

Recyclable nickel catalysed Suzuki–Miyaura reaction in the presence of polyethyleneimine under phosphine-free conditions in ethylene glycol[#]

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Abstract. In this report, Suzuki–Miyaura coupling reaction was performed in the presence of polyethyleneimine (PEI) as ligand, NiCl₂·6H₂O and K₂CO₃ in ethylene glycol at 80–100°C under phosphine-free conditions. By this method, structurally different aryl bromides and iodides were reacted with phenylboronic acid and potassium phenyltrifluoroborate. Under these simple reaction conditions a different biaryl derivatives have been prepared in high to excellent yields. Recycling experiments showed that catalyst can be used as recyclable catalyst in the Suzuki–Miyaura cross-coupling reactions.

Keywords. Suzuki–Miyaura; polyethyleneimine; nickel; Phosphine free; recyclable.

1. Introduction

Transition-metal catalysed cross-coupling reactions are powerful tools for the formation of new carbon–carbon bonds. Among the large group of transition metals, palladium complex together with (phosphorous) ligands is the most popular catalytic system.^{1–7} Palladium catalysed coupling of aryl halides with boronic acids known as the Suzuki–Miyaura coupling reaction. This is one of the most versatile and a fast growing methodologies for the selective formation of C–C bond, in particular for production of biaryls. Biaryl moieties are found in a variety of pharmaceuticals, liquid crystals, conductive polymers and natural products. For these purposes, this reaction has become very popular in both academic and industrial laboratories.^{8–12}

However, palladium is an expensive metal; description of commercial processes based on the Pd are less attractive for industrial scales. Therefore, development of palladium-free catalysts for Suzuki–Miyaura coupling reaction are attractive due to both economical and environmental concerns.^{13–25} Also, most of the used phosphorus ligands in these reactions, have drawbacks of difficulty of synthesis, poor thermal and air stability

which are the main reasons for the growing interest in N-coordinating ligands for catalysts in coupling reactions. Indeed, many N-based ligands have been reported to be efficient for the Suzuki cross-coupling reactions.^{26–32}

Recently, different homogeneous and heterogeneous nickel catalysts have been used for Suzuki–Miyaura coupling.^{33–38} Homogeneous catalysis encounters number of drawbacks such as; reuse of the catalyst, loss of expensive metals and ligands. In addition, contamination of the products by the metal residues, even after purification step, is a sharp problem for large-scale operation in pharmaceutical industries.^{39–51}

Polyethyleneimine has been widely used for preparation of polymer supported phase-transfer catalysts. Its physicochemical incompatibility with solvents and substrates most often leads to high efficiency and reactivity. Recently we have designed a synthetic polar polymeric supports such as polyvinylpyridine and polyethyleneimine. These polymers have been used as co-solvent type catalysts for nucleophilic displacement reactions under biphasic and triphasic conditions. Also, we used from these polymers as a support for the solid phase synthesis of several organic compounds, metal complex and for the preparation of a number of polymer supported reagents. These supported systems were found to have different characteristics in terms of polarity, salvations and reactivity compared to the commonly used monomeric form.^{52–56}

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[#]This paper is dedicated to Professor Habib Firouzabadi on the occasion of his 68th birthday

2. Experimental

2.1 General remarks

NMR spectra were recorded on a Bruker Avance DPX-250. The purity of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV254 plates or GC analysis using a 3-meter length column packed with DC-200 stationary phase.

2.2 General experimental procedure for the Suzuki–Miyaura reaction

In 5 mL flask containing ethylene glycol (2 mL), was added polyethyleneimine (300 mg) and stirred until solving in 80 or 100°C. To the resulting solution were added NiCl₂·6H₂O (1 mol%) aryl halide (1 mmol), phenylboronic acid or Potassium phenyltrifluoroborate (1.5 mmol) and K₂CO₃ (1.5 mmol). The progress of the reaction was monitored by TLC or GC analyses. After completion of the reaction, the reaction mixture was allowed to cool down to room temperature and extracted with ethyl acetate or diethyl ether (3 × 2 mL) and the upper organic phase was separated, washed with 3 mL water, dried over anhydrous MgSO₄ and evaporated. Further purification was performed by column chromatography (EtOAc/*n*-hexane) to obtain the desired coupling product.^{57–59}

2.3 Recycling of the catalyst

After completion of the reaction of iodobenzene (1 mmol) with phenylboronic acid (1.5 mmol), the reaction mixture was cooled down to room temperature and washed with diethyl ether (3 × 2 mL) to extract product and unreacted material. Then residue containing of polymer and NiCl₂·6H₂O was reused for the similar reaction.

2.4 Characterization data of compounds

1a⁶⁰: ¹H NMR (250 MHz, CDCl₃)δ (ppm): 7.33–7.64 (m, 10 H).

1b⁶⁰: ¹H NMR (250 MHz, CDCl₃)δ (ppm): 7.51–7.57 (m, 4H), 7.41 (t, 1H, *J* = 7.2), 7.28 (t, 1H, *J* = 7.2), 6.98 (d, 2H, *J* = 7.5), 3.85 (s, 3H); ¹³C NMR (62.9 MHz, CDCl₃)δ (ppm): 159.2, 140.9, 133.8, 128.8, 128.4, 128.2, 127.1, 114.3, 55.3.

1c⁶⁰: ¹H NMR (250 MHz, CDCl₃)δ (ppm): 8.19 (d, 2H, *J* = 9.0), 7.63 (d, 2H, *J* = 9.0), 7.53 (dd, 2 H, *J* = 7.5,

1.5), 7.36–7.43 (m, 3H); ¹³C NMR (62.9 MHz, CDCl₃)δ (ppm): 147.6, 147.0, 138.7, 129.1, 128.9, 127.7, 127.3, 124.1.

1d⁶⁰: ¹H NMR (250 MHz, CDCl₃)δ (ppm): 7.73 (m, 2H), 7.39–7.59 (m, 7H), 2.43 (s, 3H); ¹³C NMR (62.9 MHz, CDCl₃)δ (ppm): 142.0, 141.3, 135, 130.4, 129.9, 129.3, 128.9, 128.2, 127.6, 126.4, 125.9, 20.6.

1e⁶¹: ¹H NMR (250 MHz, CDCl₃)δ (ppm): 7.53–7.49 (m, 2H), 7.26–7.14 (m, 5H), 6.96–6.86 (m, 1H).

1f⁶⁰: ¹H NMR (250 MHz, CDCl₃)δ (ppm): 8.07–7.95 (m, 3H), 7.61–7.53 (m, 9H); ¹³C NMR (62.9 MHz, CDCl₃)δ (ppm): 140.9, 140.4, 133.9, 131.7 129.8, 128.8, 128.4, 127.4, 127.3, 127.0, 126.7, 126.1, 125.9, 125.5.

1g⁶⁰: ¹H NMR (250 MHz, CDCl₃)δ (ppm): 7.73 (m, 2H), 7.59–7.39 (m, 7H), 2.43 (s, 3H).

1h: ¹H NMR (250 MHz, CDCl₃)δ (ppm): 7.50–7.18 (m, 7H), 6.85–6.81(m, 2H), 4.61 (s, 1H).

1i⁶²: ¹H NMR (250 MHz, CDCl₃)δ (ppm): 8.85 (s, 1 H), 8.57 (s, 1H), 7.84 (d, 1 H, *J* = 8.0), 7.33–7.57 (m, 6 H); ¹³C NMR (62.9 MHz, CDCl₃)δ (ppm): 148.3, 148.1, 137.7, 136.7, 134.4, 129.0, 128.1, 127.1, 123.6.

1j⁶²: ¹H NMR (250 MHz, CDCl₃)δ (ppm): 7.45–7.75 (m, 9 H); ¹³C NMR (62.9 MHz, CDCl₃)δ (ppm): 141.8, 136.2, 132.4, 128.6, 126.9, 119.0, 110.5.

1k⁶⁰: ¹H NMR (250 MHz, CDCl₃)δ (ppm): 7.29–7.50 (m, 9 H); ¹³C NMR (62.9 MHz, CDCl₃)δ (ppm): 139.1, 138.4, 133.7, 129.0, 128.7, 128.3, 127.5, 126.9.

3. Results and discussion

Polyethyleneimine has been produced on the industrial scale since 1938 which is obtained mainly by the polymerization of aziridine⁶³ (figure 1).

In this article, we report using of polyethyleneimine (PEI) as ligand in the presence of NiCl₂·6H₂O for the successful recyclable Suzuki–Miyaura coupling reaction in ethylene glycol under phosphine-free and mild reaction conditions. Polyethyleneimine is stable, cheap, non-toxic polymer, and its handling in the presence of NiCl₂·6H₂O for Suzuki coupling does not need special precautions and inert atmosphere.

Optimized reaction conditions were achieved by the reaction of 4-iodoanisole (1 mmol) as a model compound with phenylboronic acid (1.5 mmol) in the presence of NiCl₂·6H₂O (1 mol%), polyethyleneimine

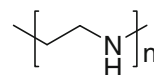
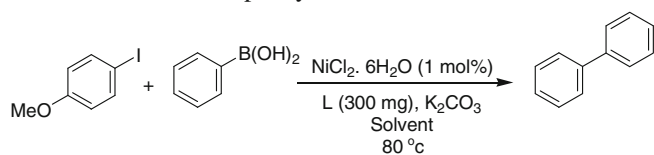


Figure 1. Polyethyleneimine.

Table 1. Screening of different solvents upon the reaction of 4-iodoanisole with phenylboronic acid.

Entry	Solvent	Isolated yield%
1	DMF	55
2	Dioxane	10
3	Toluene	trace
4	EG	91
5	NMP	62
6	Water	25

(PEI) (300 mg) and K_2CO_3 (1.5 mmol) in ethylene glycol. In order to show the effect of solvents upon the reaction, model reaction was studied in the presence of different solvents such as Toluene, DMF, THF, NMP and water (table 1).

Therefore, the subsequent reactions were performed in EG which possesses negligible vapor pressure, thermally stable, not expensive, and in comparison with many other organic solvents shows low toxicity. Recently, such similar effect of PEG has been reported for the Suzuki coupling reaction catalysed by nickel, copper and palladium catalysts.^{64–66}

In order to show the effect of polyethyleneimine (PEI) in this reaction, we performed the reaction of 4-iodoanisole with phenylboronic acid in the presence of $NiCl_2 \cdot 6H_2O$ and K_2CO_3 in ethylene glycol in the absence of polyethyleneimine at 80°C. The results of this study showed that in the absence of the polyethyleneimine the reaction was sluggish and only 53% GC yield was obtained. Also, important role of polyethyleneimine was studied by UV-Vis spectra which shows conversion of Ni(II) to Ni(0) in the presence of polyethyleneimine by the disappearance

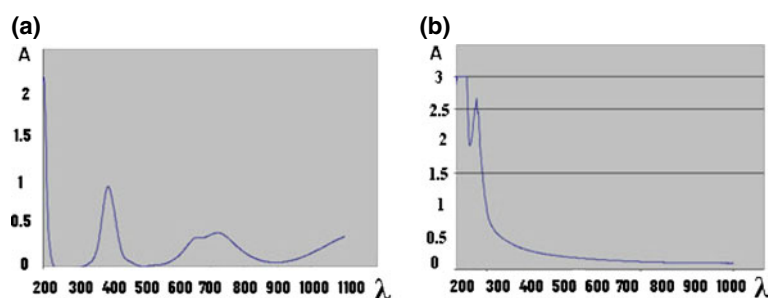
Table 2. Reactions of aryl iodides and bromides with phenylboronic acid and potassium phenyltrifluoroborate in the presence of $NiCl_2 \cdot 6H_2O$ and Polyethyleneimine (PEI) at 80–100°C.

Entry	ArX	R	T (°C)	Time (h)	Product	Isolated yield%
1		$B(OH)_2$	80	2	1a	91
2		$B(OH)_2$	80	12	1b	90
3		$B(OH)_2$	80	1	1c	93
4		$B(OH)_2$	80	10	1d	85
5		$B(OH)_2$	80	4	1e	83
6		$B(OH)_2$	80	9	1f	84
7		$B(OH)_2$	80	10	1g	82
8		$B(OH)_2$	80	10	1h	89
9		$B(OH)_2$	100	14	1a	84
10		$B(OH)_2$	100	17	1d	80
11		$B(OH)_2$	100	12	1i	75
12		$B(OH)_2$	100	9	1j	88
13		$B(OH)_2$	100	7	1c	90
14		$B(OH)_2$	100	14	1k	80
15		$B(OH)_2$	100	48	1d	trace
16		BF_3K	80	2.2	1a	90
17		BF_3K	80	13	1b	86
18		BF_3K	80	10	1c	86
19		BF_3K	100	16	1a	76
20		BF_3K	100	12	1i	78
21		BF_3K	100	10	1j	81

of the peaks related to Ni(II) at 400 and 700 nm⁶⁷ (figure 2).

We applied the optimized reaction conditions for the Suzuki–Miyaura coupling of structurally different aryl iodides and bromides with phenylboronic acid and potassium phenyltrifluoroborate at 80 or 100°C (table 2).

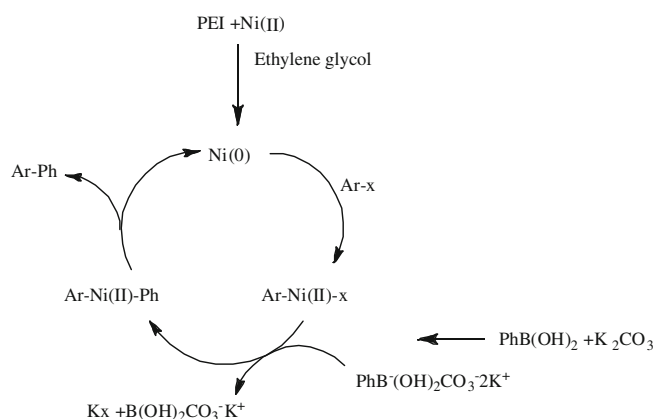
As it is evident from the results tabulated in table 2 (entries 1–9), different aryl iodides were reacted with phenylboronic acid at 80°C in appropriate reaction times. The desired biphenyl compounds were isolated in 82–93% yields. We also studied the applicability

**Figure 2.** (a) UV-Vis of $NiCl_2 \cdot 6H_2O$, (b) UV-Vis of $NiCl_2 \cdot 6H_2O$ in the presence of PEI.

of this catalyst for the reaction of aryl bromides with phenylboronic acid at 100°C, the reactions proceeded well and desired products obtained in 75–90% isolated yields. We also studied the applicability of method for the reaction of aryl chlorides with phenylboronic acid; for this purpose, reaction of 4-chlorotoluene with phenylboronic acid at 100°C was studied. The results of study showed that the reaction did not proceed and starting material was isolated intact after appropriate reaction time.

Potassium organotrifluoroborates are another substitute for boronic acids in the Suzuki–Miyaura coupling reactions. In recent years, there has been increased interest in the use of potassium organotrifluoroborates as coupling partners for this reaction.⁶⁸ In order to show the application of our method, we studied the coupling of iodobenzene, 4-iodoanisole, 4-iodotoluene, bromobenzene, 3-bromopyridine and 4-bromobenzonitrile with potassium phenyltrifluoroborate under the optimized reaction conditions. The reactions proceeded successfully and afforded the corresponding cross-coupled products in high to excellent yields (78–90%) (table 2, entries 16–21). A proposed mechanism for C–C bond formation *via* Suzuki–Miyaura reaction polyethyleneimine (PEI) and NiCl₂·6H₂O in the presence of a base is presented in scheme 1.

Recycling of the reaction was also studied. For this propose, after completion of the reaction of iodobenzene with phenylboronic acid, reaction mixture was allowed to cool down to room temperature, washed with diethyl ether and residue that contain nickel and polyethyleneimine, was reused for another reaction at the same reaction conditions. This recycling was



Scheme 1. Proposed mechanism for nickel catalysed Suzuki–Miyaura coupling reaction in the presence of polyethyleneimine (PEI).

Table 3. Recycling of the catalyst for the reaction of iodobenzene with phenylboronic acid.

Run	Time (min)	Isolated yields%
1	4	91
2	4	90
3	4	88
4	4	86

repeated for four times without significant loss of yield (table 3). This result supports that the nickel leaching should occur in low quantity. ICP analysis of nickel content of diethyl ether after first recycling run showed 1.02 ppm of nickel amount in the ether phase.

4. Conclusions

In this article, we have successfully used from NiCl₂·6H₂O in the presence of polyethyleneimine in ethylene glycol as an efficient media for phosphine-free Suzuki–Miyaura coupling of different aryl iodides and bromides with phenylboronic acid and Potassium phenyltrifluoroborate at 80 and 100°C. The catalyst can be applied for large-scale operation and is also recyclable. The recycling was repeated for four times without considerable loss of its catalytic activity.

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References

1. Negishi E and de Meijere A 2002 *Handbook of organopalladium chemistry for organic synthesis* (New York: Wiley-Interscience)
2. Miyaura N 2000 *Cross-coupling reactions. A practical guide* (Berlin: Springer-Verlag)
3. Beller M and Bolm C 2004 *Transition metals for organic synthesis, building block and fine chemicals*, 2nd Ed., (Weinheim: Wiley-VCH)
4. Alonso D A and Najera C 2010 *Chem. Soc. Rev.* **39** 2891
5. Zapf A and Beller M 2002 *Top. Catal.* **19** 101
6. Tucker C E and de Vries J G. 2002 *Top. Catal.* **19** 111
7. Brase S, Kirchhoff J H and Kobberling J 2003 *Tetrahedron* **59** 885
8. Miyaura N, Yamada K and Suzuki A 1979 *Tetrahedron Lett.* **20** 3437

9. Miyaura N and Suzuki A 1979 *J. Chem. Soc. Chem. Commun.* **866**
10. Miyaura N and Suzuki A 1995 *Chem. Rev.* **95** 2457
11. Nicolaou K C, Bulger P G and Sarlah D 2005 *Angew. Chem. Int. Ed.* **44** 4442
12. Kotha S, Lahiri K and Kashinath D 2002 *Tetrahedron* **58** 9633
13. Xu L, Li B-J, Wu Z-H, Lu X-Y, Guan B-T, Zhao K-Q and Shi Z-J 2010 *Org. Lett.* **12** 884
14. Cho C S and Tran N T 2009 *Catal. Commun.* **11** 191
15. Kuroda J-I, Inamoto K, Hiroya K and Doi T 2009 *Eur. J. Org. Chem.* **14** 2251
16. Chen C and Yang L-M 2007 *Tetrahedron Lett.* **48** 2427
17. You E, Li P and Wang L 2006 *Synthesis* **9** 1465
18. González-Bobes F and Fu G C 2005 *J. Am. Chem. Soc.* **128** 5360
19. Borhade S R and Waghmode S B 2010 *Indian J. Chem. B* **49** 565
20. Gracias V and Iyengar R 2005 *Chemtracts* **18** 339–348
21. Tang Z Y and Hu Q S 2004 *Adv. Synth. Catal.* **346** 1635
22. Tang Z Y, Spinella S and Hu Q S 2006 *Tetrahedron Lett.* **47** 2427
23. Lipshutz B H, Sclafani J A and Blomgren P A 2000 *Tetrahedron* **56** 2139
24. Leadbeater N E and Resouly S M 1999 *Tetrahedron* **55** 11889
25. Indolese A F 1997 *Tetrahedron Lett.* **38** 3513
26. Grasa G A, Viciu M S, Huang J, Zhang C, Trudell M L and Nolan S P 2002 *Organometallics* **21** 2866
27. Chahen L, Therrien B and Süß-Fink G 2007 *Eur. J. Inorg. Chem.* **5045**
28. Alonso, D A, Najera C and Pacheco M C 2000 *Org. Lett.* **2** 1823
29. Chahen L, Therrien B and Süß-Fink G 2006 *J. Organomet. Chem.* **691** 4257
30. Tao B and Boykin D W 2002 *Tetrahedron Lett.* **43** 4955
31. Tao B and Boykin D W 2004 *J. Org. Chem.* **69** 4330
32. Tao B and Boykin D W 2003 *Tetrahedron Lett.* **44** 7993
33. Reetz M T, Breinbauer R and Wanninger K 1996 *Tetrahedron Lett.* **37** 4499
34. Galland J P, Savignac M and Genêt J P 1999 *Tetrahedron Lett.* **40** 2323
35. Zim D, Lando, V R, Dupont J and Monteiro A L 2001 *Org. Lett.* **3** 3049
36. Guo Y, Young D and Hor T S A 2008 *Tetrahedron Lett.* **49** 5620
37. Zim D and Monteiro A L 2002 *Tetrahedron Lett.* **43** 4009
38. Ramarao C, Ley S V, Smith S C, Shirley, I M and De Almeida N 2002 *Chem. Commun.* **1132**
39. Ley S V, Ramarao C, Gordon R S, Holmes A B, Morrison A J, McConvey I F, Shirley I M, Smith, S C, Smith M D 2002 *Chem. Commun.* **1134**
40. Trzeciak A M, Mieczynska E, Ziolkowski W, Bukowska A, Noworol J and Okal J 2008 *New J. Chem.* **32** 1124
41. Akiyama R and Kobayashi S 2003 *J. Am. Chem. Soc.* **125** 3412
42. Okamoto K, Akiyama R and Kobayashi S 2004 *Org. Lett.* **6** 1987
43. Nishio R, Sugiura M and Kobayashi S 2005 *Org. Lett.* **7** 4831
44. Hagio H, Sugiura M and Kobayashi S 2006 *Org. Lett.* **8** 375
45. Akiyama R and Kobayashi S 2009 *Chem. Rev.* **109** 594
46. Kim J-H, Kim J-W, Shokouhimehr M and Lee Y-S 2005 *J. Org. Chem.* **70** 6714
47. Byun J-W and Lee Y-S 2004 *Tetrahedron Lett.* **45** 1837
48. Shokouhimehr M, Kim J-H and Lee Y-S 2006 *Synlett.* **4** 618
49. Schweizer S, Becht J M and Drian C L 2010 *Tetrahedron* **66** 765
50. Schweizer S, Becht J M and Drian C L 2007 *Org. Lett.* **93** 777
51. Schweizer S, Becht J M and Drian C L 2007 *Adv. Synth. Catal.* **349** 1150
52. Goudarzian N and Hosini S 1996 *Poly. Int.* **39** 61
53. Firouzabadi H, Tamami B, Goudarzian N 1991 *Synth. Commun.* **21** 2275
54. Firouzabadi H, Tamami B, Goudarzian N, Hatam M and Mansour M L 1991 *Synth. Commun.* **21** 2077
55. Tamami B and Goudarzian N 1992 *Eur. Polym. J.* **28** 1035
56. Tamami B and Goudarzian N 1994 *J. Chem. Soc. Chem. Commun.* **1079**
57. Zhou W-J, Wang, K-H, and Wang J-X 2009 *Adv. Synth. Catal.* **351** 1378
58. Firouzabadi H, Iranpoor N and Gholinejad M 2010 *Adv. Synth. Catal.* **352** 119
59. Firouzabadi H, Iranpoor N, Gholinejad M and Hoseini J 2011 *Adv. Synth. Catal.* **353** 125
60. Shi S and Zhang Y 2007 *J. Org. Chem.* **72** 5927
61. Firouzabadi H, Iranpoor N and Gholinejad M 2010 *J. Organomet. Chem.* **695** 2093
62. Feuerstein M, Doucet M and Santelli M 2003 *J. Organomet. Chem.* **687** 327
63. Zhuk D S, Gembitskii P A and Kargin V A 1965 *Russ. Chem. Rev.* **34** 515
64. Cho C S and Tran N T 2009 *Catal. Commun.* **11** 191–195
65. Mao J, Guo J, Fang F and Ji S J 2008 *Tetrahedron* **64** 3905
66. Yin L, Zhang Z-h and Wang Y-m 2006 *Tetrahedron* **62** 9359
67. Kryatov S V, Mohanraj B S, Tarasov V V, Kryatova O P, Rybak-Akimova E V, Nuthakki B, Rusling J F, Staples R J, Nazarenko A Y 2002 *Inorg. Chem.* **41** 923
68. Molander G A and Canturk B 2009 *Angew. Chem. Int. Ed.* **48** 9240