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A novel N–O ligand for palladium-catalyzed Mizoroki–Heck reaction in neat water

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ABSTRACT

1-(Morpholin-1-yl-pyridin-2-yl-methyl)-2-naphthol as a novel efficient N–O ligand has been developed for palladium-catalyzed Mizoroki–Heck reaction in neat water without the protection of an inert atmosphere. The reactions proceed smoothly and give the desired products in moderate to excellent yields. The catalyst system is reusable.

Palladium-catalyzed Mizoroki–Heck reaction is an important method for the C–C bond formation and has been extensively used for the synthesis of natural products, pharmaceutical intermediates, conducting polymers, and pesticides.[1] The efficiency of the Pd-based catalyst is strongly dependent on the nature of the phosphine ligands due to their superior donor capability and stabilization effects.[2] However, these phosphine ligands are often expensive, toxic, unrecoverable, and sensitive to oxygen and water, and these drawbacks prevented their large-scale application.[3–5] To date, many efforts have been devoted to search for more efficient and inexpensive ligands. Phosphine-free ligands such as N-heterocyclic carbene (NHC) palladium complexes and N-heterocyclic ionic liquid have been employed in the Mizoroki–Heck reaction.[6] Although these catalysts provided excellent results in many respects, unfortunately, they are expensive and some require an inert atmosphere.[7,8]

In addition, as reported in the literature, these reactions are generally carried out in organic solvents.[9–11] Thus, in view of the importance of industrial exploitation, to develop the sustainable method is becoming urgent. The media of water has many merits, such as low cost, safety, and environmentally benign nature, so reactions in aqueous media have attracted more interests of researchers for large scale industrial processes.[12] Nevertheless, only a few examples of Mizoroki–Heck reactions have been reported in aqueous media.[13,14] According to the frame work of green chemistry, we try to find an efficient ligand to promote the Mizoroki–Heck reaction to perform smoothly in water. Betti bases are attractive ligands due to their facile preparation and simple synthetic modification, both electronic and steric, and they have been used to prepare a broad range of organometallic compounds with a wide variety of applications.[15] To the best of our knowledge, the Mizoroki–Heck coupling reaction in water catalyzed by the Betti base catalyst system has not yet been reported.

Herein, we report a novel method using Betti base 1-(morpholin-1-yl-pyridin-2-yl-methyl)-2-naphthol as the ligand for the palladium-catalyzed Mizoroki–Heck reaction in water with good to excellent yields.

1-(Morpholin-1-yl-pyridin-2-yl-methyl)-2-naphthol (L) was achieved by following reaction as shown in Figure 1.[17]

Condensation of morpholine with pyridine-2-aldehyde and 2-naphthol similar to the classical Mannich reaction gives 1-(morpholin-1-yl-pyridin-2-yl-methyl)-2-naphthol (L) in good yield.[16] The ligand has the capability to coordinate with metal centres to form a six-member stable cycle chelate and could coordinate with the metal centre via the pyridyl nitrogen and oxygen

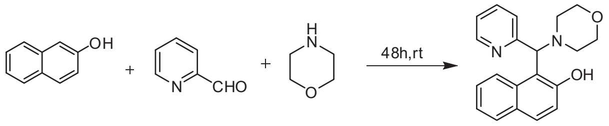

Figure 1.

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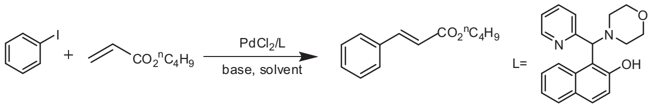


Figure 2.

Table 1
Optimization of the typical reaction conditions[a]

Entry	Base	Solvent	Catalyst/(mol %)	Time (h)	Yield[b] (%)
1	K_2CO_3	DMA	1	12	85
2	K_2CO_3	DMF	1	12	93
3	K_2CO_3	NMP	1	12	54
4	K_2CO_3	DMSO	1	12	38
5	K_2CO_3	H_2O	1	12	95
6	K_2CO_3	H_2O	0.5	12	73
7	K_2CO_3	H_2O	0.8	12	87
8	K_2CO_3	H_2O	1	12	67[c]
9	Et_3N	H_2O	1	12	77
10	KOH	H_2O	1	12	36
11	Hexamine	H_2O	1	12	15
12	K_3PO_4	H_2O	1	12	89
13	K_2CO_3	H_2O	1	8	67
14	K_2CO_3	H_2O	1[d]	12	90
15	K_2CO_3	H_2O	1	14	95
16	K_2CO_3	H_2O	1	12	56[e]
17	–	H_2O	1	12	38[f]

[a] Reaction conditions: iodobenzene (1.0 mmol), *n*-butyl acrylate (1.2 mmol.), L (5 mol %), base (1.0 mmol), solvent (3 mL), 120 °C.
[b] GC yield determined by using methoxybenzene as internal standard.
[c] Reaction temperature is 80 °C.
[d] Pd/C as catalyst.
[e] Without L.
[f] Without K_2CO_3.

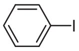
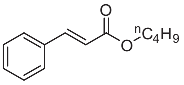
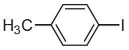
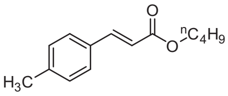
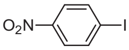
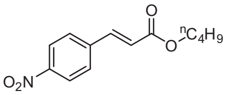
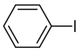
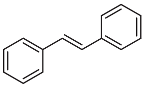
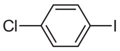
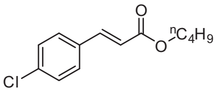
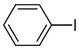
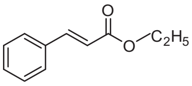
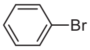
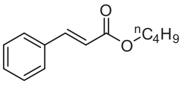
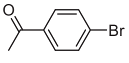
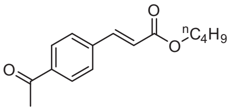
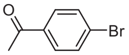
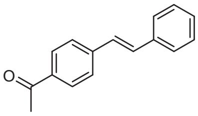
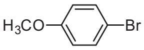
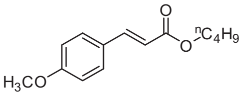
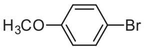
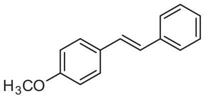
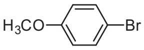
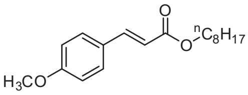
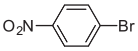
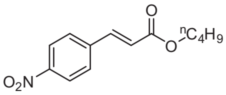
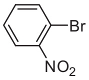
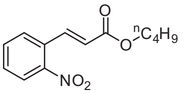
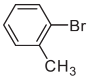
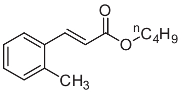
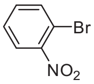
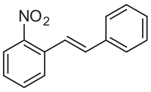
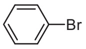
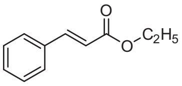
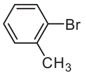
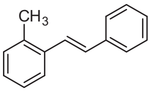
atom. Thus, it could increase the solubility of the catalyst in water and promote the reaction to proceed more smoothly.

The ligand was tested in the Heck coupling reactions. Initially, the coupling of *n*-butyl acrylate with iodobenzene was chosen as a model reaction (Fig. 2) to optimize the reaction condition.[18]

The base, reaction time, and solvent were screened. The results presented in Table 1 showed that the reactions catalyzed by the L/$PdCl_2$ catalyst system succeeded in performing in DMF with K_2CO_3 as the base at 120 °C for 12 h with good yields. In addition, we carried out intensive investigations to define the best solvent for this transformation. Several different solvents (Table 1, entries 1–5) such as DMF, NMP, DMA, DMSO, and water were tested.

The reaction performed in DMF gave a satisfactory yield of 93%. Surprisingly, the reaction performed in aqueous media showed excellent yield, with 95% yield better than DMF (Table 1, entry 5). We tend to use a green media for the Heck reaction. Thus we choose water instead of DMF as the solvent. Owing to the efficiency of the Heck reaction is also dependent on the nature of the base.[9,10] We investigated the effects of the base as depicted in Table 1. K_3PO_4 and NEt_3 were found to provide slightly lower yields (89% and 77%, respectively) than K_2CO_3 (Table 1, entries 12 and 9). Reactions using hexamine and KOH provided very low yields (Table 1, entries 10 and 11). A mass of phenyl ether was produced using KOH as the base, perhaps the strong basicity of KOH made iodobenzene hydrolyze. Compared to the result in entry 5 of Table 1, the reaction could proceed with only 56% yield in the absence of the ligand (Table 1, entry 16) and 38% yield without K_2CO_3 (Table 1, entry 17). As shown above, the Betti base is not only a ligand that could promote the reaction sharply but also a base additive in the reaction. Heterogeneous Heck reactions can run better at higher temperatures if reagents, products, and catalyst can survive such a harsh treatment.[13a] To our great delight, the yield significantly increased from 67% to 95% when the temperature increased from

Table 2
Heck reaction between aryl halides and olefins[a]

Entry	Ar-X	Product	Yield[b] (%)
1			95
2			92
3			94
4			87
5			83
6			88
7			84
8			86
9			89
10			83
11			81
12			82
13			87
14			78
15			73
16			77
17			83
18			72

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