

Synthesis of Highly Substituted Symmetrical 1,3-Dienes via Organocuprate Oxidation

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Abstract: Oxidation of alkenyl organocuprates formed from alkenyl halides allows the formation of highly substituted symmetrical 1,3-dienes. Cuprates formed from organolithiums and Grignard reagents can be tolerated and the reaction proceeds with retention of alkenyl geometry.

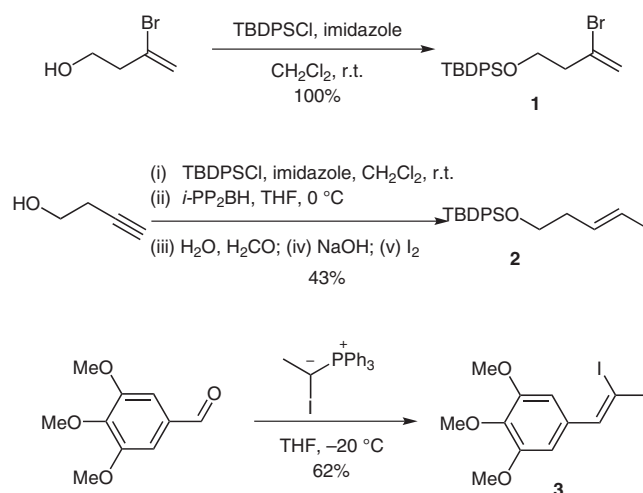
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The 1,3-diene motif is an important one in synthesis especially within the context of pericyclic reactions.¹ This functional group is also important in the development of organic materials.² Various protocols have therefore been developed to perform the homocoupling of alkenyl species; including, examples mediated by Mg,³ Ni,⁴ Pd,⁵ Mn⁶ and Cu.⁷ However, these methods suffer from a number of disadvantages such as the toxicity of the reagents or catalyst, the expense of the catalyst, the need to screen ligands and, most importantly, the possibility of geometrical scrambling occurring during coupling. This lack of stereoselectivity can also be a problem in Wittig reactions and other olefination reactions.⁸

Organocuprates are easily oxidised due to their high lying HOMO,⁹ and this has been exploited previously in the synthesis of both C–C and C–N bonds.¹⁰ Alkenyl cuprate oxidation should allow stereoselective coupling and the organocuprate structure holds apart sterically hindered ligands due to the 180° C–Cu bond angle and long (1.9 Å) C–Cu bond length.¹¹ We therefore reasoned that this methodology would provide an efficient synthesis of highly substituted 1,3-dienes. Since we had previously developed the novel, water-soluble oxidant **5** during the course of our work on aryl organocuprate oxidation,¹² we sought to apply its use to this system as it allowed for easy workup of reaction mixtures¹³ without concomitant halogenation or oxygenation side reactions.

A number of non-volatile alkenyl halides with varying alkene substitution patterns and degrees of steric hindrance were desired to test our procedure. A number of these compounds were available commercially; however, three compounds were prepared in house: protected alcohols **1** and **2** and *Z*-iodostyrenyl compound **3** (Scheme 1).

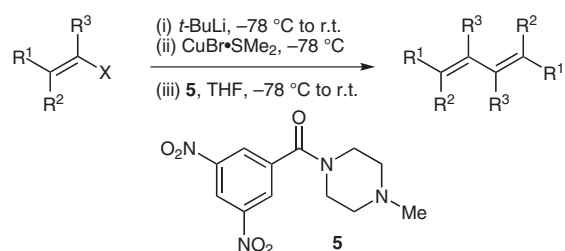
The protected alcohols were chosen as examples of alkenes bearing alkyl groups, with the alkenyl halides arranged in both *E*- and α -configurations. The synthesis of these compounds was achieved in one or two steps from commercially available species. Commercially available alkenyl bromide was protected as the TBDPS ether in quantitative yield to give **1**. *E*-Alkenyl iodide **2** was synthesised from 3-butyn-1-ol; again the alcohol was protected as the TBDPS ether in quantitative yield before the compound was treated with Snieckus reagent¹⁴ to give the boronic acid and subjected to basic conditions and iodine to furnish the desired *E*-iodoalkene in 43% yield. *Z*-Iodoalkene **3** was synthesised in 62% yield via a Wittig reaction from the corresponding aldehyde and the requisite iodo ylid.¹⁵



Scheme 1 Synthesis of alkenyl halides

Initial studies of the organocuprate oxidation centred on the homocoupling of α -bromostyrene; pleasingly the 1,3-diene product **4** was obtained in 86% yield upon oxidation of the lithio-organocuprate with oxidant **5** (Table 1, entry 1). The use of THF as a solvent was found to be necessary, as replacement with diethyl ether led to a large decrease in yield¹⁶ and the appearance of large amounts of debrominated starting material.

With these conditions in hand, the homocoupling of a range of alkenyl halides was then attempted. Gratifyingly, other alkenyl halides could be homocoupled following the

Table 1 Synthesis of Symmetrical 1,3-Dienes¹⁷

Entry	X	Product	Yield (%)
1	Br		86
2	Br		62
3	I		40
4	Br		79
5	Br		57
6	I		63 ^a

^a Reaction conditions: (i) *i*-PrMgCl·LiCl (1.1 equiv), THF, -40 °C; (ii) CuBr·SMe₂ (0.5 equiv), THF, -40 °C; (iii) oxidant **5** (1 equiv), THF, -40 °C to r.t.

same procedure: via metalation with *t*-BuLi, transmetalation to copper and oxidation (Table 1).¹⁷

The reaction was found to tolerate both alkenyl iodides and bromides and the full complement of alkene geometries. Protected alcohols **1** and **2** both successfully underwent the transformation to give **6** and **7**, in 62% and 40% yields, respectively (Table 1, entries 2 and 3).^{18,19} Fully substituted hexa-phenyl 1,3-diene **8** was also formed in good yield (79%; Table 1, entry 4), demonstrating the utility of this methodology even when using highly hindered substrates.

The reaction was also not limited to the use of lithiocuprates, as exemplified by the homocoupling of **3** via the cuprate formed from the corresponding Grignard reagent. A low temperature, functional group tolerant I/Mg exchange was performed on **3** following the procedure of Knochel and co-workers.²⁰ The resulting Grignard reagent was then transmetalated to the magnesiocuprate in good yield and upon oxidation gave a 63% yield of dimeric species **10** (Table 1, entry 6).

In conclusion, we have developed an efficient, stereoselective method for the synthesis of highly substituted 1,3-dienes from alkenyl halides using alkenyl cuprate oxidation. This discovery is a useful extension of our existing biaryl coupling methodology. As the use of mild metalation methods is possible, the reaction should be applicable to substrates possessing relatively sensitive functionality. Studies are ongoing within our laboratories to apply this method to the synthesis of natural products and in diversity-oriented synthesis.²¹

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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- (16) In Et₂O the yield dropped to ca. 5%.
- (17) **Typical Procedure for Alkenyl Halide Homocoupling:** Alkenyl halide (1 equiv) was dissolved in THF (4 mL) and the mixture was cooled to -78°C . *t*-Butyllithium (1.7 M in pentane, 2 equiv) was added dropwise and the solution was stirred at -78°C for 30 min, and then allowed to warm to r.t. over 10 min. The resultant solution was transferred via cannula onto a precooled suspension of CuBr·SMe₂ (0.5 equiv) in THF (2 mL) at -78°C and was stirred for 30 min. A solution of oxidant **5** (1 equiv) in THF (4 mL) was then added and the solution was stirred at -78°C for 30 min and at r.t. for 1 h. The resultant solution was filtered through a plug of silica eluting with PE–Et₂O (1:1) and the solvent was removed in vacuo. The residue was purified by flash column chromatography.
- (18) Selected data for compound **7**: clear oil; *R_f* 0.13 (PE–CH₂Cl₂, 5:1). IR (CDCl₃): 2930, 2857, 1427, 1105, 1088, 986, 692 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.67–7.70 (m, 8 H), 7.36–7.43 (m, 12 H), 6.03 (m, 2 H), 5.57 (m, 2 H), 3.71 (t, *J* = 6.8 Hz, 4 H), 2.34 (app q, *J* = 6.8 Hz, 4 H), 1.07 (s, 18 H). ¹³C NMR (125 MHz, CDCl₃): δ = 135.6 (CH), 134.0 (C), 132.2 (CH), 129.5 (CH), 128.8 (CH), 127.6 (CH), 63.7 (CH₂), 36.0 (CH₂), 26.8 (Me), 19.2 (C). HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₄₀H₅₀O₂Si₂Na: 641.3242; found: 641.3250.
- (19) Selected data for compound **6**: white amorphous solid; *R_f* 0.08 (PE–EtOAc, 10:1). IR (CDCl₃): 3063, 2927, 2861, 1464, 1426, 1390, 1363, 1103, 1037, 735, 757 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 7.65–7.67 (m, 8 H), 7.37–7.45 (m, 12 H), 6.08 (m, 2 H), 5.81 (d, *J* = 2.5 Hz, 2 H), 3.56 (t, *J* = 6.8 Hz, 4 H), 2.49 (app t, *J* = 6.8 Hz, 4 H), 1.21 (s, 18 H). ¹³C NMR (125 MHz, CDCl₃): δ = 143.0 (C), 136.1 (CH), 134.2 (C), 131.6 (CH₂), 129.1 (CH), 127.6 (CH), 61.3 (CH₂), 40.0 (CH₂), 28.6 (Me), 18.4 (C). HRMS (ESI): *m/z* [M + Na + 2 H]⁺ calcd for C₄₀H₅₂O₂Si₂Na: 643.3398; found: 643.3396.
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