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COMMUNICATION

Rhodium-catalysed enantioselective synthesis of 4-arylchroman-2-ones†

Joseph C. Allen, Gabriele Kociok-Köhn and Christopher G. Frost*

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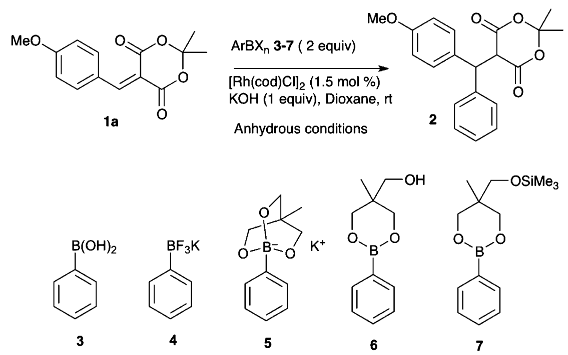
The rhodium-catalysed enantioselective 1,4-addition of organoboron reagents to arylidene Meldrum's acids as acceptors, allows convenient access to 4-arylchroman-2-ones with good to excellent levels of enantioselectivity. The use of silyl-protected dioxaborinanes as donors was found to be advantageous to achieving good yields of product under anhydrous conditions.

The enantioselective construction of C–C bonds using the rhodium-catalysed 1,4-addition of organometallics is established as an important tool for organic synthesis.[1] For the addition of aryl and alkenylboronic acids, the reaction is routinely carried out in aqueous solvents and can afford excellent enantioselectivities across a wide-range of alkene acceptors. In the majority of applications, boronic acids are the coupling partners of choice for conjugate addition reactions. However, there can be issues with purification and manipulation. Often, an excess of reagent has to be used due to competing protodeboronation processes and by competing formation of trimeric cyclic anhydrides (boroxines) in solution, leading to difficulties in being able to accurately measure reaction stoichiometry.[2] A number of elegant solutions to this problem have been presented involving the use of preformed boronate reagents that can be isolated and stored prior to use including tris(hydroxy)borates,[3] lithium trimethoxyboronate species,[4] trifluoroborate salts[5] (such as **4**) and *N*-methyliminodiacetic acid (MIDA) boronates.[6] An important addition to this range of donors are the cyclic triolborates **5** synthesised by Miyaura.[7] These boronate reagents are reported to be stable in air and water and more soluble in organic solvents than potassium trifluoroborates. In this paper we describe the utility of silyl-protected dioxaborinanes in rhodium-catalysed 1,4-addition reactions under anhydrous conditions. This allows the enantioselective addition to arylidene Meldrum's acid derivatives and a subsequent asymmetric synthesis of 4-arylchroman-2-ones.

Fillion and co-workers have shown that arylidene Meldrum's acid derivatives such as **1a** are useful substrates for the rhodium-catalysed 1,4-addition of organozinc[8] and organotin[9] donors generating a range of products with significant scope for further diversification. The lack of literature reports for the addition of organoboron reagents reflects a greater challenge due to the sterically-hindered nature of the trisubstituted alkene and the sensitivity of the malonate functionality in the product to attack by nucleophiles (*e.g.* water).[10] Indeed, our initial investigation into the rhodium-catalysed addition of phenylboronic acid **3** to the 4-methoxyphenyl alkylidene Meldrum's acid derivative **1a** in dioxane at room temperature afforded low conversion to product **2**. The anhydrous conditions and low temperature proved detrimental to the application of potassium trifluoroborate salt **4** and hydroxymethyl dioxaborinane **6** (Scheme 1).[11]



	3	4	5	6	7
Conversion to **2** after 24 h	25%	<5%	41%	<5%	65%
Isolated yield of **2** after 24 h					64%

Scheme 1 The addition of arylboron reagents to arylidene Meldrum's acids.

Pleasingly, the cyclic triolborate **5** and the silyl-protected dioxaborinane **7** gave the desired product **2** with no traces of decomposition products. The superior conversions and good isolated yield obtained with **7** prompted further investigation of this novel organoboron reagent. The silyl-protected dioxaborinanes are readily prepared in high yield by heating an arylboronic acid with 2-(hydroxymethyl)-2-methylpropane-1,3-diol under Dean–Stark conditions followed by treatment with chlorotrimethylsilane in the presence of triethylamine (See Supporting Information for full details†). The arylboron products are easily purified by flash chromatography and can be stored on the bench for several months with no evidence of decomposition. With a range of silyl-protected dioxaborinane reagents in hand, the scope of the rhodium-catalysed addition to arylidene Meldrum's acid acceptors was explored (Scheme 2).

Department of Chemistry, University of Bath, Bath, UK, BA2 7AY. E-mail: c.g.frost@bath.ac.uk; Fax: +44 1225 386231; Tel: +44 1225 386142

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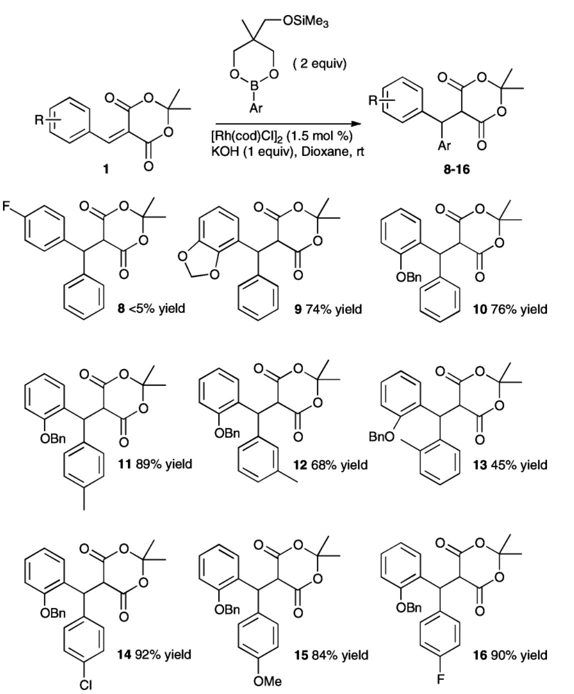
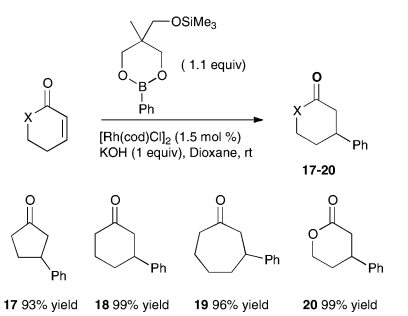


Scheme 2 Scope of addition using silyl-protected dioxaborinanes.

Employing the optimised set of reaction conditions, the isolated yields were consistently good for arylidene Meldrum's acid acceptors that possessed electron-donating ether substituents (Scheme 2, **9–16**).

In contrast, arylidene Meldrum's acid derivative **8** with the *para*-F group on the aryl ring was unreactive under the standard reaction conditions. Similarly, other electron-withdrawing substituents (Br and NO_2) were not tolerated on the acceptor. This observation can be rationalised by the inductive deactivation of the hindered trisubstituted alkene derivative to carbometallation. Substitution of the silyl-protected dioxaborinane was possible at the *ortho*, *meta*, and *para* positions. However, yields were compromised when both donor and acceptor were *ortho*-substituted (Scheme 2, **11–13**). With the optimised set of reaction conditions, we next established that silyl-protected dioxaborinane **7** could be employed for the addition to typical cyclic activated alkenes (Scheme 3).



Scheme 3 The addition to cyclic activated alkenes.

The new organoboron reagent proved to be remarkably effective for the rhodium-catalysed 1,4-addition to cyclic substrates under anhydrous conditions at room temperature. The stoichiometry of the organoboron donor could be reduced to just 1.1 equivalents and the products (Scheme 3 **17–20**) were obtained in high isolated yield. The 4-arylchroman-2-one system is of synthetic interest as it features in a number of natural flavonoid structures or as intermediates in drug synthesis.[12] The rhodium-catalysed 1,4-addition of boronic acids to coumarin derivatives has been demonstrated to afford 4-arylchroman-2-ones with high enantioselectivity.[13] However, coumarins tend to be relatively poor substrates for conjugate additions, thus up to ten equivalents of boronic acid donor were required for successful conversion to product. Our alternative strategy shown in Fig. 1 is based on an enantioselective rhodium-catalysed 1,4-addition to (2-benzyloxy)phenyl arylidene Meldrum's acid derivative followed by hydrolysis/decarboxylation of the cyclic malonate, deprotection of the benzyl ether and intramolecular esterification to provide the desired 4-arylchroman-2-one products.

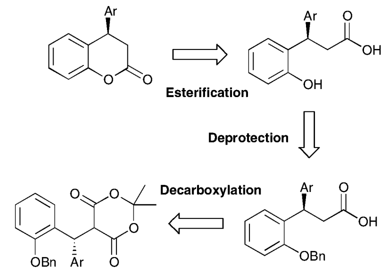
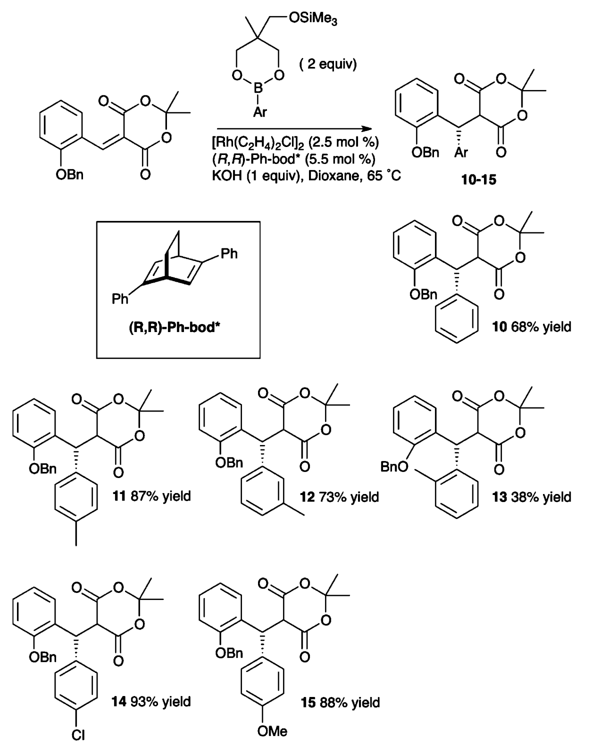


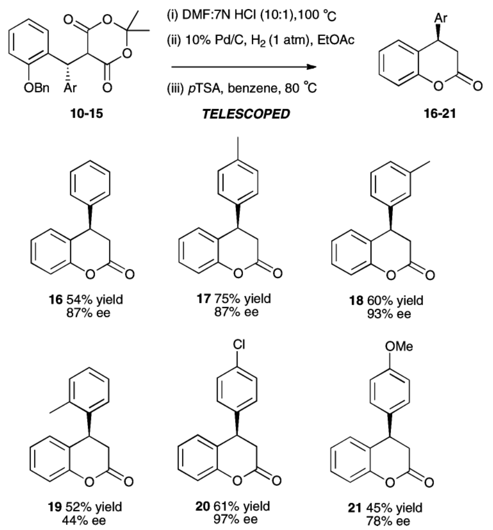
Fig. 1 Enantioselective synthesis of 4-arylchroman-2-ones.

The development of an enantioselective rhodium-catalysed 1,4-addition to (2-benzyloxy)phenyl alkylidene Meldrum's acid derivative proved to be challenging. Preliminary attempts using a $[Rh(C_2H_4)_2Cl]_2$ precatalyst in the presence of atropisomeric bidentate phosphine ligands afforded no desired product, both the silyl-protected dioxaborinane donor and the alkene were recovered intact.

Enantiopure diene ligands can substitute for chiral phosphines in enantioselective processes and often show superior reactivity and enantioselectivity.[14] Fortunately, the enantiopure diene (*R*,*R*)-Ph-bod* introduced by Hayashi and co-workers allowed the arylation to proceed with good reactivity and enantioselectivity under anhydrous conditions (Scheme 4).[15] The isolated yields obtained with the enantiopure diene ligand (*R*,*R*)-Ph-bod* were consistent with the racemic protocol. Substitution of the silyl-protected dioxaborinane at the *para* position afforded excellent yields of product (Scheme 4, **11**, **14** and **15**) with lower yields for the *meta* substituted aryl group in **12** and poor yields for the *ortho*,*ortho* substituted product **13**. The enantioselectivity was determined after conversion to the 4-arylchroman-2-one products **16–21**. Thus, the enantioenriched Meldrum's acid derivative **10–15** was heated in a stirring mixture of DMF and aqueous HCl to afford the carboxylic acid. Hydrogenation of the crude reaction mixture in ethyl acetate in the presence of palladium impregnated on carbon led to deprotection of the benzyl ether. The resulting phenol was then heated in the presence of a catalytic amount of *para*-toluenesulfonic acid to afford the desired product **16–21** over three steps (Scheme 5). The enantioselectivity was good for a range of silyl-protected dioxaborinane donors (up to 97% ee for **20**). The enantioselectivity was significantly lower when both donor and acceptor were *ortho*-substituted (Scheme 5, **9**). The absolute configuration of **20** was determined to be (*R*)- by X-ray crystallography (Fig. 2). A recent density functional



Scheme 4 Enantioselective additions with (*R*,*R*)-Ph-bod*.



Scheme 5 Enantioselective synthesis of 4-arylchroman-2-ones.

theory study of the rhodium-catalysed addition of phenylboronic acid to cyclohexenone offers useful insight into the origin of enantioselectivity with Rh(I)/Ph-bod* complexes.[16]

Conclusions

In conclusion, we have shown that silyl-protected dioxaborinanes perform exceptionally well as donors in rhodium-catalysed 1,4-addition reactions under anhydrous conditions. In the scenario presented here, this allowed an enantioselective addition to arylidene Meldrum's acid derivatives and a subsequent asymmetric synthesis of 4-arylchroman-2-ones. Further studies to explore the application of these new donors in additions to other challenging alkene acceptors and to explain their unique properties are in progress.

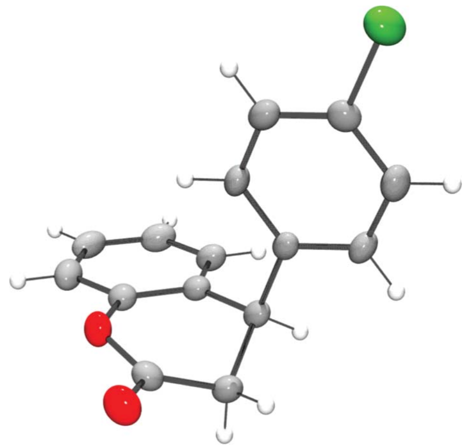


Fig. 2 ORTEP drawing of (*R*)-4-(4-chlorophenyl)chroman-2-one **20**.†

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