

Catalysts for Suzuki–Miyaura Coupling Reaction

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Among the main reactions in organic chemistry, the Suzuki–Miyaura cross-coupling reaction catalyzed by a homogeneous or heterogeneous palladium complex is undoubtedly the most important. This reaction enables the synthesis of complex and functionalized organic molecules under mild experimental conditions compatible with many functional groups in batch and in continuous flow processes [1].

A review of the Suzuki–Miyaura cross-coupling reaction using nitroarenes as electrophilic coupling reagents instead of organic halides or triflates is reported [2]. The substitution of aryl halides and derivatives with nitro compounds could have an impact in terms of sustainability even if the use of nitroarenes requires a bulky biarylphosphine ligand. This review could open up a new green and sustainable method for the future of the Suzuki–Miyaura cross-coupling reaction with important applications in the pharmaceutical domain.

Nitrogen-doped graphene (NDG) is used as a support for the preparation of an NDG@Pd nanocatalyst in a Suzuki–Miyaura cross-coupling reaction [3]. The precatalyst (Pd 5 mol%) is obtained by the simultaneous reduction of graphene oxide (GRO) and PdCl₂ in the presence of hydrazine hydrate as a reducing agent, while ammonium hydroxide is used as a source of “N” on the surface of graphene. In the presence of phenyl halides, phenyl boronic acids, and sodium dodecyl sulfate in refluxing water for 5 minutes, the cross-coupling affords the target biaryl derivatives in good yields. Under these conditions, the N-doped catalyst displays excellent reusability even after several reactions.

Three nanosized palladium catalysts (0.2 mol%) supported on graphene oxide (GO) and its composite with TiO₂ (GO–TiO₂) are prepared and fully characterized [4]. These catalysts are studied for the carbonylative coupling of iodobenzene with aryl boronic acids in anisole for 4 h at 100 °C and furnish the corresponding diarylketones at atmospheric pressure of CO. The best productivity (95%) is obtained in the presence of Pd/GO–TiO₂, which is also successfully recycled in four subsequent runs. After a few recyclings, the selectivity to ketones decreases and normal Suzuki–Miyaura coupling occurs.

Pd-nanodot-modified gold nanoparticles with or without a graphene interface layer are prepared using a wet-chemical synthetic method [5]. Among the different catalysts, Pd-rGO–AuNPs permit the highest catalytic activity for the visible-light-induced C–C bond coupling reaction. This work clearly indicates that the design and use of engineered interfaces are of importance to achieve enhanced catalytic activity with plasmonic hybrid nanomaterials. A mechanism study shows that the electron–hole pair generated by the absorption of light energy is responsible for the enhanced photocatalytic activity.

Different titanium-dioxide-supported palladium catalysts are produced and characterized for a ligand-free Suzuki–Miyaura cross-coupling reaction [6]. Among these catalysts, Pd/TiO₂ (anatase-type) obtained by acetonitrile solution impregnation between palladium acetate and anatase-type TiO₂ demonstrates the best catalytic activity. Various aryl chloride and bromide derivatives and arylboronic acids in the presence of 5–10 mol% Pd/TiO₂ in dimethylacetamide for 24 h at 80 °C furnish the target compounds in good yields.

Novel magnetically recyclable catalysts which have Fe₃O₄@Pd nanoparticles (NPs) are prepared starting from Fe₃O₄ [7]. Adding glucose in a hydrothermal treatment and then PdCl₂ in the presence of ascorbic acid furnishes Fe₃O₄@C/Pd, while adding glucose and ethylenediamine permit the creation

of $\text{Fe}_3\text{O}_4@\text{NC}/\text{Pd}$ (5 wt.%). Among the two catalysts, $\text{Fe}_3\text{O}_4@\text{NC}/\text{Pd}$ shows the highest activity in water at 90 °C for 30 minutes. As predicted, the catalyst cannot be readily isolated from the reaction liquid by an external magnet. $\text{Fe}_3\text{O}_4@\text{NC}/\text{Pd}$ can be reused at least ten times, with excellent yields achieved. Application of the method for the synthesis of the antitumoral drug crizotinib is described with success (95% yield).

The synthesis of a periodic mesoporous organosilica (PMO) structure functionalized with bipyridinium ionic liquid supported palladium ($\text{Pd}@\text{Bipy-PMO}$, 0.2 mol%) is reported and the hybrid catalysts are fully characterized [8]. Applied to the Suzuki–Miyaura cross-coupling reaction in water at 80 °C, the biaryl derivatives are obtained in good yield after more or less 1–4 h. The catalyst is successfully recovered and reused for six cycles with stable activity.

Commercial Pd-NHC such as Pd-pyridine-enhanced precatalyst preparation stabilization and initiation (PEPPSI)-type precatalysts are tested for the synthesis of ketones using Suzuki–Miyaura cross-coupling of *N*-acylphthalimides as an alternative to the carbonylative coupling of iodobenzene with aryl boronic acids in the presence of a CO atmosphere [9]. At 80 °C for 15 h, cheap, easily prepared, and broadly applicable Pd-PEPPSI-type precatalysts (3 mol%) supported by a sterically-demanding 1,3-Bis-(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) ancillary ligand provide high yields.

Two resorcinarenyl-substituted triazolium tetrafluoro borates are developed in a multi-step procedure and then coupled with palladium chloride to furnish corresponding PEPPSI-type palladium complexes [10]. Application of the catalysts (0.5 mol%) for the Suzuki–Miyaura cross-coupling reaction in the presence of aryl chloride and phenyl boronic acid in polar solvent at 100 °C permits the obtaining of various biaryl derivatives in good yields. The catalytic activity is better (by up to 5 times), with the ligand having a more accessible metal center in the catalytic intermediates.

A homogeneously modified β -cyclodextrin-supported palladium complex as a supramolecular platform for a phosphine-free Suzuki–Miyaura cross-coupling reaction is described [11]. The water soluble catalyst is prepared in four steps by the formation of the ligand and then the addition of $\text{Pd}(\text{OAc})_2$. Starting from aryl halide and boronic acid in the presence of $\text{PdLn}@\text{Et-}\beta\text{-CD}$ (2 mol%) in water at 60 °C in water under air, target biaryl derivatives which have different groups are obtained in good yields. Interestingly, the catalyst can be recovered and reused without the loss of its catalytic activity. A molecular complexation study confirms that the cavity of the cyclodextrin plays a role in this.

Salmon fish sperm DNA which have a peculiar structure and are non-toxic are used as a support for immobilization of palladium nanoparticles using palladium precursors and the support [12]. This bio-based catalyst (1 mol%) in a mixture of dioxane and water at 80 °C for 4 h permits the production of target biaryl derivatives in good yields. Moreover, the catalyst is recovered by simple phase separation and then reused in seven consecutive cycles with a high activity.

Continuous flow chemistry and specially-continuous flow has provided a real breakthrough in modern organic synthesis [13]. Integration of lithiation, borylation, and Suzuki–Miyaura coupling using a flow reactor packed with a Pd catalyst (0.5 wt.%) supported by a polymer monolith is described. After optimization of the process, a gram scale continuous flow synthesis of adapalene is reported using five monolith reactors. Due to the pressure drop caused by the series connection, a monolith reactor which has larger pore sizes is developed with success. No significant loss of activity is observed even after 15 cycle numbers. In this regard, the same group develops a system minimizing process performance degradation due to a blockage [14].

We believe that the reported contributions in this Special Issue will inspire all those involved in the field of the Suzuki–Miyaura cross-coupling reaction in batch and in flow conditions, providing useful hints for students and newcomers in this exciting field of science.

Conflicts of Interest: The author declares no conflict of interest.

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