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An efficient synthesis of chalcones based on the Suzuki reaction

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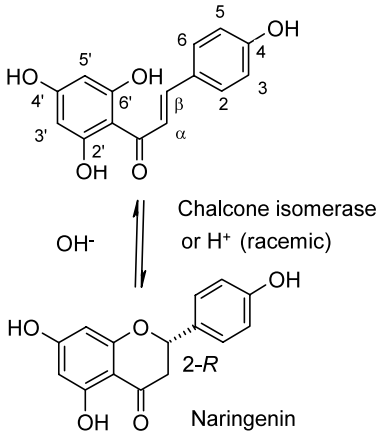
Abstract—A general method for the synthesis of chalcones based on the Suzuki reaction either between cinnamoyl chlorides and phenylboronic acids or between benzoyl chlorides and phenylvinylboronic acids is described.

Chalcones (1,3-diphenyl-2-propen-1-one) and especially chalcones bearing oxygenated function on the aromatic rings are the precursors of all the flavonoids.[1] They are biologically active molecules found in human diet as they are accumulated in many plants and vegetables.[2] During the biosynthesis, chalcones are cyclized stereospecifically into the corresponding chroman-4-one, also called flavanone, by the enzyme chalcone isomerase (CHI, EC 5.5.1.6).[1,3] Chalcones are also easily cyclized in slightly acidic conditions whereas the corresponding flavanones are opened in basic media.[4] Scheme 1 displays this relationship for the most abundant chalcone in plant 2′,4′,6′,4-tetrahydroxychalcone and the corresponding flavanone naringenin.



Scheme 1. Relationship between 2′,4′,6′-tetrahydroxychalcone and naringenin (4′,5,7-trihydroxyflavanone).

Chalcones bearing non natural substituents have been synthesized during the recent years in order to develop drugs active against cancer,[5,6] malaria,[7] leishmaniase,[8] tuberculosis[9] and cardiovascular diseases[10] or for their properties to modulate the regulation of biochemical pathways like NO[11,12] or tyrosine kinase.[13] Chalcones are usually synthesized using the Claisen–Schmidt reaction in basic medium in polar solvent and purified by separation as the reaction led very often to a complex mixture.[4] These conditions have also been used for the creation of a combinatorial library of chalcones.[14] Improved conditions using either organolithium bases in apolar solvent[15] or solid catalyst have been described recently.[16] Chalcones are key precursors in the synthesis of various flavonoids as they can be transformed easily in flavanones by cyclization in acidic medium, in flavones or aurones by oxidative cyclization in presence of hydrogen peroxide in basic medium (the so called Algar–Flynn–Oyamada reaction)[17] or other oxidants.[18] However, few new methodologies for the synthesis of chalcone have been described recently.[19,20]

We reported previously the synthesis of a series of polyoxygenated stilbenes belonging to the resveratrol family by using the Suzuki coupling reaction between a phenylvinyl bromide and a phenylboronic acid-catalyzed by zerovalent palladium (Scheme 2).[21] As phenols are very sensitive to autoxidation under even slightly basic conditions, we needed a protecting group cleavable under neutral or slightly acidic conditions. The mild conditions of the Suzuki coupling reaction allowed the use of methoxymethylether (MOM) as a protecting

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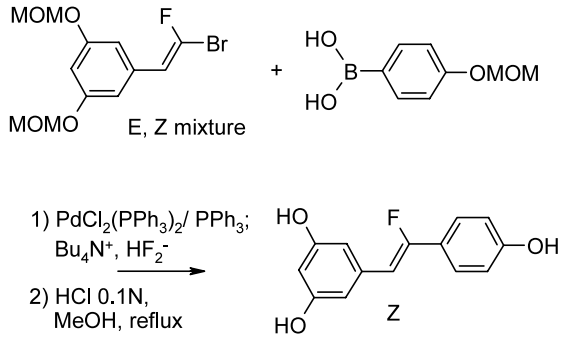


Scheme 2. Synthesis of polyoxygenated stilbenes by the Suzuki reaction.

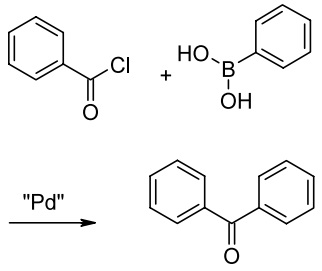
group for the phenolic functions of resveratrol allowing the synthesis of complex polyphenols.

The recently described synthesis of ketones through coupling of phenylboronic acids with acyl chlorides (Scheme 3) by McCarthy's group[22] based on the pioneering work of Cho et al.[23] prompted us to extend this strategy for the synthesis of chalcones.

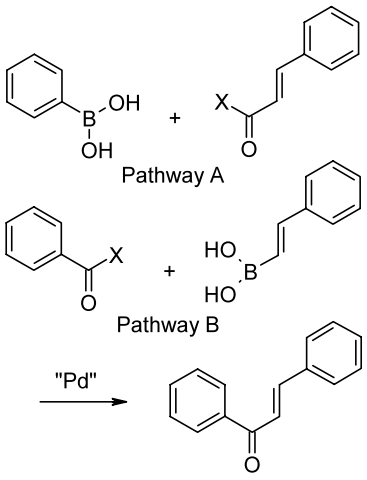
Two pathways are obviously available for the synthesis of chalcones: the coupling between activated cinnamic acids and phenylboronic acids (Scheme 4, Pathway A) and the coupling between activated benzoic acids and phenylvinylboronic acids (Scheme 4, Pathway B).

Since McCarthy's report[22] four years ago many conditions have been described for the synthesis of ketones based on the Suzuki reaction. The first variation is the activated form of the acid used. The reaction can be performed using acyl chlorides,[22,24–26] acid anhydrides,[27] acids activated by activating group usually employed in peptide synthesis,[28] acids activated in situ by pivaloyl anhydride[29] or thio-esters.[30] The second variation is related to the solvent and the nature of the palladium catalyst. Rhodium based catalyst can also be used for this purpose.[31]

We first explored the coupling between cinnamoyl chloride and various phenylboronic acids (Pathway A, Scheme 5) using the conditions we employed for the synthesis of fluorinated resveratrol (solvent: THF; catalyst: $PdCl_2(PPh_3)_2/PPh_3$ in presence of the non-basic reagent n-Bu_4N^+, HF_2^-).[21,32] Unfortunately, this catalytic system led to a complex mixture of products. The use of the protocol described by Bumagin et al.[24]



Scheme 3. Synthesis of ketones by the Suzuki reaction.

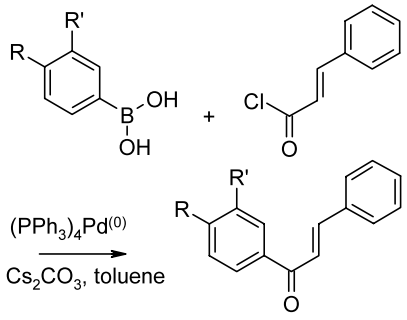


Scheme 4. Retrosynthesis of chalcones based on the Suzuki reaction.

(solvent: acetone, water 3/1; catalyst $PdCl_2$ 3%; base: Na_2CO_3) gave only a moderate yield of the expected chalcone (Table 1).

On the other hand we obtained a fair yield of chalcone (Table 2, entry 1) using McCarthy's conditions (solvent: anhydrous toluene; catalyst: tetrakis(triphenylphosphine)palladium(0); base: cesium carbonate).[22] This reaction is also efficient for phenylboronic acids bearing attracting (Table 2, entry 2) or donating groups (Table 2, entries 3, 4).

We were delighted that the coupling between benzoyl chloride and phenylvinylboronic acid (Pathway B, Scheme 6) gave the chalcones in near quantitative yield (Table 3, entry 1). Furthermore, the yield is not affected



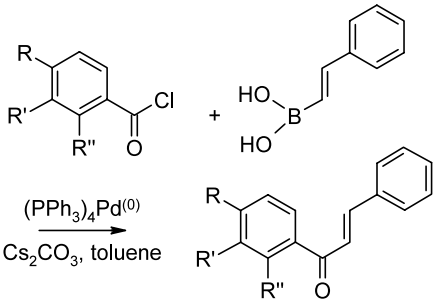
Scheme 5. Synthesis of chalcones by Suzuki coupling between cinnamoyl chloride and phenylboronic acids.

Table 1. Synthesis of chalcones by Suzuki coupling between cinnamoyl chloride and phenylboronic acids using Bumagin's conditions

Entry	R (*para*)	R′ (*meta*)	Isolated yield (%)
1	H	H	37
2	H	NO_2	27
3	OMe	H	25
4	OMe	OMe	23

Table 2. Synthesis of chalcones by Suzuki coupling between cinnamoyl chloride and phenylboronic acids using McCarthy's conditions

Entry	*R* (*para*)	R′ (*meta*)	Isolated yield (%)
1	H	H	51
2	H	NO_2	42
3	OMe	H	44
4	OMe	OMe	41



Scheme 6. Synthesis of chalcones by Suzuki coupling between benzoyl chlorides and phenylvinylboronic acid.

Table 3. Synthesis of chalcones by Suzuki coupling between benzoyl chlorides and phenylvinylboronic acid using McCarthy's conditions

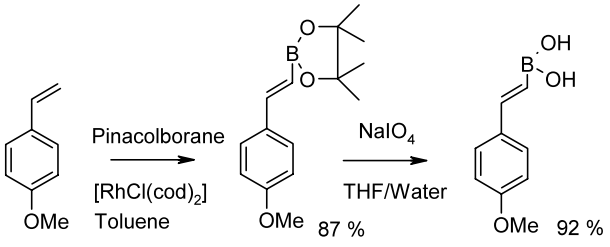
Entry	R (*para*)	R′ (*meta*)	R″ (*ortho*)	Isolated yield (%)
1	H	H	H	93
2	H	CF_3	H	77
3	H	H	CF_3	90
4	H	NO_2	H	68
5	OMe	H	H	87
6	OMe	OMe	H	80

by the substitution pattern of the benzoyl chlorides used either in the case of electron withdrawing substituents (Table 3, entries 2, 3, 4) or more interestingly in the case of electron donor substituents (Table 3, entries 5, 6).[44] These results show that the electronic requirement on the halogen leaving group for the coupling reaction between benzoyl chlorides and phenylvinylboronic acid is less than for the Heck and Suzuki reactions which both exhibit a positive ρ value in Hammett correlation.[33,34]

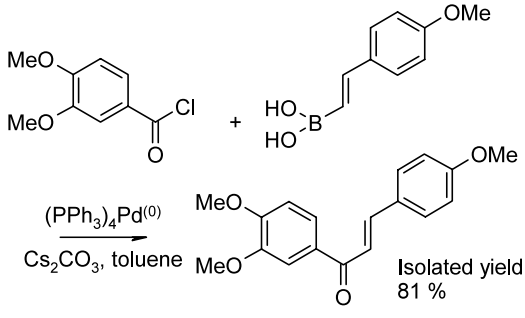
As naturally occurring chalcones are very often hydroxylated or methoxylated on both aromatic nuclei[4] we decided to investigate the effect of donor substituents on the phenylvinylboronic acid side. Phenylvinylboronic acids are accessible from the corresponding styrenes,[35] phenylvinyl bromides[36] or by homologation of the corresponding phenyl iodides[37] or benzaldehydes.[38] Among these reactions, we chose the first one, described recently by Murata et al.,[35] as all the necessary reagents are commercially available. Dehydrogenative borylation of *para*-methoxystyrene, by pinacolborane oxidative addition–dehydrogenation catalyzed by the rhodium complex $[RhCl(cod)]_2$ gave the expected *para*-methoxyphenylethenylboronic acid pinacol ester in 87% yield (Scheme 7).[35] The free boronic acid required for the Suzuki coupling step was obtained from the pinacolate ester by oxidative cleavage using sodium periodate in THF/water.[39]

Using the conditions described above, the reaction between *p*-methoxy-phenylvinylboronic acid[45] and benzoyl chloride gave the expected chalcone[40] in good yield (85%). Furthermore, coupling between *p*-methoxyphenylvinylboronic acid and 3,4-dimethoxybenzoyl chloride led to 3′,4,4′-trimethoxychalcone[41] in approximately the same yield (81%) as shown in Scheme 8.

To the best of our knowledge, the access to chalcones by the coupling between benzoyl chlorides and phenylvinylboronic acids (Pathway B) is described here for the first time, whereas the scope of coupling between cinnamoyl chlorides and phenylboronic acids described only for the simplest reagents[29,31] has been extended. The reaction is not affected by substituents located either on the acyl chloride or on the boronic acid which opens the way to a general synthesis of chalcones. The main advantage of this strategy for the synthesis of polysubstituted chalcones in comparison of the recently described alkylation of aromatic nucleus by cinnamyl alcohol catalyzed by molybdenum(IV)[42] derivatives or cinnamyl acetal catalyzed by palladium[43] is the straightforward localization of the coupling site. The synthesis of naturally occurring chalcone by this new method is under investigation in our laboratory using commercially available polyhydroxylated benzoic acids and readily synthesized substituted phenylvinylboronic acids protected by methoxymethylether (MOM) groups compatible with the Suzuki reaction.[21]



Scheme 7. Synthesis of *p*-methoxyphenylvinylboronic.



Scheme 8. Synthesis of 3′,4,4′-trimethoxychalcone.

Acknowledgements

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44. Typical procedure for the preparation of chalcones from benzoyl chlorides and phenylvinylboronic acids: *E*-2-phenylethenyl-boronic acid (74 mg, 0.5 mmol), benzoyl chloride (2 equiv., 141 mg, 1 mmol), Tetrakis(triphenylphosphine)palladium(0) (17 mg, 3%), cesium carbonate (5 equiv., 814 mg, 2.5 mmol) and 5 mL of freshly distilled toluene were added in a flask fitted with a reflux condenser. After flushing with argon the flask was heated at reflux 4 h. After cooling, the organic phase was diluted with ethyl acetate then washed with saturated sodium hydrogenocarbonate then with water and dried

over $MgSO_4$. Column chromatography on silica gel (eluent dichloromethane, petroleum ether 80/20) afforded 97 mg (yield 93%) of *E*-1,3-diphenyl-2-propen-1-one (chalcone) identical with an authentic sample (mp, TLC, ^1H and ^{13}C NMR). All boronic acids and acyl chlorides were from commercial sources, and used without further purification except *p*-methoxy-phenylvinylboronic acid synthesized as described below.

45. Synthesis of *p*-methoxyphenylvinylboronic acid. A flask was charged with di-μ-chlorobis(1,5-cyclooctadiene)dirhodium(I), ($[RhCl(cod)]_2$), (0.005 mmol, 5 mg), and dry toluene (4 mL) under an argon flow. Pinacolborane (2 mmol, 0.29 mL) and paramethoxystyrene (4 mmol, 0.536 mL) were added successively, and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with toluene, washed with water, dried over $MgSO_4$ and evaporated. Column chromatography on silica gel (eluent ethyl acetate, petroleum ether 10/90) afforded 752 mg (yield 87%) of *E*-2-(4-methoxyphenyl)ethenylboronic acid pinacol ester. Sodium periodate (3.54 mmol, 757.6 mg) was added to a room temperature solution of the above pinacolboronate ester (1.18 mmol, 307 mg) in THF/H_2O (8:2, 10 mL). The mixture was stirred until homogeneous, and then 2N HCl (0.4 mL) was added. After 12 h, the reaction mixture was extracted with ethyl acetate (3×20 mL), and the combined organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo giving 193 mg (yield 92%) of *E*-2-(4-methoxyphenyl)ethenylboronic acid.