being less expensive and exhibiting a higher bench stability.

We performed the direct alkylation of **1a** with *N*-tosylhydrazones that bear various unactivated alkyl substituents by using the $NiBr_2$/phen catalyst system (Scheme 2). In addition to **2a** with the simple cyclohexane skeleton, *N*-tosylhydrazones **2** that bear heteroatom-containing six-membered rings, that is, pyran and piperidine, directly coupled with **1a** to furnish **3ab** and **3ac** in 68% and 69% yields, respectively. The reaction with a *t*Bu-substituted cyclohexane system resulted in the formation of **3ad** with moderate diastereoselectivity. On the other hand, the reaction with an *N*-tosylhydrazone that was prepared from cycloheptanone was somewhat less efficient (**3ae**). Notably, the nickel catalysis could also be applied to acyclic systems; 5-nonyl, 2-hexyl, and homobenzyl substitution patterns were compatible, and the corresponding alkylated azoles **3af–ah** were formed in good yields. The cyclopropane-containing hydrazone underwent the direct coupling without conceivable ring opening (**3ai**). Moreover, the introduction of a sterically demanding neopentyl-type alkyl group was possible (**3aj**). The hydrazone that was derived from acetophenone, and which Wang and co-workers reported to be highly reactive,[8] participated in the reaction, albeit with moderate efficiency (**3ak**). The primary alkylation was also achieved in the case of the hydrazone of 1-octanal (**3al**). Functional-group tolerance was also good with regard to the benzoxazole moiety; methyl-, phenyl-, and chloro-substituted benzoxazoles participated in the direct alkylation with **2a** to produce the corresponding 2-cyclohexylbenzoxazoles (**3ba–da**) in synthetically useful levels.

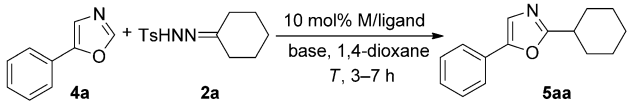


Scheme 2. Nickel-catalyzed direct C–H alkylation of benzoxazoles **1** with *N*-tosylhydrazones **2**. Reactions performed by using the conditions described in Table 1. The yields are of the isolated products. [a] The ratio of trans to cis isomers is given in parenthesis. See the Supporting Information for the stereochemical assignment.

We next attempted to apply the reaction to other 1,3-azoles and immediately found that the above-mentioned nickel catalysis was not suitable for the direct alkylation of 5-aryloxazoles. For example, the coupling of 5-phenyloxazole (**4a**) with **2a** was sluggish, and the expected product **5aa** was detected in only 1% yield (determined by GC analysis, Table 2, entry 1). Thus, more optimization studies were carried out. Elevation of the temperature or change of the base into more basic NaO*t*Bu had no positive effect on the yield (Table 2, entries 2 and 3). An investigations into the stoichiometry of the reaction resulted in no improvement (Table 2, entry 4). In these unsuccessful cases, about half the amount of starting material **4a** was recovered, and **2a** was converted to an unidentified mixture, which contained a trace amount of 1,2-dicyclohexylidenehydrazine. We then turned our attention to other transition metals, on the basis of data shown in Table 1. Pleasingly, $CoCl_2$ was found to improve the yield to 42% (Table 2, entry 5),[13] whereas $FeCl_3$ was ineffective (entry 6). Among some cobalt salts, ligands, and bases that were tested (Table 2, entries 7–12), a $CoBr_2$/phen system with LiO*t*Bu gave the best result and produced **5aa** in 71% yield of isolated product (Table 2, entry 8).[14]

With the modified $CoBr_2$/phen catalyst in hand, the scope and limitation of the reaction were examined for a variety of azoles and *N*-tosylhydrazones **2** (Scheme 3). 5-Aryloxazoles

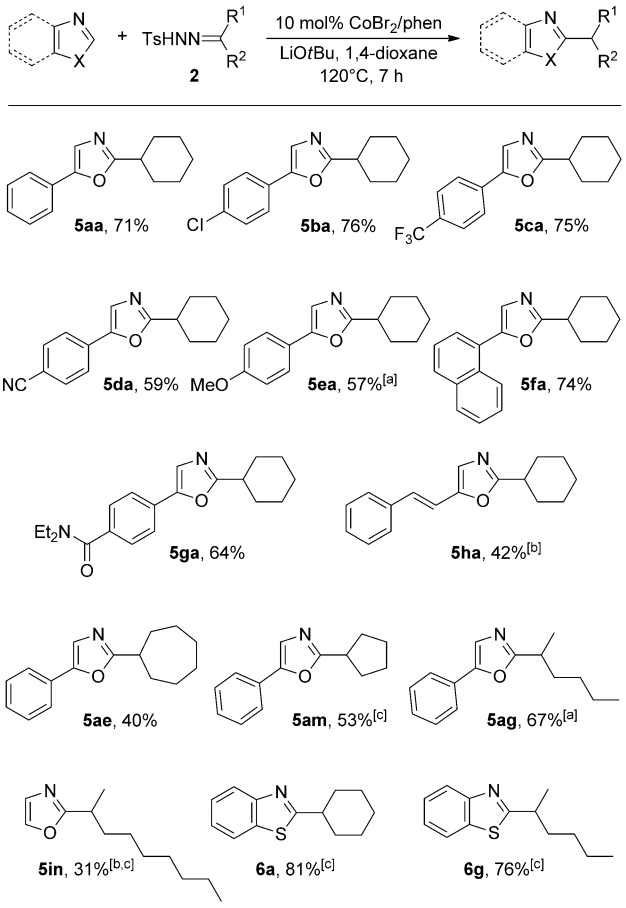
Table 2: Optimization studies for direct coupling of 5-phenyloxazole (**4a**) with *N*-tosylhydrazone **2a**.[a]



4a **2a** **5aa**

Entry	M	Ligand	Base	T [°C]	Yield [%][b]
1	$NiBr_2$	phen	LiO*t*Bu	100	1
2	$NiBr_2$	phen	LiO*t*Bu	150[c]	0
3	$NiBr_2$	phen	NaO*t*Bu	100	2
4[d]	$NiBr_2$	phen	LiO*t*Bu	120	0
5[d]	$CoCl_2$	phen	LiO*t*Bu	120	42
6[d]	$FeCl_3$	phen	LiO*t*Bu	120	3
7[d]	$CoCl_2$	–	LiO*t*Bu	120	28
8[d]	$CoBr_2$	phen	LiO*t*Bu	120	80 (71)
9[d]	$CoBr_2$	phen	NaO*t*Bu	120	67
10[d]	$CoBr_2$	PPh_3[e]	LiO*t*Bu	120	29
11[d]	CoI_2	phen	LiO*t*Bu	120	57
12[d]	$[Co(acac)_2]$	phen	LiO*t*Bu	120	57

[a] Reaction conditions: M (0.050 mmol), ligand (0.050 mmol), base (1.5 mmol), **4a** (1.0 mmol), **2a** (0.50 mmol), 1,4-dioxane (3.0 mL), N_2. [b] Yield determined by GC analysis. Yield of isolated product given in parenthesis. [c] Reaction performed in diglyme instead of 1,4-dioxane. [d] Reaction performed with **4a** (0.50 mmol), **2a** (1.0 mmol), and LiO*t*Bu (2.0 mmol). [e] Reaction performed with PPh_3 (0.10 mmol).



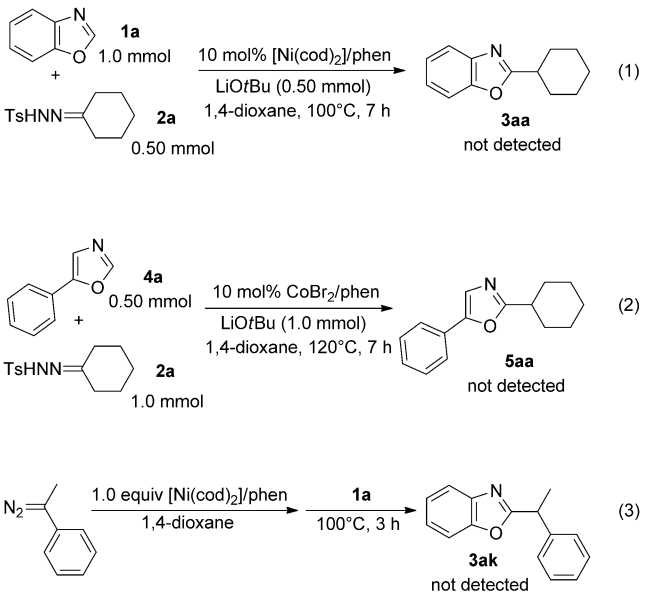
Scheme 3. Cobalt-catalyzed direct C–H alkylation of azoles with *N*-tosylhydrazones **2**. Reactions performed by using the conditions described in Table 2. The yields are of the isolated products. [a] Reaction performed with NaO*t*Bu instead of LiO*t*Bu. [b] Yield determined by ^1H NMR spectroscopy. [c] Reaction was performed with **2** (1.5 mmol), and with NaO*t*Bu and DMF instead of LiO*t*Bu and 1,4-dioxane, respectively.

with electron-withdrawing chloro, trifluoromethyl, and cyano groups underwent the alkylation smoothly under standard conditions (**5ba–da**), while the electron-donating methoxy substituent required harsher conditions, including the use of NaO*t*Bu as the base (**5ea**). A naphthyl-substituted oxazole also participated in the alkylation (**5fa**). Moreover, amide and olefin functions were compatible under these reaction conditions (**5ga–ha**). With regard to *N*-tosylhydrazone components, larger (cycloheptane) as well as smaller (cyclopentane) ring systems were also tolerated (**5ae** and **5ak**). Notably, a combination of NaO*t*Bu as the base and DMF as the solvent was necessary to obtain **5am** in a satisfactory yield. As seen in the reaction of benzoxazoles **1** with the nickel catalyst, the acyclic hydrazone could be employed in the cobalt-promoted alkylation (**5ag**). In addition to 5-aryloxazoles, unsubstituted oxazole and benzothiazole were also suitable substrates. 2-(2-Nonyl)oxazole (**5in**) as well as 2-cyclohexyl- and 2-(2-hexyl)benzothiazole (**6a** and **6g**, respectively) were obtained in moderate to good yields.[15] On the other hand, the alkylation with the hydrazone that was prepared from acetophenone and 1-octanal remained unsuccessful under cobalt-based catalysis (< 10% yield, data not shown).

A pathway including the C–H insertion of heteroarenes via metal carbenes derived from diazo compounds might be an alternative to the scenario we envisioned (Scheme 1).[16] To explore this possibility, we implemented the reactions with one equivalent (with regard to *N*-tosylhydrazones) of LiO*t*Bu under both nickel and cobalt catalysis [Eqs. (1) and (2), respectively].[8] In both cases, alkylated azoles were not detected at all.[17] Furthermore, a stoichiometric reaction (with regard to Ni) of semi-stabilized (1-diazoethyl)benzene[18] with **1a** resulted in no formation of **3ak** [Eq. (3)].

These outcomes are inconsistent with the metal carbene promoted C–H insertion. Moreover, the precedent C–H insertion reactions with diazo compounds are restricted to electron-rich arenes, such as indoles and pyrroles. Thus, the insertion into the carbene species is not plausible. At present, we consider that our postulated catalytic cycle can be operative in both nickel- and cobalt-catalyzed processes. While nickel- and cobalt-based catalyses might involve similar mechanisms, their substrate scope is quite different; the nickel complex is effective only for benzoxazoles, while the cobalt complex catalyzes the reaction of 5-aryloxazoles and benzothiazole. The reactivity differences between nickel and cobalt catalysis might arise from their capacity for 1,2 migration of azole groups of the metal species. Further efforts to clarify the detailed mechanism are ongoing.

In conclusion, we have developed efficient catalytic systems for the direct alkylation of azoles with *N*-tosylhydrazones. A nickel catalysis enables the introduction of simple secondary alkyl groups into benzoxazole compounds, whereas the alkylation of 5-aryloxazoles and benzothiazole becomes possible by using a cobalt catalyst. These catalytic



protocols could provide a concise access to azole cores that bear unactivated secondary alkyl side chains, and that are thus difficult to prepare by using the precedent C–H alkylation methodologies. Further investigations focus on the elucidation of the mechanism and the application to the stereoselective C–H alkylation.

Experimental Section

Nickel-catalyzed direct C–H alkylation of benzoxazole (**1a**) with tosylhydrazone **2a** (Table 1, entry 9): $NiBr_2$ (10.9 mg, 0.050 mmol), 1,10-phenanthroline (9.0 mg, 0.050 mmol), and LiO*t*Bu (120 mg, 1.5 mmol) were placed in a 20 mL two-necked reaction flask, which was filled with nitrogen by using standard Schlenk techniques. 1,4-Dioxane (2.0 mL) was added to the flask, and the suspension was stirred for 10 min at ambient temperature. Tosylhydrazone **2a** (133 mg, 0.50 mmol) was added in one portion. Finally, a solution of benzoxazole (**1a**, 119 mg, 1.0 mmol) in 1,4-dioxane (1.0 mL) was added dropwise. The solution was stirred at 100 °C for 8 h. The resulting mixture was quenched with water. The mixture was extracted with *n*-hexane/ethyl acetate (20:1, v/v), and the combined organic layer was dried over sodium sulfate. Concentration in vacuo and subsequent silica gel column chromatography with *n*-hexane/ethyl acetate (20:1, v/v) as eluent gave 2-cyclohexylbenzoxazole (**3aa**, 85 mg, 0.42 mmol) in 84 % yield.

Received: September 26, 2011
Revised: November 18, 2011
Published online: December 7, 2011

Keywords: alkylation · azoles · C–H functionalization · cobalt · nickel

[1] a) A. Kraft, A. C. Grimsdale, A. B. Holmes, *Angew. Chem.* **1998**, *110*, 416; *Angew. Chem. Int. Ed.* **1998**, *37*, 402; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442; c) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337.

[2] a) *Cross-Coupling Reactions: A Practical Guide* (Ed.: N. Miyaura), Springer, Berlin, **2002** (Series *Topics in Current Chemistry*, *Vol. 219*); b) *Metal-Catalyzed Cross-coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; c) *Palladium Reagents and Catalysts*, 2nd ed. (Ed.: J. Tsuji), Wiley, Chichester, **2004**.

[3] For recent reviews, see: a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; b) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200; c) L. C. Campeau, D. R. Stuart, K. Fagnou, *Aldrichimica Acta* **2007**, *40*, 35; d) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; e) Y. J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222; f) L. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013; g) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013; h) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074; i) A. A. Kulkarni, O. Daugulis, *Synthesis* **2009**, 4087; j) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; k) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; l) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677; m) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; n) A. S. Dudnik, V. Gevorgyan, *Angew. Chem.* **2010**, *122*, 2140; *Angew. Chem. Int. Ed.* **2010**, *49*, 2096; o) T. Satoh, M. Miura, *Synthesis* **2010**, 3395; p) L. Ackermann, *Chem. Commun.* **2010**, *46*, 4866; q) K. Hirano, M. Miura, *Synlett* **2011**, 294.

[4] a) C. Verrier, C. Hoarau, F. Marsais, *Org. Biomol. Chem.* **2009**, *7*, 647; b) L. Ackermann, P. Novák, R. Vicente, N. Hofmann, *Angew. Chem.* **2009**, *121*, 6161; *Angew. Chem. Int. Ed.* **2009**, *48*, 6045; c) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 6213; *Angew. Chem. Int. Ed.* **2009**, *48*, 6097; d) W. Yue, Y. Li, W. Jiang, Y. Zhen, Z. Wang, *Org. Lett.* **2009**, *11*, 5430; e) O. Vechorkin, V. Proust, X. Hu, *Angew. Chem.* **2010**, *122*, 3125; *Angew. Chem. Int. Ed.* **2010**, *49*, 3061; f) T. Yao, K. Hirano, T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 12307; g) L. D. Tran, O. Daugulis, *Org. Lett.* **2010**, *12*, 4277; h) Q. Chen, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 428; i) L. Ackermann, N. Hofmann, R. Vicente, *Org. Lett.* **2011**, *13*, 1875; j) L. Jiao, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990; k) Y. Zhao, G. Chen, *Org. Lett.* **2011**, *13*, 4850.

[5] For the methylation of acetanilide with MeI, see: a) S. J. Tremont, H. U. Rahman, *J. Am. Chem. Soc.* **1984**, *106*, 5759; b) J. S. McCallum, J. R. Gasdaska, L. S. Liebeskind, S. J. Tremont, *Tetrahedron Lett.* **1989**, *30*, 4085. For palladium-catalyzed alkylations using norbornene as the reaction mediator, see: c) M. Catellani, F. Frignani, A. Rangoni, *Angew. Chem.* **1997**, *109*, 142; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119. For an alternative approach with alkylboronic acids or alkyltin reagents, see: d) X. Chen, J.-J. Li, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 78; e) X. Chen, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 12634.

[6] For Minisci-type alkylations via radical intermediates, see: a) F. Minisci, R. Gralli, M. Cecere, V. Malatesta, T. Caronna, *Tetrahedron Lett.* **1968**, *9*, 5609; b) F. Minisci, C. Giordano, E. Vismara, S. Levi, V. Tortelli, *J. Am. Chem. Soc.* **1984**, *106*, 7146; c) W. R. Bowman, J. M. D. Storey, *Chem. Soc. Rev.* **2007**, *36*, 1803; d) G. A. Molander, V. Colombel, V. A. Braz, *Org. Lett.* **2011**, *13*, 1852.

[7] For alkylations through an oxidative addition of C–H bonds to a metal center, see: a) Y. Nakao, H. Idei, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2009**, *131*, 15996; b) T. Mukai, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 6410; c) Y. Nakao, N. Kashihara, K. S. Kanyiva, T. Hiyama, *Angew. Chem.* **2010**, *122*, 4553; *Angew. Chem. Int. Ed.* **2010**, *49*, 4451; d) Y. Nakao, Y. Yamada, N. Kashihara, T. Hiyama, *J. Am. Chem. Soc.* **2010**, *132*, 13666; e) K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2011**, *133*, 400; for Friedel–Crafts-type alkylations through π-activa-

tion of alkenes, see: f) J. Kischel, I. Jovel, K. Mertins, A. Zapf, M. Beller, *Org. Lett.* **2006**, *8*, 19; g) H.-B. Sun, B. Li, R. M. Hua, Y. W. Yin, *Eur. J. Org. Chem.* **2006**, 4231; h) M. Rueping, B. J. Nachtsheim, T. Scheidt, *Org. Lett.* **2006**, *8*, 3717; i) Z. B. Zhang, X. Wang, R. A. Widenhoefer, *Chem. Commun.* **2006**, 3717; j) M.-Z. Wang, M.-K. Wong, C.-M. Che, *Chem. Eur. J.* **2008**, *14*, 8353.

[8] X. Zhao, G. Wu, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 3296.

[9] For reviews, see: a) J. Barluenga, C. Valdés, *Angew. Chem.* **2011**, *123*, 7626; *Angew. Chem. Int. Ed.* **2011**, *50*, 7486; b) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2011**, DOI: 10.1039/c1cs15127d; for selected examples, see: c) J. Barluenga, P. Moriel, C. Valdés, F. Aznar, *Angew. Chem.* **2007**, *119*, 5683; *Angew. Chem. Int. Ed.* **2007**, *46*, 5587; d) J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Nat. Chem.* **2009**, *1*, 494; e) J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Angew. Chem.* **2010**, *122*, 5113; *Angew. Chem. Int. Ed.* **2010**, *49*, 4993; f) J. Barluenga, M. Escribano, F. Aznar, C. Valdés, *Angew. Chem.* **2010**, *122*, 7008; *Angew. Chem. Int. Ed.* **2010**, *49*, 6856; g) L. Zhou, F. Ye, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 13590; h) J. Barluenga, L. Florentino, F. Aznar, C. Valdés, *Org. Lett.* **2011**, *13*, 510; i) Q. Xiao, Y. Xia, H. Li, Y. Zhang, J. Wang, *Angew. Chem.* **2011**, *123*, 1146; *Angew. Chem. Int. Ed.* **2011**, *50*, 1114; j) J. Barluenga, N. Quiñones, M.-P. Cabal, F. Aznar, C. Valdés, *Angew. Chem.* **2011**, *123*, 2398; *Angew. Chem. Int. Ed.* **2011**, *50*, 2350; k) L. Zhou, F. Ye, J. Ma, Y. Zhang, J. Wang, *Angew. Chem.* **2011**, *123*, 3572; *Angew. Chem. Int. Ed.* **2011**, *50*, 3510; l) A. Hamze, B. Tréguier, J.-D. Brion, M. Alami, *Org. Biomol. Chem.* **2011**, *9*, 6200.

[10] For base-assisted nickelation of heteroarenes, see: a) J. Canivet, J. Yamaguchi, I. Ban, K. Itami, *Org. Lett.* **2009**, *11*, 1733; b) H. Hachiya, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 1737; c) O. Kobayashi, D. Uraguchi, T. Yamakawa, *Org. Lett.* **2009**, *11*, 2679; d) N. Matsuyama, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 4156; e) H. Hachiya, K. Hirano, T. Satoh, M. Miura, *Angew. Chem.* **2010**, *122*, 2248; *Angew. Chem. Int. Ed.* **2010**, *49*, 2202; f) N. Matsuyama, M. Kitahara, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2358; g) H. Hachiya, K. Hirano, T. Satoh, M. Miura, *ChemCatChem* **2010**, *2*, 1403; h) T. Yamamoto, K. Muto, M. Komiyama, J. Canivet, J. Yamaguchi, K. Itami, *Chem. Eur. J.* **2011**, *17*, 10113.

[11] For the decomposition of $TMSCHN_2$ in the presence of nickel complexes, see: a) Y. Ni, J. Montgomery, *J. Am. Chem. Soc.* **2004**, *126*, 11162; b) Y. Ni, J. Montgomery, *J. Am. Chem. Soc.* **2006**, *128*, 2609.

[12] Under the same conditions as reported by Wang, **3aa** was detected in 1% yield by GC analysis. In the unsuccessful cases with Ni-based catalysts, about 20–40% of benzoxazole was recovered. Under iron and cobalt catalysis, ca. 10% of the homocoupling product of benzoxazole was detected. However, the mass balance was generally not good, probably because a LiO*t*Bu-induced ring-opening side reaction of benzoxazole occurred competitively: a) H. Chikashita, M. Ishibaba, K. Ori, K. Itoh, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3637; b) G. Boche, F. Bosold, H. Hermann, M. Marsch, K. Harms, J. C. W. Lohrenz, *Chem. Eur. J.* **1998**, *4*, 814; c) R. S. Sánchez, F. A. Zhuravlev, *J. Am. Chem. Soc.* **2007**, *129*, 5824. The *N*-tosylhydrazone was completely consumed because of the instability of the corresponding diazo compound under reaction conditions.

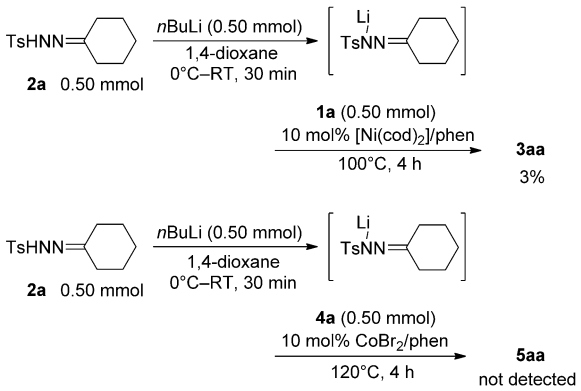
[13] For cobalt catalysis in C–H functionalization, see: a) S. Murahashi, *J. Am. Chem. Soc.* **1955**, *77*, 6403; b) S. Murahashi, S. Horie, *J. Am. Chem. Soc.* **1956**, *78*, 4816; c) C. P. Lenges, P. S. White, M. Brookhart, *J. Am. Chem. Soc.* **1998**, *120*, 6965; d) K. Gao, P.-S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.* **2010**, *132*, 12249; e) Z. Ding, N. Yoshikai, *Org. Lett.* **2010**, *12*, 4180; f) J. Y. Kim, S. H. Cho, J. Joseph, S. Chang, *Angew. Chem.* **2010**, *122*, 10095; *Angew. Chem. Int. Ed.* **2010**, *49*, 9899; g) L. Ilies, Q. Chen, X. Zeng, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 5221; h) B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *Angew. Chem.* **2011**, *123*, 1141; *Angew. Chem. Int. Ed.* **2011**, *50*, 1109; i) W. Liu, H. Cao, J. Xin, L. Jin, A. Lei, *Chem. Eur. J.* **2011**, *17*, 3588; j) K. Gao, N. Yoshikai, *Angew. Chem.* **2011**, *123*, 7020; *Angew. Chem. Int. Ed.* **2011**, *50*, 6888; k) N. Yoshikai, *Synlett* **2011**, 1047; and Ref. [4h] and [7e].

[14] Although the exact reason for the observation that a direct alkylation of benzoxazoles is not possible under cobalt catalysis is not clear at this stage, the formation of a homocoupling product of benzoxazole gives us some information: a low-valent cobalt species is probably generated through the homocoupling reaction, but might be inactive. Such a homocoupling product was not detected in the reactions of 5-aryloxazoles and benzothiazole. For a relevant reduction process of Ni^{II} to Ni^0, see Ref. [10b,h].

[15] An attempt to apply benzimidazole, benzothiophene, and polyfluoroarenes to the reaction remained unsuccessful under both nickel and cobalt catalysis.

[16] a) H. M. L. Davies, S. J. Hedley, *Chem. Soc. Rev.* **2007**, *36*, 1109; b) M. M. Díaz-Requejo, P. J. Pérez, *Chem. Rev.* **2008**, *108*, 3379.

[17] The reaction with an in situ generated lithium hydrazide also failed to give the coupling product in a satisfactory yield (see the following scheme); G. Kaufman, F. Cook, H. Shechter, J. Bayless, L. Friedman, *J. Am. Chem. Soc.* **1967**, *89*, 5736.



[18] M. I. Javed, M. Brewer, *Org. Lett.* **2007**, *9*, 1789.

