A convergent approach to γ-carbonyl vinyl boronates

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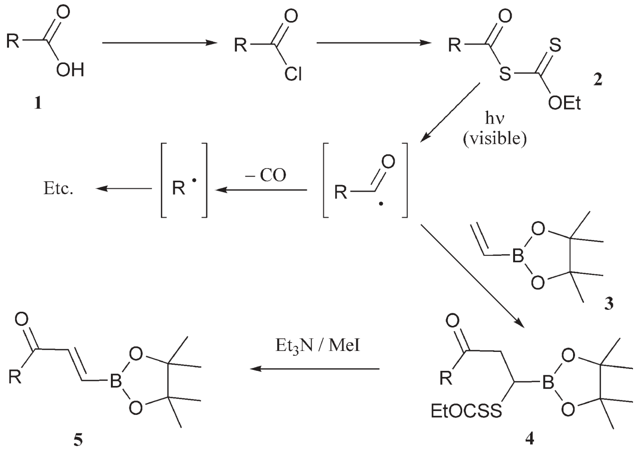
γ-Carbonyl vinyl boronates can be prepared by a visible light induced radical chain addition of an *S*-acyl dithiocarbonate (xanthate) to the pinacol ester of vinyl boronic acid, followed by treatment with base.

The palladium catalysed Suzuki–Miyaura cross coupling and related reactions of vinyl- and aryl-boronates have emerged in recent times as exceptionally powerful and useful carbon–carbon bond forming processes.[1] This has, in consequence, created a need for new methods allowing access to variously substituted vinyl boronates.[2] Vinyl boronates possessing a ketone group in the γ-position represent a rare class for which only two synthetic routes have been reported. The earliest, devised by Jehanno and Vaultier,[3] consists of a multistep sequence proceeding through the intermediacy of γ-boronyl acrolein. The second, developed by Miyaura *et al.*,[4] relies on a palladium catalysed coupling of enol triflates derived from cyclic diketones with bis(pinacolato)diboron. We now describe a radical based, expedient approach to members of this family, some of which would be difficult to obtain by existing approaches.

Our concept is summarised in Scheme 1. It hinges on the possibility of adding an acyl radical, derived from the corresponding *S*-acyl dithiocarbonate (xanthate) **2**, to the commercially available vinyl boronate **3**.[5] The key property of this process is that the xanthate group is transferred to the product **4** in a position β- to the carbonyl group and becomes therefore susceptible to elimination with base, leading thus to the desired unsaturated boronate **5**. The major side reaction that could limit the scope of this approach is the premature decarbonylation of the acyl radical to give alkyl radical R•. The severity of the competition will vary with the nature of the initial carboxylic acid **1**, since the rate of the fragmentation depends largely on the stability of R•.[6]



Scheme 1 A radical based approach to vinyl boronates.

Irradiation with a tungsten-halogen lamp of a 1,2-dichloromethane solution of xanthate **2a** derived from 3,3-dimethylbutanoic acid and a three-fold excess of vinyl boronate **3** produced the corresponding addition product **4a**, which was observed by NMR but which was not isolated. It was simply treated in the crude state with triethylamine and methyl iodide to give the desired boronate **5a** in 67% *overall* yield (Table 1).† The presence of the methyl iodide allows a cleaner elimination by irreversibly intercepting the xanthate salt and any other sulfur nucleophile that could be generated in the medium. In its absence, complex mixtures were formed.

It appeared therefore possible to capture the acyl radical derived from a primary carboxylic acid using the mildly reactive vinyl boronate trap.[7] This was further confirmed by converting the cholic acid xanthate **2b** into the corresponding boronate **5b**, albeit in lower overall yield. The use of the more hindered *O*-neopentyl xanthate (neoPn = neopentyl) is often beneficial in view of the tendency of acyl xanthates to undergo decomposition through an ionic chain reaction. In the case of xanthate **2c** derived from the secondary 4-piperidinecarboxylic acid, decarbonylation of the acyl radical is much faster and becomes a serious complication causing the yield of the desired product to drop dramatically.

Acyl radicals arising from aromatic carboxylic acids do not normally lose carbon monoxide and can therefore be successfully employed in the above sequence. This is illustrated by the synthesis of boronates **5d,e,f** starting from the respective xanthates **2d,e,f** (Table). Substituted aromatic and heteroaromatic motifs can thus be introduced into the stucture. Cyclopropylacyl radicals is the last category of acyl radicals that do not decarbonylate easily that we examined,[8] as shown by the transformation of **2g** into boronate **5g** in 46% yield (PhthN = phthalimido). Such densely functionalised boronates would not be trivial to obtain by more conventional routes.

In principle, the same approach could be applied to the synthesis of the analogous vinyl stannanes. These are also valuable intermediates in Stille's palladium catalysed cross-coupling reaction.[9] However, when acyl xanthate **2a** was irradiated in the presence of vinyl tributyltin **6**, only a low yield (24%) of the addition product **7a** was obtained (Scheme 2). The main source of difficulty was uncovered when the reaction was repeated using xanthate **2e**, as this compound allows a more convenient analysis of the reaction mixture. In addition to the expected product **7e** (31%), we isolated ethyl ester **8** in 48% yield. Such ester formation was not observed to any significant extent with the boronate reactions discussed above. Organotin derivatives are known to catalyse trans-esterification reactions[10] and

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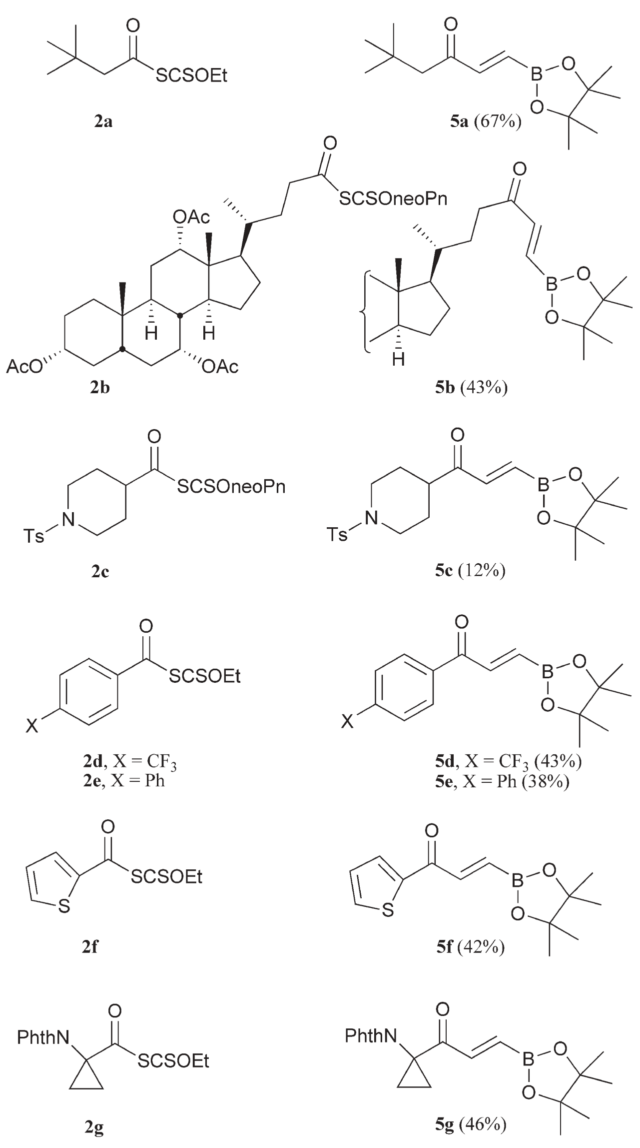
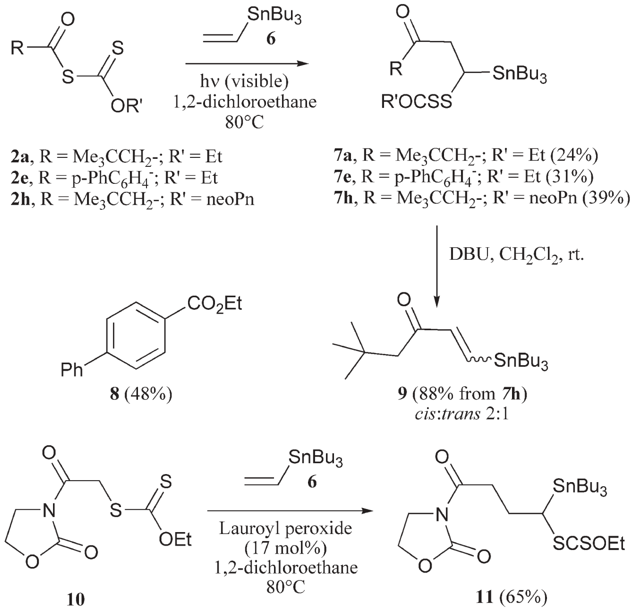
Table 1 Examples of vinyl boronates



Acyl xanthates **2**	Vinyl boronates **5**
2a	**5a** (67%)
2b	**5b** (43%)
2c	**5c** (12%)
2d, X = CF_3 **2e**, X = Ph	**5d**, X = CF_3 (43%) **5e**, X = Ph (38%)
2f	**5f** (42%)
2g	**5g** (46%)

tin-containing side-products could be causing the decomposition of the fragile starting acyl xanthate. Compounds with a geminal stannane and xanthate functions such as **7** represent hitherto unknown structures and are not inherently unstable. This is indicated by the reasonably efficient, peroxide initiated, addition of xanthate **10** to vinyl tributyltin **6** to give the corresponding adduct **11** in 65% yield. Xanthates such as **10** are much less prone to hydrolysis than acyl xanthates and no problems were therefore encountered.

In the hope of improving the reaction yield, we replaced the ethyl group in **2a** by the bulkier neopentyl group. The improvement starting from **2h** was significant since the yield of adduct **7h** increased to 39% but that is still disappointingly low. As for the elimination step, it could be accomplished from **7h** by DBU in dichloromethane in high yield (88%). Curiously, in contrast to the vinyl boronates where only the *trans* isomer was observed, vinyl stannane **9** was produced as a 2 : 1 mixture of geometric isomers in favour of the *cis* isomer. The cause for this difference in behaviour is not clear. The steric bulk and electron-releasing nature of the stannane group may be slowing down the isomerisation of the olefinic bond by a conjugate addition/elimination process, as compared with the smaller, mildly electron-attracting boronate, resulting in incomplete equilibration.



2a, R = Me_3CCH_2-; R' = Et
2e, R = p-PhC_6H_4-; R' = Et
2h, R = Me_3CCH_2-; R' = neoPn

7a, R = Me_3CCH_2-; R' = Et (24%)
7e, R = p-PhC_6H_4-; R' = Et (31%)
7h, R = Me_3CCH_2-; R' = neoPn (39%)

8 (48%)

9 (88% from **7h**)
cis:*trans* 2:1

10

11 (65%)

Scheme 2 Synthesis of vinyl stannanes.

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Notes and references

† Typical experimental procedures:

Procedure for the formation of acyl xanthates **2**: To a solution of the acid chloride in acetone (0.2 M) at −40 °C was added potassium ethyl xanthate (0.95 equiv.). After 30 minutes the solvent was removed *in vacuo* and the residue was dissolved in dichloromethane and washed with water. The organic phase was separated and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the acyl xanthate was used crude or if required could be purified by flash chromatography with protection from light.

Procedure for the synthesis of vinyl boronates **5**: A degassed solution of the acyl xanthate (0.5 mmol) in vinylboronic acid pinacol ester (250 μL) and 1,2-dichloroethane (200 μL) was irradiated at 80 °C with a tungsten halogen lamp for 3–8 hours. The solvent was removed *in vacuo* and the residue redissolved in dichloromethane (10 mL). Methyl iodide (1.05 equiv.) and triethylamine (3 equiv.) were added at room temperature. The mixture was stirred for 3 hours then washed with water and the organic phase dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the vinyl boronate was purified by flash chromatography.

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