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Microwave-assisted nickel(II) acetylacetonate-catalyzed arylation of aldehydes with arylboronic acids

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Dedicated to Professor Carmen Nájera on the occasion of her 60th birthday

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ABSTRACT

Applying sealed vessel microwave heating at 180 °C in toluene the arylation of aromatic and aliphatic aldehydes with arylboronic acids using 1–2 mol % of $Ni(acac)_2$ as a catalyst can be performed efficiently within 10–30 min providing the desired diarylmethanols or benzyl alcohols in good yields.

Owing to the importance of diarylmethanols in the context of organic synthesis and medicinal chemistry, the arylation of aromatic aldehydes using arylboron reagents has recently attracted considerable attention.[1] Miyaura and his group reported the first example of a Rh(I)-catalyzed addition reaction of arylboronic acids to aldehydes providing an entry into diarylmethanols in 1998.[2] In the following years several research groups have focused on this transformation evaluating different transition metal catalysts,[3–7] including Rh,[3] Pd,[4] Cu,[5] Fe,[6] and Ni complexes.[7–9] While the arylation generally works well applying Rh or Pd catalysts,[2–4] the corresponding 1,2-additions using Cu and Fe catalysts are restricted to aromatic aldehydes bearing strong electron-withdrawing substituents, limiting their application.[5,6] Clearly, the use of cost-effective Ni catalysts is very attractive in this context.

It was first reported by Shirakawa in 2005 that Ni(0) complexes are able to catalyze the reaction between boronic esters and aldehydes.[7] However, this protocol required expensive and air sensitive $Ni(cod)_2$ as a catalyst and the use of an alkyne as a co-catalyst.[7] Similar catalytic systems/co-catalysts were employed by other groups in subsequent years, but these published methods still required co-catalysts and/or the use of arylboroxines instead of simple and commercially available arylboronic acids as reaction partners.[8] In 2009, Bao for the first time reported the use of a Ni salt, 5 mol % of $Ni(ClO_4)_2$, for the 1,2-addition of arylboronic acids to aromatic aldehydes providing diarylmethanols in good to excellent yields after 7–14 h reaction time.[9] Herein, we wish to report a rapid and efficient microwave-assisted protocol[10] that allows the addition of arylboronic acids to both aromatic and aliphatic aldehydes to proceed within 10–30 min using only 1–2 mol % of inexpensive Ni(II) acetylacetonate [$Ni(acac)_2$] as a catalyst.

Our initial investigations focused on the 1,2-addition of phenylboronic acid (1.5 equiv) to benzaldehyde using $Ni(PCy_3)_2Cl_2$ as a catalyst and toluene as a solvent (Table 1). All reactions were performed using controlled microwave heating in a dedicated single-mode reactor using internal temperature probes.[11] As a starting point 2 mol % of $Ni(PCy_3)_2Cl_2$ catalyst and 2 equiv of K_2CO_3 as a base were chosen. As far as boronic acid stoichiometry was concerned, initial optimization studies demonstrated that 1.5 equiv of boronic acid provided optimum yields within relatively short reaction times. Applying 180 °C as reaction temperature (3–4 bar) high conversions were obtained independent of the reaction time, even after only 10 min of microwave heating (Table 1, entries 1–3). On the other hand, the amount of catalyst (Table 1, entries 1, 4, and 5) and the used base (Table 1, entries 8–12) had a significant influence on the 1,2-addition. Reducing the catalyst loading from 2 mol % to 0.5 mol % lowered the conversion from 81% to 65%. Utilizing Et_3N and Cs_2CO_3 as bases completely failed and the use of CsF provided only a low conversion. Choosing K_3PO_4 as the base

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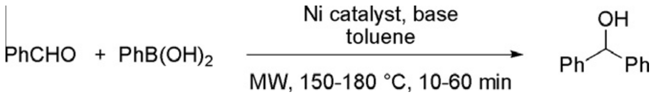
Table 1
Optimization of reaction conditions[a]



Entry	Ni catalyst (mol %)	Base (equiv)	Time (min)	T (°C)	Conversion[b] (%)
1	$Ni(PCy_3)_2Cl_2$ (2)	K_2CO_3 (2)	10	180	81
2	$Ni(PCy_3)_2Cl_2$ (2)	K_2CO_3 (2)	30	180	83
3	$Ni(PCy_3)_2Cl_2$ (2)	K_2CO_3 (2)	60	180	86
4	$Ni(PCy_3)_2Cl_2$ (1)	K_2CO_3 (2)	10	180	75
5	$Ni(PCy_3)_2Cl_2$ (0.5)	K_2CO_3 (2)	10	180	65
6	$Ni(PCy_3)_2Cl_2$ (0.5)	K_2CO_3 (2)	30	180	72
7	$Ni(PCy_3)_2Cl_2$ (1)	K_2CO_3 (0.5)	30	180	77
8	$Ni(PCy_3)_2Cl_2$ (1)	K_2CO_3 (1)	30	180	82
9	$Ni(PCy_3)_2Cl_2$ (1)	K_3PO_4 (1)	30	180	86
10	$Ni(PCy_3)_2Cl_2$ (1)	Cs_2CO_3 (1)	30	180	0
11	$Ni(PCy_3)_2Cl_2$ (1)	CsF (1)	30	180	16
12	$Ni(PCy_3)_2Cl_2$ (1)	Et_3N (1)	30	180	0
13	$Ni(PPh_3)_2Cl_2$ (1)	K_2CO_3 (1)	30	180	0
14	$NiCl_2$ (1)	K_2CO_3 (1)	30	180	0
15	$Ni(acac)_2$ (1)	K_2CO_3 (1)	30	180	100
16	$Ni(acac)_2$ (1)	K_2CO_3 (1)	10	180	93 (77)[c]
17	$Ni(acac)_2$ (1)	K_2CO_3 (1)	10	170	87
18	$Ni(acac)_2$ (1)	K_2CO_3 (1)	10	150	82
19	$Ni(acac)_2$ (1)	K_2CO_3 (1)	10	180	88[d]

[a] Reactions were performed using benzaldehyde (1.0 mmol), 1.5 equiv of phenylboronic acid, and 2 mL of anhydrous toluene. Single-mode microwave heating (Monowave 300) with internal temperature monitoring and magnetic stirring.

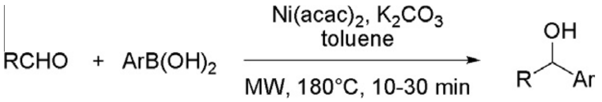
[b] Conversion based on GC–MS analysis.

[c] Isolated yields after flash chromatography.

[d] Reaction was performed in a silicon carbide vessel.

proved equally efficient to K_2CO_3 but due to the higher molecular weight of K_3PO_4, K_2CO_3 remained our preferred base. It was also found that using 1 mol % $Ni(PCy_3)_2Cl_2$ and 1 equiv of K_2CO_3 as the base for 30 min, the reaction can be carried out as efficiently as using 2 mol % $Ni(PCy_3)_2Cl_2$ and 2 equiv K_2CO_3 as the base for 10 min (Table 1, compare entries 1 and 8).

Table 2
Ni-catalyzed arylation of aromatic and aliphatic aldehydes with arylboronic acids[a]



Entry	R	Ar	$Ni(acac)_2$ (mol %)/K_2CO_3 (equiv)	Time (min)	Yield (%)[b]
1	C_6H_5	C_6H_5	1/1	10	77
2	2-Cl–C_6H_4	C_6H_5	1/1	10	73
3	3-Cl–C_6H_4	C_6H_5	1/1	10	75
4	4-Cl–C_6H_4	C_6H_5	1/1	10	67
5	2-Br–C_6H_4	C_6H_5	1/1	10	68
6	3-Br–C_6H_4	C_6H_5	1/1	10	74
7	4-Br–C_6H_4	C_6H_5	1/1	10	89
8	4-NC–C_6H_4	C_6H_5	1/1	10	NR[c]
9	2-MeO–C_6H_4	C_6H_5	1/1	10	96
10	4-MeO–C_6H_4	C_6H_5	1/1	10	74
11	2,5-$(MeO)_2$–C_6H_3	C_6H_5	1/1	10	82
12	3,4-$(MeO)_2$–C_6H_3	C_6H_5	1/1	10	75
13	3-Me–C_6H_4	C_6H_5	1/1	30	77
14	4-Me–C_6H_4	C_6H_5	1/1	30	81
15	Cyclohexyl	C_6H_5	2/2	30	69
16	*n*-Hexyl	C_6H_5	2/2	30	58
17	C_6H_5	4-Me–C_6H_4	2/2	30	47
18	C_6H_5	4-F–C_6H_4	2/2	30	70
19	4-Cl–C_6H_4	4-F–C_6H_4	2/2	30	81
20	2-MeO–C_6H_4	4-F–C_6H_4	2/2	30	74
21	C_6H_5	3-F–C_6H_4	2/2	30	72
22	C_6H_5	4-Cl–C_6H_4	2/2	30	68

[a] Reactions were performed using RCHO (1.0 mmol), 1.5 equiv (1.5 mmol) of $ArB(OH)_2$, 1 mol % of $Ni(acac)_2$, and 1 equiv of K_2CO_3 in 2 mL of anhydrous toluene. Single-mode microwave heating (Monowave 300) with internal temperature monitoring and magnetic stirring.

[b] Isolated yields after flash chromatography.

[c] No reaction occurred.

Most importantly however, when inexpensive Ni(acac)$_2$ was used as a catalyst, optimum results were obtained (Table 1, entries 15–19). After 10 min of microwave heating at 180 °C using only 1 mol % of the catalyst and 1 equiv of K_2CO_3, 93% conversion to the diarylmethane was obtained, providing a 77% isolated yield of diphenylmethanol after purification by flash chromatography (Table 1, entry 16). Reducing the reaction temperature to 170 °C or 150 °C led to somewhat reduced conversions (Table 1, entries 17 and 18).

In addition, a control experiment employing a reaction vessel made out of strongly microwave absorbing silicon carbide (SiC) using the same microwave instrument demonstrated that the improvements in reaction rate are the result of a purely thermal effect (Table 1, entry 19).[12]

With optimized reaction conditions in hand, the scope and limitations of this novel high-speed arylation protocol were examined employing a variety of aromatic and aliphatic aldehydes as well as different arylboronic acids as reaction partners. In most instances the anticipated products were obtained in good to excellent isolated yields (Table 2).[13] Aromatic aldehydes with different types of halogen substituents afforded excellent product yields (Table 2, entries 2–7). Electron-rich aldehydes such as 3-methoxy-, 4-methoxy-, and 3,4-dimethoxybenzaldehyde (Table 2, entries 9–12) provided similar high yields while for 3-methyl- and 4-methylbenzaldehyde the reaction time had to be increased to 30 min in order to obtain acceptable yields (Table 2, entries 13 and 14). On the other hand, electron-deficient aldehydes, such as 4-cyanobenzaldehyde (Table 2, entry 8), did not participate in the reaction in agreement with previous literature reports.[9] Employing aliphatic aldehydes the desired benzyl alcohols were also obtained in moderate yields, however self-aldol condensation of the aldehyde component had a negative impact on the overall reaction yield, requiring the use of longer reaction times and catalyst loadings (Table 2, entries 15 and 16). The use of substituted arylboronic acids revealed significant electronic effects, with electron-rich arylboronic acids generally providing lower yields compared to their electron-deficient counterparts (Table 2, entries 17–22).

Gratifyingly, it was also demonstrated that the microwave-assisted protocol introduced herein was readily scalable. Thus, the Ni-catalyzed addition of phenylboronic acid to benzaldehyde (Table 2, entry 1) was performed on a 10 mmol scale (20 mL solvent) in the same single-mode microwave reactor under otherwise identical conditions, but using a larger reaction vial (30 mL). From this experiment 1.36 g (74%) of diphenylmethanol was obtained, in a very similar yield and product purity as in the 1.0 mmol scale experiment.

In conclusion, we have developed a rapid and efficient protocol for the Ni-catalyzed arylation of aromatic and aliphatic aldehydes with arylboronic acids providing the corresponding benzylic alcohol derivatives. The transformations are conveniently carried out using 1–2 mol % of inexpensive Ni(acac)$_2$ in the presence of 1–2 equiv of K_2CO_3 as a base without the need for an inert atmosphere. Employing sealed vessel microwave heating at 180 °C under carefully controlled conditions the 1,2-addition reactions are completed within 10–30 min providing good to excellent product yields in most instances. The reactions are easily scalable up to gram scale (10 mmol) using larger microwave vessels.

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13. General procedure for the Ni-catalyzed arylation of aldehydes with arylboronic acids (Table 2): Aldehyde (1.0 mmol), arylboronic acid (1.5 mmol, 1.5 equiv), K_2CO_3 (138 mg, 1.0 mmol, 1 equiv), and Ni(acac)$_2$ (2.6 mg, 0.01 mmol, 1 mol %) were added to a 10 mL microwave processing vial containing a Teflon coated stir bar. After the vial was sealed dry toluene (2 mL) was transferred to the vial and mixture was pre-stirred for 5 min. The vial was placed in the microwave cavity and heated for 10 min at 180 °C (fixed hold time). After cooling, diethyl ether or ethyl acetate (10 mL) was added and the crude reaction mixture was subsequently washed with 25% aqueous NH_3 (2 × 10 mL). The aqueous ammonium layer was reextracted again with diethyl ether or ethyl acetate (2 × 10 mL). The combined organic phase was dried over $MgSO_4$ and the residue after evaporation purified by flash chromatography using a petroleum ether/ethylacetate (10:1–2.5:1) as eluent phase. All products are literature known and were identified by ^1H NMR and MS spectroscopy.