Palladium-catalyzed unsymmetrical aryl couplings in sequence leading to *o*-teraryls: dramatic olefin effect on selectivity[†]

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Selectively substituted *o*-teraryls are obtained by palladium/ norbornene-catalyzed reaction of aryl iodides, aryl bromides and aryl boronic acids in ordered sequence; high selectivity is attained thanks to the addition of diethyl maleate acting as palladium ligand.

Olefins are known to remarkably influence transition-metalcatalyzed processes.¹ In particular, oxidative addition, 1a,f reductive elimination^{1k} and coupling^{1a} steps have been reported to be quite sensitive to their influence. Controlling a sequence of several organometallic steps by olefin addition should be regarded as a very simple and effective way to arrive at complex molecules selectively. To this aim we have addressed the synthesis of *o*-teraryl derivatives, which belong to an important class of aromatic compounds exhibiting unique properties useful in the field of advanced materials and in medicinal chemistry.² In particular, *ortho*-teraryls are interesting for molecular dynamics properties^{2b} and biological activity.^{2c}

We have developed a one-pot reaction involving sequential cross-coupling of iodoarenes, containing *ortho*-electron-donating substituents, with bromoarenes bearing electron-withdrawing groups, followed by aryl coupling with arylboronic acids (Scheme 1; R^1 = electron-donating, R^2 = electron-withdrawing group). Owing to the directing action of the palladium/norbornene dual catalyst,³ the aryl halides couple



Scheme 1 Palladium/norbornene-catalyzed aryl-aryl coupling followed by Suzuki reaction.



Scheme 2 Palladium/norbornene-catalyzed aryl-aryl coupling followed by Heck reaction.

ortho to the original C–I bond, which in its turn couples with aryl boronic acids in the final step, leading to *o*-teraryls.

The selectivity in the expected cross-coupling product 3 turns out to be low, however. Thus, the reaction of *o*-iodotoluene (1; $\mathbb{R}^1 = \mathrm{Me}$), methyl *o*-bromobenzoate (2; $\mathbb{R}^2 = \mathrm{CO}_2\mathrm{Me}$) in 1:1 molar ratio with phenylboronic acid under the conditions of Scheme 1 led to a mixture of three products 3, 5⁴ and 6⁴ ($\mathbb{R}^1 = \mathrm{Me}$, $\mathbb{R}^2 = \mathrm{CO}_2\mathrm{Me}$) in 0.6:1:1 molar ratio. The lack of selectivity is in sharp contrast with the analogous reaction with olefins previously reported by us (Scheme 2),^{3e} which is highly selective.

We reasoned that the origin of this disappointing behavior had to be found in the absence of an appropriate olefin. The latter worked as a reagent in the reaction depicted in Scheme 2 but could also act as ligand. We were pleased to find that the addition of an olefin, containing electron-withdrawing substituents and not involved as reagent, increased the selectivity in compound **3** dramatically (Scheme 1).

We thus decided to explore the behavior of a series of activated olefins in the reaction of Scheme 1. They were found to be effective in the order: diethyl or dimethyl maleate \geq diethyl fumarate > methyl cinnamate > methyl crotonate. Table 1 reports the results obtained with *ortho*-substituted aryl iodides and bromides in the presence and in the absence (in parentheses) of diethyl maleate, which turned out to be the olefin of choice.

As shown in Table 1, entries 1–9, the non selective reaction leading to products **3–6** (yields reported in parentheses) can be converted into a selective one in the presence of diethyl maleate in 1.6 : 1 molar ratio to the aryl halides.⁵ Aryl iodides containing an *ortho* alkyl substituent such as the methyl and *i*-propyl ones (entries 1, 4) or additional methyl groups in *meta* and *para* positions (entries 2 and 3) lead to satisfactory results when caused to react with methyl *o*-bromobenzoate and phenylboronic acid in the presence of diethyl maleate. The added electron-poor olefin dramatically reduces, if not completely prevents, the formation of teraryls **5** and **6** resulting from homo-coupling of the corresponding iodides and bromides.⁴ A similar behavior is observed with 1-iodonaphthalene and methyl *o*-bromobenzoate (entry 5) as well as with

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 Table 1
 Reaction of ortho-substituted aryl iodides (1) and bromides (2) with phenylboronic acid^a

Entry	\mathbb{R}^1 in $\mathbb{1}$	\mathbf{R}^2 in 2	3 Yield (%) ^{b,c}	4 Yield (%) ^{b,c}	5 Yield (%) ^{<i>b,c</i>}	6 Yield (%) ^{b,c}
1	Me	CO ₂ Me	87 (30)	_	3 (50)	6 (50)
2	Me + 3-Me	CO_2Me	68 (30)	_	3 (44)	6 (53)
3	Me + 4-Me	CO_2Me	82 (24)	_	5 (48)	4 (53)
4	<i>i</i> -Pr	CO_2Me	84 (46)	_	- (30)	4 (40)
5	Naphthyl	CO_2Me	86 (65)	_	7 (25)	5 (22)
6	Me	$Me + 4-CO_2Me$	78 (55)	_	2 (37)	5 (43)
7	Me	NHCOCF ₃	83 (50)	_		
8	Me	NO ₂	78 (40)	7 (45)	2 (2)	5 (9)
9	Me	SO ₂ Me	61 (5)	3 (55)	10 (34)	- (38)
10	Me	CF_3	_ `	3 (89)	30 ()	_ ` ´
11	CF ₃	CO ₂ Me	67 (83)		_ ` ´	3 (10)

^{*a*} Reactions were carried out with $Pd(OAc)_2$ (0.022 mmol), norbornene (0.55 mmol), diethyl maleate, if used (1.76 mmol), K_2CO_3 (4.40 mmol), the aryl iodide (1.10 mmol), the aryl bromide (1.10 mmol) and phenylboronic acid (1.32 mmol) in DMF (20 mL) under nitrogen at 105 °C for 24 h. ^{*b*} Isolated yield; GC yield for values below 10%. ^{*c*} In parentheses: yield in the absence of diethyl maleate.

o-iodotoluene and *o*-bromotrifluoroacetanilide as bromide partner (entry 7). *o*-Iodotoluene in combination with methyl *p*-bromobenzoate behaves analogously, provided that a further substituent is present *ortho* to Br as in methyl 4-bromo-3-methylbenzoate (entry 6). The positive effect of the olefin is also at work in the reaction of *o*-iodotoluene and *o*-bromonitrobenzene (entry 8) to depress the formation, in this case, of teraryl **4**. With the same *ortho* substituted aryl iodide and *o*-bromo(methylsulfonyl)benzene (entry 9) the use of the olefin is needed to control the formation of teraryls **4**, **5** and **6**. Exceptions are offered by the reaction of *o*-iodotoluene with *o*-trifluoromethylbromobenzene and phenylboronic acid (entry 10) and *o*-trifluoromethylboronic acid (entry 11). These cases will be considered later.

Formation of compound **3** can be explained according to our previously reported finding^{3*a,b*} (Scheme 3). Oxidative addition of palladium(0) to the aryl iodide followed by stereoselective norbornene insertion leads to the *cis*, *exo* arylnorbornylpalladium iodide **8**.⁶ This species readily undergoes ring closure through sp² C–H bond activation,⁷ to give palladacycle **9**,⁸ which selectively reacts with the aryl bromide to afford the intermediate **10**, thus allowing the cross-coupling of two different



Scheme 3 Proposed reaction pathway for the formation of teraryl 3 through aryl–aryl coupling and Suzuki reaction. L = solvent, diethyl maleate, coordinating substrates.

aryl units, coming from the iodo- and bromo-arene, respectively. The catalytic cycle proceeds with norbornene deinsertion, likely caused by steric effects, to form the biarylpalladium intermediate 11.^{9,10} Reaction of intermediate 11 with arylboronic acid gives compound 3. Formation of the symmetrical teraryl 5, in which both rings come from the initial aryl iodide, is due to preferential reaction of the latter with palladium(0) and also with palladacycle 9. The catalytic cycle can be initiated as well by aryl bromide, more activated than the aryl iodides, thus leading to the corresponding palladacycle of type 9, and then can proceed by reaction either of the aryl bromide or of the aryl iodide. In the former case the symmetrical teraryl 6 is obtained, while in the latter the unsymmetrical product 4 is formed.

As previously reported, 3a,b,9 an *ortho*-substituent in the aryl iodide **1** is needed to cause selective aryl–aryl coupling in the reaction step from palladacycle **9** to intermediate **10** (Scheme 3). By contrast, the electron-withdrawing substituent in aryl bromide **2** is not needed in the *ortho* position. We thus carried out the reaction of an *ortho*-substituted aryl iodide, such as *o*-iodotoluene, with aryl bromides bearing electronwithdrawing substituents in the *meta* or *para* position (Table 2). Results are collected separately in Table 2 because in these cases maleic ester addition mainly affects selectivation of **14** in respect to products other than teraryls.¹²

o-Iodotoluene and 1-iodonaphthalene give good yields with variously *meta*- and *para*-substituted bromobenzenes as well as with *p*-bromopyridine. Substituted and unsubstituted aryl boronic acids behave similarly.

Addition of the maleic ester to the reaction mixture thus leads to satisfactory selectivity. As anticipated, exceptions are offered by some substituents such as the o-CF₃ in aryl iodides and bromides. In the former case (Table 1, entry 11) the substituent strongly favors the initial reaction of the aryl iodide with palladium(0) but inhibits the subsequent reaction of the aryl iodide itself with palladium(II),¹³ so that addition of the maleic ester is no longer necessary. In the latter case (Table 1, entry 10) the o-CF₃ is again unable to cause the aryl bromide to react with the palladium(II) complex but reacts with palladium(0) faster than o-iodotoluene, which instead can react with palladium(II). As a result compound 4 (entry 10) is formed. Addition of the maleic ester depresses the reaction of the aryl bromide with palladium(0) in favor of terphenyl 5.

Table 2 Reaction of *ortho*-substituted aryl iodides with aryl bromidesbearing electron-withdrawing groups, followed by coupling with arylboronic acids^a

	-R ¹ + X 12 R	+ + + 13 R ³	Pd(OAc K ₂ CO ₃ , I 105°C, 2	DMF	R ² X R ¹ 14
Entry	\mathbf{R}^1	R ²	Х	R ³	14 Yield (%) ^{b,c}
1 2 3 4	Me Me Me Me	4-CO ₂ Me 3-CF ₃ 4-CF ₃ 3-NO ₂	CH CH CH CH	H H H H	84 (61) 85 (60) 89 (66) 78 ^d (10)
5 6 7 8 9 10 11	Me Me Naphthyl Naphthyl Naphthyl Naphthyl	4-NO ₂ 4-CN H 4-CO ₂ Me H H	CH CH N CH N N N	H H H H 4-Me 4-F	90 (7) 77 (70) 70 (61) 94 (85) 88 (75) 84 (73) 95 (80)

^{*a*} Reactions were carried out with Pd(OAc)₂ (0.022 mmol), norbornene (0.55 mmol), diethyl maleate, if used (1.76 mmol), K₂CO₃ (4.40 mmol), the aryl iodide (1.10 mmol), the aryl bromide (1.10 mmol) and the aryl boronic acid (1.32 mmol) in DMF (20 mL) under nitrogen at 105 °C for 24 h. ^{*b*} Isolated yield. ^{*c*} In parentheses: yield in the absence of diethyl maleate. ^{*d*} Yield increased to 90% in 90 h.

The reason for the maleic ester effect shown in Tables 1 and 2 should be found in the ability of this olefin to coordinate palladium species and to stabilize palladium($_0$). The latter is known to intervene in the oxidative addition and in the reductive elimination steps, the former being depressed^{1a,f} and the latter accelerated.^{1k}

To account for our results the maleic ester effect should lower the reactivity of aryl bromide in respect to that of the aryl iodide. In view of the extreme complexity of a kinetic analysis of the sequences involved, however, we refrain from putting forward speculations, limiting ourselves to the synthetic results, which offer a valuable tool to the experimenter. The methodology indeed offers a valid alternative to other coupling reactions,^{2a,11e} in particular to the two-step Suzuki reaction of bifunctional arenes with aryl boronic acids, inasmuch as these products are obtained in one-pot from simple and readily available building blocks.

Some of the obtained teraryls (compounds **3** and **14**) display interesting properties in that the presence of *ortho* substituents prevents rotation of the aryl rings as evidenced by NMR spectroscopy.⁴ For example, the *ortho* and *meta* carbons of the unsubstituted phenyl ring of compound **3** ($\mathbf{R}^1 = i$ -Pr, $\mathbf{R}^2 = CO_2Me$) resonate at four distinct chemical shifts.

In conclusion we have worked out a catalytic sequential coupling methodology which leads to good selectivity thanks to the addition of maleic ester to the reaction mixture as ligand for palladium. As a matter of fact it has become possible to obtain teraryl derivatives in a one-pot reaction starting from simple aryl iodides and bromides used in equimolar amounts.

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- 12 By-products formation strongly depends on substituents. For example, in the absence of diethyl maleate *p*-bromonitrobenzene (Table 2, entry 5) gives an 80% yield of 4-nitrobiphenyl while the *meta* isomer leads to the formation of only *ca.* 20% of the corresponding biphenyl together with other by-products containing norbornene.
- 13 As we previously observed, ^{3b,e} the presence of the *o*-CF₃ in both iodobenzene and bromobenzene inhibits the reaction of these aryl halides with palladacycles of type **9** (Scheme 3). This suggests a strong interference of the *o*-CF₃ group with the palladium(II) species.