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Efficient Palladium-Catalyzed Cross-Coupling of β-Chloroalkylidene/arylidene Malonates Using Microwave Chemistry

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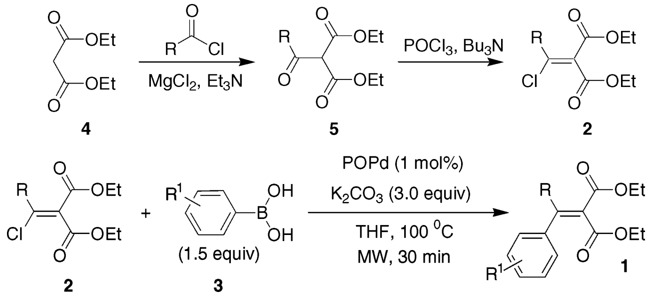
Abstract: A general method for the synthesis of β-aryl/alkylarylidene malonates is reported. The key step involves the coupling of an arylboronic acid to a β-chloroalkyl/arylidene malonate, in the presence of K_2CO_3 and 1 mol % of the air-stable palladium catalyst (POPd) under microwave irradiation, to afford β-aryl/alkylarylidene malonates in good yields. The combination of mild reaction conditions, air stable catalyst, microwave-enhanced chemistry, and high levels of functional group compatibility make this an attractive synthetic approach to this class of compounds.

Among the various reactions involving palladium-mediated coupling of sp^2-carbon atoms with organometallic compounds to form carbon−carbon bonds, the Suzuki reaction has attracted much interest due to a number of attractive features including high yields, mild reaction conditions, and tolerance of a wide variety of functional groups.[1] In view of the proven versatility of this reaction, we contemplated its use in the preparation of β-aryl/alkylarylidene malonates **1**, precursors for the synthesis of a wide range of derivatives including substituted quinolones,[2] flavones,[3] and other heterocycles[4] possessing biological activity.

Previous approaches to β-aryl/alkylarylidene malonates **1** have relied largely upon Knoevenagel condensation of diethyl malonate with the corresponding ketone. However, this reaction is limited in scope and generally only proceeds well for methyl ketones and cyclohexanone derivatives.[5] Our proposed alternative strategy centered on the palladium-catalyzed cross-coupling reaction between β-chloroalkylidine/arylidene malonates **2** and arylboronic acids **3** to yield the desired products **1** (Scheme 1). Vinyl chlorides **2** appeared to be attractive precursors since they are readily prepared in high yield and on a large scale from acyl malonates. We reasoned that **2** should possess high chemical reactivity in the Suzuki reaction and hence be amenable to coupling with a wide range of arylboronic acids. Finally, an additional aspect of our planned approach involved the use of microwave-enhanced synthesis to facilitate the coupling reactions.[6]

SCHEME 1. Synthesis of β-Aryl/alkylarylidene Malonates 1



The requisite β-chloro-alkyl/arylidene malonates **2** were prepared according to the literature procedure involving initial treatment of diethyl malonate with an acyl chloride to yield the 2-acyl malonate (yields 90−95%)[7] followed by chlorination with $POCl_3/Bu_3N$ to yield the vinyl chlorides (yields 45−60%) (Scheme 1).[8]

An initial screen of some typical palladium catalysts [e.g., $Pd(OAc)_2$, $Pd(Ph_3P)_4$, tris(dibenzylideneacetone)-dipalladium (0)] for their ability to mediate the coupling of vinyl chloride **2** (R = Me) with phenylboronic acid gave low yields of the coupled product (10−15%). We therefore turned our attention to the commercially available[9] and air-stable palladium(II) complex $[(t\text{-Bu})_2P(OH)]_2PdCl_2$ (abbreviated as POPd). This catalyst contains phosphinous acid ligands on the palladium that are generated by tautomerization of RR′P(O)H to less stable phosphinous acids in the presence of transition metals. Since the original introduction of these catalysts by Li,[10] they have become widely used for cross-coupling reactions[11] and appear to be particularly effective for coupling aryl and vinyl chlorides. Thus, Li[12] demonstrated the coupling of 1-chlorocyclopentene to arylboronic acids using POPd. Of interest to us was the performance of this catalyst not only with vinyl chlorides **2** but also under microwave heating conditions.

Initial optimization studies were carried out using a variety of different bases (Na_2CO_3, K_2CO_3, Cs_2CO_3, and K_3PO_4), and all were found to be effective for the cross-coupling of β-chloroalkyl/arylidene malonates with phen-

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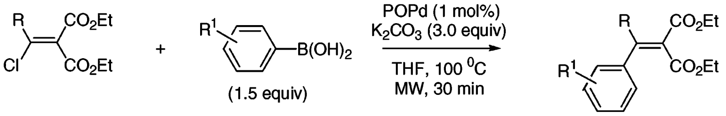
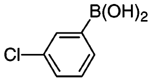
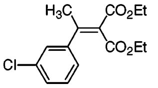
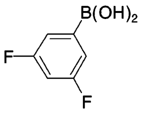
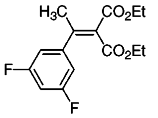
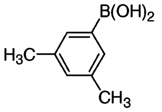
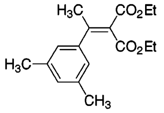
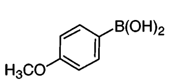
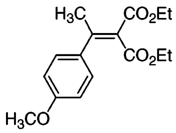
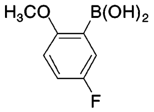
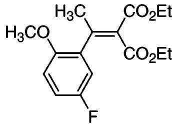
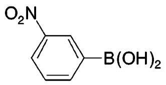
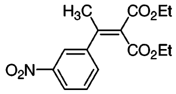
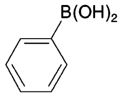
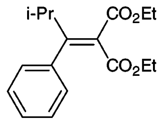
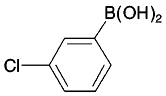
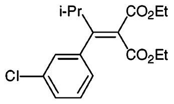
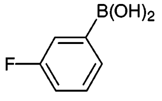
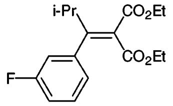
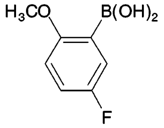
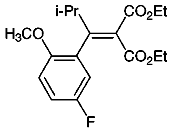
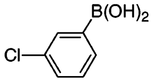
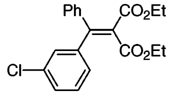
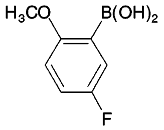
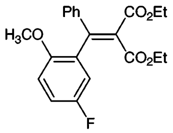
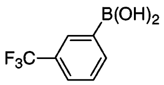
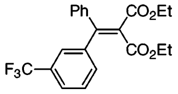
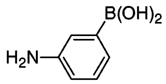
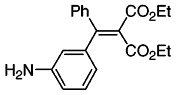
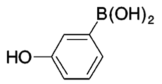
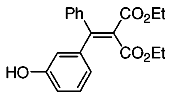
TABLE 1. Synthesis of β-Aryl/alkylarylidene Malonates[a]



entry	R	boronic acid	product	yield (%)
1[b]	Me			70
2	Me			59
3	Me			60
4	Me			65
5	Me			66
6	Me			72
7	i-Pr			71
8[b]	i-Pr			57
9	i-Pr			55
10	i-Pr			52
11[b]	Ph			55
12	Ph			50
13	Ph			68 (40)[c]
14	Ph			60 (35)[c]
15	Ph			58

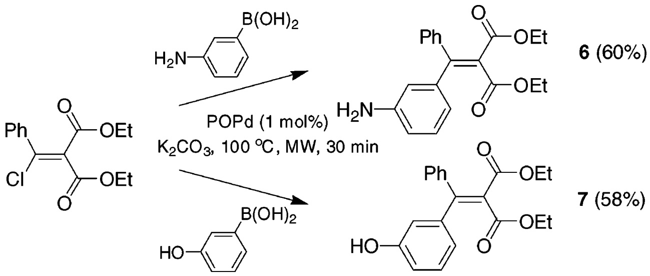
[a] The reactions of β-chloromalonates with arylboronic acids in the presence of POPd were carried out in 100 °C in THF using Explorer PLS. [b] A trace of bis-aryl product was observed. [c] Yields in parentheses are for control experiments involving heating the reaction at 100 °C for 36 h under non-microwave conditions.

ylboronic acid. We were rapidly able to identify reaction conditions under which clean and rapid coupling of the model substrate (**2**, R = Me) occurs with phenylboronic acid **3**, using the air-stable palladium catalyst POPd.

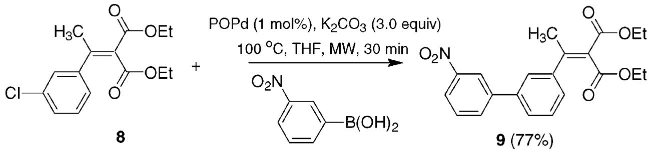
Optimized conditions were vinyl chloride **2** (1 equiv), arylboronic acid **3** (1.5 equiv), K_2CO_3 as base (3.0 equiv), and 1 mol % of POPd in THF. Reactions were irradiated with microwave heating for 30 min at 100 °C followed by workup and silica chromatography to yield the corresponding β-aryl/alkylarylidene malonates in good yields (Table 1). The Suzuki arylation reaction was found to work with a wide range of arylboronic acids including electron-rich (entries 3, 4, 7, and 14), electron-deficient (entries 2, 6, and 9) and sterically demanding (entries 5, 10, and 12) systems. As has been observed before, the Suzuki reaction was found to be compatible with $-NH_2$ and $-OH$ functionality in the arylboronic acid leading to functionalized products **6** and **7** that could be derivatized further (Scheme 2).

In view of the known ability of POPd to mediate Suzuki couplings of aryl chlorides,[10,11] the product **8** from entry 1 was subjected to a further Suzuki reaction with *o*-nitrophenylboronic acid leading to the biphenyl derivative **9** in 77% yield (Scheme 3).

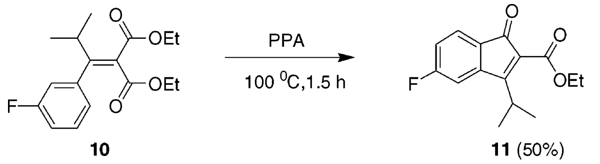
SCHEME 2



SCHEME 3



SCHEME 4



Finally, as an illustration of the further application of the β-aryl/alkylarylidene malonates reported in this paper, treatment of **10** with polyphosphoric acid resulted in cyclization to the 2-carboxyethylindenone **11** in 50% yield (Scheme 4).

In conclusion, we have developed an efficient and versatile route for the synthesis of β-aryl/alkylarylidene malonates **1** from readily available precursors, using the air-stable palladium catalyst POPd. A wide range of arylboronic acids, bearing a variety of functional groups, can be tolerated in the reaction. The use of microwave-assisted heating permits the reaction time to be reduced to as little as 30 min enabling a number of different analogues to be prepared in a short period of time.

Experimental Section

General Procedure for the Reaction of β-Chloroarylidene/alkylidene Malonates with Arylboronic Acids. POPd (1 mol %), β-chloroalkylidene/arylidene malonate (1.00 mmol), arylboronic acid (1.50 to 2.00 mmol), and K_2CO_3 (3.00 mmol) were weighed in a microwave tube, equipped with a magnetic stirrer bar, and sealed with a silicon septum. THF (2 to 3 mL) was injected into the tube via a syringe, and the reaction mixture was subjected to microwave irradiation for 30 min at 100 °C.The reaction vessel was allowed to cool to room temperature and the crude reaction mixture transferred to a separating funnel and diluted with hexane (50 mL) and H_2O (15 mL). The layers were separated; the organic layer was washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, and filtered; and solvents were removed from the filtrate by rotary evaporation. The resulting residue was chromatographed on silica gel using ethyl acetate/hexane as eluents to afford β-aryl/alkylarylidene malonates.

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Supporting Information Available: Experimental details and spectral data for all transformations and compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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