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Ni(II) source as a pre-catalyst for the cross-coupling of benzylic pivalates with arylboronic acids: facile access to tri- and diarylmethanes†

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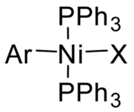
A simple and easily-used Ni^{II} complex, Ni(PPh$_3$)$_2$(1-naphthyl)Cl, was employed as a pre-catalyst in the Suzuki–Miyaura cross-coupling of benzylic pivalates with arylboronic acids, affording various tri- or diarylmethanes in good yields under mild conditions. This new protocol provides a cheap, convenient and practical alternative to synthesizing multiaryl methanes.

The study of methodologies for the construction of multi-aryl methanes has been attracting strong interest from synthetic chemists because these target molecules are valuable frameworks in medicinal and materials chemistry, as well as organic synthesis.[1] Among the synthetic strategies developed, the Suzuki–Miyaura reaction of benzylic electrophiles has emerged as a highly preferred method.[2–10] In this regard, successful examples included cross-couplings of organoboron reagents with benzylic halides,[2] carbonates,[3] acetates,[4] phosphates[5] and sulfones[6] (Pd-catalyzed processes), as well as with benzylic ammonium salts,[7] carbamates,[8] pivalates[9] and ethers[10] (Ni^0-catalyzed processes). Despite the impressive advances, improvement on the catalyst systems of those protocols remains urgently needed, since it was recognized that palladium belongs to precious metals, and the Ni^0 species is difficult to experimentally handle due to its high air-sensitivity and toxicity.

trans-Haloarylbis(triphenylphosphane)nickel(II) (Fig. 1) are a special type of nickel(II) compounds, many of which can be conveniently prepared from cheap, commercially available starting materials, and display better stability in air and moisture.[11] We previously confirmed that Ni^{II}–(σ-aryl) complexes are highly applicable catalyst precursors in Suzuki–Miyaura-type cross-couplings.[12] Therefore, we envisioned that the use of such nickel(II) pre-catalysts would be feasible in cross-couplings of benzylic pivalates with



$$\mathrm{Ar{-}\overset{\displaystyle PPh_3}{\underset{\displaystyle PPh_3}{Ni}}{-}X}$$

Fig. 1 Ni^{II}–(σ-aryl) complexes.

Table 1 Screening of conditions for Ni-catalyzed cross-coupling between the pivalate **1** and *p*-anisylboronic acid[a]

Entry	[Ni(II)] (mol%)	Ligand (mol%)	Base	Solvent	Temp. (°C)	Yield[b] (%)
1	**C-1**[c] (5)	None	K_3PO_4	Toluene	70	86
2	**C-1** (5)	PPh_3 (10)	K_3PO_4	Toluene	70	41
3	**C-1** (5)	PCy_3 (10)	K_3PO_4	Toluene	70	46
4	**C-1** (5)	DPPP (5)	K_3PO_4	Toluene	70	19
5	**C-1** (5)	DPPF (5)	K_3PO_4	Toluene	70	27
6	**C-2**[d] (5)	None	K_3PO_4	Toluene	70	0
7	**C-3**[e] (5)	None	K_3PO_4	Toluene	70	0
8	**C-4**[f] (5)	None	K_3PO_4	Toluene	70	0
9	**C-1** (5)	None	K_2CO_3	Toluene	70	12
10	**C-1** (5)	None	CsF	Toluene	70	7
11	**C-1** (5)	None	K_3PO_4	Dioxane	70	9
12	**C-1** (5)	None	K_3PO_4	THF	70	Trace
13	**C-1** (2.5)	None	K_3PO_4	Toluene	70	39
14	**C-1** (5)	None	K_3PO_4	Toluene	50	61
15	**C-1** (0)	None	K_3PO_4	Toluene	70	0

[a] Conditions: the pivalate **1** (1.0 mmol), *p*-anisylboronic acid (1.5 mmol), base (2.5 mmol), 5.0 mL of solvent, 6 h, N_2. [b] Isolated yields. [c] **C-1:** Ni(PPh$_3$)$_2$(1-naphthyl)Cl. [d] **C-2:** NiCl$_2$·6H$_2$O. [e] **C-3:** Ni(acac)$_2$. [f] **C-4:** NiCl$_2$(PPh$_3$)$_2$.

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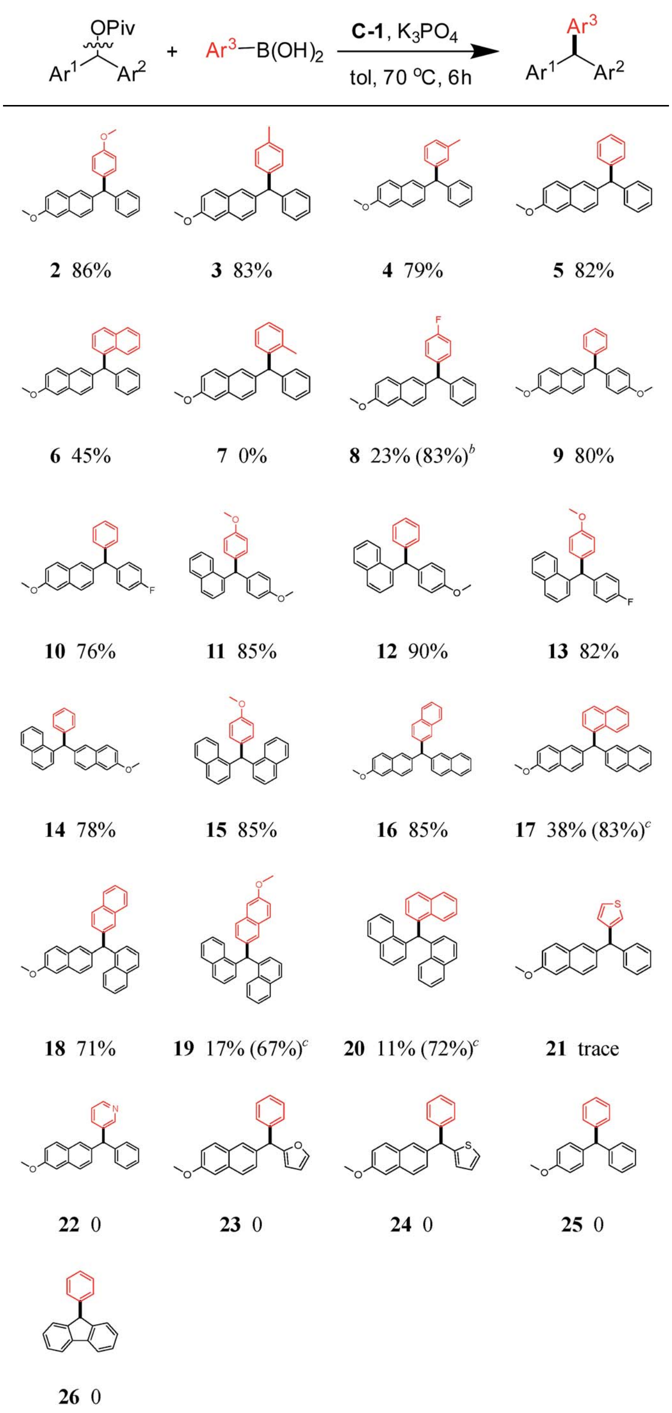
arylboronic acids. Herein, we wish to disclose our new findings.

We first attempted the cross-coupling of a diarylmethyl pivalate **1** (belonging to a type of secondary benzylic pivalates) with *p*-anisylboronic acid under the Ni^{II}–(σ-aryl) complex catalysis. $Ni(PPh_3)_2$(1-naphthyl)Cl (**C-1**) was preferably selected as pre-catalyst, as previously in our laboratory.[12] After some experimentation, the reaction was found to proceeded smoothly with a high isolated yield of 86% (entry 1), and over-loading ligands was virtually unfavourable for the reaction (entries 2–5). As expected, other types of nickel(II) sources, such as $NiCl_2 \cdot 6H_2O$, $Ni(acac)_2$ and $Ni(Ph_3P)_2Cl_2$, were ineffective for the desired C–C coupling (entries 6–8). This may be because common Ni^{II} precursors are unable to produce the catalytically active Ni^0 species in the reaction system.[12a] The type of bases is also important (entry 1 *vs.* entries 9 and 10). Toluene appeared to be the solvent of choice for the reaction and far superior to ethereal solvents such as dioxane (entry 11) and THF (entry 12). In addition, reducing the catalyst loading (entry 13) or lowering the reaction temperature (entry 14) would cause a dramatic decrease in yields. Finally, the role of the Ni^{II} complex in the reaction was demonstrated clearly in a control experiment (entry 15) (Table 1).

Next, the scope and limitations of this Ni^{II}-catalyzed benzyl–aryl coupling reactions were investigated. Under the optimized conditions we carried out the reaction of diarylmethyl pivalates (Table 2) and of primary benzylic pivalates (Table 3), respectively, with arylboronic acids.

Regarding the boronic acid component, both electron-rich (**2–4**, **11**, **13**, and **15**) and -neutral (**5**, **9**, **10**, **12**, **14**, **16**, and **18**) arylboronic acids showed excellent reactivity, providing desired products in high yields. Electron-deficient *p*-fluorophenylboronic acid (**8**) performed poorly under the standard conditions, but the outcome was improved by increasing its amounts (**8**). The reason may be that electron-deficient boronic acids are less nucleophilic and undergo a slower transmetallation as compared to electron-rich and -neutral ones. This coupling reaction is also very sensitive to the steric effects of arylboronic acids: 1-naphthyl boronic acid gave a lower yield (**6**, **17**, and **20**); the *ortho*-substituted substrate completely retarded the reaction (**7**). With respect to diarylmethyl pivalates, at least one aryl should belong to fused aromatic rings such as naphthyl group,[13] or else the reaction does not occur (comparing **25** and **26** with other cases in Table 2). For the second aryl group, the limitation is relatively less: whether electron-neutral (**2–5**), -rich (**9**, **11**, and **12**), or -poor (**10** and **13**) ones can offer good yields of the desired products, with the exception of heteroaryls (**23** and **24**). Dinaphthyl-substituted substrates appeared more favorable for the reaction (**14–20**), since even sterically congested coupling reactions (**17**, **19**, and **20**) proceeded smoothly under the slightly modified conditions.

Table 2 Ni-catalyzed cross-coupling of diarylmethyl pivalates with arylboronic acids[a]



2 86% **3** 83% **4** 79% **5** 82%

6 45% **7** 0% **8** 23% (83%)[b] **9** 80%

10 76% **11** 85% **12** 90% **13** 82%

14 78% **15** 85% **16** 85% **17** 38% (83%)[c]

18 71% **19** 17% (67%)[c] **20** 11% (72%)[c] **21** trace

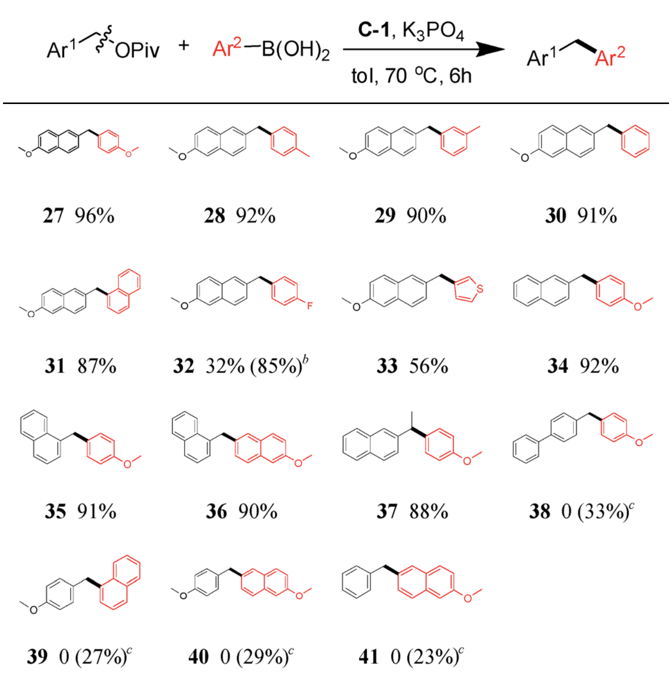
22 0 **23** 0 **24** 0 **25** 0

26 0

[a] Conditions: diarylmethyl pivalate (1.0 mmol), arylboronic acid (1.5 mmol), **C-1** (0.05 mmol), K_3PO_4 (2.5 mmol), toluene (5.0 mL), 70 °C, 6 h, N_2. [b] 2.5 mmol of *p*-fluorophenyl boronic acid, 4.0 mmol of K_3PO_4, 70 °C. [c] 2.5 mmol of arylboronic acid, 4.0 mmol of K_3PO_4, 120 °C.

To our delight, the optimized conditions can be extended with no difficulty to the Suzuki–Miyaura cross-coupling of primary benzylic pivalates for diarylmethane synthesis (Table 3). A wider array of arylboronic acids, including electron-rich (**27–29**, and **34–37**), -neutral (**30** and **31**), -deficient (**32**) and even heteroaryl (**33**) boronic acid, can be utilized in the reaction with good to excellent yields. Similarly, only benzylic pivalate containing the naphthyl substructure gave a satisfactory outcome (**27–37**).[13] Benzylic pivalates with no naphthyl group were not coupled under our standard conditions, but a sluggish conversion was achieved upon the use of DPPF as an additional

Table 3 Ni-catalyzed cross-coupling of primary benzylic pivalates with arylboronic acids[a]



27 96%
28 92%
29 90%
30 91%
31 87%
32 32% (85%)[b]
33 56%
34 92%
35 91%
36 90%
37 88%
38 0 (33%)[c]
39 0 (27%)[c]
40 0 (29%)[c]
41 0 (23%)[c]

[a] Conditions: benzylic pivalate (1.0 mmol), arylboronic acid (1.5 mmol), **C-1** (0.05 mmol), K_3PO_4 (2.5 mmol), toluene (5.0 mL), 70 °C, 6 h, N_2. [b] 2.5 mmol of *p*-fluorophenylboronic acid, 4.0 mmol of K_3PO_4, 70 °C. [c] 0.1 mmol of **C-1**, 0.1 mmol of DPPF, 120 °C, 24 h.

ligand in the Ni^{II} catalyst system (**38**–**41**). Notably, a high yield of diarylethane **37** was obtained without β-hydride elimination.

The mechanism of the reaction is believed to be almost the same as that of the well-established nickel-catalyzed Suzuki–Miyaura cross-coupling reaction: that is a typical catalytic cycle of the Ni^0–Ni^{II} shuttle involving sequential oxidative addition of the Ni^0 (*in situ* generated from the $Ni(PPh_3)_2$(1-naphthyl)Cl precursor[12]) into benzylic C–O bond, transmetallation, and reductive elimination.

In summary, we have demonstrated a facile route to tri- and diarylmethanes by a nickel-catalyzed Suzuki–Miyaura cross-coupling reaction of benzylic pivalates. This new protocol is characteristic of no using nickel(0) sources and special ligands in Ni-based catalyst systems. Further work to expand the scope of substrates and elucidate the mechanistic details is currently underway in our lab.

Acknowledgements

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