Suzuki cross-coupling reactions on the surface of carbon-coated cobalt: expanding the applicability of core–shell nano-magnets†

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To develop magnetic nanomaterials applicable to organic synthesis, the Suzuki cross-coupling method was adapted to attach a range of functional groups to carbon-coated core–shell materials *via* commercially-available substituted arylboronic acids.

The attachment of chemical or biological compounds to the surface of magnetic nanoparticles[1] offers the unique possibility of dislocating the compounds of interest by the sole action of an external magnetic field. This has led to a variety of applications in the fields of drug delivery, biotechnology[2] and separation technologies.[3] In organic synthesis such nanoparticles promise the fast and efficient removal of products, reactants or catalysts[4] from reaction mixtures (Fig. 1). To make this application feasible the particles have to be stable under typical reaction conditions. This stability not only includes the chemical inertia of the particle itself, but also the stability of the surface chemistry.

Chemically stable magnetic nanoparticles have been designed following a core–shell approach, where the core accounts for the magnetic properties and the shell gives the material its chemical inertia. Metallic cores of iron or cobalt offer advantageous ferromagnetic properties and shells of silica,[5] gold[6] and carbon[7] have been described. The extraordinary chemical stability of carbon coated nanomagnets[8] make these materials most interesting for applications involving harsh chemical conditions. Furthermore, the carbon coating allows a covalent surface functionalization based on carbon–carbon bonds. Given the structural and chemical similarity between the graphene-like carbon coatings[9] and carbon nanotubes, the extensive chemistry of carbon nanotube functionalisation[10] proved useful for covalently attaching functional groups onto the carbon surface of these particles.[11] In particular chloro- and nitro-benzene moieties have been introduced, using the respective diazonium salts,[12] generated *in situ* from the corresponding aniline derivatives. To extend the versatility of available covalent functionalizations we derived a method for the Suzuki cross-coupling reaction on the surface of these nanomagnets. This Pd-catalysed cross-coupling of an organoboronic acid and a halide or pseudohalide[13] was selected due to the high functional group tolerance and the wide variety of commercially-available substituted boronic acids.

First attempts involved bromophenyl functionalized particles **1** (Scheme 1), which were synthesized from a flame-derived carbon coated cobalt nanopowder (Fig. S6–S8, ESI†), analogous to the chlorophenyl particles previously described.[11] The particles were then subjected to classical Suzuki coupling conditions[14] (5 mol% $Pd(PPh_3)_4$ and 2 M Na_2CO_3 (aq.) under overnight reflux). This gave no reaction as determined by FT-IR and CHN element analyses. NMR analysis was impeded by the magnetic nature of the functionalized nanoparticles.

Other known protocols were investigated[15] but they too gave no reaction with bromophenyl particles. To understand why the reaction did not occur, the electronic properties of the functionalized particles were investigated. This was done by synthesizing benzoate functionalized particles **2** and evaluating the ionization properties of the benzoate moiety on the surface by titration with HCl, resulting in a pK_a value of 4.52 (benzoic acid = 4.19, for experimental details, see ESI†). Therefore, the carbon surface of the particle can be described as an electron donating *para*-substituent. The deviation to the pK_a of benzoic acid corresponds to a Hammett parameter $\sigma = -0.33$. For comparison $\sigma = -0.27$ and -0.37 are the Hammett parameters for *p*-methoxy and *p*-hydroxy groups respectively.[16]

This finding stays in line with earlier investigations on graphite[17] and agrees with the observed lack of reactivity of the bromophenyl functionalized particles **1** under Suzuki type conditions. This can be explained by the electron-donating surface increasing the electron density in the C–Br bond and, therefore, reducing the rate of oxidative addition to the Pd

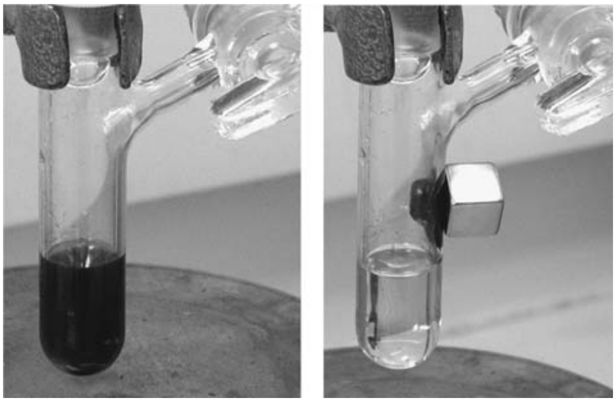

Fig. 1 Photograph of reaction mixture in a Schlenk tube (left) and the removal of the magnetic reactant by the use of an external neodymium based magnet (right). The time between the two images is 5 s.

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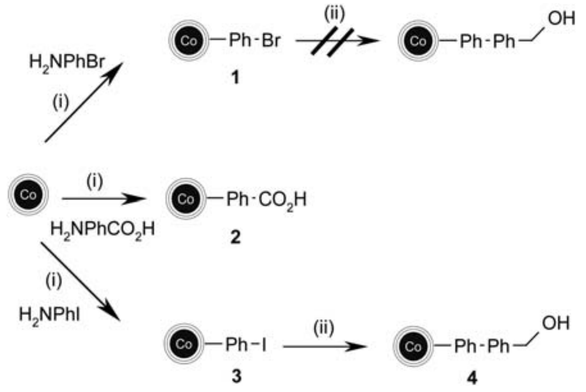


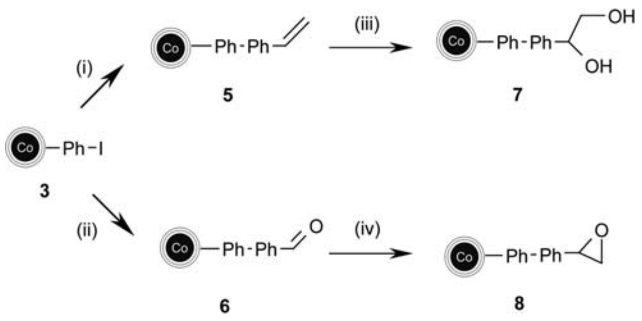
Scheme 1 Overview of functional groups introduced by diazonium intermediates **1–3**. While bromophenyl functionalized nanoparticles **1** were unreactive towards *p*-benzyloxyboronic acid, iodophenyl particles **3** could be successfully coupled under Suzuki conditions to give **4** (see Table 1). *Reagents and conditions*: (i) $NaNO_2$, H_2O, HCl, RT, 15 min; (ii) *p*-benzyloxyboronic acid, $Pd(OAc)_2$–PPh_3 (1 : 3) 5 mol%, PrOH–H_2O (1 : 1), Na_2CO_3, 16 h, reflux.

centre during the coupling. For comparison, the electron-rich arene bromoaniline requires specialised catalysts to undergo Suzuki coupling.[18] As a possible solution iodophenyl particles **3** were synthesised with the reasoning that the weaker C–I bond[19] would overcome the electronic effects of the surface. These particles were then reacted with a range of 4-substituted phenylboronic acids (see ESI†)[20] (Scheme 1, Scheme 2).

This procedure gave the expected products as analysed by FT-IR for which the product spectra were compared with those of relevant reference compounds *i.e.* substituted biphenyls. It is not expected to be a perfect match as there is no substituent with the equivalent steric and electronic properties unique to the particle surface. Nevertheless, products **4**, **5** and **6** demonstrate good correspondence with their reference spectra. (Fig. 2, Fig. S1–S3, ESI†)

The identity of the products and completion of the reaction was further confirmed by element microanalysis (Table 1). Product **5** contained only traces of Pd (<20 ppm by AAS) which confirmed that the catalyst could be effectively washed off.

The styrene and benzaldehyde functionalized particles now available (**5** and **6**, Scheme 2) motivated the transformation of these moieties to further reactive magnetic chemicals: epoxy- and diol-functionalized nanomagnets. A epoxy functionality was introduced by the Johnson–Corey–Chaykovsky reaction[21] (Scheme 2). This slightly unusual approach had to be chosen as attempts to epoxidise the 4-vinyl biphenyl particles **5** with a variety of peroxide-based agents were thwarted by the rapid decomposition of these reagents. This decomposition was possibly catalysed by Co ion impurities although the exact cause has to be determined. The Johnson–Corey–Chaykovsky reaction proceeded smoothly, as evidenced by the IR spectrum of the product (Fig. 2) wherein the strong aldehyde C=O peak at 1713 cm^{-1} of **6** is lost and peaks corresponding to the epoxide ring at 857 (sym. str.) and 762 (ring δ) cm^{-1} can be identified. In order to ascertain the reactivity of the epoxide **8** it was treated with benzylamine in water[22] in an epoxide



Scheme 2 Suzuki cross-coupling and subsequent reactions. *Reagents and conditions*: (i) *p*-vinylphenylboronic acid, $Pd(OAc)_2$–PPh_3 (1 : 3) 5 mol%, PrOH–H_2O (1 : 1), Na_2CO_3, 16 h, reflux; (ii) *p*-formylphenylboronic acid, $Pd(OAc)_2$–PPh_3 (1 : 3) 5 mol%, PrOH–H_2O (1 : 1), Na_2CO_3, 16 h, reflux; (iii) AD-mix-α, methanesulfonamide, H_2O, 2 d, 0 °C; (iv) dimethyl oxosulfonium methylide, dry DMSO, 1 h, RT.

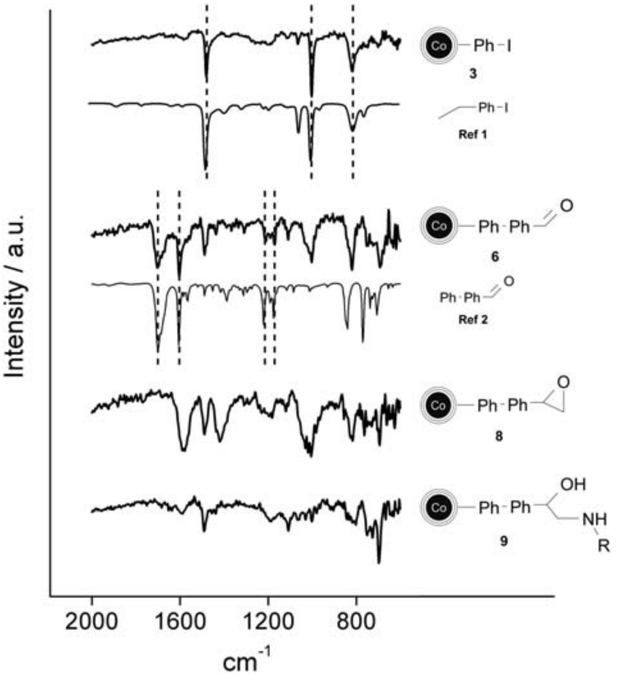


Fig. 2 FT-IR spectra‡ of iodo functionalized nanoparticles **3** (top trace with reference below) and the subsequent functionalization steps *via* the benzaldehyde **6** (third trace from top with reference below) to the epoxide **8** (second trace from bottom) as well as the ring-opened product **9** (bottom trace).

Table 1 Element analyses (wt%) for carbon, nitrogen and iodine content for samples **3–9** (where applicable)

Product	C[b]	I[b]	N[b]	Loading[b]/ mmol g^{-1}
C/Co[a]	5.3	—	—	—
3	6.5	1.7 (1.9)	—	0.16
4	7.7 (7.8)	0.1 (0)	—	0.14
5	7.8 (7.9)	0.1 (0)	—	0.14
6	7.7 (7.8)	—	—	0.14
7	7.9 (7.9)	—	—	0.16
8	7.8 (7.9)	—	0.1 (0)	0.14
9	8.8 (8.9)	—	0.3 (0.2)	0.14

[a] Reducing flame synthesis derived as-prepared powder.[11] [b] Expected values given in brackets, calculated with respect to the increase in C% for **3**, from which the functional group loading on the surface is established.

ring-opening reaction. The epoxide peaks mentioned above were not found in the significantly different ring-opened product IR-spectrum (**9**, Fig. 2) and microanalysis showed an increase in both C and N content consistent with the addition of benzylamine (Table 1). This provided good evidence that the expected reaction had taken place and that the epoxide had indeed been synthesised from **6**.

Based on the promising application of diol functionalized nanoparticles as magnetic protecting groups for ketones and aldehydes,[23] as well as the possible magnetic separation and purification of organoboronic acids,[24] the synthesis of such a material was attempted. The reaction proceeded *via* the Sharpless asymmetric dihydroxylation[25] from the olefin **5** to the 4-biphenyl ethanediol functionalized material **7**. The product spectrum showed the appearance of strong peaks between 1100–1200 cm^{-1}, which may be attributed to the C–O stretches of the diol (see Fig. S4, ESI†). There is also the obvious disappearance of the peak at 906 cm^{-1} (C=C asym. δ), demonstrating the loss of the styrene double bond. No change in the C content was seen, as anticipated, but a determination of the O content was impossible due to high metallic content of the sample. This data is consistent with the properties expected of the diol product **7**.

As the functionalization chemistry stems from work performed with carbon nanotubes, it is conceivable that methods developed for nanoparticles here may be applied to them as well. Suzuki coupling has previously been used to attach chromophores to nanotubes[26] but has not received attention otherwise. The functionalization procedures described may find use in introducing novel functional groups on both nanotubes and magnetic nanoparticles.

Of interest is the fact that these methods link the functionality to the carbon surface *via* a hydrocarbon skeleton, while most existing methods for nanoparticle functionalization utilise either amide[27] or ester[28] linkages. The additional stability afforded by a hydrocarbon linker could prove useful in more demanding applications of these materials, *e.g.* the immobilization of catalysts. Furthermore, product **7** can be described as a magnetic protection group enabling a fast and efficient way to separate intermediate compounds during multi-step organic synthesis routines.

In conclusion, a procedure based on the Suzuki coupling has been reported for the introduction of functional groups not accessible by previous methods. Products have been characterised by FT-IR and microanalysis. The electron donating properties of the particle surface were analyzed and explained the need for iodophenyl functionalized beads in Suzuki cross coupling reactions. The availability of the new formyl-, diol-, vinyl- and epoxy-groups may lead to a number of new applications for carbon-coated cobalt nanoparticles.

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Notes and references

‡ FT-IR spectra were measured on a Bruker Tensor 27 (5 wt% in KBr). For improved quality of the spectra unreacted C/Co nanoparticles were taken as background (5 wt% in KBr). Reference spectra were adapted from SDBSWeb by the National Institute of Advanced Industrial Science and Technology, Japan (http://riodb01.ibase.aist.go.jp/sdbs/)

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