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Suzuki cross-coupling reaction of aryl and heterocyclic bromides and aromatic polybromides on a Pd(II)-hydrotalcite catalyst

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The Suzuki cross-coupling reaction of various bromine-containing substrates and phenylboronic acid in toluene at 90 °C on a Pd(AcO)$_2$Py$_2$ catalyst supported on an Mg–Al hydrotalcite, using K$_2$CO$_3$ as the base, was studied. The conversion and selectivity results obtained for many of the substrates were excellent and similar to those provided by more active or even homogeneous catalysts. The reactions of aryl polybromides and phenylboronic acid gave the corresponding polyaromatic compounds in variable yields depending on the particular substrate. Arylation occurred in a consecutive manner by substitution of the different Br atoms. ICP-MS measurements of the palladium content of the catalyst performed prior to and after the reaction revealed that part of the metal is incorporated into the bulk solution; therefore, the catalytic process is not purely heterogeneous. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: Suzuki cross-coupling; palladium; hydrotalcite; arylbromide

Introduction

The Suzuki cross-coupling reaction, which involves the formation of a biphenyl molecule by coupling of an aryl halide or triflate to a phenylboronic acid in the presence of a palladium catalyst (Scheme 1), provides one of the most widely used organic synthetic tools to form carbon–carbon bonds.[1–4] The process has been extended to arylhalides with alkyl, alkenyl and heterocyclic boronic acids,[5–8] which has dramatically boosted its synthetic potential. In most cases, the reaction is conducted in the presence of a homogeneous catalyst, which provides excellent turnover results. However, removing residual palladium and its ligands is usually complicated and labour-intensive;[9] this has so far severely restricted the industrial use of these catalysts. In addition, palladium ligands are expensive and the catalyst is difficult to isolate from the reaction mass for reuse, which further restricts the use of homogeneous catalysts of this type on a large scale. These problems can in principle be minimized by using heterogeneous catalysts, which are usually more inexpensive, and also easier to prepare and remove from the reaction mass – simply by filtration. Compared with homogeneous catalysts, however, very few heterogeneous catalysts are adequately active in the Suzuki cross-coupling reaction; especially effective among such few are palladium-based catalysts supported on or anchored to inorganic supports.[10–15]

Hydrotalcites, which are also known as layered double hydroxides, have been used as supports for chelated and unchelated palladium catalysts in various carbon–carbon coupling reactions.[16–18] Our research group has used these solids as supports for various palladium forms employed as catalysts in the Suzuki reaction.[14,19,20] Hydrotalcites have aroused much interest by virtue of their potential uses in various scientific fields including organic synthesis.[21–24] The structure of these compounds is based on that of a natural mineral called hydrotalcite,[24] which is a magnesium–aluminium hydroxycarbonate of formula $Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O$, structurally similar to brucite, $Mg(OH)_2$, except for the fact that some Mg^{2+} ions are replaced with Al^{3+}; this results in the presence of layers bearing a positive charge that is countered by carbonate ions in the interlayer spacing. Replacing the magnesium, aluminium or both cations with another metal, or the carbonate with another anion, allows a large family of compounds known as hydrotalcite-like compounds (HTs) or layered double hydroxides (LDHs) to be obtained.

Based on its generally accepted mechanism (Scheme 2),[1] the Suzuki reaction requires the presence of a base in order to develop to an adequate extent. In previous work, we reported the synthesis of catalysts based on palladium complexes and salts,[14,19,20] and their use in the cross-coupling reaction of arylhalides and phenylboronic acid in the presence of various bases. The best base and solvent were found to be K$_2$CO$_3$ and toluene, respectively, and a temperature of 55 °C was found to avoid palladium leaching. In this work, we extended our previous research to other substrates (viz. some aryl and heterocyclic bromides, and aromatic polybromides), which were used at a temperature of 90 °C in order to overcome the problems encountered with some reagents at a temperature of 55 °C in previous experiments. We used a catalyst consisting of a palladium chelate with acetate and pyridine, which was reported in previous work.[14] The base and solvent used here were K$_2$CO$_3$ and toluene, respectively.

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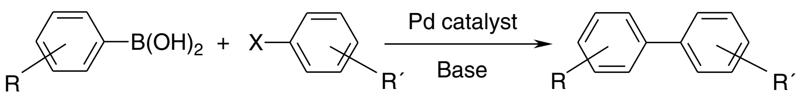
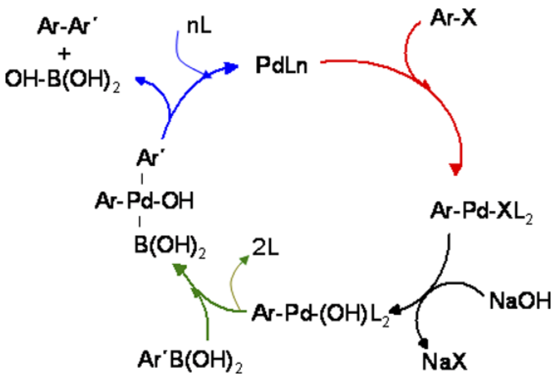
Departamento de Química Orgánica, Universidad de Córdoba, Campus de Rabanales, Edificio Marie Curie, Carretera Nacional IV-A, km 396, 14014 Córdoba, Spain



Scheme 1. General Suzuki cross-coupling reaction.



Scheme 2. Generally accepted mechanism for the Suzuki reaction in a homogeneous phase.

Results and Discussion

Suzuki reaction of monobrominated derivatives

Table 1 shows the conversion and selectivity obtained in the Suzuki cross-coupling reaction of various aryl and naphthyl bromides at 90 °C in the presence of $PdAc_2Py_2$ as catalyst and K_2CO_3 as base. Bromobenzene exhibited 100% conversion to biphenyl within a few minutes, which was also the case when the reaction was conducted at 55 °C in previous work.[14] The other brominated substrates provided variable conversion values depending on the particular substituents on the rings; in addition, they gave variable amounts of biphenyl through homocoupling of phenylboronic acid. As expected, the presence of a methyl substituent at position 2 on the bromobenzene ring resulted in considerably decreased conversion (see entry 2 in Table 1). Roughly similar conversion was obtained with the methyl group at position 3 on the bromobenzene ring; with bulkier, electron-drawing groups at position 3 (entries 5 and 6 in Table 1), conversion was substantially higher, as previously found by other authors also using heterogeneous catalysts.[25,26] Finally, the results for 1- and 2-bromonaphthalene indicate that, as expected, the position of the bromine atom has no influence on the final conversion.

Suzuki reaction of phenyl polybromides

The Suzuki cross-coupling reaction of aryl polybromides provides an efficient method for preparing polyaromatic derivatives.[27,28] The reaction with 1,4-dibromobenzene gives the corresponding *p-ter*phenyl with excellent conversion and selectivity after 1 h (entry 2, Table 2); in addition, the process gives *ca* 9% of biphenyl by effect of a homocoupling reaction. Based on the variation of the product concentrations with time, the coupling reaction takes place in a consecutive manner, first at a bromine atom and then at the other; in fact, as can be seen from Fig. 1, which shows the formation and disappearance of products over time, 4-bromophenyl begins to form at the start and then decays with time (to virtually undetectable levels after 1 h of reaction).

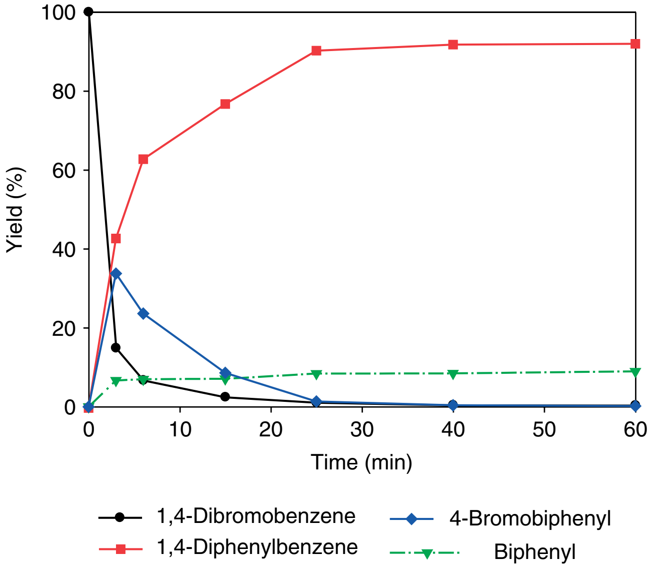


Figure 1. Product distribution as a function of time in the Suzuki cross-coupling reaction of 1,4-dibromobenzene with phenylboronic acid.

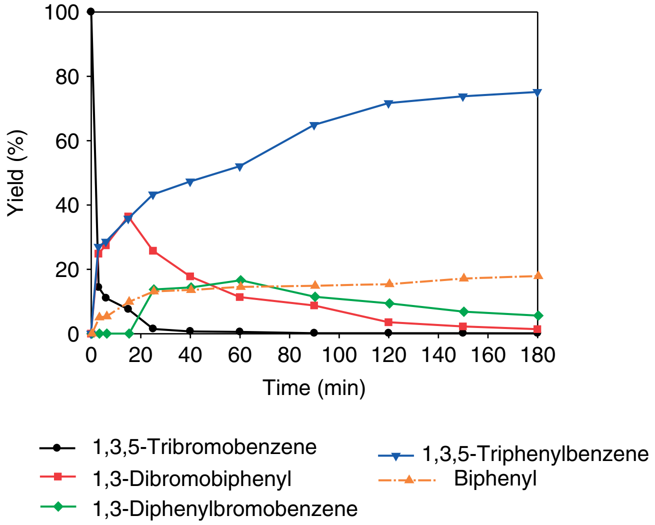
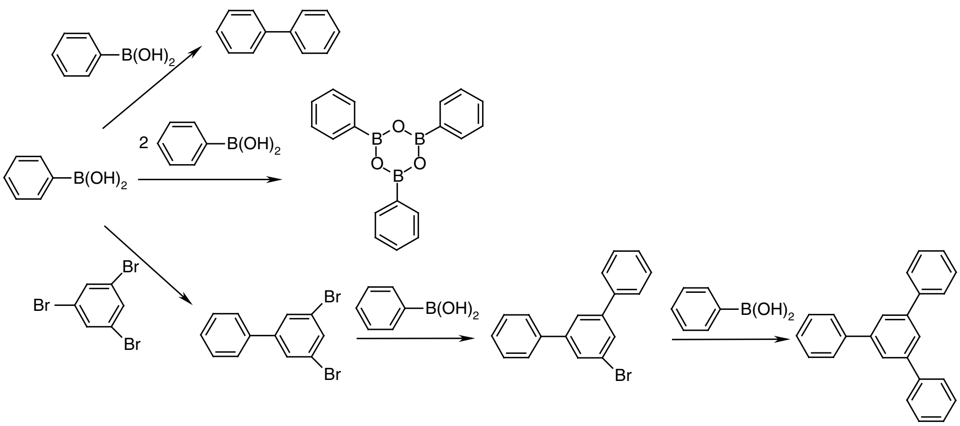


Figure 2. Product distribution as a function of time in the Suzuki cross-coupling reaction of 1,3,5-tribromobenzene with phenylboronic acid.

Figure 2 shows the variations in the products of the coupling reaction of 1,3,5-triphenylbenzene with phenylboronic acid. As can be seen, the conversion to tribromobenzene is virtually 100% after only 15 min; however, the selectivity for the sought product, triphenylbenzene, grows for 3 h, when the dibromobiphenyl and diphenylbromobenzene concentrations are very low. Also worth special note is the formation of a substantial amount of triphenylboroxine within a short time and its complete dis-



Scheme 3. Alternative processes involved in the Suzuki cross-coupling reaction between 1,3,5-triphenylbenzene and phenylboronic acid.

appearance within 1 h of reaction. The process is illustrated in Scheme 3. The formation of this product may be a result of the high phenylboronic acid concentration present in the initial solution, which is otherwise necessary as the reagent contains 3 bromine atoms and requires three times more reagent than does bromobenzene. These results suggest that, under the reaction conditions used in this work, phenylboronic acid can react with itself to form triphenylboroxine. As previously confirmed for 3-pyridylboroxine,[29] triphenylboroxine can also act as a reactant in the Suzuki reaction of 1,3,5-tribromobenzene. The medium additionally contains biphenyl formed by homocoupling of phenylboronic acid, the concentration of which increases as the reaction develops.

In one test, the reaction was allowed to develop for 24 h. The result was an 80 : 20 ratio of triphenylbromobenzene to biphenyl and the presence of 3% byproducts (dibromobiphenyl and diphenylbromobenzene).

The tests on polybrominated compounds were completed using hexabromobenzene as substrate. Again, as can be seen from Fig. 3, the process involved the sequential arylation of the different bromine atoms on the benzene ring. The monoarylation product (1,2,3,4,5-pentabromobiphenyl) prevailed at short reaction times, its conversion peaking at 1 h and then decreasing to 10% after 24 h. This pentabrominated biphenyl was then successively arylated at the different positions of the ring, the concentrations of the tetra- and tribrominated products peaking at *ca* 3 h of reaction. The concentrations of the monobrominated derivative and hexaphenylbenzene continued to increase and reached 16 and 37%, respectively, after 24 h. The reaction developed for about 48 h, when the sole reaction product detected was hexaphenylbenzene. As with 1,3,5-tribromobenzene, the reaction medium was found to contain some triphenylboroxine – a necessary ingredient of the process, the formation of which can again be ascribed to the large amount of phenylboronic acid present throughout. Finally, we should note the large amounts of biphenyl formed, which considerably detracted from selectivity by effect of the homocoupling of phenylboronic acid. Such large amounts can again be ascribed to the high concentration of phenylboronic acid initially present in the medium.

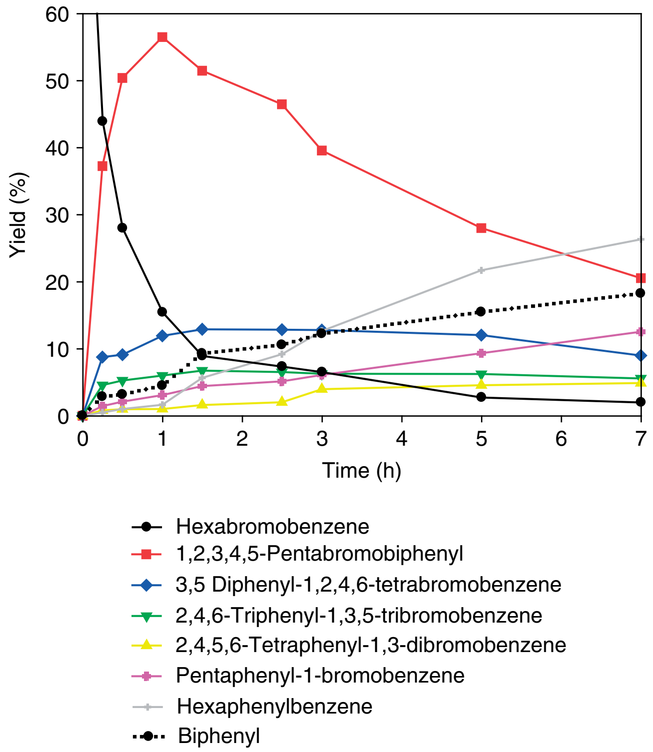
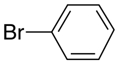
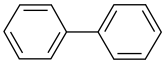
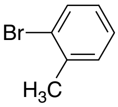
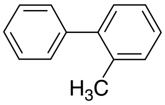
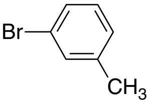
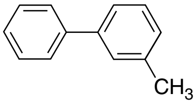
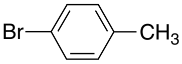
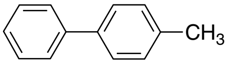
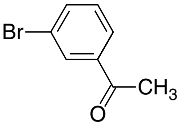
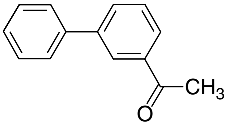
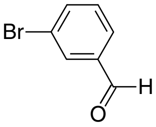
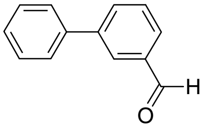
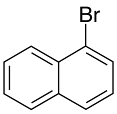
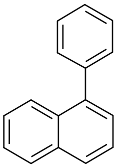
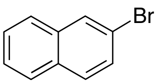
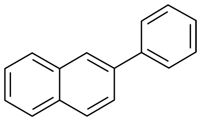


Figure 3. Product distribution as a function of time in the Suzuki cross-coupling reaction of hexabromobenzene with phenylboronic acid.

Suzuki reaction with heterocyclic brominated derivatives

Substituted heterocyclic compounds are extremely important for the synthesis of many natural and non-natural products spanning a wide range of uses in the pharmaceutical and aroma industries, as well as for the development of new materials. For example, polyphenols exhibit highly interesting electrical and optical properties. For these reasons, we initially approached the Suzuki reaction of various heterocyclic bromides with phenylboronic acid, using the same experimental conditions as in the previous tests. Table 3 shows the results. Although they are not too brilliant, they encourage further research and afford several conclusions. Thus, in thiophene, which was the substrate providing the best results (entry 3 in Table 3), introducing a second heteroatom on the ring (entry 4, 2-bromothiazole) resulted in considerably decreased conversion, the effect being even more marked when a carboxaldehyde group was introduced in α with respect to the sulfur atom (entry

Table 1. Suzuki cross-coupling reaction of various aryl bromides with phenylboronic acid

Entry[a]	Br-Ar	Product	Yield (%)[b]	Selectivity (%)[c]
1			100 (15 min)	100
2			38	63
3			35	64
4			82	94
5			84	96
6			86	92
7			81	95
8			82	96

[a] Reaction conditions: 5 ml toluene, 1.98 mmol aryl halide, 3 mmol phenylboronic acid, 3.96 mmol K_2CO_3, 0.04 mmol Pd, 90 °C. [b] Yield of cross-coupled product after 3 h of reaction (15 min for entry 1). [c] Selectivity towards the cross-coupled product after 3 h of reaction (15 min for entry 1).

5). Finally, replacing the S atom with an O atom (entry 6, 2-bromofuran) also decreased the conversion. These results are consistent with those obtained by other authors using similar heterocyclic substrates.[29,30]

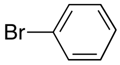
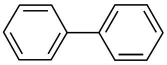
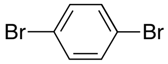
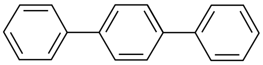
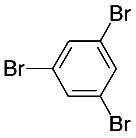
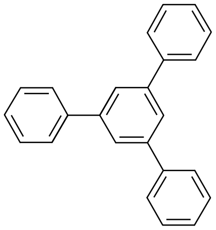
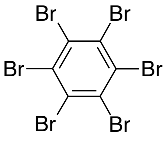
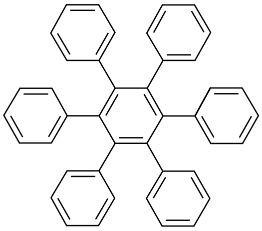
Study of the catalyst

The catalytic step of the reaction was studied by performing a hot filtration test in one of the runs. This test involves stopping the process before a preset conversion level is reached and filtering the reaction mass in order to remove the solid catalyst and then allow the reaction to proceed in its absence. Based on the results thus obtained, the filtrate was catalytically active and the reaction continued to develop in the absence of the Pd-HT catalyst. This suggests that catalysis in this process is not only of the heterogeneous type, but also of the homogeneous type as soluble palladium species which exhibit catalytic activity even after filtration is also present. The amount of palladium leached to the solution was estimated from ICP-MS measurements of the palladium content of the catalyst after three reaction times (~20% of Pd was leached).

Conclusions

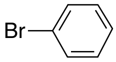
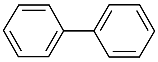
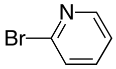
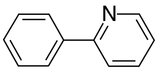
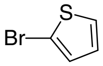
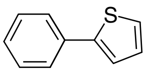
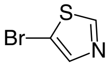
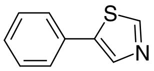
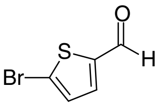
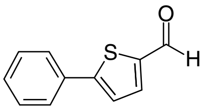
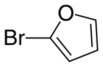
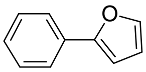
A catalyst consisting of a Pd(II) complex with acetate and pyridine supported on a 2:1 Mg–Al hydrotalcite was found to be active in the Suzuki cross-coupling reaction of various brominated substrates and phenylboronic acid. The results for monobrominated derivatives reveal a strong dependence of the electron-withdrawing or electron-releasing nature of the substituent on conversion to the cross-coupled product. Aryl polybromides give the corresponding polyaromatic compounds with excellent conversion and somewhat lower selectivity. These substrates have been found to undergo successive arylation of their brominated positions. Heterocyclic bromides provided slightly worse results. Finally, as revealed by ICP-MS measurements, some palladium is leached from the catalyst to the reaction mass.

Table 2. Suzuki cross-coupling reaction of various phenyl polybromides with phenylboronic acid

Entry[a]	Reactant	Product	Yield (%)[b]	Selectivity (%)[c]
1			100 (15 min)	100
2			93 (1 h)	93
3			75 (3 h)	76
4			37 (24 h)	38

[a] Reaction conditions: 5 ml toluene, 1.98 mmol phenyl polybromide (3 H no. Br atoms) mmol phenylboronic acid, 3.96 mmol K_2CO_3, 0.04 mmol Pd, 90 °C. [b] Yield of cross-coupled product after a variable reaction time, expressed in hours, in brackets. [c] Selectivity towards the cross-coupled product at the stated times.

Table 3. Suzuki cross-coupling reaction of various heterocyclic bromides with phenylboronic acid

Entry[a]	Reactant	Product	Yield (%)[b]	Selectivity (%)[c]
1			100 (15 min)	100
2			50	83
3			70	83
4			57	88
5			35	77
6			37	45

[a] Reaction conditions: 5 ml toluene, 1.98 mmol heterocyclic bromide, 1.98 mmol phenylboronic acid, 3.96 mmol K_2CO_3, 0.04 mmol Pd, 90 °C. [b] Yield of cross-coupled product after 3 h of reaction (15 min for entry 1). [c] Selectivity towards the cross-coupled product after 3 h of reaction (15 min for entry 1).

Experimental

General procedure for the preparation of Mg–Al hydrotalcite

The HT used was prepared from solutions of $Mg(NO_3)_2 \cdot 6H_2O$ and $Al(NO_3)_3 \cdot 9H_2O$ in an Mg(II):Al(III) ratio of 2 using a coprecipitation method described elsewhere.[31] In a typical synthetic run, a solution containing 0.2 mol of $Mg(NO_3)_2 \cdot 6H_2O$ and 0.1 mol of $Al(NO_3)_3 \cdot 9H_2O$ in 250 ml of deionized water was used. This solution was slowly dropped over 500 ml of an Na_2CO_3 solution at pH 10 at 60 °C under vigorous stirring. The pH was kept constant by adding appropriate volumes of 1 M NaOH during precipitation. The suspension thus obtained was kept at 80 °C for 24 h, after which the solid was filtered and washed with 2 l of de-ionized water. The HT solid thus obtained was ion-exchanged with carbonate to remove ions intercalated between layers. The procedure involved suspending the solid in a solution containing 0.345 g of Na_2CO_3 in 50 ml of bidistilled, de-ionized water per gram of HT at 100 °C for 2 h. Then, the solid was filtered off *in vacuo* and washed with 200 ml of bidistilled, de-ionized water. The resulting HT was subjected to a second ion-exchange operation under identical conditions. The solid was characterized from its X-ray diffraction pattern, which was consistent with the typical signals for hydrotalcite.[24] The elemental analysis performed allowed us to establish its empirical formula as $Mg_{0.70}Al_{0.35}(OH)_2(CO_3)_{0.225} \cdot 0.72H_2O$.

General procedure for the synthesis of catalyst

The HT solid was used to support the complex $Pd(CH_3COO)_2(Py)_2$ by mixing appropriate amounts of palladium acetate, pyridine and HT in toluene at 80 °C for 1 h, after which it was filtered and washed with 100 ml of toluene. The catalyst thus obtained was named HT-$PdAc_2Py_2$. The metal complex formed on the HT surface was characterized by cross-polarization magic angle spinning nuclear magnetic (^{13}C-CP/MAS NMR) spectroscopy in previous work.[14] The final palladium content as determined by ICP-MS was 0.6% by weight.[14]

Suzuki cross-coupling reaction

The Suzuki cross-coupling reaction was conducted in two-mouth flasks containing 3 mmol of phenylboronic acid, 1.98 mmol of aryl or heterocyclic bromide, 5 ml of toluene, 3.96 mmol of the base and 0.04 mmol of Pd at 90 °C. The amount of phenylboronic used with polybrominated substrates was adjusted in accordance with the number of bromine atoms in such a way as to obtain the same mole ratio as with the monobrominated substrates. One of the flask mouths was fitted with a reflux condenser and the other used for sampling at regular intervals. The system was stirred throughout the process. The resulting products were identified from their retention times by GC/MS analysis. The proportion of phenylboronic used with polybrominated substrates was 3 mmol per 1.98 mmol of bromide (e.g. hexabromobenzene was reacted with 18 mmol of the acid).

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