DOI: 10.1002/adsc.200900773

Rhodium- and Palladium-Catalyzed Hydroarylation of Propargylic Amines with Arylboronic Acids

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Received: November 6, 2009; Published online: February 10, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900773.

Abstract: The hydroarylation of 3-arylprop-2-yn-1-amine derivatives with arylboronic acids has been studied in the presence of rhodium or palladium catalysts. By using a rhodium-based catalytic system, β,γ-diarylallylamines were isolated in good yields. By contrast, the formation of the regiosomeric γ,γ-diarylallylamines was achieved by means of a palladium catalyst in the presence of acetic acid. The complementary regioselectivity displayed by these two processes is a consequence of different catalytic cycles, involving respectively carborhodation or hydropalladation of the coordinated alkyne as key steps. Calculated charge distributions in the π-complexes are in accord with the results obtained.

Keywords: alkynes; arylboronic acids; hydroarylation; palladium; propargylic amines; rhodium

Introduction

The regio- and stereoselective synthesis of multisubstituted olefins represents an important theme in organic synthesis. The transition metal-catalyzed hydroarylation of carbon-carbon triple bonds is one of the most efficient procedures towards this goal.[1]

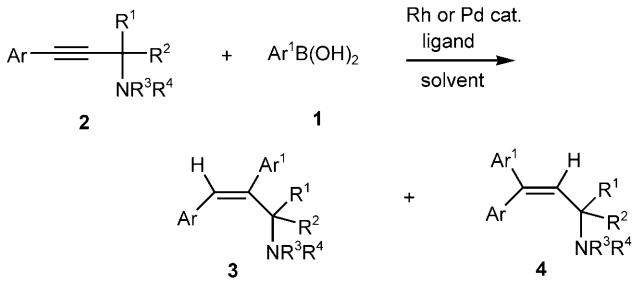
Besides unsaturated halides/triflates[2] and arenediazonium salts,[3] organoboron reagents have gained increasing attention in the last decade as possible reagents in this methodology, due to their high stability and functional group compatibility. The rhodium-catalyzed hydroarylation of disubstituted alkynes with arylboronic acids **1** in dioxane/water was first reported by Hayashi's group[4] and, since then, the reaction has been carried out in water using aza-heteroaromatic alkynes as substrates[5] and in a water-toluene biphasic system using a water-soluble ligand;[6] more recently, a phosphine-free rhodium complex has been explored as an effective catalyst.[7] As a consequence of the *syn* stereochemistry of the rhodium-catalyzed hydroarylation reaction of disubstituted alkynes, sequential heterocyclization can occur in the presence of both a nucleophilic and an electrophilic functional group close to the C≡C triple bond. We have applied such a strategy to the synthesis of butenolides[8] and quinolines[9]. Although some variation on the details of the catalytic cycle have been proposed by different authors (i.e., the occurrence of a 1-4 rhodium shift has been reported to occur in dioxane-water),[4] the reaction product is generally considered to be the result of protonolysis of the σ-vinylrhodium complex derived by the addition of an arylrhodium (I) intermediate across the C≡C triple bond of the coordinated alkyne (see Scheme 2 in the Results and Discussion section).

The regiochemical outcome of the rhodium-catalyzed hydroarylation of unsymmetrical disubstituted alkynes has been an object of study. As for phenyl-*n*-alkylacetylenes, the major[4] or unique[6] regioisomer isolated is derived from the addition of the aryl group of $ArB(OH)_2$ at the β-position with respect to the phenyl group. The replacement of the *n*-alkyl group by a $SiMe_3$ group led to a loss of regioselectivity, whereas silicon has been reported to direct the arylation of trimethylsilyl-*n*-alkylacetylenes in the β-position respect to the $SiMe_3$ group.[5] Moreover, alkynoic acid esters and alkynones were arylated exclusively at the β-position with respect to carbonyl group, likely as a consequence of electronic effects.[4,8,9] With 2-pyridyl substituents on the triple bond, chelation deter-

mined the regioselective rhodation at the position closer to the nitrogen atom.[5]

The palladium-catalyzed hyroarylation of alkynes with arylboronic acids **1** has also been investigated.[10] Usually, the reaction was carried out in the presence of acetic acid, and it was proposed that the catalytic cycle should involve an oxidative addition of a Pd(0) species to the O–H bond of AcOH[11] to give an hydridopalladium acetate. Subsequent hydropalladation of the alkyne generates a σ-vinyl palladium complex, which undergoes a transmetallation with **1** to give the reaction product after reductive elimination[10] (see Scheme 3 in the Results and Discussion section). ESI-FT-MS data concerning a related process, that is, Pd-catalyzed hydroarylation of allenes with **1** in the presence of AcOH, were in agreement with this reaction mechanism.[12] An alternative reaction path, involving the oxidative addition of Pd(0) into the C–B bond of $Ar–B(OH)_2$ followed by arylpalladation of the alkyne/protonolysis/reductive elimination, has also been suggested.[13] The stereochemical outcome of the reaction, as in the case of the Rh-catalyzed process, allowed sequential cyclization to occur.[14] The regioselectivity of the addition to unsymmetrical disubstituted alkynes was found to be influenced by steric factors and by the coordination with neighbouring groups (OH or 2-pyridyl);[13] the presence of an EWG substituent such as a keto[14b] or ester[15] group in the starting alkyne resulted in a selective β-arylation respect to the carbonyl group, but when the other substituent was a bulky tertiary alcoholic group both regioisomers were formed. A variety of ligand/solvent combinations was used in this case to direct the reaction towards the formation of one of the two regioisomers.[14a]

As part of our ongoing research activity in this field,[8,9,14b] we envisaged that the transition metal-mediated hydroarylation of propargylic amines **2** could represent a versatile new approach to diarylallylamines. It is worth noting that the reaction of propargylic amines bearing a free $-NH_2$ group failed to give the corresponding allylamine in satisfactory yield when aryl iodides were employed as organic electrophiles in the presence of formate salts and Pd catalysts.[16] Furthermore, the reaction of their corresponding *N*-tosylamide or *N*-trifluoromethanesulfonamide derivatives led to the isolation of allenes through a completely different reaction pathway involving a β-N–Pd elimination. The lack of a suitable methodology for the direct intermolecular hydroarylation made necessary, for example, the use of a two-step process (hydrostannylation/Stille coupling with aryl halides) for the conversion of a propargylic amine derivative into the γ-arylallylamine derivatives that are direct precursors of a new class of potent antagonists of the human CCR5 receptor.[17] The rhodium- or palladium-catalyzed hydroarylation of propargylic amines with arylboronic acids has not been previously explored.



Propargyl-amine	Ar =	R^1=	R^2=	R^3=	R^4=
2a	4-MeCO-C_6H_4	Me	Me	H	CH_2Ph
2b	4-$MeSO_2$-C_6H_4	Me	Me	H	CH_2Ph
2c	4-CN-C_6H_4	Me	Me	H	CH_2Ph
2d	3-CF_3-C_6H_4	Me	Me	H	CH_2Ph
2e	4-CF_3-C_6H_4	Me	Me	H	CH_2Ph
2f	3-pyridyl	Me	Me	H	CH_2Ph
2g	4-MeO-C_6H_4	Me	Me	H	CH_2Ph
2h	4-$MeSO_2$-C_6H_4	Me	Et	H	CH_2Ph
2i	4-MeCO-C_6H_4	$-(CH_2)_5-$		H	H
2j	4-MeCO-C_6H_4	n-C_5H_{11}	H	H	CH_2Ph
2k	4-MeCO-C_6H_4	H	H	$-(CH_2)_5-$	

Ar^1 =

1a: = Ph
1b: = 3-MeO-C_6H_4
1c: = 3-MeCO-C_6H_4
1d: = 4-Me-C_6H_4
1e: = 4-MeS-C_6H_4

Scheme 1. Hydroarylation of propargylic amines **2a–k** with arylboronic acids **1a–e**.

The task of our investigation was therefore to achieve the synthesis of both β,γ- and γ,γ-regioisomers **3** and **4** by determining the factors which direct the regiochemical outcome of the reaction (Scheme 1).

Results and Discussion

We began our study by investigating the rhodium-catalyzed hydroarylation of **2a** with phenylboronic acid **1a**.

The reaction was carried out using different catalyst/solvent/temperature combinations (Table 1). All reactions afforded β,γ-diarylallylamine **3aa** as a single isomer (purity >95% by GC-MS analysis), and its structure was unambiguously assigned by NOE experiments (see Supporting Information). Under the hydroarylation conditions reported by Hayashi and co-workers,[4] **3aa** was obtained in moderate yield

Table 1. Rh-catalyzed hydroarylation of **2a** with $PhB(OH)_2$ **1a**.[a]

Entry	Catalyst	Ligand	Equiv. of **1a**	Solvent	**3aa**% yield[c]
1	$Rh(acac)(C_2H_4)_2$	dppf	5	dioxane/water[b]	50[d]
2	$Rh(acac)(C_2H_4)_2$	dppf	5	dioxane/water[b]	70
3	$Rh(acac)(C_2H_4)_2$	dppf	3	dioxane/water[b]	68
4	$Rh(acac)(C_2H_4)_2$	dppf	3	EtOH	87
5	$Rh(acac)(C_2H_4)_2$	dppf	3	EtOH/water[b]	88
6	$[Rh(cod)OH]_2$	dppf	3	EtOH/water[b]	86
7	$[Rh(cod)OH]_2$	dppf	3	EtOH/water[b]	82[e]
8	$[Rh(cod)OH]_2$	dppp	3	EtOH/water[b]	92[f]
9	$[Rh(cod)OH]_2$	dppp	2	EtOH/water[b]	67 g]
10	$[Rh(cod)OH]_2$	dppb	3	EtOH/water[b]	76
11	$[Rh(cod)OH]_2$	dppe	3	EtOH/water[b]	85
12	$[Rh(cod)OH]_2$	binap	3	EtOH/water[b]	70

[a] Unless otherwise stated reactions were carried out on a 0.25 mmol scale with 3.5 mol% of Rh and 3.5 mol% of ligand, using 1.5 mL of solvent at 80 °C under an N_2 atmosphere for 8 h.
[b] 95:5 v/v.
[c] HPLC yields.
[d] Carried out at 100 °C.
[e] Carried out at 60 °C for 24 h.
[f] Isolated yield.
[g] Reaction time: 16 h.

(entry 1). Carrying out the process at 80 °C afforded better results (entry 2). The molar excess of **1a** can be reduced to 300% without significative yield lowering (entry 3). Interestingly, dioxane can be replaced by the more environmentally friendly ethanol or ethanol/water mixture 95:5 v/v (entries 4 and 5). The cheaper binuclear $[Rh(cod)OH]_2$ was as efficient as $Rh(acac)(C_2H_4)_2$ (entries 5 and 6) and the reaction can be carried out also at 60 °C with longer reaction times (entry 7). A screening of some chelating phosphines revealed that all those tested were effective, and 1,2-bis(diphenylphosphino)propane (dppp) afforded the best result (entry 8). Using the latter ligand, a good yield was obtained even with further reduction of the molar excess of **1a** (entry 9).

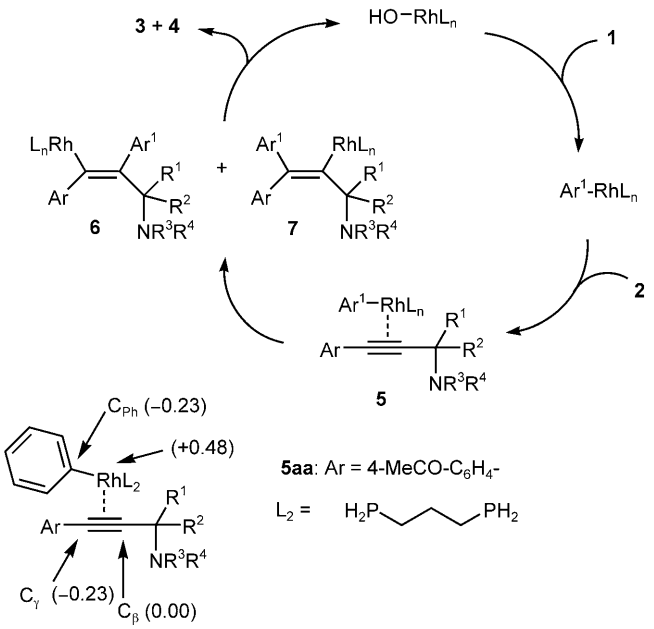
The procedure was then extended to include different propargylic amine/boronic acid combinations, and the results are summarized in Table 2.

The rhodium-catalyzed reaction of tertiary, secondary and primary propargylic amine derivatives with various arylboronic acids afforded the β,γ-diarylallylamines **3** in moderate to excellent yields. According to the literature,[4–6] a plausible catalytic cycle for this reaction is depicted in Scheme 2. The process proved to be highly regioselective, and the observed **3**:**4** ratios (determined by GC-MS analysis of crude reaction mixtures) were higher than 95:5; only in the hydroarylation of **2d** was the regioisomer **4da** detected in a significative amount (entry 9). Interestingly, the hindrance of propargylic groups did not affect the regioselectivity: that is, with substrates **2j** (bearing as substituent an *N*-benzyl group bonded to a secondary carbon) and **2i** (bearing a free amino group bonded to a tertiary carbon) the regioselectivity control was accomplished as well as with the substrate **2k**, whose substitution pattern around the triple bond resembles that of the aforementioned *n*-alkylacetylenes.[4,6] Our results can be rationalized by taking into account various considerations. The general predominance of re-

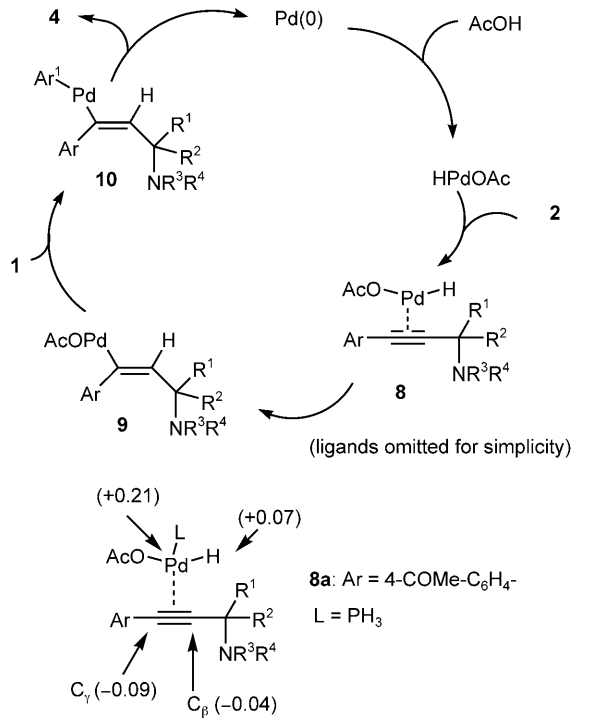
Table 2. Rh-catalyzed hydroarylation of propargylicamines **2** with arylboronic acids **1**.[a]

Entry	Propargylic amine **2**	Arylboronic acid **1**	Time [h]	Product (Yield [%])[b]
1	**2a**	**1b**	8	**3ab** (88)
2	**2a**	**1c**	24	**3ac** (84)
3	**2a**	**1d**	7	**3ad** (83)
4	**2b**	**1a**	5	**3ba** (86)
5	**2b**	**1d**	4	**3bc** (81)
6	**2b**	**1d**	4	**3bd** (95)
7	**2b**	**1e**	3.5	**3be** (97)
8	**2c**	**1a**	6	**3ca** (78)
9	**2d**	**1a**	11	**3da** (40)[d]
10	**2f**	**1a**	5	**3fa** (89)
11	**2g**	**1a**	24	**3ga** (42)[c]
12	**2h**	**1a**	5.5	**3ha** (73)
13	**2i**	**1a**	6	**3ia** (49)
14	**2j**	**1a**	22	**3ja** (77)
15	**2k**	**1a**	4	**3ka** (47)

[a] Reactions were carried out on a 0.5 mmol scale in 3 mL of ethanol/water 95:5 v/v at 80 °C under N_2 atmosphere using the following molar ratios: **2**:**1**:$[Rh(COD)OH]_2$:dppp = 1:3:0.0017:0.0035.
[b] Isolated yields.
[c] **2**:**1**: $[Rh(COD)OH]_2$:dppp = 1:3:0.0035:0.007.
[d] The regioisomer **4da** was obtained in 20% yield



Scheme 2. Proposed catalytic cycle for the Rh-catalyzed hydroarylation of propargylic amines **2**.



Scheme 3. Proposed catalytic cycle for the Pd-catalyzed hydroarylation of propargylic amines **2**.

gioisomer **3** suggests that the reaction outcome is not under the influence of steric factors: it is conceivable that, if those factors were determinant, the formation of regioisomers **4** should be favoured, according to the general trend observed, for example, in the Pd-catalyzed hydroarylation of alkynes with aryl halides or vinyl triflates[2] (in which, as in the present process, carbometallation of coordinated alkyne is the regioselectivity-determining step). Coordination of the neighbouring amino group to rhodium[5] would, also, result in the formation of **4** through the intermediate **7**.

As reported in the Introduction section, the presence of a carbonyl group conjugated to the triple bond determined the regioselectivity of the rhodium-catalyzed hydroarylation of internal alkynes;[4,8,9] showing that electronic effects can be of primary importance in controlling the carborhodation step. We therefore carried out quantum-chemical calculations, with the aim to evaluate the charge distribution in the π-complexes **5** that undergo carborhodation in the present case. Atomic point charges of **5aa** (derived from **2a**) are shown in Scheme 2, while the results relative to other π-complexes are reported in the Supporting Information. In all cases the calculated negative charge on C_γ was higher than that on C_β, whereas the rhodium atom showed a positive charge and the C_{Ph} a negative charge. As a consequence, the formation of C_γ–Rh and C_β–Ph bonds should be favoured, giving rise preferentially to σ-vinylrhodium intermediates **6**, in accord with the experimental results.

We next turned out to consider charge distribution for π- complex **8** that should be formed in the palladium-catalyzed hydroarylation of **2** with **1**. Our previous results, using β-(2-aminophenyl)-α,β-ynones as substrates in the hydroarylation reaction with organoboron compounds, revealed that palladium catalysts in the presence of AcOH were as efficient as rhodium catalysts.[9,14b] The calculations applied to the π-complex **8a**, deriving from the coordination of propargylamine **2a** to hydridopalladium acetate, showed a strong positive charge on the palladium atom, while the negative charge on C_γ was higher than that on C_β (Scheme 3).

On the basis of this charge distribution, we envisaged that the use of palladium catalysis could result in an inversion of the regiochemistry, providing a straightforward entry into regioisomers **4**. To verify this hypothesis, the reaction of **2a** with **1a** was then carried out, and the results are reported in Table 3. The use of 0.15 equivalents of acetic acid with $Pd(OAc)_2$/dppe in ethanol (Table 3, entry 1) did not produce any detectable amount of product, although these reaction conditions were found to be suitable for the hydroarylation of β-(2-aminophenyl)-α,β-ynones. Likely, the higher basicity of **2a** could account for this result, determining the deprotonation of acetic acid and the reaction inhibition. We therefore increased the amount of AcOH (Table 3, entries 2 and 3), and we were pleased to find that **4aa** was obtained as the sole product, although with unsatisfactory yields.

The structure of **4aa** was assigned on the basis of the chemical shift of the vinylic proton (that occurs at

Table 3. Pd-catalyzed hydroarylation of **2a** with **1a**.[a]

Entry	Catalyst (equiv. %)	Ligand (equiv. %)	Equiv. of acetic acid	**4aa** Yield[b] [%]
1	$P(OAc)_2$ (5)	dppe (5)	0.1	–
2	$P(OAc)_2$ (5)	dppe (5)	1.3	20
3	$P(OAc)_2$ (5)	dppe (5)	1.3	17[c]
4	$P(OAc)_2$ (5)	$P(Cy)_3$ (10)	1.3	82

[a] Reactions were carried out on a 0.25 mmol scale in ethanol at 80 °C using 3 equiv. of **1a**, unless otherwise stated.
[b] Isolated yield.
[c] Carried out at 100 °C with 5 equiv. of **1a**.

higher field with respect to **3aa**)[2c] and was confirmed unambiguously by NOE experiments (see Supporting Information). Finally, the use of tricyclohexylphosphine as ligand instead of dppe resulted in a dramatic improvement of the yield of **4aa** (entry 4).

The Pd-catalyzed hydroarylation was then extended to include different propargylic amines and boronic acids (Table 4). Allylamines **4** were isolated in moderate to good yields, and in all the experiments **4**:**3** ratios (GC/MS analysis) were higher than 96:4. Pd(0) can be used as catalyst in place of Pd(II) with similar results (entries 10 and 11).

In addition to charge distribution, steric hindrance around the propargylic carbon could be responsible for the observed regioselectivity. Hydroarylation of propargylic amines **2j** and **2k**, bearing secondary and primary propargylic groups afforded, however, product distributions (entries 9–11) similar to that observed in the presence of tertiary propargylic groups (entries 1–8). This observation points out that, at least within the examples tested, steric effects play a minor role in controlling the reaction outcome.

Table 4. Pd-catalyzed hydroarylation of propargylic amines **2** with arylboronic acids **1**.[a]

Entry	Propargylic amine **2**	Arylboronic acid **1**	Time [h]	Product (Yield [%])[b]
1	**2a**	**1b**	3.5	**4ab** (77)
2	**2a**	**1c**	3.5	**4ac** (78)
3	**2b**	**1e**	6	**4be** (43)
4	**2c**	**1a**	6.5	**4ca** (85)
5	**2d**	**1a**	3.5	**4da** (78)
6	**2e**	**1a**	8	**4ea** (60)
7	**2f**	**1a**	36	**4fa** (69)
8	**2i**	**1a**	36	**4ia** (54)
9	**2j**	**1a**	4.5	**4ja** (70)
10	**2k**	**1a**	2	**4ka** (78)
11	**2k**	**1a**	4	**4ka** (80)[c]

[a] Reactions were carried out on a 0.5 mmol scale in 3 mL of ethanol at 80 °C under N_2 atmosphere using the following molar ratios: **2**:**1**:AcOH:$Pd(OAc)_2$:$(Cy)_3P$ = 1:2:1.2:0.05:0.10.
[b] Isolated yields.
[c] Carried out using 0.0025 equiv. of $Pd_2(dba)_3$ as Pd source.

The results obtained in the Rh- and Pd-catalyzed reactions are in agreement with the hypothesis that, in both cases, the main product is generated through migration of the metal atom towards C_γ. According to this view, the inversion of regioselectivity observed can be rationalized taking into account the difference between the two catalytic cycles, involving respectively arylrhodation and hydropalladation of the coordinated triple bond: in the former case the aryl group migrates to the C_β position, while in the latter it is introduced in the position occupied by the Pd, that is, C_γ, by subsequent transmetallation.

Conclusions

In conclusion, we have developed an efficient procedure for the hydroarylation of propargylic amines **1**, opening a new route towards β,γ-diarylallylamines **3** and γ,γ-diarylallylamines **4**. The reaction tolerates a variety of functional groups, and can be applied to primary, secondary and tertiary propargylic amines. While in the presence of Rh the arylation occurred mainly on the *sp* carbon closer to the nitrogen, the use of a Pd catalyst under acidic conditions resulted in the complete inversion of regioselectivity, showing the complementary character of the two processes. In both cases, the calculated charge distribution in the intermediate π-complexes that undergo carborhodation or hydropalladation is in accord with the observed regioselectivity.

Experimental Section

General

All reactions were carried out under a nitrogen atmosphere, and were monitored using T.L.C. and/or GC/MS analysis. The syntheses of propargylic amines **2a, 2d, 2f** and **2h** were previously described.[18] Propargylic amines **2b**, **2c**, **2e**, **2g**, **2i**, **2j** and **2k** were obtained in a similar manner by Sonogashira coupling of the corresponding terminal alkynes with aryl halides (see Supporting Information).

General Procedure for the Rh-Catalyzed Hydroarylation

To a solution of propargylic amine **2** (0.5 mmol) in 3 mL of ethanol/water (95:5 v/v) were added the arylboronic acid **1** (1.5 mmol), $[Rh(COD)OH]_2$ (0.0035 mmol) and dppp (0.017 mmol). The mixture was stirred at 80 °C under N_2 atmosphere for the appropriate time and monitored by TLC and/or GC-MS analysis. After completion, the mixture was purified by chromatography on silica gel eluting with hex-

anes/ethyl acetate mixtures to afford the pure derivative **3**. Characterization data for products **3** can be found in the Supporting Information.

General Procedure for the Pd-Catalyzed Hydroarylation

To a solution of propargylic amine **2** (0.5 mmol) in 3 mL of ethanol were added the arylboronic acid **1** (1.5 mmol), acetic acid (0.6 mmol), $Pd(OAc)_2$ (0.025 mmol) and tricyclohexylphosphine (0.05 mmol). The mixture was stirred at 80 °C under N_2 atmosphere for the appropriate time and monitored by TLC and/or GC-MS analysis. After completion, the mixture was purified by chromatography on silica gel eluting with hexanes/ethyl acetate mixtures to afford the pure derivative **4**. Characterization data for products **4** can be found in the Supporting Information.

Acknowledgements

This work was supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome, and by the University of L'Aquila. The authors would like to thank CASPUR (Roma) for the use of Gaussian 03 program.

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