

Biaryl synthesis via Suzuki coupling promoted by catalytic amounts of quaternary ammonium salts

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Abstract

Palladium-catalyzed Suzuki cross-coupling reaction (between phenylboronic acid and 4-bromobenzonitrile) in presence of catalytic quaternary ammonium salts is described. With Aliquat 336 (tricaprylmethylammonium chloride), the rates of the reaction were increased in DME and toluene allowing to work with lower stirring and at lower temperatures in some cases. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Suzuki couplings which produce biaryl products are currently among the most highly prized processes in synthetic chemistry [1]. In its original form, it consists in the palladium-catalyzed cross-coupling of an aryl halide with an aryl boronic acid in the presence of a common aqueous base (for example Na_2CO_3) [2].

From mechanistic studies, it is likely that the boron reagent first reacts with the base to give the corresponding boronate which serves as the actual nucleophile. It transfers its organic ligand to the alkoxypalladium(II) complex formed by insertion of the Pd(0) into the C–X bond followed by the displacement of X by the hydroxide ion [3,4]. In this system the aqueous layer contains the base, the organic phase contains the aryl halide, the palladium catalyst and

the boronate salt is partitioned between aqueous and organic phase.

Phase transfer catalysis enables reactions between anions or molecules soluble in one phase (usually aqueous) and organic substrates soluble in organic phase. The most commonly used catalysts are quaternary ammonium and phosphonium salts [5], crown ethers [6] and cryptates [7].

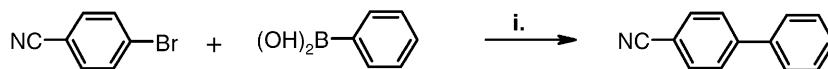
Recently Oehme [8] described an efficient two phase Suzuki reaction catalyzed by palladium complexes with water-soluble phosphine ligands and amphiphiles (20–50 mol%) as phase transfer agent. Badone et al. [9] reported a “ligandless” palladium acetate-catalyzed Suzuki cross-coupling reaction in water in the presence of a stoichiometric amount of tetrabutylammonium bromide.

Arenediazonium tetrafluoroborates derived from aromatic amines are very efficient partners in cross-coupling reactions with organoboronic acids [10]. Palladium-catalyzed cross-coupling of organoboron compounds with iodonium salts were also reported [11]. All these examples are in agreement with the

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Scheme 1. (i) 1 eq. 4-bromobenzonitrile; 1.05 eq. $\text{PhB}(\text{OH})_2$; solvent/ H_2O : 1.5/1; 0.02 eq. $\text{Pd}(\text{PPh}_3)_4$; 1.5 eq. Na_2CO_3 ; 0.2 eq. Aliquat 336.

potentiality to add some surfactants during Suzuki coupling reaction.

In this paper we present the effect of catalytic amounts (5–20 mol%) of a quaternary ammonium salt in Suzuki cross-coupling reaction. We studied the cross-coupling reaction of phenylboronic acid and 4-bromobenzonitrile in the presence of catalytic Aliquat 336 (tricaprylmethylammonium chloride) and $\text{Pd}(\text{PPh}_3)_4$ as catalyst in two phase system (Scheme 1). This coupling reaction in presence of surfactant was investigated in various solvents, with various stirring rates and at various temperatures.

2. Experimental

The chemicals were purchased from Aldrich and Strem. All reactions were performed in oxygen-free solvents under an argon atmosphere. The ^1H and ^{13}C NMR spectra were recorded on Bruker spectrometer AC 200 in CDCl_3 as solvent.

2.1. General procedure

To the tetrakis(triphenylphosphine) palladium (0.02 mmol) in 10 ml of solvent (DME or toluene) were added at room temperature 6.7 ml of distilled water, Na_2CO_3 (1.5 mmol) and 1.05 mmol phenylboronic acid.

To this mixture were added Aliquat 336 (0.2 mmol) and 4-bromobenzonitrile (1 mmol). Then the reaction mixture was heated at 60–85 °C in DME or 20–85 °C in toluene with various stirring (1500 or 750 rpm) during 3 h. After 0.5, 1, 1.5, 2, 3 h, samples were analyzed by GLC (column HP 5; program: first 40 °C then 40 °C/min up to 300 °C and 5 min at 300 °C) after filtration on SiO_2 with ethyl acetate.

After 3 h the mixture was cooled at room temperature, 10 ml ethyl acetate was added and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (2 × 10 ml). The organic phases were combined, washed with saturated NaCl , dried over

magnesium sulfate and the solvents were removed under reduced pressure. After dilution in ethyl acetate the crude product was filtrated on silica gel. After evaporation of ethyl acetate, the solid was recrystallized in *n*-hexane to give 4-cyanobiphenyl as a white solid.

3. Results and discussion

3.1. Coupling reactions performed in DME

3.1.1. Influence of stirring rates

The coupling reaction of phenylboronic acid with 4-bromobenzonitrile (Scheme 1) without any surfactant and under vigorous stirring of 1500 rpm afforded after 3 h at 85 °C 4-cyanobiphenyl (98% yield). The yield of the reaction dropped to 67% with stirring of 750 rpm at 85 °C. By using a catalytic amount (20%) of Aliquat 336 at 85 °C and 750 rpm, the yield increased from 67 to 98% after 3 h (Fig. 1).

3.1.2. Temperature effect

Then we studied the influence of Aliquat 336 at 60 °C. 4-Cyanobiphenyl was obtained in 67% yield at 60 °C and under vigorous stirring (1500 rpm). The use of Aliquat 336 did not allow to increase the yield. With a stirring of 750 rpm at 60 °C, yield of biaryl was increased from 25 to 39% in presence of this quaternary ammonium salt (Fig. 2).

3.1.3. Conclusion

In conclusion, when the reaction was performed in DME, catalytic quaternary ammonium salt allowed to work under lower stirring (750 rpm instead of 1500 rpm) at 85 °C.

3.2. Coupling reaction performed in toluene

3.2.1. Influence of stirring rates

Many Suzuki biaryl coupling reaction are performed in benzene or toluene. These solvents are less miscible to water than DME but are frequently used at low temperatures.

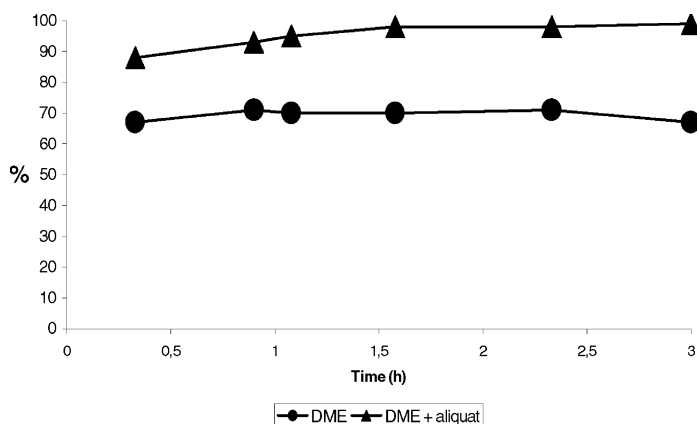


Fig. 1. Coupling reaction of phenylboronic acid with 4-bromobenzonitrile (reflux of DME (85 °C), 750 rpm) without Aliquat 336 or in presence of Aliquat 336.

We found at 85 °C under vigorous stirring an acceleration of the reaction by the use of Aliquat 336 in toluene. After 20 min we obtained 95% of biaryl instead of 77% without Aliquat 336 (Fig. 3). Consequently at 750 rpm and 85 °C the effect of Aliquat 336 was more important; we obtained a conversion of 94% in 3 h instead of 65% without surfactant (Fig. 3).

3.2.2. Temperature effect

In toluene, decreasing the temperature from 85 to 60 °C at 1500 rpm decreased the yield from 96 to

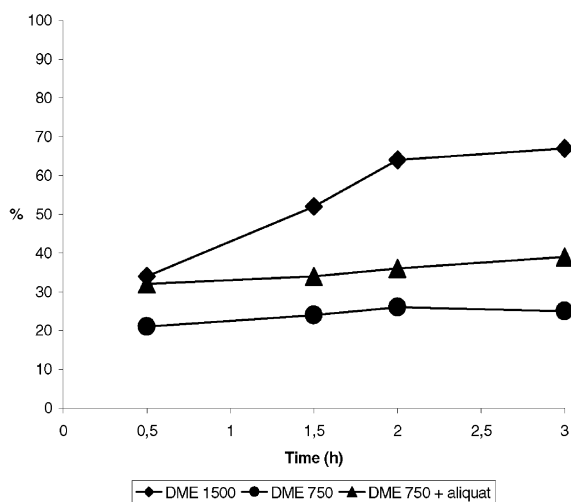


Fig. 2. Coupling reaction of phenylboronic acid with 4-bromobenzonitrile (DME, 60 °C, 1500 and 750 rpm) without Aliquat 336 or in presence of Aliquat 336.

80% in 3 h. Addition of Aliquat 336 at 60 °C and 1500 rpm allowed to obtain the coupling product in 100% yield in 3 h (Fig. 4). At 750 rpm and 60 °C the effect of Aliquat 336 was slightly more important; a 97% conversion was obtained instead of 71% without Aliquat 336 (Fig. 4).

Furthermore if we decreased the temperature to 20 °C, we observed an acceleration of the reaction: after 30 min the yield is 40% with ammonium salt instead of a few percent without (Fig. 5).

3.2.3. Conclusion

In conclusion, when the coupling reaction was performed in toluene, Aliquat 336 allowed to work under lower stirring and at lower temperatures.

3.3. Comparison between DME and toluene

If we compared the better results in DME and toluene at 60 °C under vigorous stirring (1500 rpm) without Aliquat 336, we observed a better yield of coupling product in toluene than in DME (80% in toluene and 67% in DME) (Fig. 6). This is in agreement with a work of Anderson et al. [12] who described a Suzuki coupling reaction between mesitylboronic acid and bromobenzene at low temperature (20 °C) and obtained better yields in benzene than in DME.

Furthermore, as we have seen before, adding Aliquat 336 at 60 °C under stirring of 1500 or 750 rpm in toluene increased the yield to 100 or 97% in 3 h (Figs. 6 and 7).

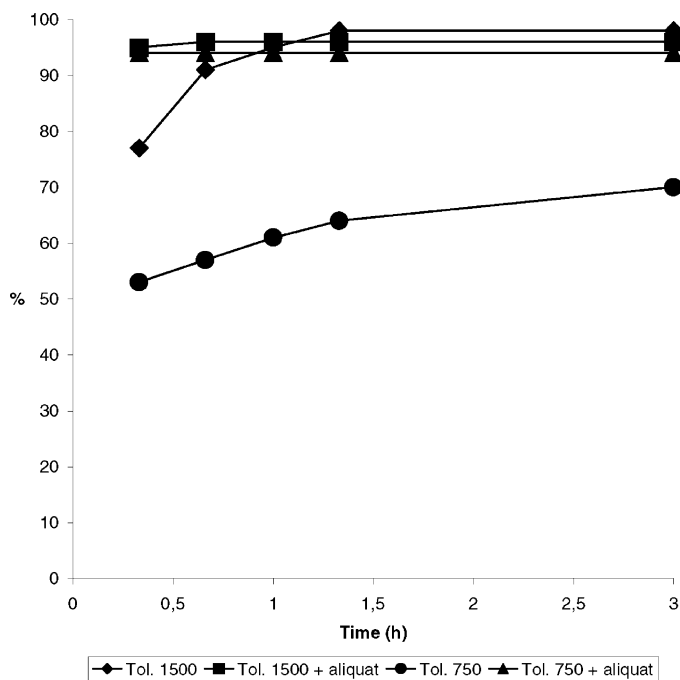


Fig. 3. Coupling reaction of phenylboronic acid with 4-bromobenzonitrile (toluene (Tol.), 85 °C, 1500 and 750rpm) without Aliquat 336 or in presence of Aliquat 336.

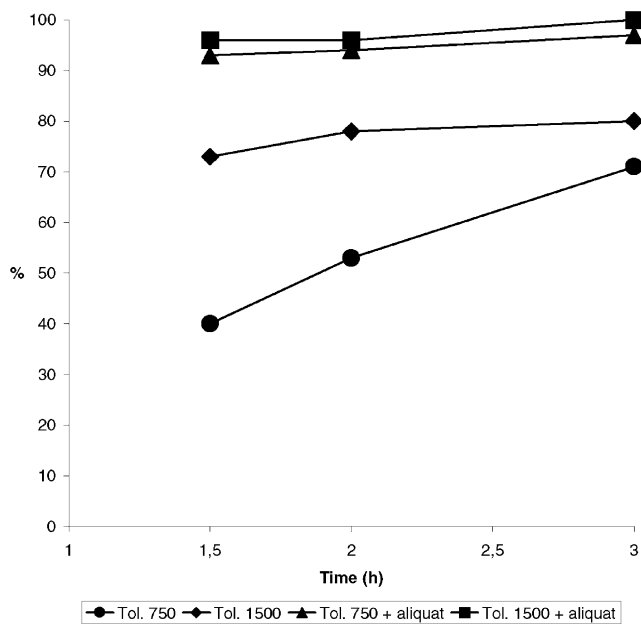


Fig. 4. Coupling reaction of phenylboronic acid with 4-bromobenzonitrile (toluene (Tol.), 60 °C, 1500 and 750rpm) without Aliquat 336 or in presence of Aliquat 336.

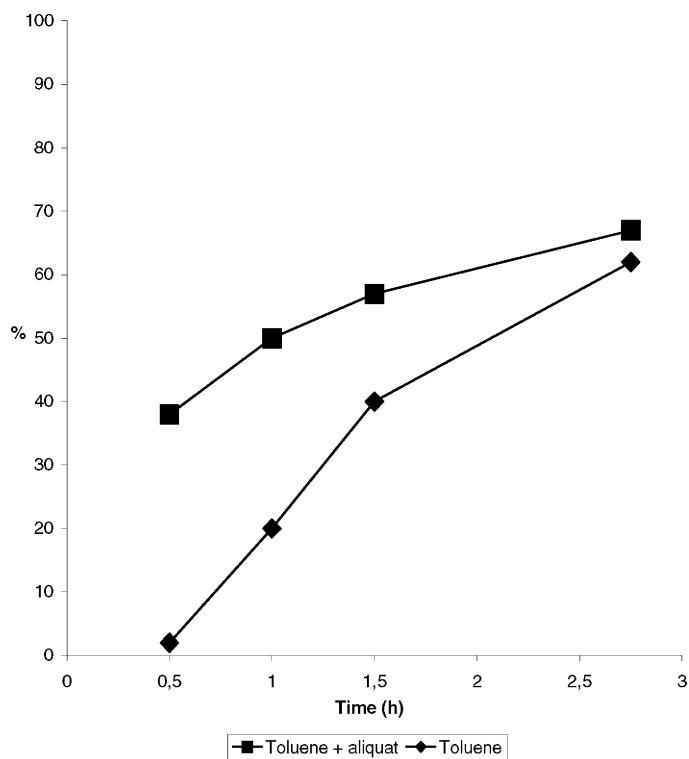


Fig. 5. Coupling reaction of phenylboronic acid with 4-bromobenzonitrile (toluene, 20 °C, 1500 rpm) without Aliquat 336 or in presence of Aliquat 336.

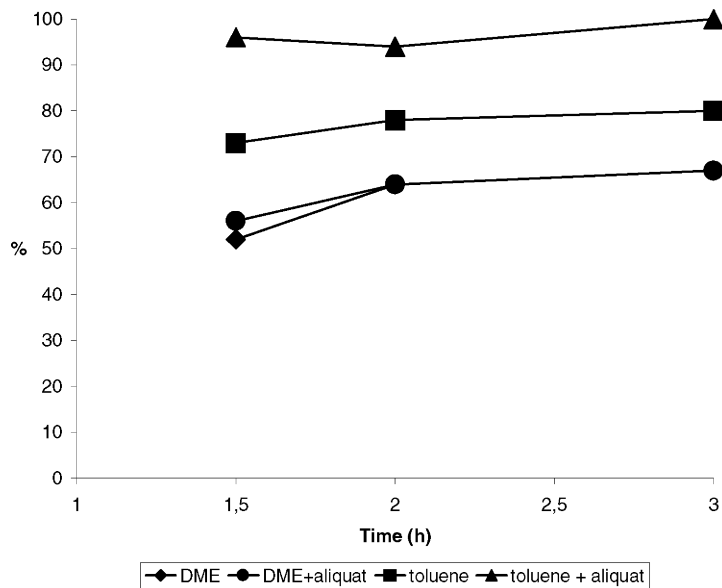


Fig. 6. Coupling reaction of phenylboronic acid with 4-bromobenzonitrile (DME or toluene, 60 °C, 1500 rpm) without Aliquat 336 or in presence of Aliquat 336.

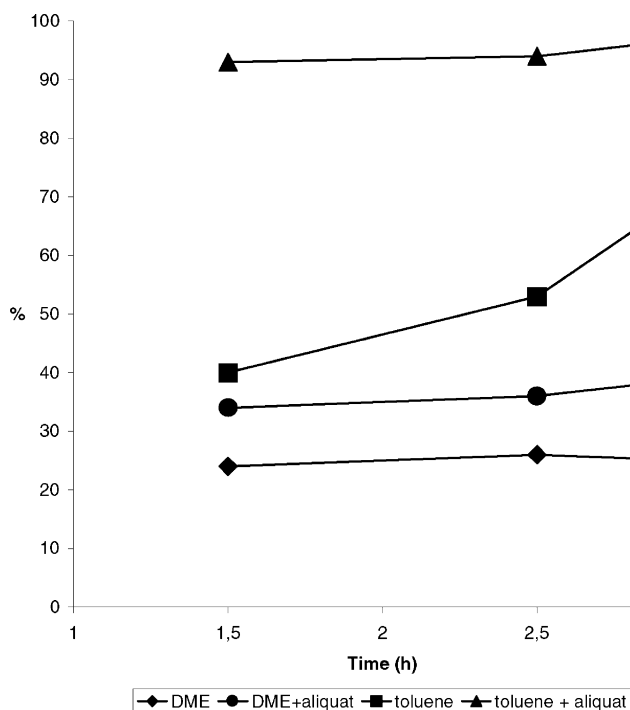


Fig. 7. Coupling reaction of phenylboronic acid with 4-bromobenzonitrile (DME or toluene, 60 °C, 750 rpm) without Aliquat 336 or in presence of Aliquat 336.

3.4. Effect on sterically hindered biaryl synthesis

In asymmetric biaryl formation, sterically hindered arylboronic acids did not provide satisfactory results due to steric hindrance or competitive hydrolytic deboronation [13].

Furthermore to obtain acceptable yield of hindered biaryls under Suzuki conditions, high temperatures (80–100 °C) are needed with multihour reaction times [14]. In asymmetric synthesis, high temperature would lead to racemization.

One solution is the addition of stronger bases: Anderson and Namli [15] have reported that certain biaryls can be formed in good yield via Suzuki couplings at room temperature using toxic thallium(I) hydroxide as base in DMA.

We report our results on the influence of steric hindrance in the Suzuki coupling reaction at lower temperatures in presence of catalytic amount of Aliquat 336.

We first tried the coupling reaction between 4-bromobenzonitrile and *o*-tolylboronic acid in toluene at

55 °C under vigorous stirring (1500 rpm). Without Aliquat 336, the yield after 3 h was 53% instead of 98% in presence of this additive (Fig. 8).

Unfortunately with mesitylboronic acid and 4-bromobenzonitrile at 70 °C, the addition of Aliquat 336 did not prevent completely the deboronation.

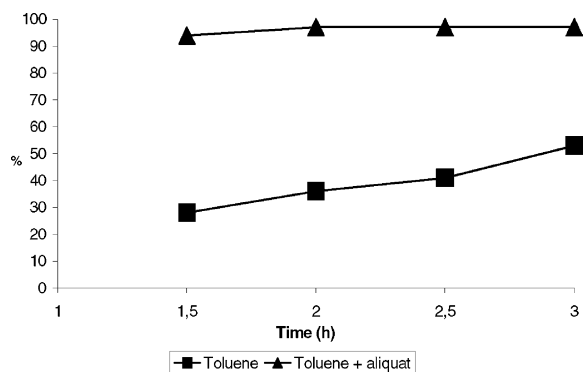


Fig. 8. Coupling reaction of *o*-tolylboronic acid with 4-bromobenzonitrile (toluene, 55 °C, 1500 rpm) without Aliquat 336 or in presence of Aliquat 336.

3.5. Dependence of Aliquat 336 concentration

In the previously described coupling reactions, we used 20 mol% of Aliquat 336. We tried to reduce this amount to 5 mol% in the coupling reaction of 4-bromobenzonitrile and phenylboronic acid at reflux of DME (85 °C) under 750 rpm (Fig. 1) and we observed the same yield increasing from 67 to 98%.

3.6. Use of other detergents

The use of tetrabutylammoniumbromide in toluene at 1500 rpm and 60 °C led to the same effect than with Aliquat 336. Furthermore we found an acceleration of the reaction by the use of sodiumdodecansulfate in toluene at 750 rpm and 85 °C.

4. Conclusions

The Suzuki carbon–carbon bond formation between aryl bromide and arylboronic acid was generally performed at high temperature (boiling point of the solvent) and under vigorous stirring (about 1500 rpm).

Large industrial application on tonne scale did not allow vigorous stirring in the reactors. By use of quaternary ammonium salts in catalytic amount (5–20 mol%), it is possible to work at lower stirring in DME and toluene.

Furthermore working in toluene with detergents allowed to work at lower temperatures especially with orthosubstituted boronic acid.

Acknowledgements

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