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Pd-catalyzed synthesis of arylacetic acid derivatives from boronic acids†

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A palladium(0)-catalyzed cross-coupling reaction between arylboronic acids or esters and α-bromoacetic acid derivatives is described which allows the synthesis of various functionalized arylacetic acid derivatives under mild conditions.

Methylenecarboxy groups are key functionalities in many biologically active compounds such as the antiinflammatory and analgesic drugs Indomethacin or Aclofenac.[1] A mild and efficient procedure for the introduction of the methylenecarboxy group into functionalized molecules is thus of great interest. Traditional syntheses involve multistep procedures that are often incompatible with sensitive functionalities.[2] Alternatively, transition metal-catalyzed cross-coupling reactions between aryl halides and Reformatsky reagents,[3] tin,[4] copper,[5] and other enolates,[6] or ketene acetals have been employed.[7] Some electrochemical syntheses have also been reported.[8] However, especially for applications in combinatorial chemistry, most of these syntheses are quite inconvenient due to the instability or toxicity of the reagents or the required bases.

We imagined that the inverse approach of combining an arylmetal species with an α-halocarbonyl derivative might be an interesting alternative, especially for substrates containing sensitive functions such as enolizable keto-groups. Due to their easy handling and long shelf life, arylboronic acid derivatives would be the starting materials of choice, particularly for small-scale reactions. Arylboronic esters have recently become widely accessible from aryl halides by *in situ* coupling reactions that tolerate many functional groups.[9,10] In order to permit an application of the outlined coupling reaction in drug discovery, it is of utmost importance to overcome the necessity of using highly toxic reagents such as thallium carbonate.[11] Initial studies were carried out with phenylboronic acid and ethyl bromoacetate (Scheme 1).

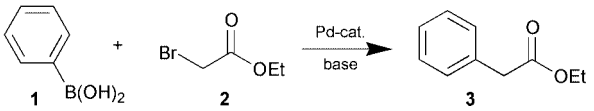
Under standard Suzuki conditions using tetrakis(triphenylphosphine)palladium and potassium carbonate in DMF,[12] only trace amounts of the expected product **3** were detected. Instead, redox reactions between the arylboronic acid and ethyl bromoacetate predominated, leading to large amounts of biphenyl **4** and benzene **5**. This is not surprising since similar systems have purposely been used in the synthesis of symmetrical biaryls.[13] We have now discovered that the selectivity of the reaction can be completely inverted when bulky, moderately electron-donating phosphines are employed as ligands on palladium. Selected results are shown in Table 1.

Changing the ligand from triphenylphosphine to tri(*o*-tolyl)phosphine significantly improves the selectivity towards the desired coupling product and allows smooth conversions even at room temperature. In order to determine the origin of this effect, we varied both the steric and the electronic properties of the ligand (entries 1–9). Tri(*m*-tolyl)phosphine gives only poor selectivities, which led us to conclude that the steric bulk of the tri(*o*-tolyl)phosphine is responsible for the good selectivities. Additionally, the lower selectivities observed for tri(*o*-ethylphenyl)-, tri(*m*-xylyl)-, tri(mesityl)-, and di-*tert*-butylbiphenyl-2-ylphosphine indicate that the ligand must not be too electron-rich. These combined requirements are best fulfilled with tri(1-naphthyl)phosphine, and indeed, this ligand leads to enhanced product selectivity. Chelating phosphines such as (±)-BINAP totally inhibited the reaction, suggesting that the catalytic cycle proceeds through mono-ligated palladium complexes.

Both palladium(II) acetate and tris(dibenzylideneacetone) dipalladium(0) can be used as palladium(0) precursors and show no significant differences in activity (entries 3, 14). However, the amount of biaryl formed is slightly higher when palladium(II) acetate is used. This suggests that the boronic acid initially acts as a reducing agent for the palladium(II). Since a slight excess of boronic acid is usually added, this reaction has no influence on the isolated yields.

The choice of the base also affects the product selectivity (entries 3, 10, 11 and 8, 15). Both K_2CO_3 and K_3PO_4 are equally suitable as bases. However, at room temperature, shorter reaction times were often observed with potassium phosphate. KF was inferior for most substrates since larger amounts of the reduction products were formed. Only in the case of some electron-poor boronic acids did KF become the base of choice (see also Table 2). Other bases, for instance triethylamine, were significantly less active. Best results were obtained with excess amounts of base.

THF proved to be by far the most effective solvent. In acetonitrile, the reaction was much slower and the use of more polar solvents, *e.g.* DMF, drastically decreased the amount of isolable products. This could indicate that hydrolysis of the ester occurs. In THF, however, the presence of small quantities of



Scheme 1 Coupling of benzeneboronic acid and ethyl bromoacetate.

† Dedicated to Professor K. B. Sharpless on the occasion of his 60th birthday.

Table 1 Effects of the reaction conditions on the product distribution

	Ligand	Conv. (%)	**3**[a] (%)	**4**[a] (%)	**5**[a] (%)
1	PPh_3	95	34	38	< 5
2	P(*m*-Tol)$_3$	75	3	23	75
3	P(*o*-Tol)$_3$	100	86	12	< 1
4	P(*o*-EtPh)$_3$	100	51	19	10
5	P(*m*-Xyl)$_3$	100	80	15	5
6	P(Mes)$_3$	80	80	15	5
7	P(*t*-Bu)$_2$Biph	100	67	31	2
8	P(Nap)$_3$	100	88	7	5
9	BINAP	< 5	—	< 1	< 1
10[b]	P(*o*-Tol)$_3$	100	78	15	7
11[c]	P(*o*-Tol)$_3$	100	36	20	28
12[d]	P(*o*-Tol)$_3$	90	14	6	< 1
13[e]	P(*o*-Tol)$_{33}$CN	82	35	6	< 1
14[f]	P(*o*-Tol)$_3$	100	89	10	< 1
15[g]	P(Nap)$_3$	100	91	7	2

Conditions: 3 mol% $Pd(OAc)_2$, 9 mol% ligand, 5 equiv. base, 2 equiv. H_2O, THF, 20 °C. [a] Selectivities determined by GC. [b] KF as base. [c] NEt_3 as base. [d] In DMF. [e] In acetonitrile. [f] $(dba)_3Pd_2$ instead of $Pd(OAc)_2$. [g] K_3PO_4 as base.

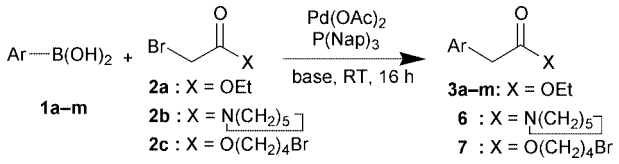
Table 2 Pd-catalyzed synthesis of arylacetic acid derivatives

Comp.	Ar	X	Method A Yield (%)[a]	Method B Yield (%)[a]
3a	Phenyl	OEt	85 (90)	87 (91)
3b	*o*-Tolyl	OEt	90 (90)	75 (79)
3c	1-Naphthyl	OEt	80 (84)	68 (70)
3d	*p*-MeO-Phenyl	OEt	84 (85)	76 (79)
3e	*p*-Acetylphenyl	OEt	79 (80[c]	60 (65)
3f	*p*-Tolyl	OEt	90 (93)	
3g	*m*-Chlorophenyl	OEt	70 (75)[b]	
3h	*p*-Formylphenyl	OEt	67 (74)[c]	
3i	*m*-Nitrophenyl	OEt	40 (40)[b]	
3k	*m*-AcNH-Phenyl	OEt	63 (70)	
3l	2-Thienyl	OEt	33 (33)[b]	
3m	2-Fluorophenyl	OEt	31 (42)[c]	
6	Phenyl	$N(C_5H_{10})$	81 (89)	
7	Phenyl	$O(C_4H_8)Br$	72 (90)	68 (72)

Conditions: (A) 1.2 equiv. arylboronic acid, 3 mol% $Pd(OAc)_2$, 9 mol% $P(Nap)_3$, 5 equiv. K_3PO_4, 2 equiv. H_2O, 20 °C, THF; (B) 1.2 equiv. pinacol boronate, 3 mol% $Pd(OAc)_2$, 9 mol% $P(Nap)_3$, 5 equiv. K_3PO_4, 2 equiv. H_2O, 20 °C, THF. [a] Isolated yields (GC-determined yields in parentheses). [b] KF instead of K_3PO_4. [c] K_2CO_3 instead of K_3PO_4

water had no adverse effect on the reaction outcome so that special drying of the solvent and the reagents is not required.

The generality and selectivity of the reaction were investigated using a number of arylboronic acids **1a**–**m** in combination with several alkyl halides (Scheme 2).

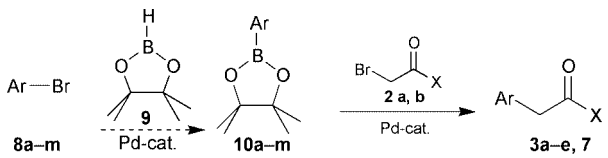


Scheme 2 Pd-catalyzed synthesis of arylacetic acid derivatives.

As can be seen in Table 2 (Method A), most substrates give good yields. Electron-poor and electron-rich compounds are equally suitable for the transformation. Even sterically hindered compounds (*o*-tolylboronic acid) or substrates that are sometimes problematic in palladium-catalyzed reactions (nitro- or heteroarenes) were successfully employed. Moreover, products containing enolizable keto-groups are readily formed without any signs of side products arising from undesired aldol condensations.

Besides ethyl bromoacetate (**2a**), other bromoacetates (**2c**) or -amides (**2b**) can be used. The high selectivity of the transformation is demonstrated by the formation of compound **7**‡ (Table 2): the arylation of 4-bromobutyl bromoacetate (**2c**) takes place exclusively α to the carbonyl group even though a primary alkyl bromide functionality is present.

Many functionalized pinacol boronates§ (**10**) are conveniently accessible from aryl halides (**8**) and bispinacol diboron[9] or pinacol borane (**9**).[10] We thus considered it to be important to extend our reaction to this substrate class (Scheme 3).



Scheme 3

We were pleased to find that the best conditions for the conversion of the boronic acids turned out also to be optimum conditions for pinacol boronate and that the reaction usually gives similar yields for both starting materials (Table 2, 'method B').

In summary, the disclosed palladium-catalyzed cross-coupling reaction between arylboronic acids or esters and α-bromoacetic esters or α-bromoacetic amides represents a mild and general approach to arylacetic acid derivatives. The simple reaction protocol which involves only air-stable chemicals and does not require absolutely dry solvents makes this reaction a valuable alternative to the existing protocols, especially for applications in combinatorial chemistry and drug discovery.

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Notes and references

‡ *Synthesis of 4-bromobutyl phenylacetate* (**7**): A 100 mL flask was charged with palladium acetate (67.3 mg, 0.30 mmol), tri-1-naphthylphosphine (371 mg, 0.90 mmol), 4-bromobutyl bromoacetate (**2b**) (2.74 g, 10.0 mmol) and an excess of potassium phosphate (10.61 g, 50.0 mmol). The reaction vessel was purged with argon, a solution of benzeneboronic acid (1.46 g, 12.0 mmol) in THF (40 ml) was added and the reaction mixture was stirred at 20 °C overnight. The reaction slurry was then poured into water (300 mL) and extracted 3× with 100 mL portions of dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by fractional distillation. A colorless oil (2.41 g, 89%) boiling at 91 °C/0.01 mbar was collected and identified as the desired product. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.33–7.26 (m, 5H), 4.12 (t, ^3J (H,H) = 6 Hz, 2H), 3.62 (s, 2H), 3.38 (t, ^3J (H,H) = 6 Hz, 2H), 1.87 (m, 2H), 1.79 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 171.5, 134.0, 129.2, 128.6, 127.1, 63.8, 41.4, 32.9, 29.2, 27.2 ppm; MS (70 eV): *m/z* (%): 270(6) [M^+], 191(4), 179(4), 136(23), 91(100); HRMS: calcd. for $C_{12}H_{15}BrO_2$ [M^+]: 270.02555; found: 270.02546; anal. calcd. for $C_{12}H_{15}BrO_2$ (271.16): C, 53.16; H, 5.58; N, 0.0; found: C, 52.96; H, 5.65; N, 0.0. The reactions in Table 1 and Table 2 were performed at least twice on 1 mmol scale using 0.05 mL tetradecane as an internal GC standard. The products were isolated by column chromatography (SiO_2, hexane–ethyl acetate 10 : 1) and characterized by means of ^{1}H and ^{13}C NMR as well as by GC-MS.

§ The IUPAC name for pinacol boronates and pinacol borane is 2,3-boranediyldioxy-2,3-dimethylbutane.

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