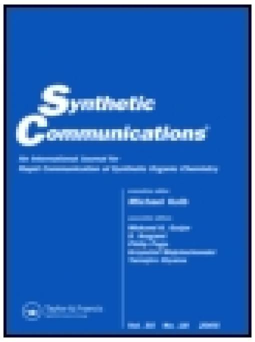

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Yang Liao, Weisen Yang, Ting Wei & Mingzhong Cai (2019): A highly efficient and recyclable $NiCl_2$(dppp)/PEG-400 system for Suzuki-Miyaura reaction of aryl chlorides with arylboronic acids, Synthetic Communications, DOI: 10.1080/00397911.2019.1584318

To link to this article: https://doi.org/10.1080/00397911.2019.1584318

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https://doi.org/10.1080/00397911.2019.1584318

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A highly efficient and recyclable $NiCl_2$(dppp)/PEG-400 system for Suzuki-Miyaura reaction of aryl chlorides with arylboronic acids

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ABSTRACT

$NiCl_2$(dppp) in PEG-400 is shown to be a highly efficient catalyst for Suzuki-Miyaura coupling of aryl chlorides with arylboronic acids. The reaction could be conducted at 100 °C using K_3PO_4 as base, yielding a variety of biaryls in good to excellent yields. The isolation of the products was readily performed by extraction with petroleum ether and $NiCl_2$(dppp)/PEG-400 system could be easily recycled and reused up to five times without significant loss of activity. Our system not only avoids the use of easily volatile and toxic dioxane or toluene as a solvent but also solves the basic problem of nickel catalyst reuse.

ARTICLE HISTORY
Received 9 August 2018
Accepted 11 February 2019

KEYWORDS
Nickel; Suzuki-Miyaura coupling; aryl chloride; PEG-400; green chemistry

GRAPHICAL ABSTRACT

$$\underset{\mathbf{1}}{\text{Ar—Cl}} + \underset{\mathbf{2}}{(HO)_2B\text{—}Ar^1} \xrightarrow[K_3PO_4,\ \text{PEG-400},\ 100\ ^\circ C]{NiCl_2(\text{dppp})\ (2\ \text{mol\%})} \underset{\mathbf{3}}{\text{Ar—}Ar^1}$$

Recyclable catalytic system!

27 examples
up to 95% yield

Introduction

Suzuki-Miyaura coupling is a very important and widely used reaction in organic synthesis because it provides a highly efficient and powerful tool for constructing a biaryl structure, which is found in many biologically active molecules, liquid crystals, and EL materials.[1,2] During the past decades, palladium-based catalysts have been extensively investigated for Suzuki-Miyaura coupling reactions[3] and great success has been achieved with the help of ligand design.[4–6] On the other hand, since the first $NiCl_2$(dppf)-catalyzed Suzuki-Miyaura coupling of aryl sulfonates in the presence of a zinc reductant has been reported by Percec and coworkers,[7] the development of inexpensive nickel-based catalysts has attracted considerable interest and a number of nickel complexes including $NiCl_2(PPh_3)_2$, $NiCl_2(PCy_3)_2$, $Ni(cod)_2$, $NiCl_2$(dppp), and nickel/*N*-heterocyclic carbene (NHC) system have proven to be efficient catalysts in

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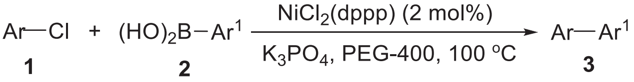


Scheme 1. $NiCl_2$(dppp)-catalyzed Suzuki-Miyaura coupling of aryl chlorides with arylboronic acids in PEG-400.

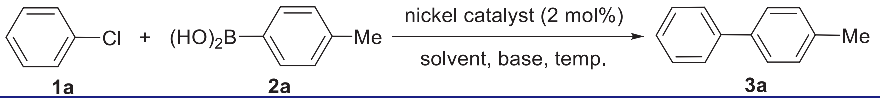
Suzuki-Miyaura reactions.[8] Despite significant progress made in nickel-catalyzed Suzuki-Miyaura reactions, a limited substrate scope or a high loading of the nickel catalyst (typically 3–10 mol%) and need for the extra addition of a large excess of supporting ligands (1–5 equiv.) have restricted their wide applications. Moreover, the reactions usually proceed in easily volatile and toxic organic solvents such as dioxane, THF, and toluene in the presence of homogeneous nickel catalysts, which makes the recovery of the catalytic system tedious if not impossible and might give rise to unacceptable metal contamination of the desired product. These problems are of particular environmental and economic concerns in large-scale syntheses and in industry. Therefore, from the standpoint of green and sustainable chemistry, development of a recyclable and reusable nickel catalyst system that allows for highly efficient Suzuki-Miyaura coupling of a wide range of aryl halides with arylboronic acids in a green solvent is highly desirable.

With the development of green organic synthesis, to avoid the use of any easily volatile and toxic organic solvent is becoming more and more important. In order to satisfy both catalyst recycle and environmental concerns, a simple and practical method is to immobilize the catalyst in a liquid phase by dissolving it into a nonvolatile and nonmixing liquid, such as room temperature ionic liquids[9] and poly(ethylene glycols) (PEGs).[10] However, ionic liquids have some disadvantages, such as a complicated preparative procedure as well as their environmental safety, which is still being debated since the toxicity and environmental burden data are unknown for the most of ionic liquids. PEGs are commercially readily available and cheap, thermally stable, recoverable, biodegradable, and nontoxic hydrophilic polymers, which serve as efficient media for environmentally friendly and safe chemical reactions. In recent years, PEGs have been successfully used as reaction media for the palladium-catalyzed carbon–carbon bond formation reactions with facile recyclability of the solvents and palladium catalysts.[11] In addition, some organic reactions catalyzed by other metals including ruthenium,[12] platinum,[13] nickel,[14] and copper[15] in PEGs have also been reported. Recently, Cho and Tran reported the Suzuki-Miyaura coupling of aryl iodides and bromides with arylboronic acids in PEG-400 using 5 mol% nickel(0) powder as catalyst, but the reaction was not compatible with the less reactive aryl chlorides and no recycling of the catalytic system was mentioned.[14a] Aryl chlorides are more appearing as substrates compared with the analogous aryl bromides and iodides due to the lower cost and the ready availability. However, the low reactivity of aryl chlorides makes their coupling reactions more challenging. In continuing our efforts to develop green synthetic pathways for organic transformations,[11h,12b,13b,14c] herein, we report the application of $NiCl_2$(dppp)/PEG-400 system as an extremely efficient and recyclable catalytic medium for the Suzuki-Miyaura coupling of aryl chlorides with arylboronic acids (Scheme 1).

Results and discussion

In our initial screening experiments, the Suzuki-Miyaura coupling of unactivated chloro benzene (**1a**) with 4-methylphenylboronic acid (**2a**) was selected as model reaction to optimize the reaction conditions. The influences of nickel catalyst, solvent, base and reaction temperature on the reaction were investigated and the results are summarized in Table 1. At first, the nickel catalyst effect was examined in PEG-400 with K_3PO_4 as base, and a significant nickel catalyst effect was observed (Table 1, entries 1–5). When $NiCl_2(PPh_3)_2$ and $NiCl_2$(dppe) were used as catalysts, the desired product **3a** was obtained in low yields (entries 1 and 2), whereas $NiCl_2$(dppf), $NiCl_2$(dppp), and $NiCl_2$(dppb) afforded good to excellent yields and $NiCl_2$(dppp) was the best choice (entries 3–5). Among the bases examined, K_2CO_3 also gave a good yield, but both Cs_2CO_3 and Na_2CO_3 were less effective and NaOAc was ineffective (entries 6–9), so K_3PO_4 was the most efficient base (entry 4). We next examined the effect of reaction temperature on the model reaction. Raising temperature to 110 °C did not improve the yield (entry 10), whilst reducing temperature to 90 °C resulted in a decreased yield and required a longer reaction time (entry 11). Besides, the efficiency of various chain length PEGs on the model reaction was also examined under the same reaction conditions (entries 4, 12, and 13). PEG-400 was found to be superior to PEG-600 and PEG-1000. Finally, the amount of $NiCl_2$(dppp) was also screened (entries 14 and 15). Lower yield was observed and a longer reaction time was required when the amount of the nickel catalyst was reduced to 1.0 mol%. Increasing the amount of $NiCl_2$(dppp) could shorten the reaction time but had no significant improvement in the yield of **3a**. Thus, the

Table 1. Reaction condition screening for the Suzuki-Miyaura coupling of unactivated chlorobenzene with 4-methylphenylboronic acid.[a]



Entry	Ni source	Solvent	Base	Temp (°C)	Yield (%)[b]
1	$NiCl_2(PPh_3)_2$	PEG-400	K_3PO_4	100	34
2	$NiCl_2$(dppe)	PEG-400	K_3PO_4	100	56
3	$NiCl_2$(dppf)	PEG-400	K_3PO_4	100	85
4	$NiCl_2$(dppp)	PEG-400	K_3PO_4	100	92
5	$NiCl_2$(dppb)	PEG-400	K_3PO_4	100	75
6	$NiCl_2$(dppp)	PEG-400	K_2CO_3	100	79
7	$NiCl_2$(dppp)	PEG-400	Cs_2CO_3	100	47
8	$NiCl_2$(dppp)	PEG-400	Na_2CO_3	100	31
9	$NiCl_2$(dppp)	PEG-400	NaOAc	100	0
10	$NiCl_2$(dppp)	PEG-400	K_3PO_4	110	91
11[c]	$NiCl_2$(dppp)	PEG-400	K_3PO_4	90	74
12	$NiCl_2$(dppp)	PEG-600	K_3PO_4	100	86
13	$NiCl_2$(dppp)	PEG-1000	K_3PO_4	100	78
14[d]	$NiCl_2(PPh_3)_2$	PEG-400	K_3PO_4	100	84
15[e]	$NiCl_2(PPh_3)_2$	PEG-400	K_3PO_4	100	93

[a] Reaction conditions: chlorobenzene (0.5 mmol), 4-methylphenylboronic acid (1.0 mmol), nickel catalyst (2 mol%), base (2.0 mmol), solvent (3.0 mL) under Ar for 12 h.

[b] Isolated yield.

[c] For 24 h.

[d] 1.0 mol% $NiCl_2$(dppp) was used for 24 h.

[e] 4 mol% $NiCl_2$(dppp) was used for 8 h.

Table 2. $NiCl_2$(dppp)-catalyzed Suzuki-Miyaura coupling of aryl chlorides with arylboronic acids in PEG-400.[a]

$$\underset{\mathbf{1}}{\text{Ar—Cl}} + \underset{\mathbf{2}}{(HO)_2B\text{—}Ar^1} \xrightarrow[K_3PO_4\text{, PEG-400, 100 °C}]{NiCl_2\text{(dppp) (2 mol\%)}} \underset{\mathbf{3}}{Ar\text{—}Ar^1}$$

Entry	Ar	Ar^1	Time (h)	Product	Yield (%)[b]
1	Ph (**1a**)	4-MeC_6H_4 (**2a**)	12	**3a**	92
2	Ph (**1a**)	4-$MeOC_6H_4$ (**2b**)	10	**3b**	95
3	Ph (**1a**)	Ph (**2c**)	12	**3c**	90
4	Ph (**1a**)	4-ClC_6H_4 (**2d**)	12	**3d**	89
5	Ph (**1a**)	4-$MeCOC_6H_4$ (**2e**)	18	**3e**	86
6	Ph (**1a**)	4-$MeOCOC_6H_4$ (**2f**)	18	**3f**	87
7	Ph (**1a**)	2-MeC_6H_4 (**2g**)	20	**3g**	81
8	4-$MeCOC_6H_4$ (**1b**)	4-$MeOC_6H_4$ (**2b**)	8	**3h**	90
9	4-$MeOCOC_6H_4$ (**1c**)	4-ClC_6H_4 (**2d**)	12	**3i**	91
10	4-NCC_6H_4 (**1d**)	4-ClC_6H_4 (**2d**)	12	**3j**	92
11	4-$OHCC_6H_4$ (**1e**)	Ph (**2c**)	10	**3k**	87
12	2-NCC_6H_4 (**1f**)	4-$MeOC_6H_4$ (**2b**)	10	**3l**	93
13	2-$OHCC_6H_4$ (**1g**)	4-$MeOC_6H_4$ (**2b**)	10	**3m**	85
14[c]	4-MeC_6H_4 (**1h**)	4-$MeOC_6H_4$ (**2b**)	18	**3n**	79
15[c]	4-$MeOC_6H_4$ (**1i**)	4-MeC_6H_4 (**2a**)	24	**3n**	71
16[c]	3-$Me_2NC_6H_4$ (**1j**)	4-$MeOC_6H_4$ (**2b**)	24	**3o**	69
17	1-naphthyl (**1k**)	4-$MeOC_6H_4$ (**2b**)	16	**3p**	94
18	1-naphthyl (**1k**)	4-MeC_6H_4 (**2a**)	16	**3q**	92
19	1-naphthyl (**1k**)	4-ClC_6H_4 (**2d**)	18	**3r**	86
20	1-naphthyl (**1k**)	4-$MeOCOC_6H_4$ (**2f**)	20	**3s**	87
21	1-naphthyl (**1k**)	Ph (**2c**)	16	**3t**	91
22	2-pyridyl (**1l**)	4-MeC_6H_4 (**2a**)	14	**3u**	82
23	3-pyridyl (**1m**)	4-$MeOC_6H_4$ (**2b**)	12	**3v**	95
24	4-pyridyl (**1n**)	4-$MeOC_6H_4$ (**2b**)	12	**3w**	92
25	2-thienyl (**1o**)	Ph (**2c**)	16	**3x**	86
26	2-thienyl (**1o**)	4-MeC_6H_4 (**2a**)	14	**3y**	88
27	2-thienyl (**1o**)	4-ClC_6H_4 (**2d**)	18	**3z**	81

[a] Reaction conditions: aryl chloride (0.5 mmol), arylboronic acid (1.0 mmol), $NiCl_2$(dppp) (2 mol%), K_3PO_4 (2.0 mmol), PEG-400 (3.0 mL) at 100 °C under Ar.

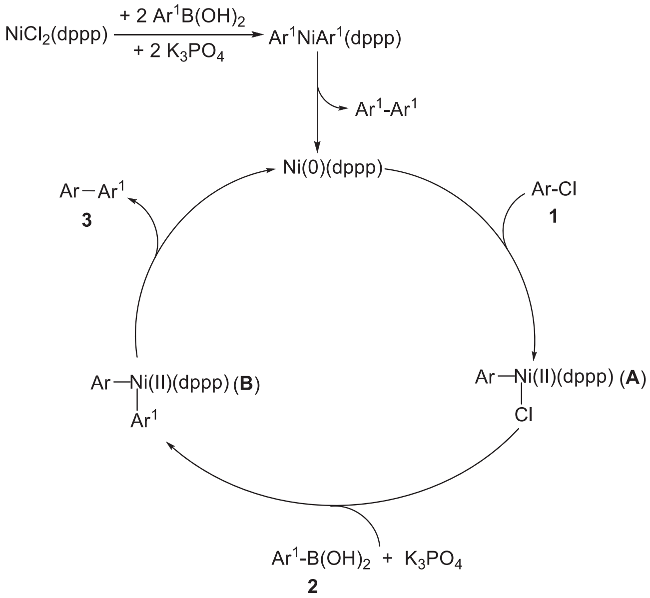
[b] Isolated yield.

[c] Reaction was run at 110 °C.

optimal catalytic system involved the use of $NiCl_2$(dppp) (2 mol%), K_3PO_4 (4.0 equiv.) as base in PEG-400 at 100 °C under Ar for 12 h (Table 1, entry 4).

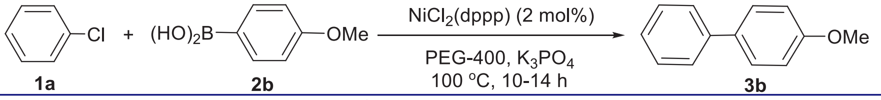
Having obtained satisfactory results in the Suzuki-Miyaura coupling of chlorobenzene with 4-methylphenylboronic acid, then, a variety of aryl chlorides and arylboronic acids were examined to explore the scope of substrates under the optimized reaction conditions and the results are listed in Table 2. As shown in Table 2, the Suzuki-Miyaura coupling reactions of a variety of electron-neutral, electron-rich and electron-deficient arylboronic acids **2a–2f** with unactivated chlorobenzene **1a** proceeded smoothly to afford the corresponding biaryls **3a–3f** in good to excellent yields under the standard reaction conditions (Table 2, entries 1–6). The reaction of sterically hindered 2-methylphenylboronic acid **2g** with **1a** also gave the desired product **3g** in 81% yield (entry 7). The reaction was also tolerant of various activated aryl chlorides having a range of functional groups such as ketone, ester, cyano and aldehyde. For example, the reactions of *para*-substituted electron-deficient aryl chlorides such as 1-(4-chlorophenyl)ethanone **1b**, methyl 4-chlorobenzoate **1c**, 4-chlorobenzonitrile **1d** and 4-chlorobenzaldehyde **1e** with various arylboronic acids afforded the desired coupling products **3h–3k** in 87–92% yields (entries 8–11). It is noteworthy that the aryl chlorides bearing a cyano or aldehyde group at the *ortho*-position **1f** and **1g** proved to be also good coupling partners and furnished the corresponding biaryls **3l** and **3m** in 93% and 85% yield, respectively (entries 12 and 13). These results, together with that observed from the sterically hindered boronic acid **2g** (entry 7), indicate that the coupling reaction exhibits good tolerance of steric hindrance not only on aryl chlorides but also on arylboronic acids. More importantly, the deactivated aryl chlorides **1h–1j** are also viable substrates, affording the desired coupled products in good yields although the reaction required higher temperature (110 °C) and longer reaction times (entries 14–16). In addition, bulky 1-chloronaphthalene **1k** could undergo smooth cross-coupling with various arylboronic acids, furnishing the corresponding biaryls **3p–3t** in 86–94% yields (entries 17–21). Finally, the developed methodology also displays good compatibility to heteroaryl chlorides (entries 22–27). For instance, 2-, 3-, and 4-chloropyridines **1l–1n** were coupled with arylboronic acids effectively to give the desired biaryls **3u–3w** in good to excellent yields (entries 22–24). The reactions of 2-chlorothiophene **1o** with various arylboronic acids produced the expected products **3x–3z** in high yields (entries 25–27). Noteworthy was that a variety of functional groups of both aryl chlorides and arylboronic acids tolerate to this reaction condition, which include methyl, methoxy, amino, ketone, ester, aldehyde, cyano, pyridyl, and thienyl groups.

A possible mechanism for the $NiCl_2$(dppp)-catalyzed Suzuki-Miyaura coupling of aryl chlorides with arylboronic acids in PEG-400 is shown in Scheme 2. First, Ni(0)(dppp) as catalytically active species is formed from the sequence involving arylboronic acid transmetalation and reductive elimination.[16] Indeed, in all cases, 4–5% of the homo-coupled products of arylboronic acids were observed. Subsequent oxidative addition of Ar-Cl (**1**) to Ni(0)(dppp) forms ArNi(II)Cl(dppp) intermediate **A**, which undergoes the transmetalation with Ar^1-$B(OH)_2$ (**2**) by the aid of K_3PO_4 to give ArNi(II)Ar1(dppp)



Scheme 2. Possible mechanism for $NiCl_2$(dppp)-catalyzed Suzuki-Miyaura coupling of aryl chlorides.

Table 3. Recyclability of $NiCl_2(dppp)$/PEG-400 system.[a]



Cycle	Time (h)	Yield (%)[b]	Cycle	Time (h)	Yield (%)[b]
1	10	95	4	10	93
2	10	94	5	12	93
3	10	94	6	14	92

[a] Reaction conditions: chlorobenzene (0.5 mmol), 4-methoxyphenylboronic acid (1.0 mmol), $NiCl_2(dppp)$ (2 mol%), K_3PO_4 (2.0 mmol), PEG-400 (3.0 mL) at 100 °C under Ar.

[b] Isolated yield.

intermediate **B**. Finally, reductive elimination of intermediate **B** affords the desired coupling product **3** and regenerates Ni(0)(dppp) to complete the catalytic cycle.

To examine the recyclability of the solvent as well as the catalytic system, the reaction of chlorobenzene **1a** (0.5 mmol) with 4-methoxyphenylboronic acid **2b** (1.0 mmol) was evaluated in the presence of $NiCl_2(dppp)$ (2 mol%) and K_3PO_4 (4.0 equiv.) in PEG-400 (3.0 mL) at 100 °C under Ar. As shown in Table 3, we were pleased to observe that the $NiCl_2(dppp)$/PEG-400 system could be recycled and reused five times without significant loss of activity. After initial experimentation, the reaction mixture was extracted with petroleum ether three times (3 × 10 mL), and the left $NiCl_2(dppp)$/PEG-400 system was heated to 60 °C in vacuum for 20 min and then subjected to a second run of the reaction by charging with the same substrates (chlorobenzene, 4-methoxyphenylboronic acid, and K_3PO_4) without addition of $NiCl_2(dppp)$. In addition, the leaching of nickel in the product was also determined. ICP analysis of the product showed that nickel content was less than 0.8 ppm.

Conclusions

In conclusion, a highly efficient and reusable $NiCl_2(dppp)$/PEG-400 system for the Suzuki-Miyaura coupling reaction of aryl chlorides with arylboronic acids has been developed. In the presence of 2 mol% $NiCl_2(dppp)$, the cross-coupling reactions of a variety of aryl chlorides with various arylboronic acids proceeded smoothly at 100 °C in PEG-400 with K_3PO_4 as base to afford the corresponding biaryls in good to excellent yields. Furthermore, the $NiCl_2(dppp)$/PEG-400 system could be recycled and reused at least five times without significant loss of catalytic activity. Our system not only avoids the use of easily volatile and toxic organic solvents but also solves the basic problem of the catalyst reuse and this protocol will serve as an efficient and green way to prepare a variety of biaryls.

Experimental

All chemicals and nickel catalysts were reagent grade and used as purchased. All coupling products were characterized by comparison of their spectra and physical data with authentic samples. ^1H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer with TMS as an internal standard in $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer in $CDCl_3$ as solvent. Melting points are uncorrected.

General procedure for the nickel-catalyzed Suzuki-Miyaura coupling reaction of aryl chlorides with arylboronic acids in PEG-400

To a 25 mL Schlenk tube equipped with a magnetic stir bar were added $NiCl_2$(dppp) (0.01 mmol), aryl chloride (0.5 mmol), arylboronic acid (1.0 mmol), K_3PO_4 (2.0 mmol), and PEG-400 (3.0 mL) under Ar. The reaction mixture was stirred at 100–110 °C until the aryl chloride had disappeared as monitored by TLC. After being cooled to room temperature, the resulting mixture was extracted three times with petroleum ether (3 × 10 mL). The residue of the extraction was heated to 60 °C in vacuum for 20 min to remove the residual petroleum ether and then subjected to a second run of the Suzuki-Miyaura reaction by charging with the same substrates (aryl chloride, arylboronic acid, and K_3PO_4) under the same conditions without further addition of $NiCl_2$(dppp). The combined ether phase was concentrated under reduced pressure. The residue was purified using flash column chromatography on silica gel using petroleum ether or a mixture of petroleum ether and EtOAc as eluent to give the desired cross-coupled products.

Full experimental detail, characterization data of all compounds can be found via the "Supplementary Content" section of this article's webpage.

Funding

We thank the National Natural Science Foundation of China [No. 21462021], the Natural Science Foundation of Jiangxi Province of China [No. 20161BAB203086] and Key Laboratory of Functional Small Organic Molecule, Ministry of Education [No. KLFS-KF-201704] for financial support.

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