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Carbonylative and direct Suzuki–Miyaura cross-coupling reactions with 1-iodo-cyclohexene

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Abstract

The Suzuki–Miyaura reaction of 1-iodo-cyclohexene and phenylboronic acid (or 3-trifluoromethoxy-phenylboronic acid) was investigated concerning the detailed analyses of the catalytic mixtures. The reaction was carried out both under argon ('direct' Suzuki–Miyaura coupling) and carbon monoxide ('carbonylative' Suzuki–Miyaura reaction). Palladium(II) acetate based in situ formed palladium(0) catalysts were used as catalytic system. The detailed analysis revealed the importance of the formation of the Heck-products and the homo-coupling of the substrate. The corresponding alkenyl-aryl-ketone was obtained by carbon monoxide insertion into palladium(II)-aryl bond.
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1. Introduction

The activation of a C−X bond with a transition metal complex leading to C−C bond formation has furnished an enormous variety of fascinating transformations in organic synthesis [1–4]. Although the vast majority of the reactions require substrates having sp or sp^2 carbons at or immediately adjacent to an electrophilic center, there are also a number of examples for the use of aliphatic C−X compounds (i.e. sp^3 carbon attached to halide) and have been reviewed [5].
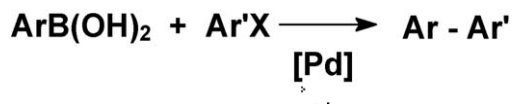
Among these C−C bond forming reactions, the palladium catalysed cross-coupling of organoboronic acids or organoboronates with organic electrophiles (referred usually as Suzuki–Miyaura (SM) reaction [6]) turned out to be a successful one due to its versatility as shown by several reviews [7–10] (Scheme 1).

Its importance lies mainly in the straightforward synthesis of oligoaryls (oligoheteroaryls) or dienes in aromatic or vinylic couplings, respectively, under mild reaction conditions. The Suzuki–Miyaura reaction has gained a special importance in the last few years because the conditions developed for this reaction have many desirable features for large-scale synthesis of pharmaceuticals and fine chemicals. The boronic acids and esters proved to be more user-friendly and environmentally safer than the other main-group organometallic reagents like Grignard reagents and organostannanes. A review focused also on these topics has been published [11].

Among the substrates, various aryl halides or triflates predominate. However, related to the topic of this paper, there are also some examples for the use of alkenyl halides or alkenyl triflates. The SM coupling using geminal dibromo-olefins or iodo-alkene substrates provided bromo-dienes or polyolefins, respectively [12–14]. The enol-triflate functionality involved in a six-membered ring gave good yields under mild conditions, whereas the five-membered analogues showed poor reactivity [15]. A synthetic analogue cyclohexenylphosphate reacts also with a variety of arylboronic acids [16]. The electron-poor iodo-quinone underwent coupling with phenylboronic acid to produce the reduced form of the corresponding phenylquinones [17]. It is worth mentioning that bromo-naphthoquinone with similar structure was decomposed under same conditions [18]. Fluorinated olefins with bromoalkene moiety have been transferred to 1-aryl-1-fluoro-olefins [19] or trifluoromethyl-containing tetrasubstituted enol ethers [20]. The consecutive use of Sonogashira and SM reactions led to the formation of geometrically pure alkenyl substituted branched

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Scheme 1. The general scheme of the Suzuki–Miyaura coupling.

Scheme 3. Ketone synthesis via Pd-catalysed reaction of acyl chloride and aryl-boronic acid.

enynes by using 1,1-dibromo-1-alkene substrate [21]. Various 4-substituted 1-methylimidazoles have been synthesised by using the corresponding 4-bromo-1-methyl-imidazoles and the organoboronic acids in the presence of Pd(PPh$_3$)$_4$ precursor [22]. The synthesis of 17-(3′-pyridyl)-androst-5,16-dien-3β-ol (abiraterone) and 17-(5′-pyronyl)-androst-16-enes has been carried out by reacting the appropriate 17-iodo-16-ene compounds with diethyl(3-pyridyl)borane and 2-pyrone-5-boronate derivative, respectively [23,24].

If carbon monoxide insertion during the Suzuki coupling reaction took place, ketones from simple building blocks (organic halide, carbon monoxide and boronic acid derivative) would be available even in those cases when the synthesis of the corresponding acylchloride is not feasible. There are only sporadic results for this protocol only, where diarylketones [25] (Scheme 2) and indol-2-yl ketones [26] were synthesised.

Although there are many results on the synthesis of *diaryl ketones* via SM reaction *of acylchlorides/anhydrides and aryl-boronic acid* derivatives [27–31] (Scheme 3), the facile synthesis of *aryl-alkenyl ketones* still remained a challenge.

Although the SM reaction proved to be of high importance for the synthesis of the great variety of compounds under certain conditions (after optimisation), there are a number of 'undesired' reactions which are often overlooked. In this paper, we describe our results on the systematic catalytic investigation of the reaction conditions in the SM reaction, as well as that on carbonylative SM reaction with 1-iodo-cyclohexene as modell substrate.

2. Results and discussion

1-Iodo-cyclohexene (**1**) and phenylboronic acid (**2**) (or 3-trifluoromethoxy-phenylboronic acid, (**3**)) were reacted under carbon monoxide (1 bar) atmosphere in the presence of in situ formed palladium(0) catalysts. Palladium(II) acetate served as catalytic precursor and its reduction with phosphine provided the highly reactive, coordinatively unsaturated palladium(0) catalyst.

The expected carbonylative products (**4a** or **5a**, respectively, Scheme 4) have been formed in all cases depending on the reaction conditions (vide infra). Their formation is explained by the oxidative addition of **1** to Pd(0) species, which is followed by carbon monoxide activation, its insertion to palladium-alkenyl bond and arylation of the resulted palladium–acyl
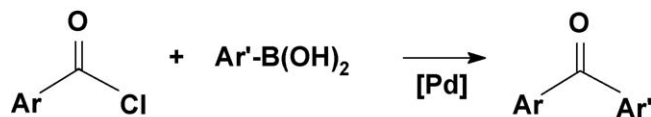
(palladium–cyclohexenoyl) complex in the product forming step (Scheme 5, cycle A).

The formation of the expected unsaturated ketones is accompanied by further parallel and consecutive coupling reactions. In most cases, the 'direct' coupling reaction, including the arylation of the Pd-cyclohexenyl species, prevails. The reaction gives 1-phenyl-cyclohexene (**4b**) or 1-(3′-trifluoromethoxy-phenyl)-cyclohexene (**5b**) (Scheme 5, cycle B). The direct SM coupling is followed by Heck reaction between **4b** (or **5b**) and iodo-cyclohexene (**1**) resulting in the formation of 1-phenyl-2-(cyclohexen-1-yl)-cyclohexene (**4c**) or 1-(3′-trifluoromethoxy-phenyl)-2-(cyclohexen-1-yl)-cyclohexene (**5c**), respectively (Scheme 5, cycle C). The isomerization products of **4c** and **5c** have been also detected in traces. (The olefinic side-products were not isolated as pure substances from the reaction mixtures. They were identified by GC-MS and by using the corresponding reference compounds for GC-MS and TLC.) It is worth noting that the similar Heck reaction between the unsaturated ketones (**4a** or **5a**) and iodo-cyclohexene (**1**) has not been observed. The deactivation of the olefin by the acyl group might result in the lack of these compounds in the reaction mixture.

Depending on the reaction conditions, further side reactions have been observed. The carboxamidation with dimethylformamide resulted in 1-(dimethylcarboxamido)-cyclohexene (**1a**). Symmetrical homo-coupling of **1** yielded **1b**, while the similar reaction with the corresponding acyl-intermediate (formed upon oxidative addition of **1** to Pd(0) species, followed by carbon monoxide insertion) resulted in bis(1-cyclohexenyl)-glyoxal (**1c**). The reaction of a Pd-acyl intermediate with **1** gave di-(cyclohexen-1-yl)-ketone (**1d**).

Although the starting compound **1** can totally be converted in 6 h under carbon monoxide in all cases, the reactivity of the two arylboronic acids differs substantially (Table 1). While the application of **3** resulted in low chemoselectivities towards carbonylation product (**5a**) with all catalytic systems (entries 7–10) that of **2** could result in practically complete chemoselectivity towards **4a** in the presence of DPPF (entry 4). The reaction shows a strong dependence on the solvent. While complete ketone selectivity has been obtained with DMF by using Pd(OAc)$_2$—DPPF system, various further side-products obtained in direct Suzuki coupling (as well as in consecutive Heck reaction) are dominating by using DMSO as solvent (entries 3 and 5). A further
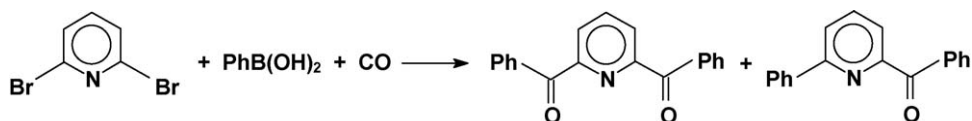
Scheme 2. Carbonylative arylation by using a carbonylative Suzuki–Miyaura coupling.
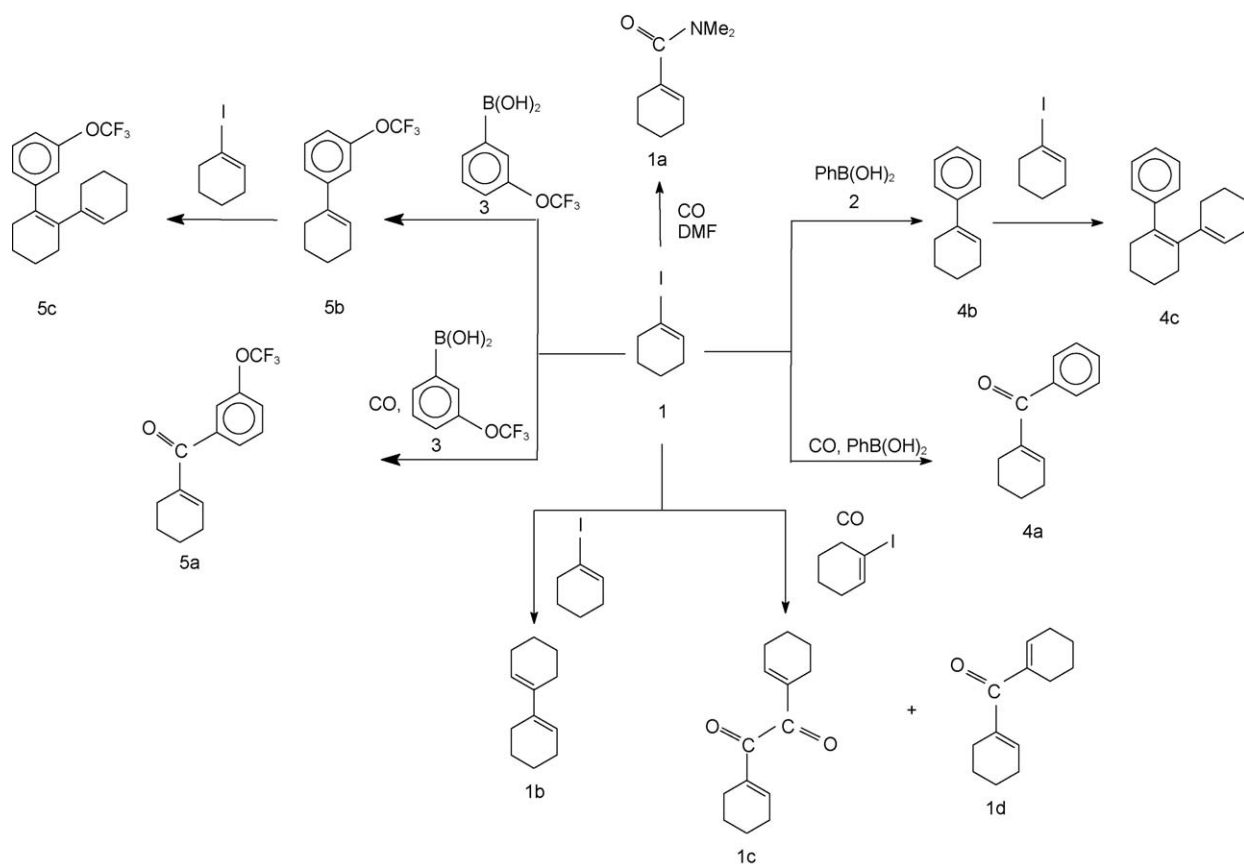
Scheme 4. The products (including side-products) formed in the 1-iodo-cyclohexene—arylboronic acid coupling reaction under carbonylative conditions.

interesting feature is the influence of increased carbon monoxide pressure on product selectivity. The higher the carbon monoxide pressure was, the lower the selectivity towards **4a/5a** was found. A possible explanation could be the higher ratio of palladium carbonyls that are not able to activate the substrate in the coordination sphere, i.e. a part of the catalyst is deactivated (entries 6 and 9). It has to be added that the amount of cyclohexen-1-yl formiate (**1a′**) could be high especially in those cases where the carbonyl insertion into cyclohexen-1-yl-palladium bond is not favoured (entries 2, 8 and 9). Its formation can be explained by the presence of the water content of the solvent.

Table 1
Carbonylative Suzuki–Miyaura coupling of 1-iodo-cyclohexene (**1**) with phenylboronic acid (**2**) or 3-trifluoromethoxy-phenylboronic acid (**3**)

Run	Phosphine[a]	RB(OH)$_2$	Conversion[b] (%)	Composition of the reaction mixture (%)[b]				Other products
				1a′	**4b/5b**	**4a/5a**	**1b, 1c** and **1d**	
1	PPh$_3$	2	94	15	30	22	33	
2	DPPB	2	100	75	25	0	0	
3[c]	DPPB	2	100	33	24	4	27	10% cHex$_2$O; 2% **4c**
4	DPPF	2	100	0	0	100	0	
5[c]	DPPF	2	100	25	44	0	23	2% cHex$_2$O; 6% **4c**
6[d]	DPPF	2	100	0	75	25	0	
7	PPh$_3$	3	100	27	15	13	44	
8	DPPF	3	99	49	16	7	27	
9[e]	DPPP	3	98	82	6	0	10	
10	DPPB	3	95	38	29	5	28	

Reaction conditions (unless otherwise stated): 0.5 mmol **1**; 0.025 mmol Pd(OAc)$_2$; 0.025 mmol diphosphine (or 0.05 mmol PPh$_3$); 0.5 mmol RB(OH)$_2$ (**2** or **3**); reaction time: 6 h; 1 bar carbon monoxide; solvent: DMF.
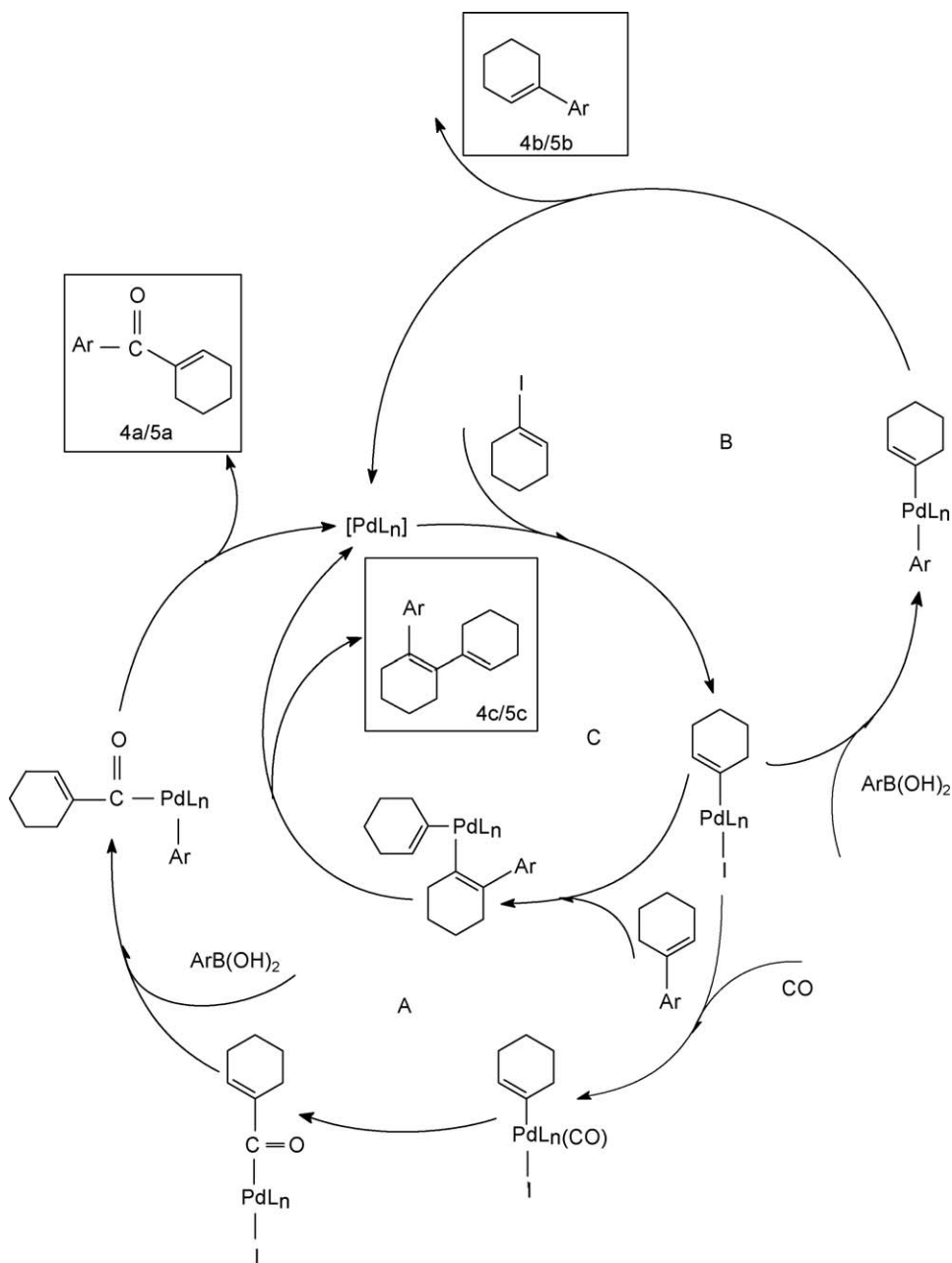[a] DPPE = 1,2-bis(diphenylphosphino)ethane; DPPP = 1,3-bis(diphenylphosphino)propane; DPPB = 1,4-bis(diphenylphosphino)butane; DPPF = 1,1′-bis(diphenylphosphino)ferrocene.
[b] Determined by GC.
[c] Solvent: DMSO.
[d] 42 bar Carbon monoxide.
[e] 12 bar Carbon monoxide.

Scheme 5. Simplified catalytic cycles showing the formation of the major products (Ar stands for aryl (phenyl or 3-trifluoromethoxy-phenyl) groups) both in carbonylative and direct SM reactions.

The two systems containing either **2** or **3** behave in completely different way also under normal 'Suzuki-conditions' (under argon atmosphere) (Table 2). Considering **2** as an 'aryl-source', the highest conversions have been obtained with DPPB forming seven-member chelate ring (entry 4) in 6 h. (The conversion can be improved by the application of elevated reaction times, e.g. the conversion can be increased from 36% (6 h) to 56% (24 h) by the application of DPPP containing catalyst (entry 6 and 8). In case of **3** the best activities have been obtained with PPh$_3$ and DPPE that is able to form five-membered chelate ring (entries 10 and 15, respectively).

The chemoselectivity towards Suzuki-products **4b** and **5b** are the highest in case of DPPF and DPPP, DPPB, respectively (com-

pare entries 3 and 13, 14). (The application of a rigid diphosphine or a flexible chelating phosphines proved to be superior by using **2** or **3**, respectively.) The extent of side-reactions leading to Heck-products (**4c, 5c**) and their isomers (**4c', 4c'', 5c', 5c''**) is unexpectedly high in the absence of phosphine ligand regardless the type of arylboronic acid used. The above Heck-products are dominating when palladium(II) acetate is used without any phosphine, and their amount reach 70% of the total products (entries 1 and 9). In case of **3** their amount can be diminished by the application of DPPP or DPPB to as low as 7 or 10%, respectively (entries 14 and 14). By using **2**, 20% of Heck-products have been detected even with the most selective DPPF containing catalyst (entry 3).

Table 2
Suzuki coupling of 1-iodo-cyclohexene (**1**) with phenylboronic acid (**2**) or 3-trifluoromethoxy-phenylboronic acid (**3**)

Run	Phosphine[a]	ArB(OH)$_2$	Reaction time (h)	Conversion[b] (%)	Composition of the product mixture[b] (%)			
					4b/5b	4c/5c	4c′/5c′	4c″/5c″
1	–	2	6	10	30	10	10	50
2	PPh$_3$	2	6	30	47	13	10	30
3	DPPF	2	6	29	80	7	3	10
4	DPPB	2	6	51	41	12	14	33
5	DPPE	2	6	30	79	7	2	12
6	DPPP	2	6	36	64	11	6	19
7	DPPF	2	24	34	74	12	6	9
8	DPPP	2	24	56	43	13	23	21
9	–	3	6	100	30	20	28	22
10	PPh$_3$	3	6	100	62	11	17	10
11	PPh$_3$	3	2	74	64	4	28	4
12	DPPF	3	6	84	75	<1	24	<1
13	DPPB	3	4	50	90	0	10	0
14	DPPP	3	4	55	93	0	7	0
15	DPPE	3	8	100	73	<1	26	<1

Reaction conditions: 0.01 mmol Pd(OAc)$_2$; 0.02 mmol PPh$_3$ (or 0.01 mmol diphosphine); 1 mmol **1**; 50 °C; argon atmosphere; solvent DMF.

[a] For abbreviations see: Table 1.
[b] Determined by GC.

3. Conclusions

As a summary, it can be stated that under appropriate ('carbonylative Suzuki') conditions conjugated unsaturated arylalkenyl ketones can be synthesised from arylboronic acids and iodo-alkenes. The yields, however, are strongly dependent both on the reaction conditions (carbon monoxide pressure, solvent) and the type of the arylboronic acid. The detailed analysis of the reaction mixture revealed that great variety of side-products may be formed both under 'direct' and 'carbonylative' SM reactions.

4. Experimental

4.1. Reagents

Palladium(II) acetate, triphenylphosphine, DPPE, DPPP, DPPB, DPPF, phenylboronic acid and 3-trifluoromethoxy-phenylboronic acid (Aldrich) were used without further purification. Solvents were dried according to standard procedures.

1-Iodo-cyclohexene was prepared according to a described method [32]. Cyclohexanone hydrazone, obtained from cyclohexanone, was treated with iodine in the presence of tetramethyl guanidine (TMG) as a base.

Samples of the catalytic reactions were analysed with a Hewlett Packard 5830A gas chromatograph fitted with a capillary column coated with OV-1. For the identification in of the products of the model reaction reference compounds have been used [33–37].

4.2. Carbonylative coupling reaction

In a typical reaction, Pd(OAc)$_2$ (5.6 mg, 0.025 mmol) and PPh$_3$ (13.1 mg, 0.05 mmol) (or 0.025 mmol of bidentate phosphine) was dissolved in 10 ml DMF under argon. After the formation of a pale brown homogeneous solution, phenylboronic acid (61 mg, 0.5 mmol) (or 3-trifluoromethoxy-phenylboronic acid (103 mg, 0.5 mmol)) and 1-iodo-cyclohexene (67.8 μl, 0.5 mmol) were added. The atmosphere was changed to carbon monoxide and the reaction mixture was kept at 50 °C for 6 h. The reaction mixture was analysed immediately by GC-MS.

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