MINIREVIEW / MINISYNTHÈSE

Review on green chemistry — Suzuki cross coupling in aqueous media

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Abstract: The Suzuki cross-coupling reaction is a very efficient, reliable, and environmentally friendly method for the introduction of novel carbon–carbon bonds into molecules. This review summarizes recent advances in the use of the reaction in aqueous media with a focus on different types of ligands and the ligandless protocols currently in use. Several synthetic targets for the reaction have been mentioned. The work summarizes recent results from studies on asymmetric Suzuki reactions performed in organic – aqueous mixed solvents.

Key words: Suzuki reaction, green chemistry, metal-catalyzed cross-coupling reactions, aqueous synthesis media.

Résumé : La réaction de couplage croisé de Suzuki est une méthode très efficace, fiable et environnementalement correcte pour l'introduction de nouvelles liaisons carbone–carbone dans des molécules. Cette revue résume les progrès récents réalisés dans l'utilisation de la réaction en milieu aqueux, en se concentrant sur les divers types de ligands et les protocoles sans ligands actuellement en usage. Plusieurs cibles de synthèse pour cette réaction sont mentionnées. Le travail résume les résultats récents obtenus à partir d'études sur les réactions de Suzuki asymétriques effectuées dans des solvants mixtes organique – aqueux.

Mots clés : réaction de Suzuki, chimie verte, réactions de couplage croisé catalysées par les métaux, milieu de synthèse aqueux.

[Traduit par la Rédaction]

Introduction

The chemical industry is a major contributor to environmental pollution, largely because of the use of hazardous solvents. These solvents released or disposed by the chemical industry include methanol, toluene, xylene, methyl ethyl ketone, and methylene chloride (1). With sharpened regulatory pressure focusing on organic solvents, the search for alternatives is of increasing importance. In this respect, organic transformations in aqueous media (2), have received much attention because water is easily available, economical, and harmless to the environment. The cross-coupling reaction of alkenyl and aryl halides with organoborane derivatives in the presence of a palladium catalyst and a base, known as the Suzuki reaction, has often been carried out in an organic–aqueous mixed solvent. Although Davidson and Triggs (3) discovered in 1968 that arylboronic acids reacted with palladium(II) acetate to give corresponding biaryls, and Garves (4) in 1970 that arylsulfinic acids could be coupled

to biaryls using Pd(II) in aqueous solvents, it was not until 1979 when biaryls could efficiently be prepared by a palladium-catalyzed reaction. Miyaura and Suzuki (5) reported that cross-coupling reactions between alkenylboranes and organic halides were efficiently catalyzed by a catalytic amount of tetrakis(triphenylphoshine) palladium (Pd(PPh$_3$)$_4$) in the presence of a suitable base. Starting from these observations, the reaction has developed to become one of the most utilized methods for the introduction of novel carbon–carbon bonds in solution (6) and on solid phase (7). This current paper summarizes recent developments in Suzuki-type, palladium-catalyzed coupling reactions in water. This short review summarizes the advantages of using the Suzuki protocol instead of other similar cross-coupling reactions in aqueous media, several structurally different ligands that promote the reaction in water, recent results from ligandless Suzuki protocols, and target molecules mainly produced by the method. The paper ends with a few examples for the utilization of the reaction in an asymmetric manner.

Fig. 1. Selected palladium-catalyzed cross-coupling reactions.

Suzuki coupling: Pd-catalyzed cross coupling of organic halides or perfluorinated sulfonates with organoboron derivatives.

$$R_1-BY_2 \ + \ R_2-X \ \xrightarrow[\text{base}]{\text{Pd}} \ R_1-R_2$$

$X = I, Br, Cl, OSO_2$
$BY_2 = B(OR_2), \text{9-BBN}, B(\text{alkyl})_2$
$R_1 \text{ or } R_2 = \text{various aromatic or alifatic}$
hydrocarbons
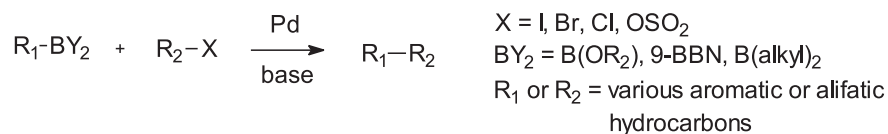
Heck reaction: Pd-catalyzed coupling of an alkyl, aryl, or vinyl entity to an alkene

$$\underset{R_1}{\overset{H}{\diagdown}}C=C\underset{R_2}{\overset{R_3}{\diagup}} \ + \ R_4-X \ \xrightarrow[\text{base}]{\text{Pd}^0-L} \ \underset{R_1}{\overset{R_4}{\diagdown}}C=C\underset{R_2}{\overset{R_3}{\diagup}}$$
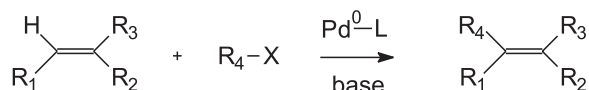
Kumada coupling: Ni- or Pd-catalyzed substitution of aryl halides with Grignard reagents

$$Ar\text{-}X \ + \ R_1MgBr \ \xrightarrow{\text{[Pd] / [Ni]}} \ ArR_1$$
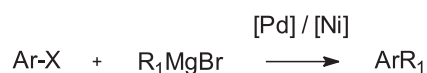
Stille coupling: Pd-catalyzed reaction of organostannanes with halides, acetates, or perfluorinated sulfonates lacking a sp^3-hybridized β-hydrogen

$$R-\underset{R}{\overset{R}{Sn}}-R_1 \ + \ R_2-X \ \xrightarrow{\text{[Pd]}} \ R_1-R_2 \ + \ R-\underset{R}{\overset{R}{Sn}}-X$$
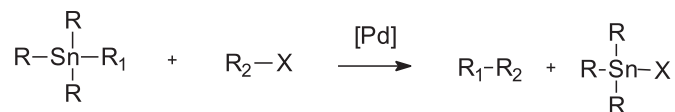
Negishi coupling: Ni- or Pd-catalyzed coupling of a alkenyl, aryl, allylic, or benzylic halide with alkyl- or arylzinc reagents

$$R_1-Y \ + \ R_2-Zn-X \ \xrightarrow{\text{[Pd] / [Ni]}} \ R_1-R_2 \ + \ ZnXY$$
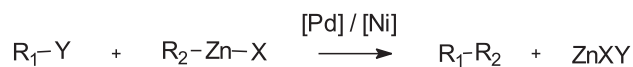
Sonogashira coupling: Cu(I) mediated and Pd-driven alkyne coupling to aromatic halides in the presence of a base

$$Ar\text{-}X \ + \ \equiv\!\!\diagup^{R_1} \ \xrightarrow[\text{base}]{\text{[Pd] , CuI}} \ Ar\!\!-\!\!\equiv\!\!\diagup^{R_1}$$
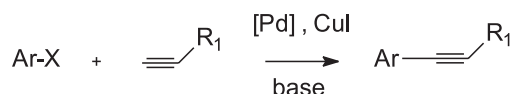
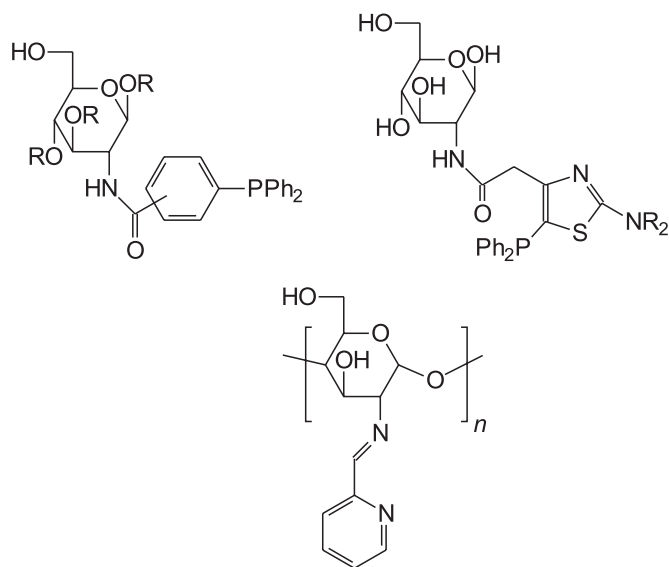## Suzuki cross coupling vs. other palladium-catalyzed reactions

In the Suzuki reaction (5, 6), the Heck reaction (8), the Kumada reaction (9), the Stille reaction (10), the Negishi reaction (11), and the Sonogashira reaction (12), palladium is known to be particularly effective in activating sp^2-carbon–halogen bonds even in aqueous media (13) (Fig. 1). All reaction types have drawbacks that limit the use in synthesis. Suzuki cross coupling has, on the other hand, less limitations than the other reactions mentioned. In the Heck reaction, for example, where an aryl or vinyl halide and an alkene are converted to a more highly substituted alkene under Pd catalysis, the intermolecular reaction often proceeds well when the alkene is electrophilic. With nucleophilic substituents, the reaction gives less satisfactory results. The Kumada coupling is very sensitive to air and the presence of radical inhibitors, and this has limited the use of the reaction in aqueous media. In the Stille reaction, stannates are used as substrates, and many of these are environmentally hazardous. There is no toxicity issue involved in organoborane reagents. For a large-scale setting, a Suzuki coupling is an attractive choice. The organoborane reagents are usually more easy to prepare in the laboratory, and the workup procedures are more simple than using other cross-coupling methods (14–17).

Ligands

The vast majority of ligands applied in modern synthesis possess low water solubility. Many strategies have been used to enhance the solubility of metal–ligand complexes in water of which three are mostly utilized (18). The catalytic reaction is performed in the presence of micelle-forming surfactants, solubilizing functionalities are added to the ligand, i.e., ionic groups to poorly soluble ligands and easily accessible, water-soluble sources from nature are utilized as ligands. These include, for example, carbohydrates and the

Fig. 2. Ligand alternatives from nature suitable for Suzuki cross coupling.

Fig. 3. Pd/C-catalyzed ligandless Suzuki coupling.

LeBlond et al. (29*a*):

Sakurai et al. (29*b*):

Tagata et al. (29*c*):

biopolymer chitosan suitable for the Suzuki reaction (19) (Fig. 2). Ligands based on monosaccharides usually have only moderate solubility in water and often require incorporation of extra hydrophilic groups to improve the ligand property. Also, a co-solvent or a surfactant is sometimes needed for optimum efficiency. Dissaccharide ligands have the advantage of higher aqueous solubility, but the synthesis of these is usually tedious. Chitosan, on the other hand (20–23), has proven to be a very promising material for organic synthesis and catalysis. For example, Suzuki and Heck reactions have successfully been completed using metal–chitosan complexes as catalysts in aqueous solutions (24). The complexes have offered both economically and environmentally more favourable conditions for many reactions. Catalysts for the Suzuki reaction heterogenized through co-valent attachment to organic or inorganic supports have also been synthesized (25). The supports have included organic polymers (7, 26), silica (27), and layered clays (28).

## Ligandless Suzuki cross coupling

From an environmental point of view, development of a new catalytic system without the use of stabilizing phosphine ligands in aqueous media under mild conditions has attracted much attention. The reaction with ligandless catalysts such as Pd/C in water has, for example, very recently been investigated (16, 29) (Fig.3). Compared to air-sensitive and expensive homogenous palladium catalysts, palladium charcoal can safely be handled and removed from the reaction mixture by simple filtration. The recovered palladium charcoal can be purified and reused as palladium metal. These features are also of great advantage in industrial processes. Other palladium catalysts useful for the ligandless Suzuki reaction in water include Pd(OAc)$_2$ and PdCl$_2$ (30, 31).
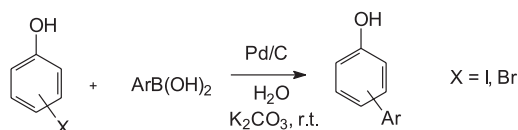
Targets for the Suzuki cross coupling

The synthesis of biaryl compounds, reviewed by Stanforth (32), is of importance for numerous agrochemical and phar-
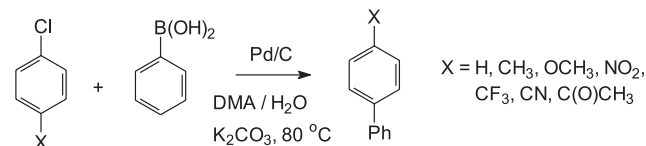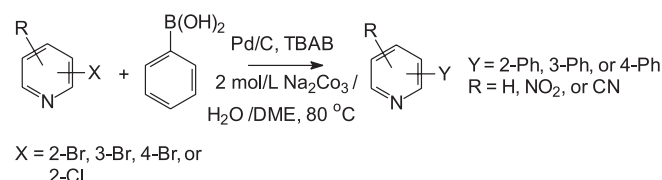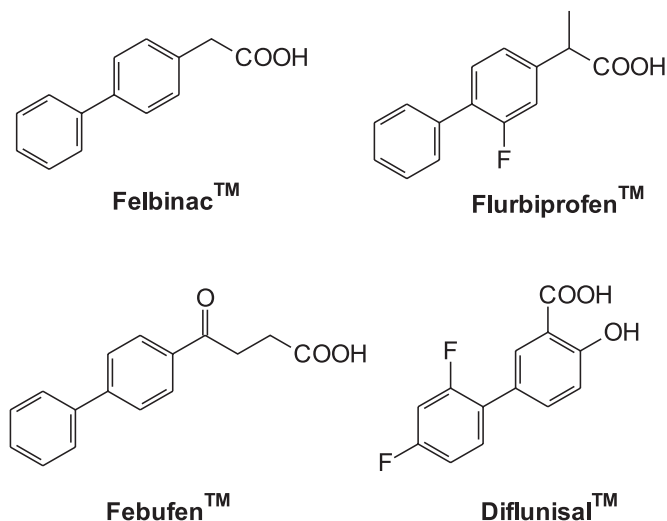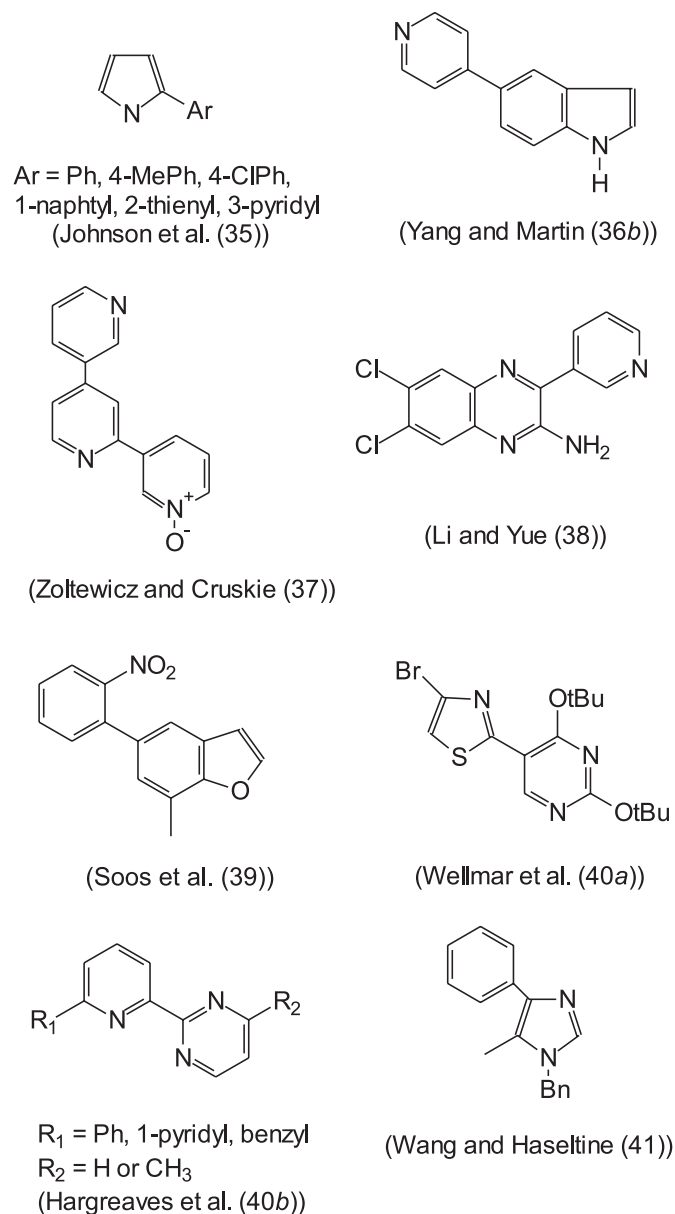
Fig. 4. Examples of non-steroidal anti-inflammatory drugs bearing biaryl fragments.

maceutical applications (Fig. 4). The classic Ullmann methology (33) is well-known in this context. Owing, on the other hand, to the versatile chemistry of palladium compounds in carbon–carbon bond-forming reactions, several palladium-catalyzed prosesses have been proposed as eco-friendly replacement for this stoichiometric protocol. Essentially based on the Pd(II)–Pd(0) redox cycle, these processes require in situ regeneration of the active palladium catalyst, which can be achieved, for example, during the Suzuki reaction by various reagents, e.g., 2-propanol, hydrogen gas, or aqueous alkali salts. In the synthesis of heterocyclic compounds, the aqueous Suzuki reaction has found many applications (34). A few examples include the structural modifications and preparations of pyrroles (35), indoles (36), pyridines (37), quinoxalines (38), benzofurans (39),

Fig. 5. Examples of heterocycles prepared by an aqueous Suzuki reaction.

Fig. 6. Two recent examples of the utilization of the Suzuki reaction in the preparation of polymers.

Ar = Ph, 4-MePh, 4-ClPh,
1-naphtyl, 2-thienyl, 3-pyridyl
(Johnson et al. (35))

(Yang and Martin (36*b*))

(Wallow and Novak (44))

(Zoltewicz and Cruskie (37))

(Li and Yue (38))

(Martina and Schluter (45))

(Soos et al. (39))

(Wellmar et al. (40*a*))

Fig. 7. Complex organic molecules prepared using a Suzuki reaction as the key step.

R₁ = Ph, 1-pyridyl, benzyl
R₂ = H or CH₃
(Hargreaves et al. (40*b*))

(Wang and Haseltine (41))

4,5-Dioxoaporphines
(Suau et al. (47))

Oximidine II
(Molander and Dehmel (48))

Phomactin A
(Mohr and Halcomb (49))

Nemertelline
(Bouillon et al (51))

pyrimidyl thiazoles (40*a*), pyridyl pyrimidines (40*b*), and imidazoles (41) (Fig. 5). The Suzuki reaction of boronic acids in water and a variety of heteroaryl halides has been conducted to prepare 5-substitued heteroaryl pyrimidines, which can be hydrolyzed to 5-substituted uracils as potential antiviral agents (42*a*). Using a palladium(0) complex having a monosulfated phosphine as a ligand, Casalnuovo and Calabrese (42*b*) performed an alkylation of biomolecules in an aqueous medium. The reaction could tolerate a broad range of functional groups, including those present in unprotected nucleotides and amino acids. In the preparation of purines on solid phase, Pd catalyses have also successfully been utilized (43). In the synthesis of polymeric materials (Fig. 6), the Suzuki reaction has found applications in water. A hydrocarbon nonmetallic conducting polymer with a rigid rod of benzene rings was synthesized recently in water (44). Another example is the synthesis of phenyl–pyrrole mixed
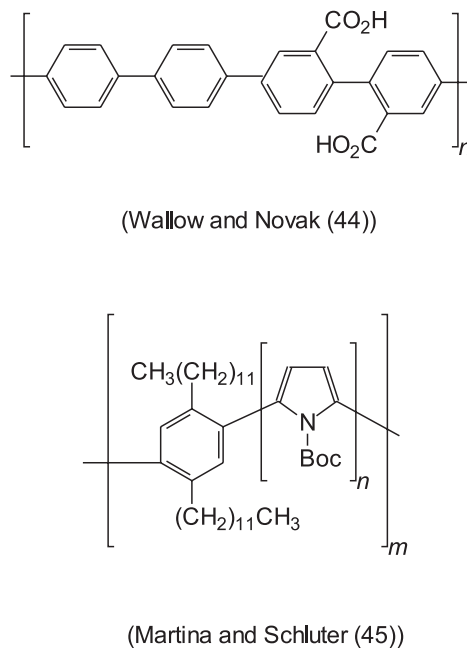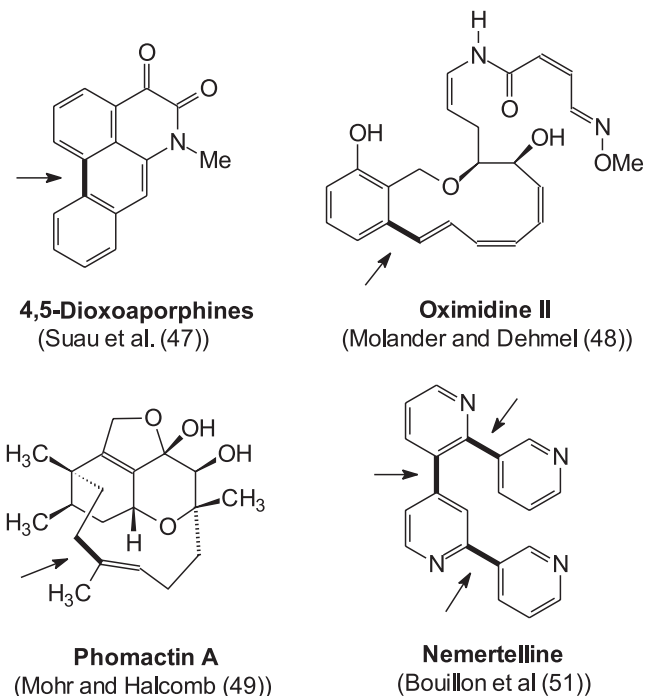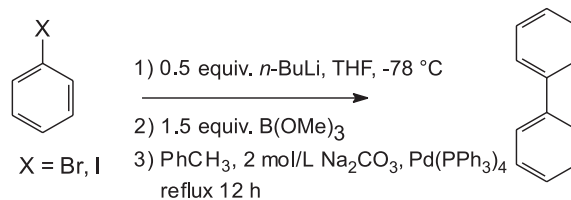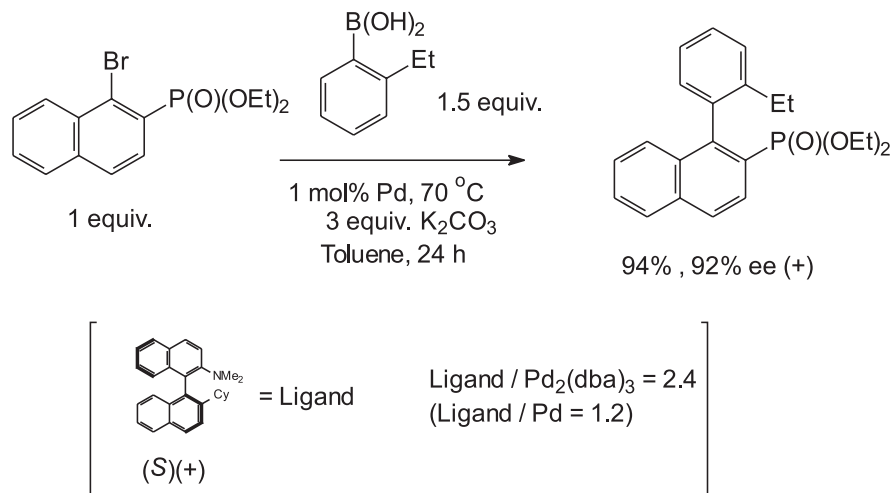
Fig. 8. Initial attempts to prepare C_2-symmetric biaryls.

1) 0.5 equiv. *n*-BuLi, THF, -78 °C

2) 1.5 equiv. B(OMe)₃

X = Br, I   3) PhCH₃, 2 mol/L Na₂CO₃, Pd(PPh₃)₄
reflux 12 h

Fig. 9. Preparation of axially chiral biaryls.

Fig. 10. Asymmetric Suzuki cross coupling performed in organic–aqueous mixed solvents for the preparation of binaphtalene derivatives.

polymers (45) using a method where originally β-octasubstituted tetramethylporphyrins were crafted by various arylboronic acids (46). In the total synthesis of complex molecules, such as aporphinoids (47), oximidine II (48), (+)-phomactin (49), gymnocin-A (50), quaterpyridine nemertelline (51), and ristocetin aglycon (52), an organic solvent – aqueous mixed Suzuki reaction has successfully been used as a key step (Fig. 7). These mentioned molecules are only a few very recent examples. The Suzuki cross coupling has, since its discovery, been used for a large group of different natural products (53).

Catalytic asymmetric Suzuki cross coupling

The asymmetric Suzuki cross-coupling reaction has successfully been accomplished in both organic solvents and inorganic–aqueous mixed solvents. For the preparation of C_2-symmetric biaryls, a modified Suzuki cross-coupling method of haloarenes was designed in 1996 by Keay and co-workers (54) (Fig. 8). The catalytic asymmetric version of the reaction for the synthesis of axially chiral biaryl compounds was later developed by the Buchwald group (55) (Fig. 9). The first, asymmetric Suzuki cross coupling performed in an organic–aqueous mixed solvent resulting in binaphthalene derivatives in up to 63% ee, was described by Cammidge and

Crepy (56) (Fig. 10). In DME, the reaction gave up to 85% ee. Following these discoveries, other reports on the asymmetric synthesis for chiral binaphhyls or biaryls have been reported, for example, by Castanet et al. (57) in the study on chirality reverseal depending on the palladium – chiral phosphine ratio in the reaction of sterically hindered arylboronic acids. The reaction was performed in DME–water or toluene–EtOH–water. An atropo-enantioselective Suzuki cross coupling towards an axially chiral antimitotic biaryl has very recently been prepared by Herrbach et al. (58) in dioxane–water. Chiral atropisomeric binaphthalenes have also been synthesized in water–DME and a mixture of water–EtOH–toluene.

Concluding remarks

Suzuki cross coupling as a method for carbon–carbon bond formation has been a highly useful and versatile method needed for the development of modern drug discovery and in the synthesis of many natural products and polymers. Although the method has found many applications in synthesizing hitherto different molecules, there is still much work on the development towards an efficient catalyst applicable for structurally different substrates. The work on developing a catalyst working entirely in water has resulted in

a few remarkable discoveries. However, during the next few years, it is anticipated that new and more efficient catalysts will be discovered, giving even more excellent results in aqueous media.

Acknowledgements

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