B-Alkyl Suzuki couplings for the stereoselective synthesis of substituted pyrans†

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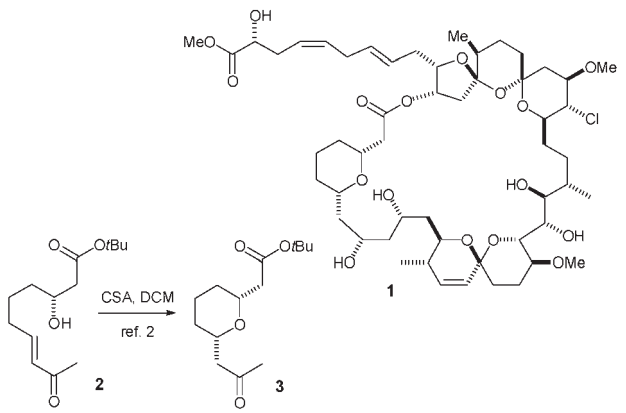
Unprotected homoallylic alcohols can be directly converted to *cis*-2,6-disubstituted pyrans by palladium catalyzed *B*-alkyl Suzuki coupling and subsequent Michael addition.

Substituted pyrans represent a structural motif common to a wide range of natural products. Given their highly varying degrees of functionalization, they remain a significant synthetic challenge. Hence, a number of methods have been developed for their selective preparation.[1] Our own synthetic efforts toward a synthesis of the tetrahydropyran containing natural product spirastrellolide A (**1**) made use of a thermodynamically controlled 6-*exo*-trig cyclization of an intermediate α,β-unsaturated hydroxyketone **2**, affording the *cis*-2,6-disubstituted pyran **3** (Scheme 1).[2]

We questioned whether this same compound could be obtained by Suzuki reaction[3] of an *in situ* prepared alkyl boronate of type **4** and iodobutenone **5**[4] (Fig. 1).

It was anticipated that the use of two equivalents of 9-BBN would allow for the reaction to be carried out without prior hydroxyl group protection. To test this hypothesis, Brown allylation adduct **6**[5] was treated with two equivalents of 9-BBN and subsequently exposed to sodium hydroxide and $(dppf)PdCl_2$ in the presence of iodide **5** in THF at room temperature (Scheme 2). Gratifyingly, upon aqueous acidic workup, the cyclized product itself was obtained in good yield as a >10 : 1 (NMR) diastereomeric mixture in favor of the *cis*-2,6-disubstituted pyran **7**.[6]



Scheme 1 Acid-catalyzed 6-*exo*-trig cyclization.

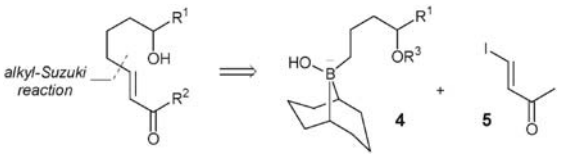


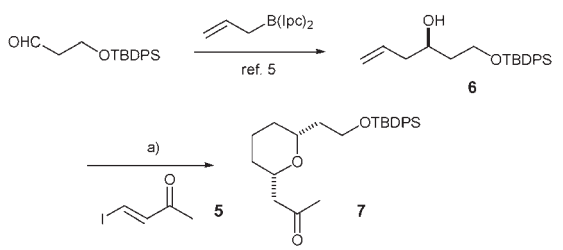
Fig. 1 Pyran retrosynthesis.

In order to investigate the generality of this method for the stereoselective construction of 2,6-substituted pyrans, readily available homoallylic alcohol **8**[7] was first treated with 2 equivalents of 9-BBN. The alkyl borane thus obtained was exposed to aqueous sodium hydroxide before stirring with iodide **5** in the presence of $(dppf)PdCl_2$ at ambient temperature. To our delight, upon acidic hydrolysis, *cis*-2,6 pyran **9** was obtained in good yield and again with excellent levels of diastereocontrol. (Scheme 3).[8] As a demonstration of this methodology in the context of natural product synthesis, **9** was converted to the olfactory (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid **10**,[9] a glandular secretion from the civet cat (*Viverra civetta*), using the conditions previously described by Ley and co-workers.[10]

To further explore the scope of this reaction, 1-allylcyclohexanol (**11**)[11] was subjected to the optimized tandem Suzuki-coupling/oxy-Michael conditions in the presence of iodide **5**, affording the structurally unique spiro-pyran **12** in 70% isolated yield (Scheme 4).

This reaction is not limited to the preparation of 2,6-substituted pyrans. For instance, known crotylation adduct **13**[12] also underwent a productive alkyl-Suzuki coupling with iodide **5** to generate selectively the *anti*-2,3-*cis*-2,6 trisubstituted pyran **14** (Scheme 5).[13]

An extension of this method would be toward the synthesis of five-membered substituted heterocycles. To that end, allylic



Scheme 2 *Reagents and conditions*: (a) 9-BBN (2 eq.), aq. NaOH, $(dppf)PdCl_2$ (10 mol%), $AsPh_3$ (10 mol%), THF, then HCl (1 M), 62%.

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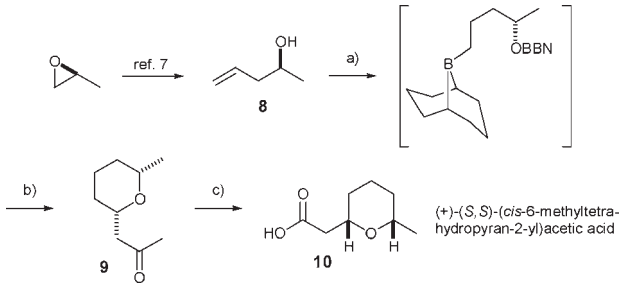
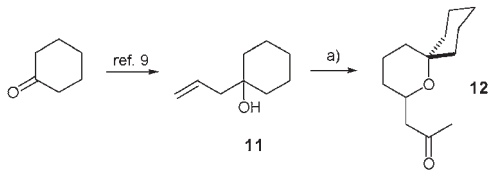
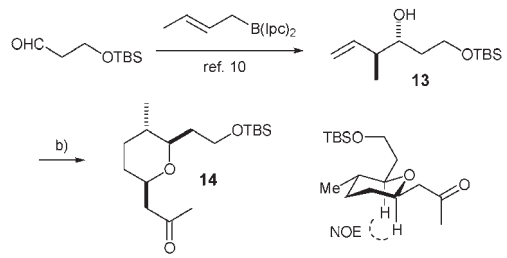


Scheme 3 *Reagents and conditions*: (a) 9-BBN (2 eq.), THF; (b) aq. NaOH then **5**, (dppf)$PdCl_2$ (10 mol%), $AsPh_3$ (10 mol%), THF, then HCl (1 M), 73% (d.r. > 10 : 1) (c) NaOBr (aq), dioxane, 65%.

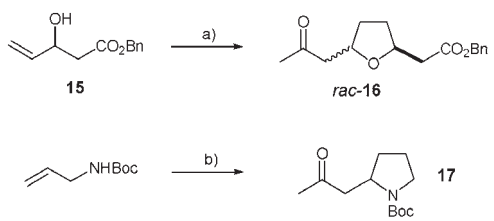


Scheme 4 *Reagents and conditions*: (a) 9-BBN (2 eq.), aq. NaOH, **5**, (dppf)$PdCl_2$ (10 mol%), $AsPh_3$ (10 mol%), THF, then HCl (1 M), 70%.

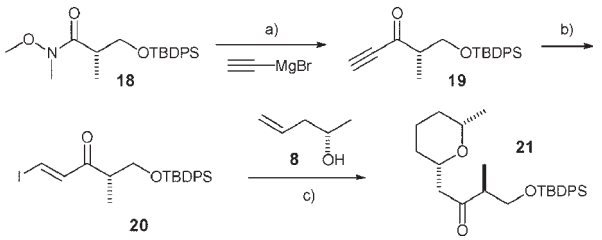


Scheme 5 *Reagents and conditions*: (a) 9-BBN (2 eq.), aq. NaOH, **5**, (dppf)$PdCl_2$ (10 mol%), $AsPh_3$ (10 mol%), THF, then HCl (1 M), 64% (d.r > 10 : 1).

alcohol **15**[14] was first transformed to the corresponding alkyl borane in the presence of 9-BBN, and subsequently exposed to Suzuki coupling conditions in the presence of iodide **5** (Scheme 6). Indeed, the desired 2,5-disubstituted tetrahydrofuran **16** was obtained in good yield, albeit as a 1.7 : 1 mixture of diastereomers. This same sequence can also be applied to the synthesis of nitrogen-containing heterocycles exemplified by the conversion of *N*-allylcarbamate to the corresponding 2-substituted pyrrolidine **17**.[15]



Scheme 6 *Reagents and conditions*: (a) 9-BBN (2 eq.), aq. NaOH, **5**, (dppf)$PdCl_2$ (10 mol%), $AsPh_3$ (10 mol%), THF, then HCl (1 M), 61% (d.r. = 1.7 : 1); (b) 9-BBN then aq. NaOH, **5**, (dppf)$PdCl_2$ (10 mol%), $AsPh_3$ (10 mol%), THF, then aq. NH_4Cl, 55%.



Scheme 7 *Reagents and conditions*: (a) THF, 88%; (b) TMSI, CH_2Cl_2 then *i*-Pr_2NEt, 96%; (c) 9-BBN then aq. NaOH, (dppf)$PdCl_2$ (10 mol%), $AsPh_3$ (10 mol%), THF, then HCl (1 M), 63% (d.r. = 6.5 : 1).

This method may prove highly useful in the context of fragment couplings. As a demonstration, a more complex iodide **20** was chosen as a suitable Suzuki coupling partner, available in two steps from known Weinreb amide **18**[16] *via* an intermediate alkynone **19** (Scheme 7). As expected, **20** underwent a smooth Suzuki reaction with a homoallylic alcohol **8** derived alkyl borane in the presence of (dppf)$PdCl_2$ and sodium hydroxide in THF at room temperature. The corresponding 2,6-substituted pyran **21** was obtained under the described reaction conditions as a separable 6.5 : 1 *cis* : *trans* mixture of diastereomers in 64% overall yield.[17]

In conclusion, Suzuki couplings of homoallylic alcohols with α,β-unsaturated iodoketones afford upon aqueous acidic work-up the corresponding *cis*-2,6-disubstituted pyrans in good yield and with high levels of diastereoselectivity. The reaction has been extended to include the synthesis of substituted tetrahydrofurans and pyrrolidines from the corresponding allylic alcohols and allylcarbamates, respectively. Given the plethora of conditions available for the preparation of both coupling partners and the avoidance of protecting groups, we hope this reaction will find further application to the synthesis of complex substituted heterocycle containing natural products.

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Notes and references

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