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Synthesis of sulfur-containing aryl and heteroaryl vinyls via Suzuki–Miyaura cross-coupling for the preparation of SERS-active polymers

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ABSTRACT

The preparation of sulfur-containing aryl and heteroaryl vinyl co-monomers via Suzuki–Miyaura cross-coupling between the corresponding mercaptomethyl arylboronates and in situ-generated vinyl bromides is described. Surface-enhanced Raman scattering (SERS) studies of the target compounds on gold nanoparticles confirmed their potential as spectroscopic tags in the fabrication of SERS-encoded polymers for combinatorial screening and biomedical diagnostics.

The bar-coded resins (BCRs) were recently introduced for applications in combinatorial synthesis and screening,[1] and for biomedical diagnostics.[2] The defining characteristic of the BCRs is their preparation from spectroscopically active styrene co-monomers displaying unique IR and Raman vibrational fingerprints. Using the styrene co-monomers' substitution pattern as the source of spectral diversity, over 600 BCRs were generated from a small set of unique styrene co-monomers.[3] The BCRs can be identified using hyperspectral[4] and/or time-of-flight secondary ion mass spectrometry[5] imaging/mapping.

A potentially important application for the BCRs is in Dual REcursive Deconvolution (DRED), a strategy devised for the rapid screening of resin-supported combinatorial libraries.[6] DRED operates through the iterative identification of the first and last randomized positions of active members in a combinatorial library generated through split synthesis. The last building block can be readily obtained from pool screening after the last step of library generation while identification of the first randomized position could be determined from the BCR's vibrational fingerprint. To this end we developed a rapid bead-identification strategy based on Raman spectroscopy.[4] Although this method is limited by low signal-to-noise ratio, we have been able to record reliable spectra of the BCRs in 10 ms using state-of-the-art instrumentation,[4] which translates into a screening speed of 10–100 beads/s. To further push this limit and reduce the cost associated with the Raman detection set-up, we opted to design a new family of metal nanoparticle–BCR (NP–BCR) composites that can be detected with very high sensitivity using surface-enhanced Raman scattering (SERS).[7] With enhancement factors reaching 10^{11} relative to Raman scattering, thousands of beads could in principle be classified in a fraction of a second.[8] To take advantage of the SERS effect, the encoded polymer must be chemically or physically adsorbed on the surface of a SERS-active nanoparticle (silver or gold).[9] A key step toward this goal requires the synthesis of a new family of methylthio styrene derivatives that we describe in this report along with their characterization by Raman and SERS spectroscopies. Because of their high affinity for metallic surfaces, we reasoned that the thioether groups would adsorb on the nanoparticle surface to generate a self-assembled monolayer, which can then be copolymerized with a styrene co-monomer in a suspension polymerization set-up[1] to generate SERS-active BCRs.

Chart 1 shows sulfide-containing aryl and heteroaryl vinyl compounds obtained via Pd-catalyzed Suzuki cross-coupling between

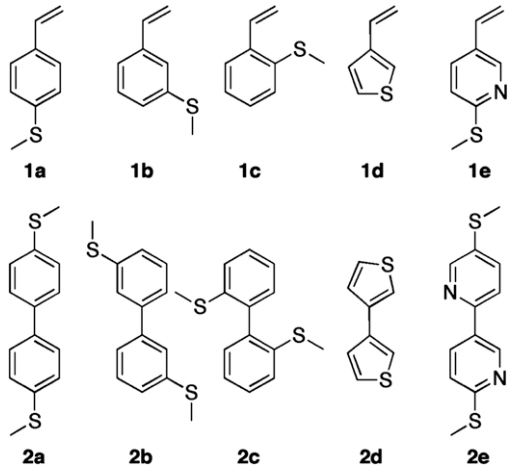

Chart 1.

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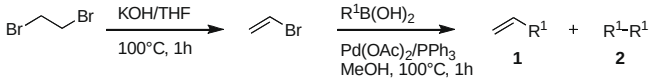
vinyl bromide generated in situ and the corresponding aryl/heteroaryl boronic acids. This strategy differs from our previously reported method[10] for thioacetyl styrene derivatives not only from the synthetic point of view but also from a practical perspective. The thioethers prepared here are anticipated to be chemically more stable, thus preventing undesired cross-linking, known to dramatically affect the physical properties of the beads such as swelling, porosity, and on-bead reactivity.[1b]

Mercaptomethyl styrenes have previously been obtained either by dehydration of (methylthiophenyl) methanol in the presence of Al_2O_3[11] or by reaction of Grignard reagents from halo-(alkyl)styrenes with dimethyl disulfide.[12] Palladium-catalyzed cross-coupling reactions are efficient to introduce a vinyl group onto aromatic rings. Examples covering the use of potassium vinyl-trifluorborate,[13] vinyl-tributyltin,[14] trivinyl-indium,[15] vinyl-magnesium,[16] vinyl-polysiloxane,[17] and vinyl-triethylsilane[18] have been extensively reviewed in the recent literature. However, the use of sulfur-containing substrates in vinylation reactions has not received as much attention.[19,20] Recently Lando et al. reported a simple and efficient protocol for the synthesis of several functionalized styrenes via Pd-catalyzed Suzuki cross-coupling between arylboronic acids and vinyl bromide generated in situ from 1,2-dibromo ethane.[20] Taking into account the simplicity of this experimental procedure, the use of mild reaction conditions, and its functional group tolerance, we decided to extend its scope to the preparation of sulfur-containing aryl and heteroaryl vinyl co-monomers.

Monitoring of the reaction progress by GC–MS confirmed the formation of the desired compounds. After final work-up and purification by flash chromatography, the three mercaptomethyl styrene isomers, Table 1 (entry a–c), were isolated in moderate yields as the main reaction products. Interestingly, the most sterically hindered *ortho*-mercaptomethyl styrene derivative **1c** was obtained in higher yield. A possible explanation for this result could lie in the co-existence of a parallel competing homocoupling reaction inferred from the concomitant formation of the corresponding *bis*-mercaptomethyl-biphenyls **2a–c** (Chart 1). We then explored the synthesis of vinyl heterocyclic compounds. The 3-vinylthiophene co-monomer (**1d**) was previously obtained via Pd-catalyzed cross-coupling of 3-bromo thiophene with potassium vinyltrifluorborate[13] or triethyl vinylsilanes.[18] However, these procedures tend to have long reaction times and/or poor yields, commonly associated with an inefficient oxidative addition step of the thiophene ring to the Pd(0) complex. In this context we have found that involvement of this heterocycle in the transmetalation step to the Pd(II) center, as a thiophene-3-ylboronic acid derivative, greatly improves the synthetic outcome of co-monomer **1d**. Consistent with this result, a successful catalytic coupling reaction between thiophene boronic acid with heteroaryl bromides or activated heteroaryl chlorides in the presence of Pd(II) and monophosphines was recently reported.[21] Finally, the cross-coupling reaction of 6-(mercaptomethyl)pyridin-3-ylboronic acid was also tested and the corresponding vinyl derivative **1e** was obtained in low yields. In this case the major reaction product identified was the 2-(methylthio)pyridine resulting from a thermal protodeboronation process upon prolonged heating.

To test the potential of compounds **1a–e** in the preparation of SERS-active BCRs, the Raman spectra of co-monomers **1a–e** were recorded and compared with the corresponding predicted spectra. Furthermore the SERS spectra were recorded in the presence of a Au(0) nanoparticle (Au–NP) solution[22] (Fig. 1). In all cases, the predicted spectra for the pure compounds correlated well with the experimental Raman and SERS spectra. While the Raman experiments were carried out on the bulk material, the SERS spectra were recorded using dilute solutions of each co-monomer ($\sim 10^{-5}$ M), thus confirming the coordination of the mercaptomethyl moiety onto the Au–NP. The significant enhancement of the C–S stretching vibrational mode is further evidence of the coordination to the Au–NP surface. Table S1 summarizes the assignment of the most characteristic Raman and SERS bands for each co-monomer. From these data, it is clear that each co-monomer features a unique vibrational spectrum, which is a key requisite for their utilization in the preparation of a library of SERS-active BCRs.[1]

Table 1
Results of the Pd-catalyzed cross-coupling reaction between 1,2-dibromoethane and the corresponding aryl or heteroaryl boronic acids



Entry	Product **1**	Yield[a] (%) **1:2**
a	**1a**	41:4.8
b	**1b**	33:12
c	**1c**	51:2.5
d	**1d**	60:2.8
e	**1e**	17:0

[a] Isolated yields for cross-coupling product. All compounds were characterized by $^1H/^{13}C$ NMR, Raman, SERS, GC/MS, and MS.

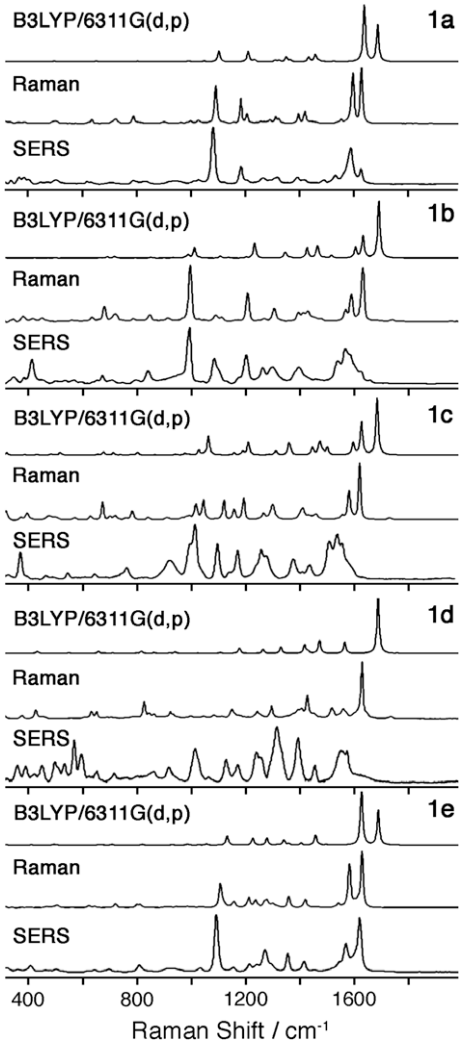


Figure 1. Calculated, Raman, and SERS spectra for compounds **1a–e**.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.061.

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