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Boronate Titanium Alkylidene Reagents for Diversity-Based Synthesis of Benzofurans

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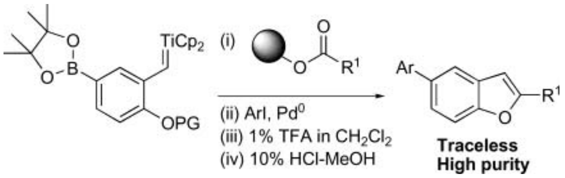
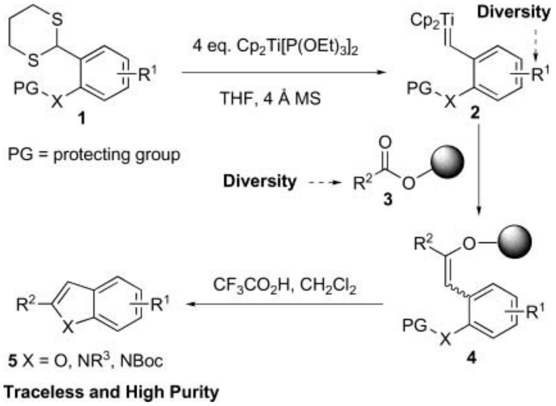
ABSTRACT



Novel titanium benzylidenes (Schrock carbenes) bearing an arylboronate group are generated from thioacetals with low valent titanium species, $Cp_2Ti[P(OEt)_3]_2$, and alkylidenate Merrifield resin-bound esters to give enol ethers. Treatment with 1% TFA gives 2-substituted (benzo[*b*]furan-5-yl)boronates, and solid-phase Suzuki cross-coupling gives 2,5-disubstituted benzofurans. Steps in the syntheses of thioacetal substrates include selective lithiation-boronation, hydrolysis of a MOM group without affecting a boronate ester, and cross-coupling with bis(pinacolato)-diboron.

We have recently demonstrated[1,2] that titanium benzylidenes **2**, bearing a masked oxygen or nitrogen nucleophile in the *ortho* position, can be generated by the reduction of thioacetals **1**[3] and used to convert resin-bound esters **3** into enol ethers **4** (Scheme 1). The resulting enol ethers **4** react with mild acid to give benzofurans or indoles **5** in high purity, because any unreacted ester **3** remains attached to resin under these conditions. These solid-phase syntheses of bicyclic heterocycles are traceless[4] in that, theoretically, substituents are allowed at any site. Although we have used a range of esters and a number of different titanium benzylidenes to generate small libraries of pure benzofurans and indoles, we felt that it would be desirable if extra sites of diversity could be introduced by the titanium reagents. Unfortunately, $Cp_2Ti[P(OEt)_3]_2$ reduces aryl bromides and aryl chlorides,[2] which could act as substrates for palladium-catalyzed cross-coupling reactions.[5] We therefore turned our attention to incorporating the organometallic coupling partner in the titanium reagent.

Scheme 1. Synthesis of Indoles and Benzofurans



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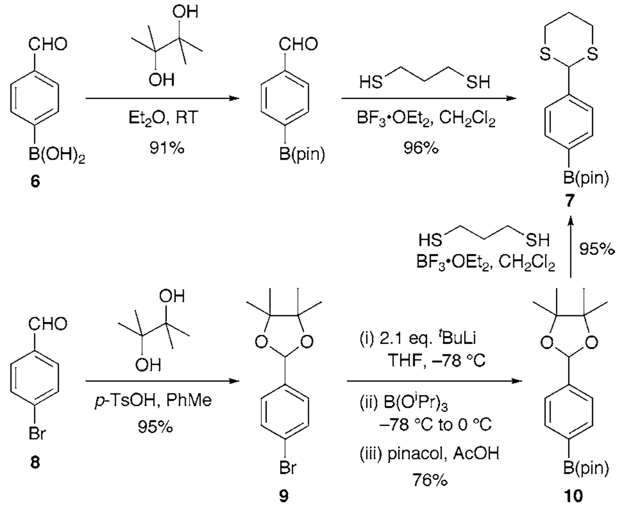
We could find no examples of Schrock carbenes (nucleophilic metal alkylidenes[6]) bearing organoboronates or organotin moieties. Chromium-containing 1,1-bimetallics bearing such groups were known and had been used to alkylidenate aldehydes,[7] but they do not react with carboxylic acid derivatives. Trimethylsilyl groups are tolerated in the titanium alkylidenes[8] and 1,1-bimetallics[9] that alkylidenate esters.[10] However, unlike (alken-1-yl)trimethylsilanes, aryltrimethylsilanes are not substrates for palladium-catalyzed cross-couplings.[11]

We decided that organoboronate functionality would be the most useful for introducing diversity. Although Suzuki cross-couplings[12] of resin-bound halides or triflates are some of the most common reactions in combinatorial library synthesis,[13] polymer-bound boronates have rarely been employed. This is surprising as there are many more commercially available aryl halides than arylboronates. The few reported examples involve using resin-bound boronates in polymer functionalization,[14] in standard solid-phase synthesis,[5,15] in soluble polymer-supported convergent synthesis,[16] and as linkers that are cleaved during cross-coupling reactions.[17]

Initially, we wished to determine whether a titanium alkylidene bearing an arylboronate group could be generated from a thioacetal and used to alkylidenate esters. Therefore, we prepared thioacetal **7** in high yield from commercially available boronic acid **6** (Scheme 2). A cheaper route, which involved no chromatography and was amenable to multigram scale, began from 4-bromobenzaldehyde **8**. Aldehyde **8** was protected as tetramethyldioxolane **9**. Lithium−bromine exchange, reaction with triisopropylborate, and transesterification of the resulting arylboronate gave acetal **10**.[18] Reaction with propanedithiol then gave the desired thioacetal **7**. It is important to match the acetal and boronate ester, as partial transesterification of the pinacolatoboronate occurred in this step when a 1,3-dioxane protecting group was used. Acetal protection was necessary as neither lithiation−boronation nor Grignard formation−boronation were successful using the 1,3-dithiane formed from aldehyde **8**.

Scheme 2. Synthesis of Simple Boronate Substrate



Thioacetal **7** reacted with 4 equiv of $Cp_2Ti[P(OEt)_3]_2$ to give a titanium reagent, presumably titanium benzylidene **12**, that converted Merrifield resin-bound ester **11a** contained in an IRORI macrokan into enol ether **13**. Treatment with mild acid then gave boronate **14** cleanly and in high yield (based on resin loading of commercial Merrifield resin) following solvent removal. We then investigated Suzuki cross-couplings on solid support in DMF. A range of bases (K_3PO_4, K_2CO_3, Tl_2CO_3, CsF, Ag_2CO_3 and Cs_2CO_3) and water−DMF mixtures (including anhydrous DMF) were tested. Under the optimum conditions (1 equiv of water with cesium carbonate as nucleophilic base), both electron-rich *p*-iodotoluene and electron-poor *p*-nitrophenyl iodide coupled smoothly, and ketones **15** and **16** were isolated in high yield and purity following cleavage from resin and solvent removal (with no further purification required; see Supporting Information for ^{1}H NMR spectra). We had previously shown that benzylic thioacetals with an *ortho* trimethylsiloxy group can be used to make benzofurans,[2] so we embarked on a synthesis of benzylic thioacetal **22** (Scheme 4). Methoxymethyl protection of bromosalicylaldehyde **17** gave aryl bromide **18**, which underwent cross-coupling with bis(pinacolato)diboron[19] **19** to give boronate **20**. The mild conditions reported

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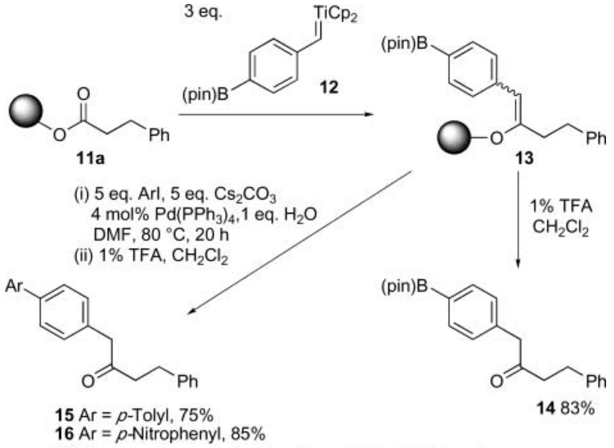
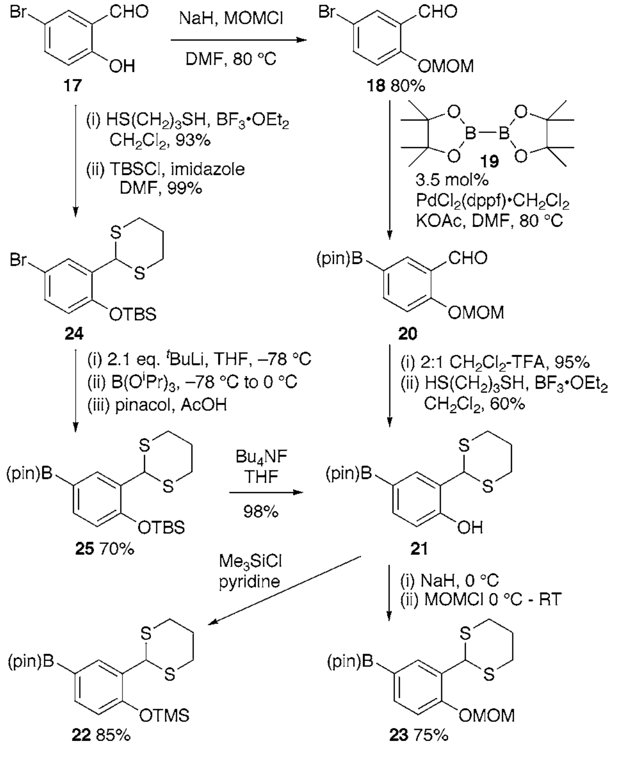
Scheme 3. Synthesis of Simple Boronate Substrate



Yields based on original loading of Merrifield resin

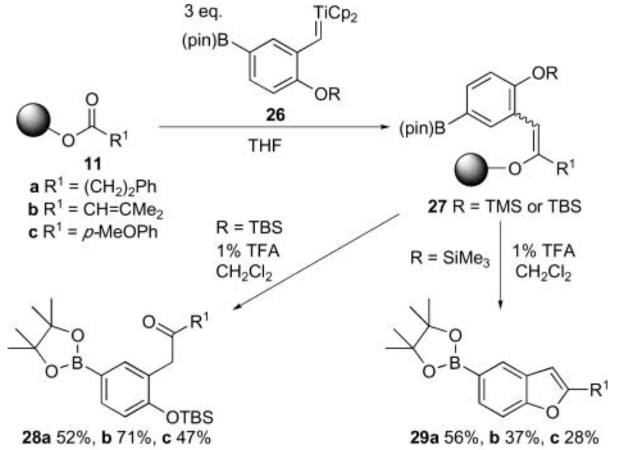
by Weyermann and Diederich[20] allowed selective hydrolysis of MOM without affecting the boronate ester. Thioacetal formation then gave dithiane **21**. Trimethylsilyl protection produced TMS ether **22**, while MOM protection with control of the temperature to prevent opening of the thioacetal gave acetal **23**. Although high yielding, this route was not amenable to scale-up because of problems with the cross-coupling reaction: both the palladium catalyst[21] and bis(pinacolato)diboron are expensive and in mass terms a large amount of catalyst is used. Furthermore, the product boronate **20** was difficult to separate from boron-containing side products. Therefore, we developed an alternative route. Bromosalicylaldehyde **17** was converted into the corresponding 1,3-dithiane, and the phenolic hydroxyl was protected as *tert*-butyldimethylsilyl (TBS) ether **24**. The X-ray crystal structure of this compound shows that the TBS group shields the hydrogen atom at C2, so lithiation−boronation proceeds smoothly to give boronate **25** following transesterification. This contrasts with the MOM analogue of aryl bromide **24**, which gives an intractable mixture of products under the same conditions. Finally, removal of the TBS group gave phenol **21**.

Scheme 4. Synthesis of Substrates for Benzofuran Formation



Thioacetals **22**, **23**, and **25** are all potential substrates for titanium benzylidene formation. Indeed, titanium reagents (presumably titanium benzylidenes **26**), generated from thioacetals **22** and **25** using 4 equiv of $Cp_2Ti[P(OEt)_3]_2$, benzylidenated Merrifield resin-bound esters **11a**−**c** to give enol ethers **27**. Treatment with mild acid then gave ketones **28**, in the case of TBS protection, and benzofurans **29**, when TMS protection was used. The yield was moderate to good, and compounds were isolated in excellent purity following solvent evaporation (^{1}H NMR spectra in Supporting Information). Unfortunately, neither TBS nor TMS protection could stand the cross-coupling conditions, so thioacetal **23** was investigated as an alternative substrate.

Scheme 5. Solid-Phase Synthesis of Boronates



Yields based on original loading of Merrifield resin

Merrifield resin-bound esters **11a**−**c** reacted with the titanium benzylidene **30** generated from thioacetal **23** to give enol ethers **31** (Scheme 6). The alkylidenation reaction had to be heated under reflux for good conversion to occur. It is possible that the MOM group coordinates to the titanium atom in a precursor to benzylidene **30**, stabilizing it so that a higher temperature is necessary for generation of the benzylidene.[22] Cross-coupling followed by resin-washing and

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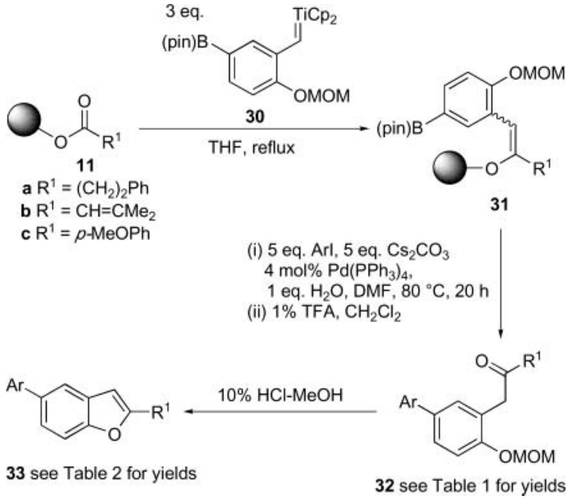
Scheme 6. Solid-Phase Synthesis of Boronates



treatment with 1% trifluoroacetic acid in dichloromethane gave ketones **32** in moderate to good yield (Table 1) and excellent purity following solvent removal. Heating ketones **32** with 10% concentrated hydrochloric acid in methanol and evaporating the solvent gave benzofurans **33** in high purity without any need for further purification (see ^{1}H NMR spectra in Supporting Information). Electron-rich arenes took only 5 min to cyclize, while electron-poor arenes **32ac′**, **32bc′**, and **32cc′** required 20 min exposure to acid.

Table 1. Yields[a] of Ketones **32**

	Ar		
R^1	**a′**, *p*-MePh	**b′**, *p*-MeOPh	**c′**, *p*-NO_2Ph
a, $Ph(CH_2)_2$	51%	53%	56%
b, $Me_2C{=}CH$	57%	56%	57%
c, *p*-MeOPh	22%	26%	25%

[a] Yields based on original loading of Merrifield resin.

In summary, we have developed novel boronate-containing titanium benzylidenes that allow the diversity-based synthesis[23] of benzofurans.

Table 2. Yields of Benzofurans **33** from Ketones **32**

	Ar		
R^1	**a′**, *p*-MePh	**b′**, *p*-MeOPh	**c′**, *p*-NO_2Ph
a, $Ph(CH_2)_2$	90%	92%	54%
b, $Me_2C{=}CH$	95%	80%	96%
c, *p*-MeOPh	83%	87%	100%

Acknowledgment. We thank EPSRC for funding and Dr. L. J. Farrugia for X-ray crystallography.

Supporting Information Available: ^{1}H NMR spectra of ketones **14**−**16**, **28a**−**c**, **29a**−**c**, and **32aa′**−**cc′** as released from resin after solvent removal and benzofurans **33aa′**−**cc′** after solvent removal (all without further purification). Procedure for the preparation of titanium benzylidene **30** and conversion of esters **12** into ketones **32** and benzofurans **33**. ORTEP structure of thioacetal **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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