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One step synthesis of Diflunisal using a Pd-diamine complex

Research Article

Tuula Kylmälä[1], Jan Tois[1], Youjun Xu[2], Robert Franzén[1]*

[1] *Department of Chemistry and Bioengineering, Laboratory of Chemistry, Tampere University of Technology, Tampere, FIN-33720, Finland*

[2] *School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, 110016, China*

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Abstract: Diflunisal and Felbinac , two FDA-approved NSAIDs and other biphenyl carboxylic acids were prepared in one step by a simple and clean Suzuki cross-coupling reaction using an easily synthesized, air and moisture stable, palladium-diamine complex. The yield (93%) for the one-step preparation of Diflunisal is the best reported without using a glovebox and a phoshine-based catalyst.

Keywords: *Diflunisal • Felbinac • NSAID • Biphenyl carboxylic acid • Suzuki cross-coupling • Pd-diamine complex*

1. Introduction

Biaryl functionalities are present in a wide range of therapeutic classes, including antifungal, anti-inflammatory, antirheumatic, antitumor, and antihypertensive agents [1]. The biaryl moiety interacts favorably with polar groups such as amides and hydroxyl groups. Because of these unique physicochemical properties it has become a privileged substructure in pharmaceuticals [1,2] The biaryl moiety is present in drugs like Diflunisal **1**, Felbinac **2**, Flurbiprofen, Fenbufen and Xenbucin [3-5]. Also many larger molecules, for example natural cyclic peptide antibiotics including the Biphenomycins A–C [6], anti-HIV agents Chloropeptin I and II [7] and Sartan-type drugs (for example Irbesartan for the treatment of arterial hypertension [8]), contain a biaryl moiety (Fig. 1). Diflunisal **1** is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects [9]. The compound, also referred to as Dolobid, is a nonacetylated phenyl-derivative of salicylic acid. It is 20 times more effective in a hyperestesia assay and 9 times more effective in adjuvant arthritis than Aspirin [3]. Unlike Aspirin, Diflunisal which is unesterified is chemically incapable of acetylating cyclo-oxygenase and may therefore contribute to better tolerance in humans [9].

1.1. Conventional preparation of Diflunisal

Recently Diflunisal has been prepared with different synthetic routes which can be divided into conventional methods and catalytic methods. In conventional methods, Diflunisal is prepared in several steps starting from fluorinated aniline. Hannah and co-workers have prepared Dilflunisal in a five step synthesis (Scheme 1) consisting of benzene arylation using a Gomberg-Bachmann-Hey reaction (GBH), Friedel-Crafts acylation, Bayer-Villiger oxidation, saponification and finally carbonation of phenol through a Kolbe-Schmitt reaction achieving Diflunisal in 35.78% yield [3]. In the GBH reaction the aromatic radical formed from aryldiazoniumhydroxide reacts with a different aromatic substrate. Yields are generally less than 50% in GBH-reactions due to the uncontrollable formation of regioisomers. Even with symmetrical reactants yields are low because of several side-reactions, for example formation of arylazo compounds [10]. Friedel Crafts

* *E-mail: robert.franzen@tut.fi*

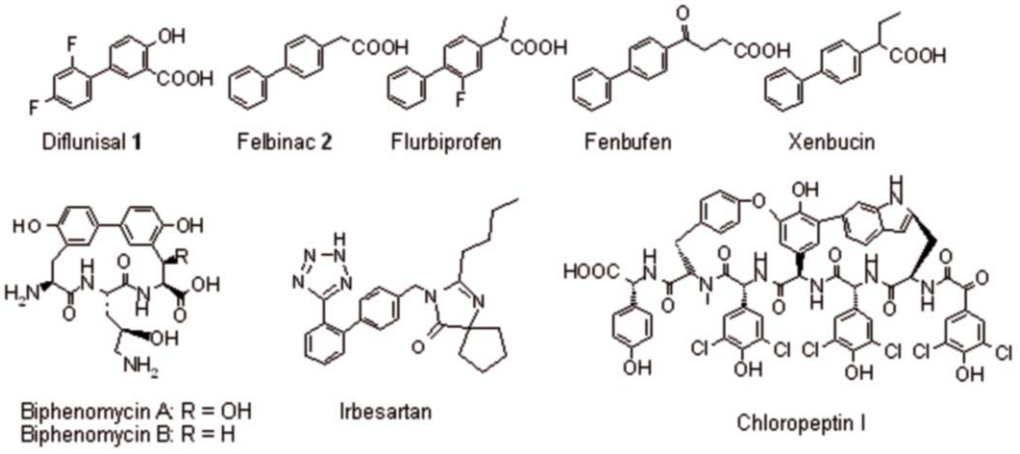
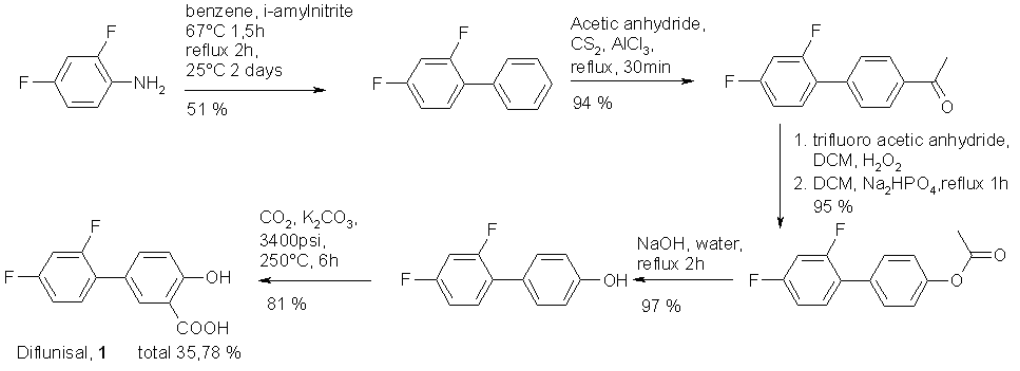


Figure 1. Examples of drugs containing a biaryl moiety.



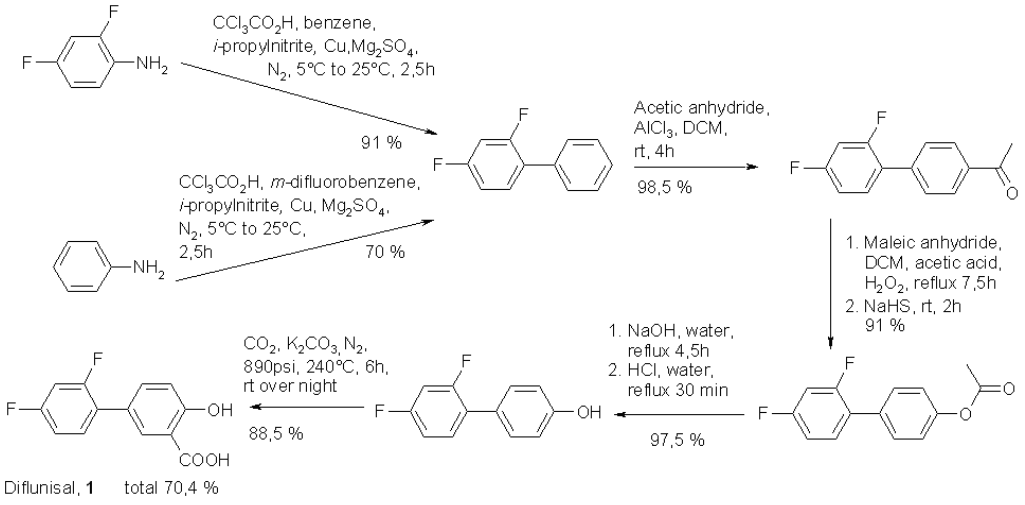
Scheme 1. Five step syntheses of Diflunisal by Hannah *et al.*

acylation and Bayer-Villiger oxidation proceed well. Finally the phenol is heated with anhydrous carbonate in carbon dioxide under high pressure (3400 psi, 6 h at 250°C). Under these drastic conditions phenoxides are reactive enough to add to carbon dioxide [11]. Hannah *et al.* tried to improve the route and utilized anisole instead of benzene. However, the selectivity of the GBH-reaction was poor and the desired *para*-isomer was obtained as a minor product [3].

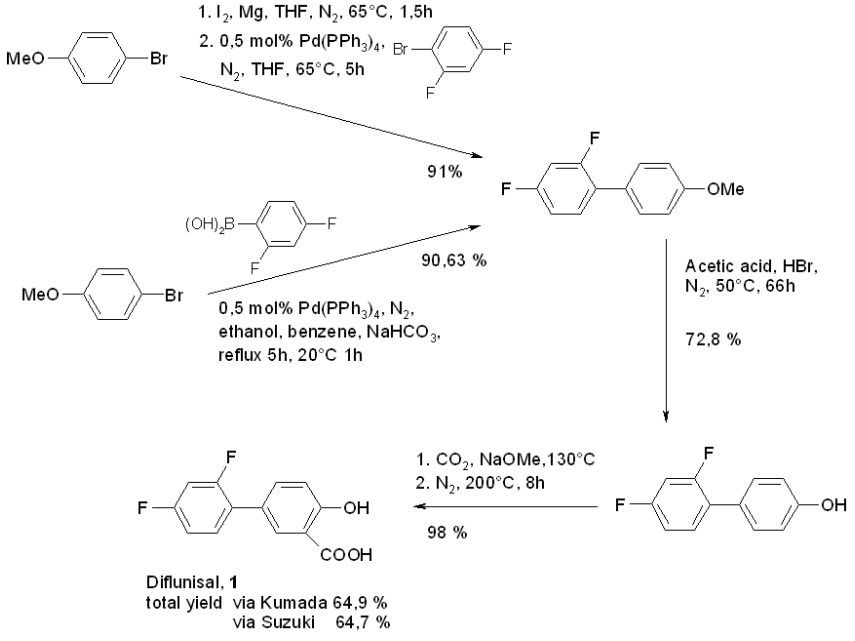
Jones *et al.* (Merck & Co. Inc.) prepared Diflunisal also in five steps (Scheme 2) [12]. They improved the Gomberg-Bachmann-Hey reaction by adding copper and anhydrous Mg_2SO_4 and the reaction was conducted under an inert atmosphere. These additives improved the yield and shortened the reaction time. An interesting detail is that they managed to perform the GBH-reaction also for unsymmetrical 2,4-difluorobenzene in good yield (70%). After these improvements in the GBH-reaction as well as in Friedel-Crafts acylation the total yield of Diflunisal was 70.4% (Scheme 2). Even though the yields are increased, it is still a five-step synthesis and the reaction conditions are still harsh especially in the last step where carbonation of phenol is conducted in 890 psi, 6 h at 240°C and continuing over night at room temperature [12].

1.2. Catalytic preparation of Diflunisal

Transition metal catalyzed cross-coupling reactions are efficient methods to prepare the carbon-carbon bond found in biaryls [13-16]. For example Suzuki coupling reactions provide a general approach to aryl-aryl C-C bond formation [17,18]. Giordano *et al.* have prepared Diflunisal *via* bromoanisoles (Scheme 3) [19]. Commonly used palladium tetrakis(triphenylphosphine) was used as a catalyst in Suzuki and Kumada reactions to achieve phenylanisole. In the Kumada reaction the Grignard reagent was prepared in an inert atmosphere *in situ* followed by slow addition of preheated and de-aerated 1-bromo-2,4-difluorobenzene and catalyst. The demethylation reaction was the true bottleneck of this route; this slow reaction was conducted in HBr/AcOH at 50°C and yielded the phenol in 72.8% yield. A more readily removed protective group could have improved the total yield.



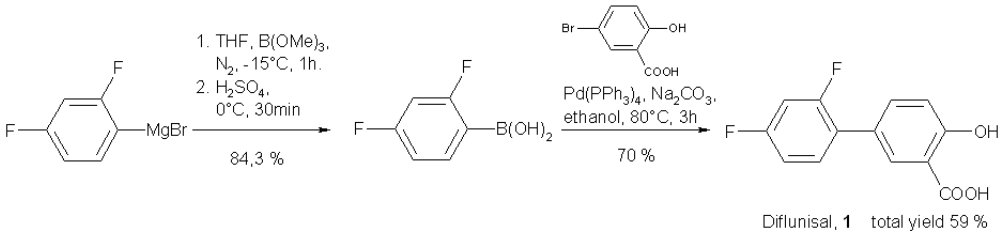
Scheme 2. Five step synthesis of Diflunisal by Jones et al.



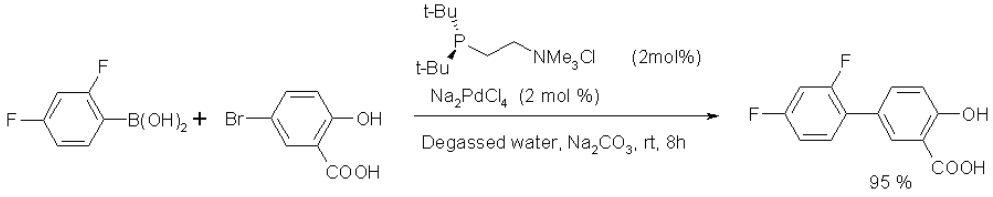
Scheme 3. Preparation of Diflunisal via three steps by Giordano et al.

Diflunisal has also been synthesized by Suzuki reaction using commercially available 5-bromosalicylic acid. However, phosphine ligands are required to achieve the product [19,20]. Giordano *et al.* prepared Diflunisal in two steps starting with preparation of a phenylboronic acid from the corresponding Grignard reagent in 84.3% yield (2,4-difluorophenylboronic acid is also commercially available at present time) and continued through the Suzuki reaction. Phosphine based $Pd(PPh_3)_4$ was required in this successful reaction sequence, achieving Diflunisal in 59% total yield (Scheme 4) [19].

Many small molecule drugs, including Diflunisal and Felbinac, contain carboxyl group functionalities in biaryl moiety (Fig. 1).] Compounds derived from Diflunisal are still of interest as potential NSAIDs [21-24]. Although, Diflunisal has been prepared in one step by Suzuki coupling, excellent yield was obtained only by using a phosphine based catalyst, glovebox and degassed water (Scheme 5) [20]. Also, Felbinac has been prepared by Suzuki coupling using either phenylboronic acid [25,26] or tetraphenylborate [5,27] as reactant (Scheme 6). Suzuki coupling with free hydroxyl or carboxylic acid



Scheme 4. Preparation of Diflunisal via two steps by Giordano et al.

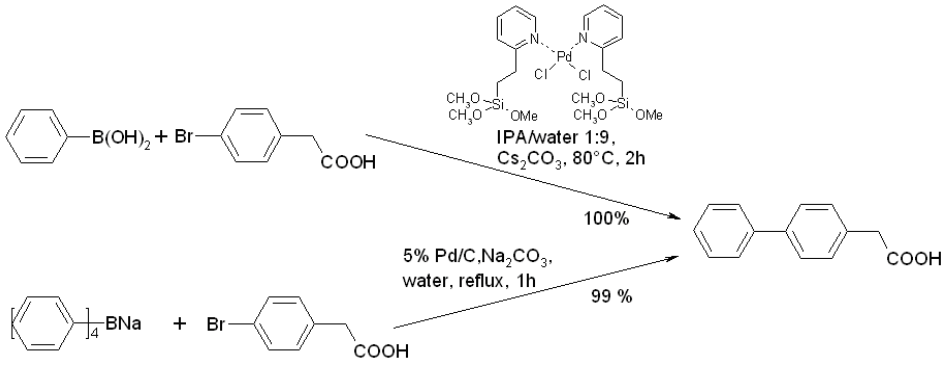


Scheme 5. Preparation of Diflunisal by Suzuki reaction using Phosphine based catalyst, glovebox and degassed water.

functionalities present in the aromatic halide have been reported but, aryltrifluoroborates, strong bases (KO^{t}Bu, LiOH, KF), microwave or phosphine based palladium catalysts have been utilized [28-33]. Generally, when coupling partners containing substituents other than in the para-position with respect to the halide or boron, a phosphine based palladium catalyst has been required [33-38]. Halogenated biaryls which contain a hydroxyl group are usually prepared by Suzuki reactions using anisoles followed by demethylation [39-41]. Development of efficient phosphine free catalysts for preparation of hydrophilic substrates are of interest and reactions without a phosphine ligand, strong base and free hydroxyl groups in arylhalide have been reported recently [43,44]. As part of our ongoing projects considering synthesis of biphenyl carboxylic acids and low-molecural sized drugs employing Pd-catalysts [5,14,27,45], we have noticed that Pd/C has turned out to be a good catalyst for arylation of bromobenzoic acids [27]. Pd/C is also reported to catalyze reactions of halophenols, though in these reactions iodine is required as the halide and/or the use of microwave power for effective reactions [46,47]. We examined our novel palladium diamine and diimine catalysts and Pd/C as well as some commonly used palladium phosphine complexes in Diflunisal syntheses.

2. Experimental Part

Solvents and reagents were purchased from Sigma-Aldrich or Merck and were used without further purification. Thin-layer chromatography (TLC) was performed on precoated (Kieselgel 60 F_{254}) aluminium plates with detection by UV light. Silica gel 100, particle size 0.063-0.2 mm, was used for column chromatography. Melting points were determined with a Stuart 110 meltingpoint apparatus. ^{1}H and ^{13}C NMR spectra were acquired with a Varian Mercury 300 MHz spectrometer using $CDCl_3$, methanol-d_4 or DMSO as solvent. Chemical shifts are reported as δ values (ppm) relative to tetramethylsilane which was used as an



Scheme 6. Pd-Catalyzed Preparation of Felbinac

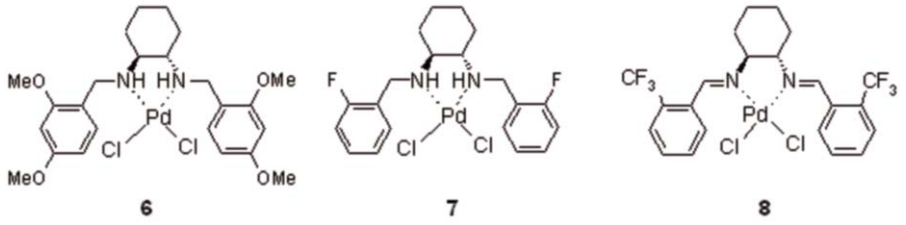


Figure 2. Structure of Pd-diamine and Pd-diimine complexes.

internal standard. Yields for the Suzuki reactions were determined from isolated products by quantitative NMR analyses [48] and nitromethane was used as standard. Purification by column chromatography (Chloroform: Methanol 4:1) was performed after all reactions.

2.1. Catalysts

Pd-diamine **6-7** and Pd-diimine **8** complexes (Fig. 2) were prepared as previously reported [14]. Pd/C (5%) was purchased from Sigma-Aldrich and used as water wet 50% without purification.

2.2. Suzuki reaction

We have recently noticed that 3 eq K_2CO_3 is the optimal amount of base to be employed in Suzuki reactions when using catalysts **6-8** [14]. Therefore, 4 or 5 eq of base, depending on free acid and hydroxyl groups on the reactants, were used so that accessible amount of base for the Suzuki reaction itself was 3 eq (Schemes 7 and 8). General procedure of Suzuki reaction; catalyst (0.002 mmol, 1 mol%), arylbromide (0.20 mmol, 1.0 eq), phenylboronic acid (0.24 mmol, 1.2 eq), K_2CO_3 (1.00 mmol, 5 eq or 0.8 mmol, 4 eq) and solvent (1.0 mL) were added while exposed to air. In some cases TBAB (0.26 mmol, 1.3 eq) was also added to the reaction mixture. Thereafter, the reaction mixture was stirred for 24 h at constant temperature. The mixture was cooled to room temperature, water (ca. 15 mL) was added and by-products were extracted with diethyl ether. After addition of aqueous HCl (3M) followed by extraction into diethyl ether, the organic phase was dried with $MgSO_4$, filtered and evaporated to yield the corresponding biphenyl. NMR data for the products were in accordance with literature values [20,22,27,32,49].

2.2.1. 5-(2,4-difluorophenyl)-2-hydroxybenzoic acid, Diflunisal, 1

White solid. m.p. 209-210°C (Lit. 210-211°C), ^{1}H NMR (DMSO-d_6) 7.62 – 7.59 (m, Ar, 4H), 7.46 (t, Ar, 2H), 7.34 – 7.39 (m, Ar, 3H), 3.62 (s, CH_2, 2H); ^{13}C NMR (DMSO-d_6) 172.1, 140.9, 139.7, 134.5, 130.2, 129.1, 127.5, 127.1, 127.0, 40.3 [20].

2.2.2. 4-biphenylacetic acid, Felbinac, 2

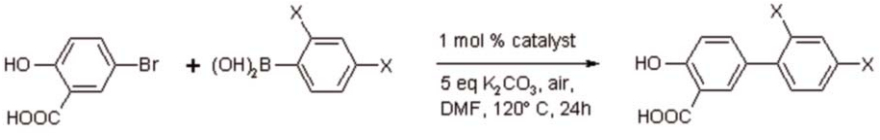
White solid. m.p. 162-164°C (Lit. 163-164°C), ^{1}H NMR(DMSO-d_6) 7.62 – 7.59 (m, Ar, 4H), 7.46 (t, Ar, 2H), 7.34 – 7.39 (m, Ar, 3H), 3.62 (s, CH2, 2H); ^{13}C NMR(DMSO-d_6) 172.1, 140.9, 139.7, 134.5, 130.2, 129.1, 127.5, 127.1, 127.0, 40.3 [27].

2.2.3. 5-phenyl-2-hydroxybenzoic acid, 3

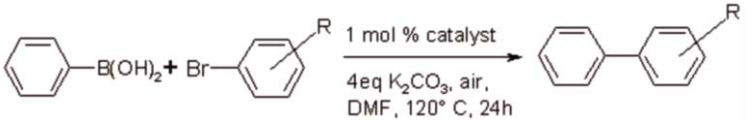
White solid. m.p. 211-214°C (Lit.210-212°C), ^{1}H NMR(methanol-d_4) 8.07 (d, Ar, 1H), 7.72 (dd, Ar, 1H), 7.53 (m, Ar, 2H), 7.40 (tt, Ar, 2H), 7.28 (tt, Ar, 1H), 7.00(d, Ar, 1H) ^{13}C NMR(methanol-d_4) 173.3, 162.5, 141.1, 135.1, 129.9, 129.5, 128.0, 127.4, 118.7, 114.0 [22].

2.2.4. 3-biphenylacetic acid, 10

White solid. m.p. 139-140°C (Lit. 141-143°C), ^{1}H NMR(DMSO-d_6) 8.74(br, OH, 1H), 7.63 (d, Ar, 2H), 7.54



Scheme 7. Preparation of Diflunisal and its non-fluorinated analogue.



Scheme 8. Preparation of Felbinac 2 and other carboxylic acid and hydroxybiphenyls.

(d, Ar, 2H), 7.48-7.33 (m, Ar, 4H), 7.26 (d, Ar, 1H), 3.64 (s, CH_2, 2H); ^{13}C NMR(DMSO-d_6) 172.9, 140.4, 140.4, 140.3,129.1, 129.0, 128.6, 128.0, 127.6, 126.8, 125.1, 40.8 [49].

2.2.5. 2-biphenylacetic acid, 11

White solid. m.p. 111-113°C (Lit. 111-113°C), ^{1}H NMR ($CDCl_3$) 11.52 (br, OH, 1H), 7.41-7.24 (m, Ar, 9H), 3.62 (s, CH_2, 2H); ^{13}C NMR ($CDCl_3$) 142.7, 141.0, 131.2, 130.5, 130.4, 129.3, 128.4127.7, 127.5, 127.4 [27].

2.2.6. 4-biphenyl carbocylic acid, 12

White solid, m.p. 224-225°C (Lit. 223-225°C), ^{1}H NMR (DMSO-d_6) 8.06 (d, Ar, 2H), 7.79 (d, Ar, 2H), 7.72(d, Ar, 2H), 7.48 (t, Ar, 2H), 7.42 (d, Ar, 1H); ^{13}C NMR (DMSO-d_6) 167.3, 144.5, 139.2, 130.1, 129.7, 129.2, 128.4, 127.1, 126.9 [22].

2.2.6. 3-biphenyl carbocylic acid, 13

White solid, m.p. 160-162°C (Lit. 160-161°C), ^{1}H NMR (DMSO-d_6)7.98-7.87 (m, Ar, 3H), 7.69 (d, Ar, 2H), 7.60 (t, Ar, 1H), 7.47 (t, Ar, 2H), 7.40 (d, Ar, 1H); ^{13}C NMR (DMSO-d_6) 167.4, 140.7, 139.4, 131.2, 129.4, 129.2, 128.4, 128.0, 127.5, 126.9 [46].

2.2.7. 4-hydroxybiphenyl, 14

White solid. m.p. 164°C (Lit. 164-165°C), ^{1}H NMR ($CDCl_3$) 7.54-7.27 (m, Ar, 7H), 6.90(d, Ar, 2H), 2.75(br, OH, 1H); ^{13}C NMR ($CDCl_3$) 156.0, 141.0, 133.2, 128.8, 128.4, 126.7, 126.6, 115.7 [32]

3. Results and Discussion

In this report we present the preparation of Diflunisal **1**, Felbinac **2** and other biphenyl carboxylic acids (Fig. 3), by different catalyst methods: the tested catalysts were $Pd(PPh_3)_2Cl_2$ and $PdCl_2$(dppf), Pd/C and novel Pd-diamine and - diimine complexes **6-8** (Fig. 2). Phosphine-based complexes catalyzed the reaction but in ethanol Diflunisal was achieved only in moderate to good yields (Table 1, entries 1 and 3). Giordano *et al.* have used another commonly used phosphine catalyst, $Pd(PPh_3)_4$, and achieved 70% in Suzuki reaction in ethanol (Scheme 4) [19].

When preparing Diflunisal from 2,4-difluorophenylboronic acid using Pd/C as catalyst, the reaction proceeded in low yield or did not occur (Table 1, entries 5 and 6). $PdCl_2$ without being complexed

Table 1. The synthesis of Diflunisal with different catalysts.

Entry	Catalyst	Solvent	Temperature	Yield %
1	$Pd(PPh_3)_2Cl_2$	Ethanol	80°C	30
2	$Pd(PPh_3)_2Cl_2$	DMF	150°C	67
3	$PdCl_2$(dppf)	Ethanol	80°C	61
4	$PdCl_2$(dppf)	DMF	150°C	89[a]
5	Pd/C	DMF	150°C	Nr
6	Pd/C	Water	100°C	3
7	$PdCl_2$	DMF	150°C	58
8	6	DMF	150°C	93[a]
9	6	DMF	120°C	78
10	6	DMF	120°C	52[b]
11	6	DMF	80°C	26
12	6	Toluene	110°C	6
13	6	Toluene	110°C	18[b]
14	6	Ethanol	80°C	20
15	6	Ethanol	80°C	13[b]
16	6	i-propanol	80°C	5
17	6	Toluene : water 1:1	80°C	10[b]
18	6	Ethanol : water 1:1	80°C	19[b]
19	7	DMF	150°C	58
20	7	DMF	120°C	45
21	7	DMF	120°C	20[b]
22	8	DMF	150°C	10
23	8	DMF	120°C	10
24	8	DMF	120°C	29[b]

[a] *average yield of three reactions,* [b] *1.3 eq. of TBAB was added, nr = no reaction*

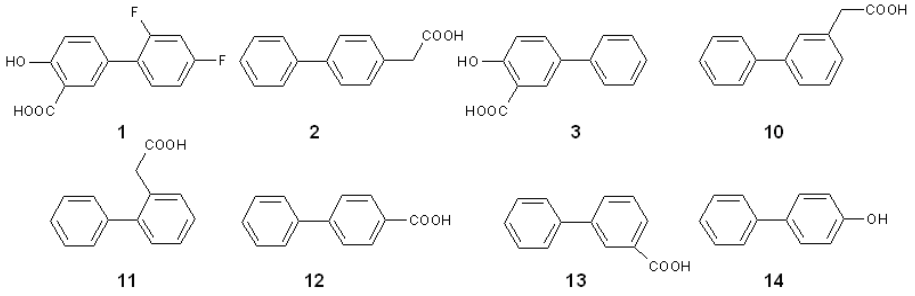


Figure 3. Prepared biaryls.

to a nitrogenous ligand, catalysed the reaction in 58% (Table 1, entry 7). Palladium-diamine complexes (**6** and **7**), however, turned out to be the most efficient catalysts tested, exhibiting yields up to 93% (Table 1, entry 8). The reaction proceeded under air and yielded highly pure crystalline Diflunisal after very simple purification on a slilica column to remove the palladium catalyst. The palladium-diimine complex (**8**) was also examined in the Suzuki reaction because of its demonstrated catalytic abilities in PCB syntheses [14]. However, in the case of Diflunisal synthesis, the reaction proceeded in low yield (Table 1, entries 22-24). We obtained less satisfactory results for the Suzuki reaction in toluene, ethanol, or water but good results in DMF. It was found that the reaction proceeded best in harsh conditions, with temperatures up to 150°C. At lower temperatures less satisfactory results were obtained (Table 1, entries 6, 11 and 17). Although the reactions had to be performed at higher temperatures, the advantage was to obtain the products in higher purity. Finally, we added TBAB to the reaction mixture to form a boronate complex $ArB(OH)_3^-Bu_4N^+$ which has been thought to play an active role in the transmetallation step [50-52]. Unfortunately with DMF as the solvent, we could not significantly improve the yields for the preparation of Diflunisal by adding TBAB to the reaction mixture. The best yield for the preparation of Diflunisal remained as 93% without using TBAB (Table 1, entry 8).

The aromatic fluorine atoms in Diflunisal are chemically inert and relatively stable metabolically. Diflunisal and its monofluoro analogue are almost equal inhibitors of PG synthetase [1]. Diflunisal is also known to be more active than its ester congener [9]. Thus the free carboxylate enhances inhibition more than the presence of fluorine. Defluorination is the initial photochemical decomposition product of Diflunisal [53], therefore we prepared molecules where fluorine was replaced with hydrogen (**3**). A satisfactory preparation of 5-phenyl-2-hydroxybenzoic acid **3** (70% yield) was obtained by using the same harsh conditions (Table 2, entry 2). Also another NSAID drug, Felbinac **2** and two of its analogues **10** and **11** (Fig. 3) were prepared in excellent yields using the same reaction conditions (Table 2, entries 3-5). Even though free hydroxyl group containing arylhalides are rarely used in coupling reactions due to the typically low yields, Diflunisal can be prepared in excellent yield without hydroxyl protection. This exceptional behavior may be due to the internal hydrogen bond formation which prevents the side reactions usually observed in coupling reactions without protection. For example, moderate yields of 3-carboxylic acid biphenyl **13** and 4-hydroxybiphenyl **14** syntheses (Table 2, entries 7 and 8), but excellent yields in Diflunisal preparation qualify this supposition.

Table 2. Syntheses of Diflunisal non-fluorinated analogue **3**, Felbinac and biaryls in DMF using catalyst **6**.

Entry	Temperature	Product	Yield %
1	120°C	3	50
2	150°C	3	70
3	150°C	2	99
4	150°C	10	87
5	150°C	11	93
6	150°C	12	99
7	150°C	13	77
8	150°C	14	42

4. Conclusions

In summary, a straightforward and clean synthesis of biphenyl carboxylic acids has been demonstrated. A novel air stable, easily prepared phosphine free Pd-diamine complex **6** catalyzes Suzuki coupling reactions in only 1 mol% of catalyst loading without any need of dry solvents or inert atmosphere. Several biphenyl carboxylic acids and 4-hydroxylbiphenyl could be synthesized without any requirement for protection of either the carboxyl or hydroxyl groups. Use of this novel Pd-diamine catalyst is a convenient and reasonably efficient method to prepare Diflunisal and Felbinac and their analogues in only one step. After the Suzuki reaction, very pure products may be obtained by chromatographic separation on a short silica column.

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