Pergamon

Tetrahedron Letters, Vol. 35, No. 20, pp. 3277-3280, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0578-L

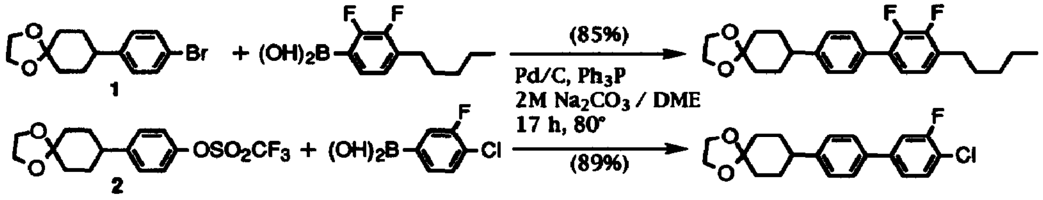
Aryl Couplings with Heterogeneous Palladium Catalysts

Guy Marck, Alois Villiger and Richard Buchecker*
F. Hoffmann-La Roche Inc., Dept. RLCR, 4002 Basel, Switzerland

Abstract: The coupling reaction of diverse phenylboronic acids with aryl halogenides and -triflates has been performed by the use of simple palladium hydrogenation catalysts. Evidence for a heterogeneous type of catalysis has been obtained.

The palladium catalysed cross-coupling of organoboronic acids with organic electrophiles in the presence of a base, sometimes referred as Suzuki reaction [1], has gained increasing attraction during the last few years (see recent review) [2]. Its usefulness lies mainly in the fields of aromatic or vinylic couplings where oligoaryls with differing rings, oligoheteroaryls or dienes can be obtained under mild conditions. The reaction has recently also been used for the synthesis of liquid crystals [3], which often are incorporating biphenyl subunits in their molecular structures. In order to check its potential for liquid crystal synthesis in more detail, we decided to investigate the reaction conditions more systematically.

According to the literature a broad selection of different palladium complexes can be used for the catalysis of the Suzuki reaction. By far the most frequently employed is the relatively expensive tetrakis(triphenylphosphine)palladium(0) ((TPP)$_4$Pd). In connection with another project we came across a paper of De la Rosa et al [4]. The authors reported on a successful coupling of phenyl bromides with acetylenes catalysed by copper(I)iodide, palladium on carbon and triphenylphosphine. This lead us to the question whether (TPP)$_4$Pd could be replaced analogously for the synthesis of phenylboronic acids. Our first experiments in this direction are depicted in *Scheme 1.* The results clearly show that the bromide and even the usually less reactive triflate are easily brought to reaction by this alternative catalytic system. Although the reaction times are remarkably longer than the time usually reported for the conventional couplings catalysed by (TPP)$_4$Pd, the isolated yields are of the same magnitude. It is reasonable to assume that the increased reaction time is due to the precedent formation of the triphenylphosphine-palladium



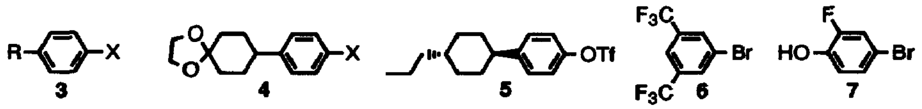
Scheme 1. *Coupling with Pd/C in the presence of triphenylhosphine. Typical procedure see ref. 5. Yields refer to isolated and purified products.*

complex. Our later series of experiments however indicate, that this explanation is not necessarily correct.

In a further experiment with p-bromobenzaldehyde in ethanol/water (9:1) and triethylamine as base, the addition of triphenylphosphine was omitted (see *Table*, entry *1*). To our surprise the coupling was finished in less than five hours and the isolated yield again reached more than 80 percent. This new result prompted us to further investigate the conditions, under which such uncomplexed hydrogenation catalysts can be used. The results are collated in the *Table*.

Entry	*Electrophile* [a] *(R, X)*	*Phenylboronic acid*	*Catalyst* [b]	*Base* [c]	*Solvent*	*Time [h]*	*Conversion [%]*	*Yield* [d] *[%]*
1	**3** (CHO, Br)	4-fluoro-	E101 N/D	TEA	EtOH	5	97	84 [e]
2	**3** (CN, Br)	3-fluoro-4-chloro-	E10 N/D	Na_2CO_3	EtOH	1	100	94
3	**6**	4-n-propyl-	E101 N/D	Na_2CO_3	EtOH	0.5	100	90
4	**3** (n-propyl, Br)	3,5-difluoro-	E10 N/D	Na_2CO_3	EtOH	19	97	88
5	**7**	4-n-pentyl-	E10 N/D	2M Na_2CO_3	DME	19	95	80
6	**3** ($N(CH_3)_2$, Br)	3-fluoro-4-chloro-	E10 N/D	Na_2CO_3	EtOH	19	98	95
7	**3** (H, I)	" "	E10 N/D	Na_2CO_3	EtOH	19	96	91
8	**4** (--, Br)	2,3-difluoro-	E10 N/D	Na_2CO_3	EtOH	19	97	94
9	**4** (--, Cl)	3-fluoro-4-chloro-	E10 N/D	Na_2CO_3	EtOH	19	40	6
10	**4** (--, OTf)	" "	E10 N/D	Na_2CO_3	EtOH	19	0	0
11	**3** (ethyl, Br)	" "	E10 N/D	2M Na_2CO_3	DME	19	98	87
12	**3** "	" "	E10 N/D	TEA	DME	19	12	6
13	**3** "	" "	E10 N/D	TEA	EtOH	19	49	41
14	**3** "	" "	E101 R/D	2M Na_2CO_3	DME	19	82	78
15	**3** "	unsubstituted	E207 N	Na_2CO_3	EtOH	19	98	96
16	**3** (CN, OTf)	"	E10 N/D	2M Na_2CO_3	DME	19	0	0
17	**5**	"	E10 N/D +LiCl [f]	2M Na_2CO_3	DME	2.5	0	0
18	**3** (CN, OTf)	"	E10 N/D	$NaHCO_3$	EtOH	19	83	50
19	**5**	"	E10 N/D	Na_2CO_3	DMF	19	74	62 [g]
20	**5**	"	E101 R/D	Na_2CO_3	DMF	24	68	68
21	**5**	"	E101 R/D + LiCl [f]	Na_2CO_3	DMF	18	90	84
22	**5**	"	$Pd(AcO)_2$	Na_2CO_3	DMF	19	50	35 [h]

Table. *Coupling reactions with Pd/C catalyst without ligands. Typical procedure see ref. 6. All couplings were, if not otherwise mentioned, analysed by GLC. a) see also Scheme 2. b) supplier: Degussa . c) TEA = triethylamine,* Na_2CO_3 *= solid soda, 2M* Na_2CO_3 *= aqueous solution. d) yield relative to starting materials. e) isdolaed yield, reaction conditions analogous to ref. 5 but without addition of triphenylphosphine. f) 2 equiv. (related to electrophile) of solid LiCl , g) plus 10% biphenyl . h) plus 16% biphenyl .*



Scheme 2. *Starting materials (meaning of R and X see Table)*

With activated aromatic electrophiles (incorporating electron withdrawing groups), reaction times down to 30 min. were registered (*1-3*). The activation by substituents with mesomeric (*1, 2*) or inductive effects (*3*) seems to be of similar quality. However the reaction proceeds also with nucleophiles that are not activated (*4*) or even deactivated by electron donating groups (*5, 6*), although longer reaction times are necessary for completion. In entries *7-10* the reactivities of electrophiles possessing different leaving groups are compared. The iodide and the bromide react smoothly (*7, 8*), while the triflate does not react under the applied conditions (*10*). The chloride shows at least some reactivity (*9*), but the main path is rather the hydrogenolysis than the coupling. The reactivities observed here are in principle similar to previously published results with other palladium catalysts, except that triflates are usually reacting smoothly, if palladium complexes are used. The discrimination of the triflates with Pd/C allows the concept of a one-pot synthesis of mixed terphenyls from p-bromophenyl triflates if triphenylphosphine and a second boronic acid is added after the reaction of the bromide with a first, different phenylboronic acid and with Pd/C without ligand has taken place .

Comparison of different base/solvent systems shows that the common system 2M aqueous soda/dimethoxyethane (2M Na_2CO_3/DME) is also suitable for the Pd/C catalysis (*14*). The best yields were however obtained if powdered soda was added to ethanol (*8, 15*). With triethylamine as base a sharp decrease of reactivity was observed . This deactivation is less pronounced in ethanol than in DME (*12, 13*) and is not of practical importance with activated electrophiles (cf. *1* and *2*).

The following experiments were designed to enhance the reactivities of triflates. Entry *16* shows, that even activated triflates are not reactive in the common 2M soda/DME system. Addition of lithium chloride, known for its accelerating effect [7] was neither successful (*17*). With solid sodium bicarbonate in ethanol however at least a 50% yield could be achieved (*18*). Bicarbonate reduces the hydrolysis of the triflate, which is the main reaction with soda in ethanol . Still better results were obtained with powdered soda and DMF (*19, 20*) and an excellent yield was finally achieved by the addition of solid lithium chloride to the above reaction mixture (*21*).

All catalysts used in entries *1-21* are commercial hydrogenation catalysts differing in the supporting material (E10, E101 = charcoal, E207 = aluminium oxide) or in the oxidation state (N = not reduced (Pd^{II}), R = reduced (Pd^0)). According to our experiments all these types are able to catalyse the coupling. The Pd^{II} of the N-types is first reduced to Pd^0 by one equivalent of the boronic acid [8] leading to some dimerisation by-products (cf. entry 19). This also happens with unsupported Pd(II)acetate, a catalyst recently used by Bumagin et al. [9] (see also entry *21*). In most mechanistic studies met in the literature Pd(0) is postulated to be active as a complexed homogeneous species. The results obtained here lead rather to the conclusion that Pd(0) is acting in a heterogeneous form. In order to clarify this question, some additional experiments were performed.

Some first experiments with addition of mercury, a method described to suppress heterogeneous catalysis by amalgamation of Rh(0) [10], gave contradictory results. More conclusive was the following procedure. The reaction was started in the usual way. When approximately 50% of the coupling product was formed, the reaction mixture was subjected to centrifugation (3 min., 3000 rpm) and subsequently filtrated through a 0.22 μm Millipore filter. Then the initial quantity of solid Na_2CO_3 was added and the reaction was allowed to continue under the same reaction conditions as at the beginning. The reactions with Pd/C catalyst completely stopped after this procedure, while analogous parallel reactions, where $(TPP)_4Pd$ was used instead of Pd/C, were not affected. The procedure has obviously eliminated the metallic particles of the heterogeneous catalyst while the homogeneous, complexed catalyst could not be separated from the reaction mixture. When new Pd/C catalyst was added to the reaction which stopped, it succeeded to completion as usual. To exclude the possibility of adsorption on the supporting charcoal of a hypothetical homogeneous catalyst, the experiment with $(TPP)_4Pd$ was repeated in the presence of charcoal. No difference was registered. *These results represent strong evidence, that the coupling reactions with Pd/C catalysts under the conditions presented here are occurring by heterogeneous catalysis.*

In conclusion the use of Pd/C catalysts provides a simple and cheap synthetic alternative to the classical Suzuki coupling. In addition the aryl-aryl exchange between palladium centre and phosphine ligand (mostly phenyl), which is sometimes observed when complexed catalysts are used [11], can be avoided by the method reported here.

References and Notes:

1. Miyaura N.; Suginome H.; Suzuki A.; *Synth. Commun.* **1981**, *11*, 513.
2. Martin A.R.; Yang Y.; *Acta Chem. Scand.* **1993**, *47*, 221.
3. Hird M.; Gray G.W.; Toyne K.J.; *Mol Cryst. Liq. Cryst.* **1991**, *206*, 187.
4. De la Rosa J. M. A.; Velarde E.; Guzman A.; *Synth. Commun* . 1990, *20*, 2059.
5. Typical procedure for coupling with TPP ligand: Under nitrogen protection a mixture of 976 mg (2,66 mmol) 2, 560 mg (3.21 mmol) 4-chloro-3-fluorophenylboronic acid, 125 mg (0.12 mmol) 10% Pd/C (type E101 N/D), 122 mg (0.47 mmol) triphenylphosphine in 10 ml dimethoxyethane was stirred during 15 min. at ambient temperature. Then 5 ml 2 M aqueous Na_2CO_3 was added and the stirred mixture heated to 80° over night. The cold reaction mixture was then diluted with ether, filtrated trough Celite and washed several times with water. Then the organic phase was dried over $MgSO_4$, the solvent evaporated and the residue purified over 100 g silicagel . Thus 820 mg (88.9%) of coupling product (GLC-purity 98.8%) were obtained as white crystals (mp. 112 - 112.4 °C). 1H-NMR, IR and MS were in accordance with the structure.
6. Typical procedure: In a 10 ml glass vessel provided with a magnetic stirrer and a reflux condenser a mixture of 500 mg (2.7 mmol) 1-bromo-4-ethylbenzene, 362 mg (2.97 mmol) phenylboronic acid, 230 mg (0.11 mmol) 5% Pd/C (type E101 R/D) in 5 ml 95% ethanol was heated to 80° C under nitrogen over night. The mixture was then cooled down and diluted with a mixture of water and ether. The organic phase was separated, washed with brine and water and dried over $MgSO_4$. After filtration and evaporation of the solvent the residue was analysed by GLC
7. Huth, A.; Beetz I.; Schumann I.; *Tetrahedron* **1989**, *45*, 6679.
8. Davidson J. M.; Triggs C.; *Chem. Ind. (London)* **1966**, 457.
9. Bumagin N. A.; Bykov V. V.; Beletskaya I. P.; *Bull. Acad. Sci. USSR* **1989**, *38*, 2206.
10. Brown J. N.; Hall S. A.;*Tetrahedron Lett.* **1984**, *25*, 1393.
11. O'Keefe, D. F.; Dannock, M., C.; Marcuccio, S. M.; *Tetrahedron Lett.* **1992**, *33*, 6679.

(*Received in Germany* 3 *March* 1994; *accepted* 17 *March* 1994)