Catal Lett (2012) 142:557–565
DOI 10.1007/s10562-012-0806-4

Application of a Nickel-Bispidine Complex as Pre-Catalyst for C(sp^2)–C(sp^3) Bond Formations

Michael Haberberger · Chika I. Someya · Anna Company · Elisabeth Irran · Stephan Enthaler

Received: 3 February 2012 / Accepted: 10 March 2012 / Published online: 3 April 2012

Abstract In the present study, the nickel-catalyzed cross coupling of aryl halides with benzyl zinc bromides or dialkyl zinc reagents to create C(sp^2)–C(sp^3) bonds has been explored. As pre-catalyst the well-defined and easy-accessible (bispidine)Ni(NO_3)$_2$ complex has been applied. After investigation of different reaction parameters a broad scope of C(sp^2)–C(sp^3) bond formations were feasible under mild reaction conditions.

Keywords Nickel · Catalysis · Nitrogen ligand · Cross coupling

1 Introduction

The construction of carbon–carbon bonds is one of the key transformations in organic chemistry and over the years manifold methodologies have been established [1]. Especially, transition metal-catalyzed coupling reactions have been proven to be a versatile and powerful technique [2–6]. For instance carbon nucleophiles can be coupled with carbon electrophiles including *sp*, sp^2 as well as sp^3 carbons applying nickel catalysts [7, 8]. However, the reaction of sp^3 carbon nucleophiles or electrophiles is still a challenging task, because of various difficulties, e.g., β-hydride elimination, slow reductive elimination steps, and high catalyst loadings [9]. To overcome these limitations the design and fine-tuning of the catalyst structure has been found to be a crucial parameter. Especially, the coordination of ligands to the metal influences significantly the catalyst activity and selectivity; hence the search for new ligands to improve the reaction is worthwhile [10–14]. In this regard, the application of tridentate nitrogen ligands, especially terpyridine based systems, has been proven to be efficient for those transformations (Scheme 1) [13]. Recently, the effect of substitution of the pyridines in 2,2′-position by e.g., oxazolines, on the reaction outcome has been studied, while the central pyridine unit was unchanged (Scheme 1a). On the other hand, the influence of the central nitrogen donor is an interesting target to investigate. Based on that, the replacement of the pyridine by a more basic piperidine unit should significantly effect on the substituent in the *trans*-position during the catalytic cycle. Furthermore, an additional donor functionality could be useful to stabilize reactive intermediates and increase the life-time of the catalyst (Scheme 1b).

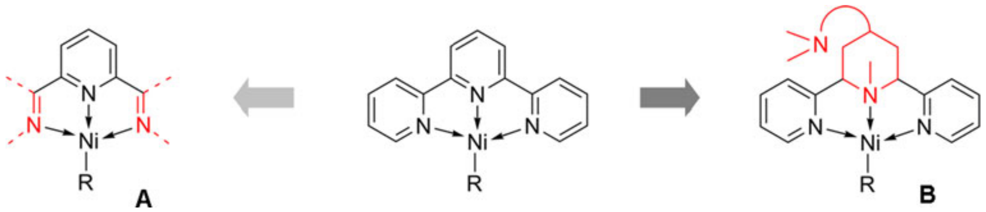
Recently the group of Comba presented the straightforward synthesis of tetradentate and pentadentate nitrogen ligands based on the bispidine motif as key structural element and furthermore the abilities in coordination chemistry were studied [15–37]. Some of the metal complexes based on the bispidine ligand have been applied in catalysis (Scheme 2) [38–41].

However, so far the potential of nickel bispidine complexes has not been evaluated in cross coupling reactions; hence we report herein the successful application of a homogeneous cross coupling catalyst based on nickel(II)

M. Haberberger · C. I. Someya · S. Enthaler (✉)
Department of Chemistry, Cluster of Excellence “Unifying Concepts in Catalysis”, Technische Universität Berlin, Straße des 17. Juni 135/C2, 10623 Berlin, Germany
e-mail: stephan.enthaler@tu-berlin.de

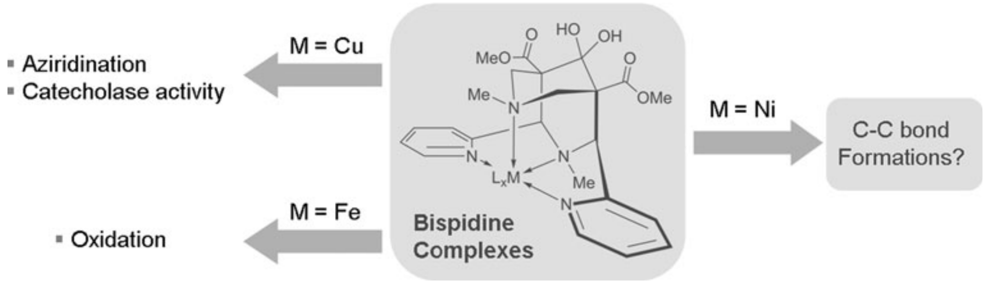
A. Company
Departament de Química, Universitat de Girona, Campus de Montilivi, E17071 Girona, Catalonia, Spain

E. Irran
Department of Chemistry: Metalorganics and Inorganic Materials, Technische Universität Berlin, Straße des 17. Juni 135/C2, 10623 Berlin, Germany

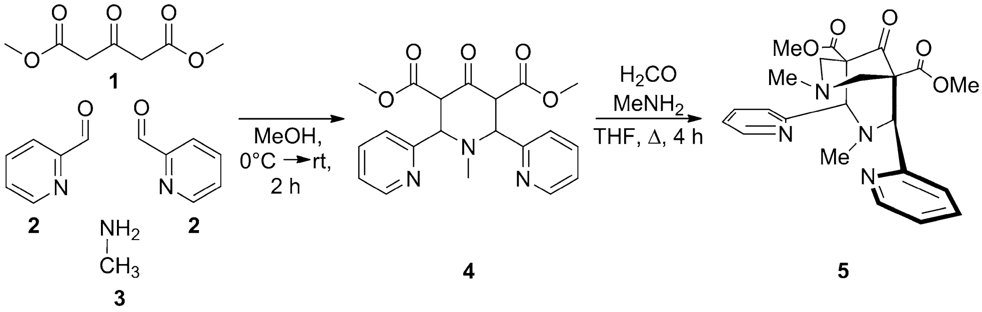


Scheme 1 Strategic modifications of nickel terpyridine complexes

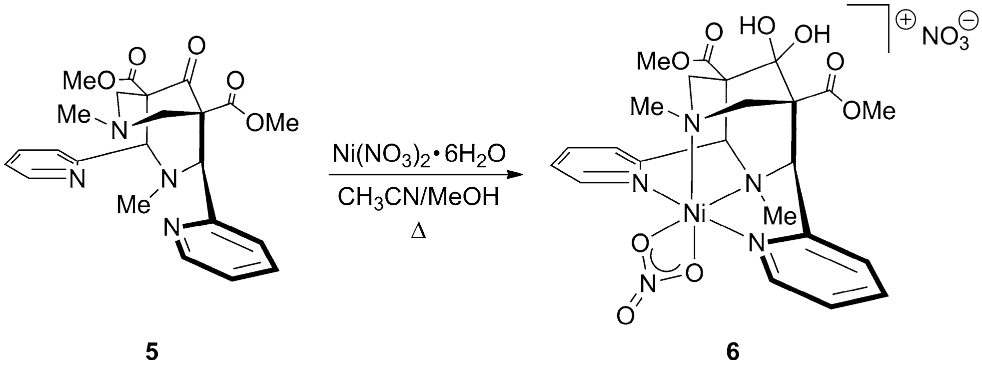
Scheme 2 Selection of applications of bispidine complexes in catalysis



Scheme 3 Synthesis of the bispidine ligand **5**



Scheme 4 Synthesis of the bispidine nickel complex **6**



nitrate modified by the tetradentate bispidine ligand; this catalyst showed good performance and is capable of coupling a variety of aryl halides with benzyl zinc bromides or dialkyl zinc reagents [42].

2 Results and Discussion

The bispidine ligand **5** was synthesized in a two-step synthesis in accordance to the method reported by Holzgrabe, Comba and co-workers (Scheme 3) [32, 43, 44]. First, the piperidone **4** is obtained in a one-pot Mannich reaction of dimethyl-1,3-acetonedicarboxylate (**1**), pyridine-2-carbaldehyde (2.2 equiv.), and methylamine (**3**). After isolation, **4** was reacted with formaldehyde and methylamine to attain the desired bispidine **5** in 65 % yield.

With this ligand in hand we examined the coordination to nickel (Scheme 4). In agreement to the previously reported procedure a nickel(II) nitrate solution in acetonitrile/methanol was added to a warm solution of the ligand in acetonitrile/methanol [16, 22]. The mixture was refluxed

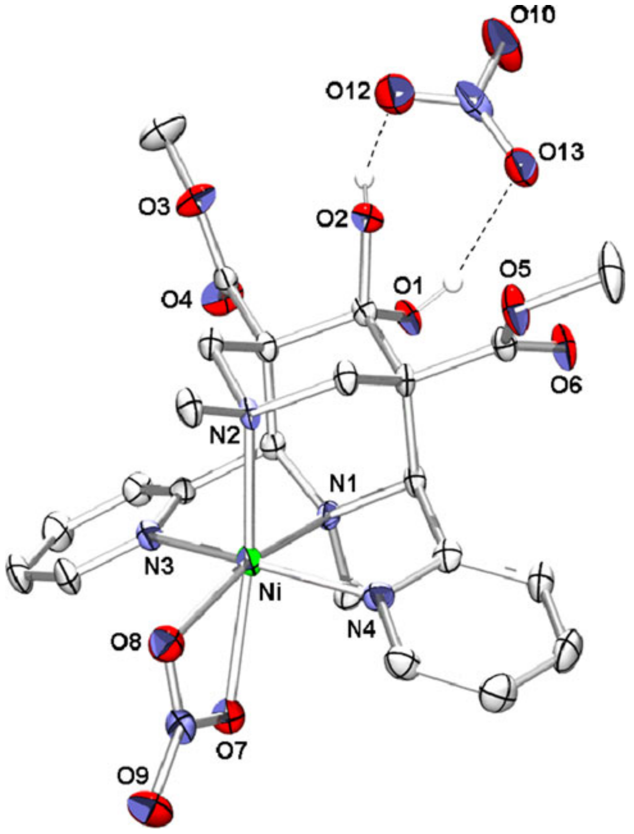


Fig. 1 Molecular structure of **6**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at the 50 % probability level

for a few seconds until a colour change from pale green to purple appeared. The complex [(**5**)Ni(NO_3)$_2$] (**6**) was obtained as a purple powder after removal of the solvent in vacuum. Dark purple crystals suitable for X-ray measurements were grown from a concentrated acetonitrile solution by diethyl ether diffusion. The solid-state structure of complex **6** was characterized by single-crystal X-ray diffraction analysis. Thermal ellipsoid plots are shown in Fig. 1. In Table 1 selected bond lengths and angles are summarized.

The equatorial nickel nitrogen bonds showed distances in the range of 2.044–2.074 Å, which is in contrast to the axial nickel nitrogen bond (2.090 Å) [35]. The N1–Ni–N2 angle (87.71°) is slightly squeezed and differs from the ideal 90°. In the case of the angle spanned by the pyridyl residues (N4–Ni–N3) a distortion is observed (160.68°). The distances of the oxygen atoms of the η^2-coordinated nitrate anion attached to the nickel are in a different range (2.161–2.105 Å). The second nitrate anion is connected via hydrogen interactions to the hydrated keto functionality in the backbone of the ligand. IR measurements revealed a brought absorption between 3,700 and 3,100 cm^{-1} which could be dedicated to the hydrogen bridges between the hydrated keto group and the nitrate anion. A strong absorption at 1,358 cm^{-1} can be attributed to the ester groups. Additionally the occurrence of a strong absorption at 1,385 cm^{-1} can be probably assigned to the nitrate functionality and a further band gives hint to the hydrated keto group (1,271 cm^{-1}) [45].

Table 1 Selected bond lengths and angles of **6**

	6
Ni–N1 (Å)	2.044(3)
Ni–N2 (Å)	2.090(2)
Ni–N3 (Å)	2.052(2)
Ni–N4 (Å)	2.074(3)
Ni–O7 (Å)	2.161(2)
Ni–O8 (Å)	2.105(2)
N1···N2 (Å)	2.864
N3···N4 (Å)	4.067
N1–Ni–N2 (°)	87.71(10)
N4–Ni–N3 (°)	160.68(10)
N2–Ni–O8 (°)	105.72(9)
O8–Ni–O7 (°)	60.79(9)
O1H···O13 (Å)	1.899
O2H···O12 (Å)	1.966

The catalytic abilities of the complex **6** were investigated in the coupling of aryl halides with benzyl zinc bromides and dialkyl zinc reagents (Table 2). After initial optimization we established that 2.0 mol% of the nickel complex **6** in THF performed the C(sp^2)–C(sp^3) bond formation during 24 h at 70 °C in excellent yield (>99 %) (Table 2, entry 2). Decreasing the reaction time to 3 h resulted in an excellent yield for the coupling of 1-iodo-4-methoxybenzene (**9**) and benzyl zinc bromide (**8**) (Table 2, entry 3). Moreover, the catalyst loading was decreased to 0.5 mol% showing an unchanged activity (Table 2, entry 4). Noteworthy, as reported recently by our group in the absence of any nickel source no reaction took place; hence the nickel complex did operate as the pre-catalyst [42]. When subjecting aryl bromides to catalysis a diminished yield was observed compared to aryl iodides, while for aryl chlorides the reaction was hampered (Table 2, entries 1, 2, 5, 9 and 22). Furthermore, fluorine substituents are untouched by the system (Table 2, entry 10). For alkyl substituted aryl bromides low conversions were observed (Table 2, entries 6–8). For substrates containing an electron withdrawing function the complex **6** showed good to excellent performance except for a substrate containing a nitro functionality (Table 2, entries 10–15). Remarkably, applying pyridyl bromides as substrates led to excellent yields of >99 % (Table 2, entry 19–21). To study the effect of β-hydride elimination α-methylbenzyl zinc bromide was used instead of benzyl zinc bromide (Table 2, entry 23–26). Along with the desired coupling products the

Table 2 Nickel–catalyzed C–C bond formation of benzyl zinc bromides with aryl halides

$$R^1\text{-}X \quad + \quad \underset{1.5\ \text{equiv.}}{R^2\text{–}Zn\text{–}R^3} \quad \xrightarrow[\text{THF, 70 °C, 24h}]{2.0\ \text{mol\%}\ \mathbf{6}} \quad R^1\text{-}R^2$$

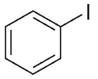
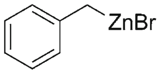
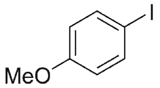
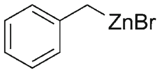
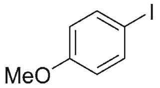
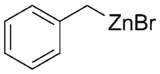
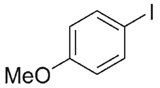
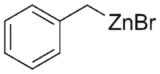
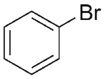
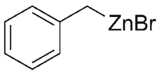
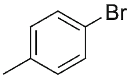
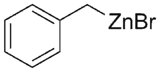
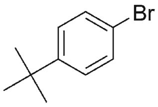
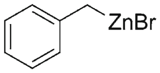
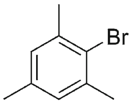
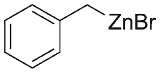
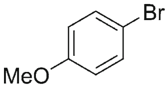
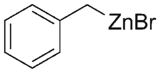
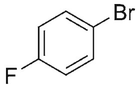
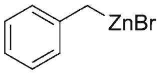
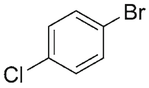
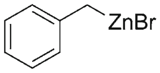
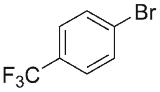
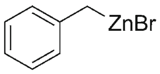
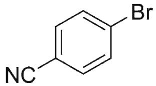
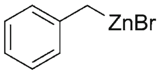
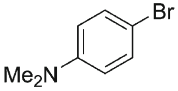
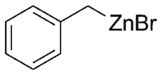
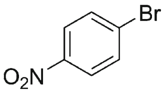
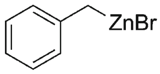
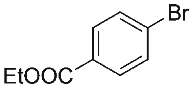
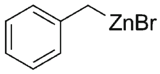
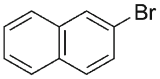
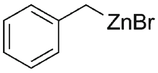
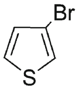
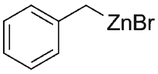
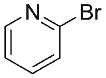
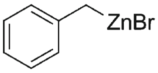
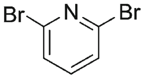
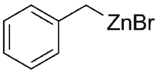
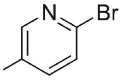
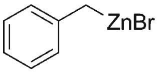
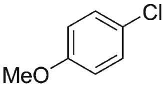
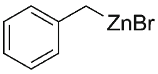
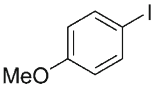
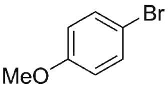
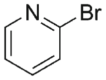
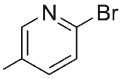
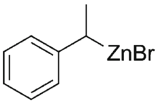
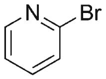
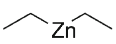
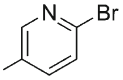
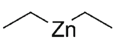
Entry	Substrate	Zn-source	Product	Yield (%)
1	 **7**	 **8**	**30**	>99
2	 **9**	 **8**	**31**	>99
3[a]	 **9**	 **8**	**31**	>99
4[b]	 **9**	 **8**	**31**	>99
5	 **10**	 **8**	**30**	57[c]
6	 **11**	 **8**	**32**	33
7	 **12**	 **8**	**33**	<1
8	 **13**	 **8**	**34**	<1
9	 **14**	 **8**	**31**	26
10	 **15**	 **8**	**35**	44[d]
11	 **16**	 **8**	**36**	60
12	 **17**	 **8**	**37**	80[e]
13	 **18**	 **8**	**38**	>99
14	 **19**	 **8**	**39**	16
15	 **20**	 **8**	**40**	<1
16	 **21**	 **8**	**41**	70

Table 2 continued

Entry	Substrate		Zn-source		Product	Yield (%)
17		**22**		**8**	**42**	71
18		**23**		**8**	**43**	11
19		**24**		**8**	**44**	>99
20[f]		**25**		**8**	**45**	>99
21		**26**		**8**	**46**	>99
22		**27**		**8**	**31**	<1
23		**9**		**28**	**47**	52[g]
24		**14**		**28**	**47**	14[h]
25		**24**		**28**	**48**	<1
26		**26**		**28**	**49**	12[i]
27		**24**		**29**	**50**	>99
28		**26**		**29**	**51**	>99

Reaction conditions substrate (0.72 mmol), benzyl zinc bromide (1.08 mmol, 0.5 M in THF), pre-catalyst (2.0 mol%), 70 °C, 24 h. The yield was determined by GC–MS and ^{1}H NMR

[a] *Reaction time* 3 h

[b] Catalyst loading 0.5 mol%

[c] Homocoupling product of **10**: 15 %

[d] Homocoupling product of **15**: 6 %

[e] Homocoupling product of **17**: 16 %

[f] 2 equivalents of benzyl zinc bromide (1.16 mmol, 0.5 M in THF)

[g] Homocoupling product of **9**: 27 %, β-hydride elimination of 28 yielded styrene in 10 %

[h] Homocoupling product of **14**: 13 %, β-hydride elimination of 28 yielded styrene in 5 %

[i] β-hydride elimination of **28** yielded styrene in 3 %, other side products occurred but were not determined

homocoupling products of the aryl bromides and the homocoupling product of the α-methylbenzyl zinc bromide were determined. Additionally styrene (3–10 %) was detected as β-hydride elimination product. Moreover, the coupling reaction was also performed by the use of diethyl zinc yielding 2-ethyl pyridine and 2-ethyl-5-methyl pyridine in quantitative yields (Table 2, entry 27 and 28).

In addition, we investigated the reaction of the aryl iodide **9** and the heteroaryl bromide **26** with benzyl zinc bromide in more detail (Fig. 2). For this purpose the coupling reaction was performed in the presence of the pre-catalyst (2.0 mol% of the complex **6**) and the product formation over time was evaluated by GC–MS. High activity of complex **6** was observed for the substrate 1-iodo-4-methoxybenzene (**9**) and full conversion was reached within 5 min (TOF > 600 h^{-1}). For comparison the half-life value could be drawn into account [t(50 % yield) for **31**: 1.5 min and t(50 % yield) for **46**: 29 min]. To compare the activity of the complex **6** with the parent terpyridine nickel complex, a mixture of $Ni(NO_3)_2 \cdot 6H_2O$ (2 mol%) and 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine (2 mol%) was applied as pre-catalyst in the coupling of substrate 26 and benzyl zinc bromide **8** (see for the reaction conditions: Fig. 2). For comparison the yield after 29 min [t(50 % yield) of pre-catalyst **6**] was monitored. After 29 min a yield of 82 % was observed, which is to some extent higher.

With regard to the underlying processes in Scheme 5 a reaction mechanism in accordance to reported protocols is proposed [7, 8]. First, the pre-catalyst is reduced to a nickel(0) species, which can undergo oxidative addition of the organic halide to form a nickel(II) complex. After transmetalation with the organic zinc compound, a new carbon carbon bond will be formed by reductive elimination. Moreover, the nickel(0) species is regenerated, which can perform the next C–C bond formation.

3 Conclusion

In summary, we have demonstrated the value of a nickel complex modified by the easy-accessible bispidine ligand for C(sp^2)–C(sp^3) bond formations. A broad scope of aryl halides were successfully coupled with alkyl zinc compounds in the presence of catalytic amounts of the nickel bispidine complex under mild reaction conditions. Especially for the transformation of heteroaryl bromides excellent performance was attained.

4 Experimental Section

4.1 General

All compounds were used as received without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AFM 200 spectrometer (^{1}H: 200.13 MHz, ^{13}C: 50.32 MHz) using the proton signals of the deuterated solvents as reference. GC–MS measurements were carried out on a Shimadzu GC-2010 gas chromatograph (30 m Rxi-5 ms column) linked with a Shimadzu GCMA-QP 2010 Plus mass spectrometer.

4.2 Synthesis of the Ligand **5**

The ligand was synthesized as described in the literature [43, 44]. In a round bottom flask dimethyl-1,3-acetonedicarboxylate (7.9 g, 45.5 mmol) was dissolved in methanol (50 mL) and cooled to 0 °C. Afterwards a mixture of pyridine-2-carbaldehyde (9.7 g, 90.9 mmol) and aqueous methylamine solution (3.5 g, 45.5 mmol, 40 %) was added dropwise to the stirred solution until the colour of the reaction mixture turned to deep red. The solution was allowed to warm to room temperature and stirring was continued for 2 h. After placing the reaction mixture at −20 °C overnight a white precipitate was formed, which was collected by suction filtration and was washed several times with cold methanol. After removal of the solvent a white powder **4** (4.7 g, 12.4 mmol, yield: 27 %) was obtained. The product **4** was dissolved in THF (50 mL) then an aqueous solution of formaldehyde (2.6 g, 32.2 mmol, 37 %) and an aqueous methylamine solution (1.3 g, 16.1 mmol, 40 %) were added dropwise. After refluxing the reaction mixture for 4 h and cooling to room temperature the solvent was removed in vacuum. The brown solid was recrystallized from ethanol (50 mL) and stored at −20 °C overnight. The white precipitate was collected by suction filtration and washed several times with cold ethanol to obtain a white powder. Yield: 65 % (3.5 g, 8.1 mmol); Mp: 168 °C; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 8.44$–8.52 (m, 2H), 8.06 (d, 2H, $J = 7.9$ Hz), 7.77 (td, 2H, $J = 7.6$ Hz, $J = 1.4$ Hz), 7.08–7.33 (m, 2H), 4.73 (s, 2H), 3.80 (s, 6H), 2.95 (d, 2H, $J = 12.5$ Hz), 2.50 (d, 2H, $J = 12.1$ Hz), 2.23 (s, 3H), 2.02 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) $\delta = 203.6$, 168.5, 159.1, 149.2, 136.3, 123.5, 122.9, 73.8, 62.2, 60.8, 52.4, 44.4, 43.2 ppm; IR (KBr): $\nu = 2952$ w, 2846 w, 2796 w, 1738 s, 1590 m, 1570 w, 1471 w, 1433 m, 1363 w, 1332 w, 1288 s, 1254 m, 1171 w, 1092 w, 1040 w, 996 w, 968 w, 787 w, 763 w, 750 w, 620 w, 532 w, cm^{-1};

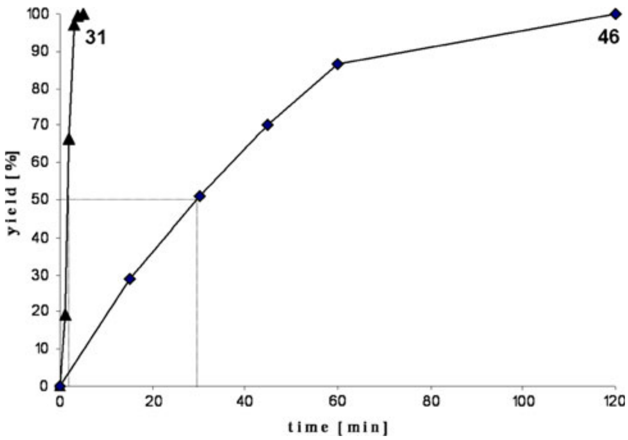
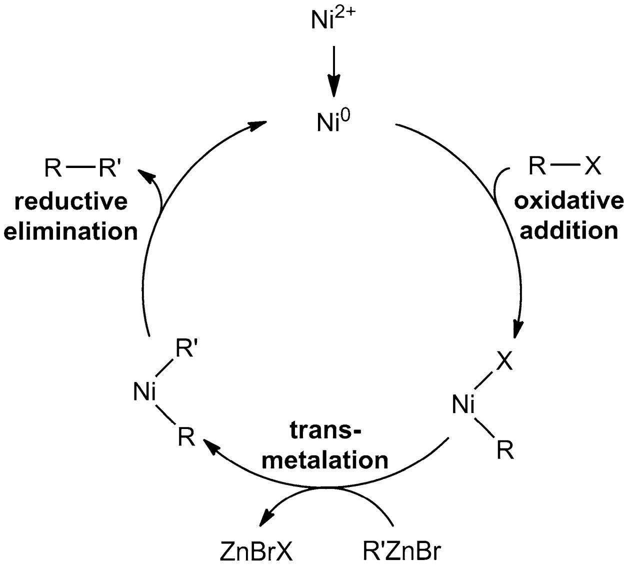


Fig. 2 Comparison of different aromatic halides. Reaction conditions: substrate (0.78 mmol), benzyl zinc bromide (1.17 mmol, 0.5 M in THF), pre-catalyst (2.0 mol%), 70 °C



Scheme 5 Catalytic cycle for nickel-catalyzed coupling reactions

HRMS calc. for $C_{23}H_{26}N_4O_5 + H$: 439.19814, found: 439.19709.

4.3 Synthesis of the Complex **6**

The complex was synthesized in accordance to the literature [16, 23]. To a solution of bispidine **5** (200.0 mg, 456.1 µmol) in acetonitrile/methanol (3.0 mL, 1:1 by vol.) a solution of $Ni(NO_3)_2 \cdot 6H_2O$ (132.6 mg, 456.1 µmol) in acetonitrile/methanol (3.0 mL, 1:1 by vol.) was added. The combined reaction mixture was heated to reflux for a few seconds until the colour changed from pale green to purple. Evaporation of the clear purple solution to dryness yielded **6** as a pink powder (285.2 mg, 446.2 µmol). Crystallization from a concentrated acetonitrile solution by diethyl ether diffusion yielded dark purple crystals suitable for X-ray diffraction. Yield: 98 %; Mp 220 °C (decomp.); IR (KBr): $v = 3215$ br, 2955 m, 1734 s, 1643 m, 1607 m, 1574 w, 1499 m, 1475 m, 1451 m, 1385 s, 1271 s, 1157 m, 1104 m, 1078 m, 1047 m, 1024 m, 1016 m, 971 w, 911 w, 889 w, 829 w, 808 w, 781 m, 648 w, 582 w, 532 w, cm^{-1}; HRMS calc. for $C_{23}H_{28}N_6NiO_{12}$–NO_3: 576.12350, found: 576.12302; $C_{23}H_{28}N_6NiO_{12}$: calc. C 43.22, H 4.42, N 13.02; found C 43.64, H 4.40, N 13.30.

4.4 General Procedure for the C–C Coupling Reaction

A Schlenk flask was charged with an appropriate amount of complex 6 (0.016 mmol, 2.0 mol%) and the corresponding halo arene (0.78 mmol). The flask was cycled with nitrogen and vacuum and benzyl zinc bromide (1.17 mmol, 0.5 M in THF) was added. The flask was sealed and heated at 70 °C for 24 h. The mixture was cooled on an ice bath. Dichloromethane and water were added. The aqueous layer was extracted with dichloromethane and the collected organic layers were washed with water, brine and dried with Na_2SO_4. After filtration and removal of the solvent the residue was dissolved in diethyl ether and purified by a short plug of silica gel. The analytical properties of the products are in agreement with literature. In case of low yields the compounds were not isolated and were only characterized by GC–MS.

*4.4.1 Diphenylmethane (**30**) [46]*

^1H NMR ($CDCl_3$, 200 MHz) $\delta = 7.11$–7.35 (m, 10H), 3.95 (s, 2H, CH_2) ppm; MS (EI) m/z = 168 (M^+, 100), 165 (40), 153 (28), 91 (27), 83 (16), 65 (16).

*4.4.2 1-Benzyl 4-methoxybenzene (**31**) [42]*

^1H NMR ($CDCl_3$, 200 MHz) $\delta = 7.02$–7.38 (m, 7H), 6.75–6.86 (m, 2H), 3.89 (s, 2H, CH_2), 3.70 (s, 3H, CH_3) ppm; MS (EI) m/z = 198 (M^+, 100), 183 (17), 167 (40), 153 (15), 121 (33), 91 (14).

*4.4.3 1-Benzyl 4-methylbenzene (**32**) [47]*

MS (EI) m/z = 182 (M^+, 69), 167 (100), 165 (34), 152 (15), 89 (14).

*4.4.4 1-Benzyl-4-fluorobenzene (**35**) [48]*

^1H NMR ($CDCl_3$, 200 MHz) $\delta = 7.05$–7.42 (m, 9H), 4.70 (s, 2H, CH_2) ppm; MS (EI) m/z = 186 (M^+, 100), 171 (14), 165 (43), 109 (22), 91 (18).

*4.4.5 1-Benzyl-4-chlorobenzene (**36**) [46]*

^1H NMR ($CDCl_3$, 200 MHz) $\delta = 7.38$–7.05 (m, 9H, ArH), 3.93 (s, 2H, CH2) ppm; MS (EI): m/z = 202 (M^+, 47), 167 (100), 165 (42), 152 (19), 91 (7), 82 (20).

*4.4.6 1-Benzyl-4-(trifluoromethyl)benzene (**37**) [49]*

^1H NMR ($CDCl_3$, 200 MHz) $\delta = 7.66$–7.82 (m, 2H), 7.51–7.63 (m, 2H), 7.02–7.45 (m, 5H), 4.06 (s, 2H, CH_2) ppm; MS (EI) m/z = 236 (M^+, 90), 217 (8), 215 (10), 168 (14), 167 (100), 166 (17), 165 (36), 152 (12), 91 (17).

*4.4.7 4-Benzylbenzonitrile (**38**) [49]*

^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.51$–7.68 (m, 2H), 7.05–7.42 (m, 5H), 3.98 (s, 2H, CH_2) ppm; MS (EI): m/z = 193 (M^+, 100), 192 (34), 191 (9), 190 (15), 178 (6), 165 (25), 91 (14).

*4.4.8 4-Benzyl-N,N-dimethylaniline (**39**) [49]*

MS (EI) m/z = 211 (M^+, 100), 210 (60), 167 (18), 165 (14), 134 (50), 91 (14).

*4.4.9 Ethyl 4-benzylbenzoate (**41**) [49]*

^1H NMR ($CDCl_3$, 200 MHz) $\delta = 8.02$ (d, $J = 7.6$ Hz, 2H), 7.03–7.54 (m, 7H), 4.39 (q, $J = 6.7$ Hz, 2H), 4.04 (s, 2H, CH_2), 1.40 (t, $J = 6.9$ Hz, 3H, CH_3) ppm; MS (EI) m/z = 240 (M, 77), 212 (16), 196 (15), 195 (96), 168 (15), 167 (100), 166 (18), 165 (50), 152 (32), 91 (15).

*4.4.10 2-Benzylnaphthalene (**42**) [50]*

^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.03$–8.02 (m, 12H) 4.11 (s, 2H, CH_2) ppm; MS (EI): m/z = 218 (M^+, 100), 217 (67), 215 (31), 203 (31), 202 (32), 141 (13) 108 (14).

*4.4.11 3-Benzylthiophene (**43**) [48]*

MS (EI) m/z = 174 (M^+, 100), 173 (80), 141 (15), 129 (22), 115 (13), 97 (63), 86 (8), 65 (12).

*4.4.12 2-Benzylpyridine (**44**) [51]*

^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 9.01$–9.1 (m, 1H), 7.81–7.95 (m, 1H), 7.08–7.49 (m, 7 H), 4.61 (s, 2H) ppm; MS (EI): m/z = 168 (M^+, 100), 91 (6), 84 (12).

*4.4.13 2,6-Dibenzylpyridine (**45**) [52]*

^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 8{,}08$ (t, J = 7.9 Hz, 1H), 7.01-7.39 (m, 12H), 4.50 (s, 4H) ppm; MS (EI) m/z = 259 (M^+, 52), 258 (100), 180 (30), 168 (14), 115 (7), 91 (15).

*4.4.14 2-Benzyl-5-methylpyridine (**46**) [42]*

^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 8.89$ (s, 1H), 7.58–7.69 (m, 1H), 7.00–7.42 (m, 6H), 4.45 (s, 2H, CH_2), 2.35 (s, 3H, CH_3) ppm; MS (EI) m/z = 182 (M^+, 100), 167 (17), 40 (91).

*4.4.15 1-Methoxy-4-(1-phenylethyl)benzene (**47**) [49]*

MS (EI) m/z = 212 (M^+, 48), 198 (16), 197 (100), 182 (9), 165 (16), 165 (22), 153 (12).

*4.4.16 5-Methyl-2-(1-phenylethyl)pyridine (**49**)*

MS (EI) m/z = 197 (M^+, 43), 196 (100), 182 (10), 181 (33), 180 (11), 120 (17), 93 (8).

*4.4.17 2-Ethylpyridine (**50**) [53, 54]*

^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 9.01$–9.14 (s, 1H), 7.81–7.96 (m, 1H), 7.32–7.45 (m, 1H), 3.15 (q, 2H, $J = 7.5$ Hz), 1.23 (t, 3H, $J = 7.6$ Hz) ppm; MS (EI) m/z = 107 (M^+, 42), 106 (100), 79 (23) 78 (14), 52 (12), 51 (11).

*4.4.18 2-Ethyl-5-methylpyridine (**51**) [55, 56]*

^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 8.36$ (s, 1H), 7.34–7.44 (m, 1H), 6.98–7.09 (m, 1H), 2.76 (q, 2H, $J = 7.5$ Hz), 2.27 (s, 1H), 1.24 (t, 3H, $J = 7.6$ Hz) ppm; MS (EI) m/z = 121 (M^+, 49), 120 (93), 93 (18), 40 (100).

4.5 Single-Crystal X-ray Structure Determination

Crystals were each mounted on a glass capillary in perfluorinated oil and measured in a cold N_2 flow. The data were collected using an Oxford Diffraction Xcalibur S Sapphire at 150(2) K ($Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å). The structures were solved by direct methods and refined on F^2 with the SHELX-97 software package [57]. The positions of the hydrogen atoms were calculated and considered isotropically according to a riding model.

CCDC-865067 (for **6**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements Financial support from the Cluster of Excellence "Unifying Concepts in Catalysis" (funded by the Deutsche Forschungsgemeinschaft and administered by the Technische Universität Berlin) is gratefully acknowledged.

References

1. Corey EJ, Cheng XM (1989) The logic of chemical synthesis. Wiley, New York, pp 1–91
2. Suzuki A (2011) Angew Chem 123:6854–6869, Angew Chem Int Ed 2011, 50: 6722–6737
3. Negishi E (2011) Angew Chem Int Ed 50:6738–6764
4. de Meijere F, Diederich (eds) (2004) Metal-catalyzed cross-coupling reactions. Wiley-VCH, Weinheim
5. Negishi E (ed) (2002) Handbook of organopalladium chemistry for organic synthesis. Wiley-InterScience, New York
6. Diederich F, Stang PJ (eds) (1998) Metal-catalyzed cross-coupling reactions. Wiley-VCH, Weinheim
7. Jana R, Pathak TP, Sigman MS (2011) Chem Rev 111:1417–1492
8. Hu X (2011) Chem Sci 2:1867–1886
9. Rilatt RFW, Jackson J (2008) Org Chem 73:8694–8704
10. Zhou S, Fu GC (2003) J Am Chem Soc 125:14726–14727
11. Phapale VB, Buñuel E, García-Iglesias M, Cárdenas DJ (2007) Angew Chem Int Ed 46:8790–8795
12. Smith SW, Fu GC (2008) Angew Chem 120: 9474–9476, Angew Chem Int Ed 2008, 47:9334–9336
13. Jones GD, Martin JL, McFarland C, Allen OR, Hall RE, Haley AD, Brandon RJ, Konovalova T, Desrochers PJ, Pulay P, Vicic DA (2006) J Am Chem Soc 128:13175–13183
14. Joshi-Pangu A, Ganesh M, Biscoe MR (2011) Org Lett 13:1218–1221
15. Comba P, Kanellakopulos B, Katsichtis C, Lienke A, Pritzkow H, Rominger F (1998) J Chem Soc Dalton Trans 23:3997–4001
16. Börzel H, Comba P, Katsichtis C, Kiefer W, Lienke A, Nagel V, Pritzkow H (1999) Chem Eur J 5:1716–1721
17. Börzel H, Comba P, Hagen KS, Katsichtis C, Pritzkow H (2000) Chem Eur J 6:914–919
18. Börzel H, Comba P, Pritzkow H (2001) Chem Commun 97–98
19. Comba P, Kerscher M, Merz M, Müller V, Pritzkow H, Remenyi R, Schiek W, Xiong Y (2002) Chem Eur J 8:5750–5760
20. Börzel H, Comba P, Hagen KS, Kerscher M, Pritzkow H, Schatz M, Schindler S, Walter O (2002) Inorg Chem 41:5440–5452
21. Börzel H, Comba P, Hagen KS, Lampeka YD, Lienke A, Linti G, Merz M, Pritzkow H, Tsymbal LV (2002) Inorg Chim Acta 337:407–419
22. Comba P, Hauser A, Kerscher M, Pritzkow H (2003) Angew Chem Int Ed 42:4536–4540
23. Comba P, de Laorden CL, Pritzkow H (2005) Helv Chim Acta 88:647–664

24. Bautz J, Comba P, Que L Jr (2006) Inorg Chem 45:7077–7082
25. Anastasi AE, Lienke A, Comba P, Rohwer H, McGrady JE (2007) Eur J Inorg Chem 65–73
26. Born K, Comba P, Ferrari R, Lawrance GA, Wadepohl H (2007) Inorg Chem 46:458–464
27. Comba P, Kuwata S, Linti G, Tarnai M, Wadepohl H (2007) Eur J Inorg Chem 657–664
28. Anastasi AE, Comba P, McGrady J, Lienke A, Rohwer H (2007) Inorg Chem 46:6420–6426
29. Bentz A, Comba P, Deeth RJ, Kerscher M, Seibold B, Wadepohl H (2008) Inorg Chem 47:9518–9527
30. Born K, Comba P, Kerscher M, Linti G, Pritzkow H, Rohwer H (2009) Dalton Trans 362–367
31. Comba P, Daumann L, Lefebvre J, Linti G, Martin B, Straub J, Zessin T (2009) Aust J Chem 62:1238–1245
32. Black DSC, Deacon GB, Rose M (1995) Tetrahedron 51:2055–2076
33. Barnes NA, Brooker AT, Godfrey SM, Mallender PR, Pritchard RG, Sadler M (2008) Eur J Org Chem 1019–1030
34. Walther M, Matterna M, Juran S, Fähnemann S, Stephan H, Kraus W, Emmerling F (2011) Z Naturforsch 66b:721–728
35. Bleiholder C, Börzel H, Comba P, Ferrari R, Heydt M, Kerscher M, Kuwata S, Laurenczy G, Lawrance GA, Lienke A, Martin B, Merz M, Nuber B, Pritzkow H (2005) Inorg Chem 44:8145–8155
36. Comba P, Haaf C, Wadepohl H (2009) Inorg Chem 48: 6604–6614
37. Atanasov M, Busche C, Comba P, El Hallak F, Martin B, Rajaraman G, van Slageren J, Wadepohl H (2008) Inorg Chem 47:8112–8125
38. Comba P, Merz M, Pritzkow H (2003) Eur J Inorg Chem 1711–1718
39. Born K, Comba P, Daubinet A, Fuchs A, Wadepohl H (2007) J Biol Inorg Chem 12:36–48
40. Comba P, Lang C, de Laorden CL, Muruganantham A, Rajaraman G, Wadepohl H, Zajaczkowski M (2008) Chem Eur J 14:5313–5328
41. Bukowski MR, Comba P, Lienke A, Limberg C, de Laorden CL, Mas-Ballesté R, Merz M, Que L Jr (2006) Angew Chem Int Ed 45:3446–3449
42. Someya CI, Inoue S, Krackl S, Irran E, Enthaler S (2012) Eur J Inorg Chem 1269–1277
43. Sammhammer A, Holzgrabe U, Haller R (1989) Arch Pharm 322:551–555
44. Holzgrabe U, Erciyas E (1992) Arch Pharm 325:657–663
45. Comba P, Nuber B, Ramlow A (1997) J Chem Soc Dalton Trans 3:347–352
46. Alacid E, Nájera C (2008) Org Lett 10:5011–5014
47. Sun G, Wang Z (2008) Tetrahedron Lett 49:4929–4932
48. Burns MJ, Fairlamb IJS, Kapdi AR, Sehnal P, Taylor RJK (2007) Org Lett 26:5397–5400
49. Amatore M, Gosmini C (2008) Chem Commun 5019–5021
50. Cho C-H, Sun M, Seo Y-S, Kim C-B, Park K (2005) J Org Chem 70:1482–1485
51. Wu GG, Chen FX, LaFrance D, Liu Z, Greene SG, Wong Y-S, Xie J (2011) Org Lett 13:5220–5223
52. Blachut D, Szawkalo J, Czarnocki Z (2011) Synthesis 21: 3496–3506
53. Smit C, Fraaije MW, Minnaard AJ (2008) J Org Chem 73: 9482–9485
54. Rubottom GM, Evain EJ (1990) Tetrahedron 46:5055–5064
55. Kutney JP, Cable J, Gladstone WAF, Hanssen HW, Nair GV, Torupka EJ, Warnock WDC (1975) Can J Chem 53:1796–1817
56. Kato S, Kurata T, Ishiguro S, Fujimaki M (1973) Agric Biol Chem 37:1759–1761
57. Sheldrick GM (1997) SHELXL93, Program for the refinement of crystal structures. University of Göttingen, Göttingen