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A bifunctional palladated rasta resin for Mizoroki–Heck reactions

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ABSTRACT

Bifunctional palladated rasta resins **2b** and **2c** bearing both phosphino and basic amino groups have been successfully used for Mizoroki–Heck reactions between aryl iodides and alkenes without adding a soluble base. We have also shown that **2c** can be easily regenerated after reaction and reused. To the best of our knowledge, this work represents the first use of a bifunctional palladated polymer for a C—C bond forming reaction.

The Mizoroki–Heck cross-coupling reaction is one of the most powerful tools for the creation of alkenyl–aryl bonds.[1] It finds widespread applications for the syntheses of elaborated molecules presenting interesting physical,[2] biological,[3] or pharmaceutical[4] properties. The Mizoroki–Heck reaction is generally performed by reacting aryl iodides or bromides with alkenes in the presence of a soluble base (traditionally a tertiary amine) and a homogeneous palladium catalyst.[5] Versatile alkenes can be prepared in high yields under mild reaction conditions. However some drawbacks lie in the use of an expensive palladium catalyst that cannot be recovered for reuse and the presence of sizeable amounts of precious metal in products and wastes.[6] In the last decades tremendous work has been devoted to the replacement of soluble palladium catalysts by heterogeneous reusable catalysts at least as efficient as their soluble analogs. For this purpose, the precious metal is generally adsorbed on inorganic supports or grafted on mineral[7] or organic[8] supports bearing carbene, phosphino, or amino ligands.[9] We have reported efficient Mizoroki–Heck reactions using reusable palladated polystyrenes bearing various phosphino groups.[10,11]

In the last decade, some bifunctional heterogeneous reusable systems bearing both a palladium catalyst and basic groups have emerged as a promising class of reusable reagents. For example, the group of Baba has reported allylation of phenols, carboxylic acids, or 1,3-dicarbonyl derivatives in the presence of a bifunctional heterogeneous palladium tertiary amine system.[12] Carbon—carbon bond forming reactions have also been reported in the presence of reusable bifunctional palladium catalysts supported on basic zeolites,[13] sepiolites,[14] mesoporous molecular sieves,[15] and silica particles.[16,17]

Rasta polymers constitute a unique class of heterogeneous supports composed of very long straight and flexible polymeric chains bound to a reticulated core.[18] Their major advantage is that the supported reagents are grafted on flexible and solvent-accessible polymeric chains rather than in the interior of a reticulated polymer bead. However, to date, rasta resins have been only sparsely used in organic synthesis, for carbonyl cyanosilylations,[19] additions of carbon dioxide to epoxides,[20] Wittig reactions,[21] tandem Michael–Henry reactions,[22] and transesterifications.[23] We have also reported the first use of palladated rasta resins bearing diphenylphosphino groups for Suzuki–Miyaura[24] reactions and Mizoroki–Heck couplings in the presence of a soluble base.[25]

Recently we prepared bifunctional rasta resins **1a** and **1b** bearing both amino and diphenylphosphino groups[26] for chromatography-free Wittig olefinations. It was found that **1b** gave superior results than **1a** because of decreased nucleophilicity of the amino group.[26b] These resins represent the first polymer-supported bifunctional reagents. We thought that they could be used, after introduction of palladium, as bifunctional reagents for the Mizoroki–Heck reaction. We obtained resin **2b** according to our previously published procedure (Scheme 1).[24,25] Since NBu_3 is in some cases more efficient than NEt_3 in the Mizoroki–Heck reaction[25] and since the synthesis of these rasta resins is easy and versatile, we also prepared resin **1c** (according to a procedure analogous to that reported for **1b**[26]) which gave **2c** (Scheme 1). TEM images

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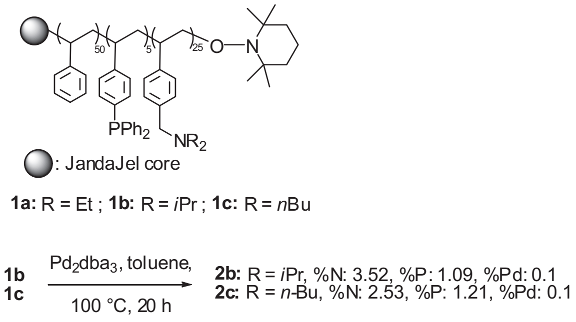
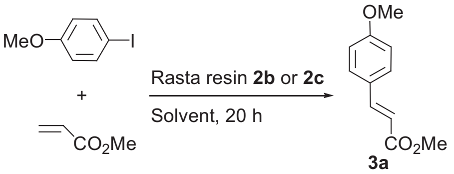


Scheme 1. Preparation of palladated rasta resins **2b** and **2c**.

Table 1

Optimization of the reaction conditions



Entry[a]	Catalyst	Solvent[c]	Yield (%)
1[b]	**2b**	Toluene	No reaction[d]
2[b]	**2b**	1,4-Dioxane	No reaction[d]
3[c]	**2b**	Acetonitrile	No reaction[d]
4[c]	**2b**	EtOH	No reaction[d]
5[b]	**2b**	DMA	No reaction[e]
6[b]	**2b**	DMSO	<10[e]
7[b]	**2b**	DMF/toluene 1:2	No reaction[d]
8[b]	**2b**	DMF	90[e]
9[b]	**2c**	DMF	99[e]

[a] Reactions performed with 4-iodoanisole (1.0 equiv, 0.2 mmol), methyl acrylate (2.0 equiv, 0.4 mmol), resin **2b**, (containing ca. 1.2 equiv of base and 4.5 mequiv of supported Pd, 96 mg) or **2c** (containing ca. 1.2 equiv of base and 6.2 mequiv of supported Pd, 133 mg) in 2 mL of solvent.

[b] Reactions performed at 100 °C.

[c] Reactions performed in refluxing solvent.

[d] Aryl iodide was recovered unchanged after reaction.

[e] Isolated yields.

(Fig. 1a) of catalyst **2c** show the presence of nanoaggregates of palladium, as was found in our previous work with phosphinated resins.[25] Herein we present the use of palladated resins **2b** and **2c** obtained from **1b** and **1c** (Scheme 1) for the Mizoroki–Heck reaction. With these resins this coupling can be performed without addition of any soluble reagent.

Noteworthily, **2b** and **2c** can be handled and stored without particular precautions. The reaction conditions were then optimized using 4-iodoanisole and methyl acrylate as model substrates (Table 1).

It turned out that running the reaction in toluene, 1,4-dioxane, acetonitrile, EtOH, DMA, DMSO, or in a 1:2 DMF/toluene mixture[11] was unsuccessful (entries 1–7). Gratifyingly, excellent yields were obtained using either **2b** or **2c** in DMF (entries 8 and 9). Noteworthily, no reaction was observed by replacing aryl iodide by a bromide such as 4-bromoanisole or 4-bromoacetophenone.

A hot filtration test was then performed in order to determine if soluble palladium entities participate in this coupling. For this purpose, the reaction was performed according to Table 1, entry 9. After 7 h of reaction at 100 °C, the rasta resin **2c** was filtered off on a 0.2 μm membrane (yield at that point: 47%), NBu_3 (1.2 equiv) was added and the filtrate was heated for another 13 h at 100 °C (yield at that point: 99%). In accordance with a previous report from our group,[25] we conclude therefore that soluble palladium entities catalyze the Mizoroki–Heck reaction. However, the exact nature of the catalytic species is not well known.[27] We also measured that the amount of palladium present in the reaction mixture at the normal end of the cross-coupling was variable: 5–12%. We determined that, on average, 90% of the initial amount of palladium was still present in the catalyst after each use.[28]

The possibility to reuse **2c** was then ascertained (Table 2): after reaction the rasta resin was filtered on a 0.2 μm membrane, the basic groups were regenerated by treatment with NBu_3 in DMF at rt for 1 h[26b] and the recovered **2c** was reused in another Mizoroki–Heck reaction. We found that **2c** could be used five times with yields ranging from 99% to 70%.

TEM images of catalyst **2c** before use, after one use (Fig. 1), and after five uses showed also that no significant change was observed since palladium aggregates of ca. 10 nm size were observed in each case.

Mizoroki–Heck couplings were then performed by reacting various aryl iodides and alkenes in the presence of **2c** (Table 3).[29] The desired alkenes were obtained using aryl iodides bearing electron-donating or electron-attracting groups with yields ranging from 69% to 99% (entries 1–9). It is noteworthy that sterically hindered aryl iodides were reacted successfully (entries 4–6). Replacing methyl acrylate by styrene afforded the corresponding alkene in 83% yield (entry 10). However, acrylonitrile gave only traces of alkene.

In conclusion, we have described the first bifunctionalized polymer bearing both a supported palladium catalyst and a supported base for Mizoroki–Heck reactions. According to Green Chemistry principles, the purification step of the product can then be avoided and the use of a scarce natural resource, palladium, is minimized.

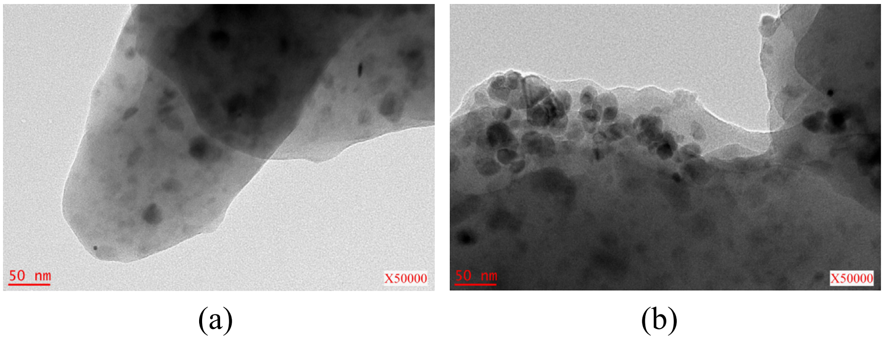


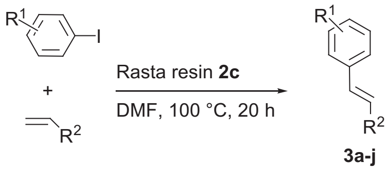
Figure 1. TEM images of catalyst **2c**: (a) freshly prepared; (b) after one use.

Table 2
Recycling tests (conditions of Table 1, entry 9)

Run	1	2	3	4	5
Yield[a]	99	99	90	78	70

[a] Isolated yields.

Table 3
Mizoroki–Heck reactions (conditions of Table 1, entry 9)



Entry[a]	R^1	R^2	Compound	Yield[b] (%)
1	4-OMe	CO_2Me	**3a**	99
2	4-Me	CO_2Me	**3b**	99
3	3-Me	CO_2Me	**3c**	99
4	2-Me	CO_2Me	**3d**	98
5	2-iPr	CO_2Me	**3e**	69
6	2-Br	CO_2Me	**3f**	98
7	H	CO_2Me	**3g**	99
8	3-CF_3	CO_2Me	**3h**	98
9	4-Ac	CO_2Me	**3i**	95
10	4-OMe	Ph	**3j**	83

[a] Reactions performed with aryl iodide (1.0 equiv, 0.2 mmol), alkene (2.0 equiv, 0.4 mmol), and resin **2c** (containing ca. 1.2 equiv of base and 6.2 mequiv of supported Pd, 133 mg) in 2 mL of DMF.

[b] Isolated yields.

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28. For the method of palladium determination see Ref. 24.
29. *Synthesis of alkenes **3a–j**.* Catalyst **2c** (prepared according Ref. 26b, 133 mg, 6.2 equiv of Pd) was added to a solution of aryl iodide (0.20 mmol, 1.0 m equiv), alkene (0.40 mmol, 2.0 equiv) in DMF (2 mL). The reaction mixture was heated at 100 °C for 20 h. After cooling to rt, compound **2c** was filtered off under vacuum using a 0.2 μm membrane. The mixture of solvents was concentrated under vacuum to afford pure **3a–j** after drying under vacuum (0.1 mbar). The catalyst **2c** was then regenerated by reaction with NBu_3 (0.16 mL, 0.66 mmol, 3.3 equiv) in DMF at rt for 3 h. Compound **2c** was then filtered under vacuum, washed with Et_2O (2 mL), and dried under vacuum.