The use of monosaccharides in metal-catalyzed coupling reactions

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Abstract

The addition of monosaccharides to metal-catalyzed coupling reactions can be beneficial in terms of decreasing the time required, chemical waste products and overall cost of the process. Monosaccharides are used in a number of different ways, including: (a) acting as a ligand for the metal, (b) providing the appropriate reduction potential for a chemical process and (c) acting as a reducing agent for the formation and stabilization of catalytically active metal nanoparticles. Recently, there has been a significant amount of research in this growing field and there is thus the potential for the addition of monosaccharides to coupling reactions to have significant impact on the synthesis of the important small molecules on which we have all come to rely. This Perspectives Article will cover recent developments in the addition of monosaccharides to metal-catalyzed coupling reactions with an emphasis on their utility and limitations in order to facilitate the further development of this exciting area of research.

Keywords: *Monosaccharide, Bio-renewables, Metal Catalysis, Green Chemistry, Nanoparticle*

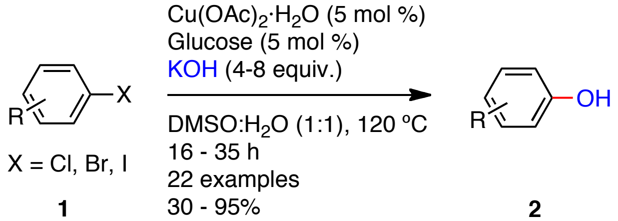
Introduction

Metal-catalyzed coupling processes are a ubiquitous part of the modern chemists' toolkit for the synthesis of added-value small molecules on which we have all come to rely. In order to make these processes more efficient, in terms of time, expense and cost to the environment, unmodified monosaccharides have been added to metal-catalyzed reactions as part of research into the use of bio-renewables in catalytic / chemical reactions. The addition of monosaccharides can serve many purposes in these reactions, including: (a) acting as a ligand for the metal, (b) providing the reduction potential for a chemical process and (c) acting as a reducing agent for the formation and stabilization of catalytically active metal nanoparticles. The ability of monosaccharides to reduce metals has been known for decades,[1] for example Benedict's[2] or Fehling's tests,[3] but their use in cross-coupling reactions has flourished in recent years. This review will focus on the latest uses of monosaccharides in metal-catalyzed coupling reactions. Due to recent reviews and full publications the following areas will not be covered in this review: polysaccharides,[4,5,6,7,8,9] smaller sugar derived aldehydes / carboxylic acids (Leuckart-Wallach reaction)[10,11,12,13,14,15,16] or reactions in which sugars are used as starting materials or incorporated into the molecule.[17,18,19,20,21,22,23,24]

Monosaccharides as ligands

One of the most common uses of monosaccharides in metal-catalyzed reactions are as ligands for a catalytically active metal species.[25] For example, Sekar and Thakur recently disclosed the synthesis of phenols **2** from aryl halides **1** in a process that was catalyzed by a copper/glucose system (Scheme 1).[26] Aryl iodides and bromides **1** were reacted with excess potassium hydroxide (4-8 equiv.) in the presence of copper(II) acetate (5 mol %) and D-glucose (5 mol %) to give good to excellent yields of the corresponding phenols **2**. The reactivity of aryl chlorides depended on the nature of the electron withdrawing group with substrates containing a nitro group giving an excellent yield of phenol **2**.

Scheme 1.

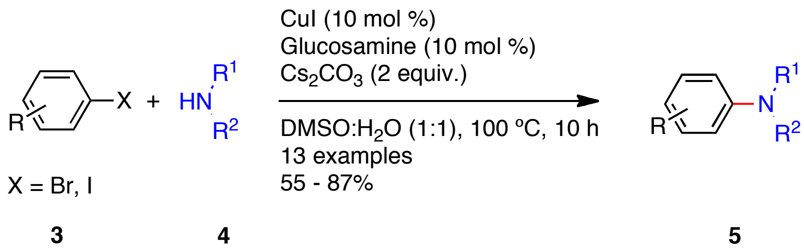


The use of monosaccharides in metal-catalyzed coupling reactions

Sara H. Kyne,[†*] and Jason E. Camp[‡*]

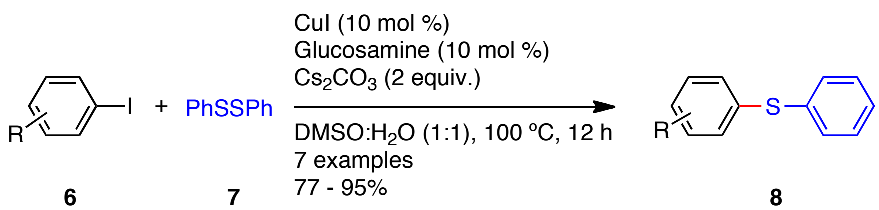
Recently a number of carbon-nitrogen cross-coupling reactions have been developed employing a catalytic system formed *in situ* from copper(I) iodide and D-glucosamine in the presence of base.[27] For example, anilines were formed from aryl halides in the presence of excess aqueous ammonia (10 equiv.) or sodium azide (3 equiv.).[28,29] Zhang *et al*. reported the use of similar conditions for the cross-coupling of aryl halides **3** with nitrogen heterocycles **4** **(**1.2 equiv.; Scheme 2).[30] Most of the examples used imidazole as the heterocycle **4**, and good yields were observed for aryl iodides **3** bearing electron-withdrawing groups. Unfortunately, the reaction did not occur with aryl chlorides.

Scheme 2.



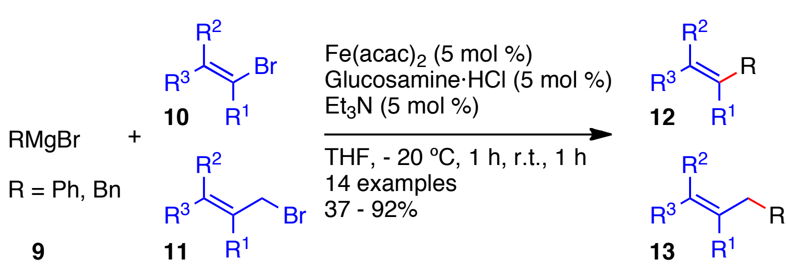
Zhang *et al*. extended this methodology to carbon-sulfur cross-coupling reactions. In this work, aryl iodides **6** were reacted with diphenyl disulfide (**7**, 0.6 equiv.) in the presence of copper(I) iodide (10 mol %), D-glucosamine (10 mol %) and cesium carbonate (2 equiv.) to give the corresponding unsymmetrical diaryl sulfide **8** (Scheme 3).[30] When aryl bromides were tested the reaction occurred, but required 24 hours to go to completion. Similar methodology was used by the same group to synthesize a variety of diaryl sulfones from aryl halides and sodium benzenesulfonates.[31]

Scheme 3.



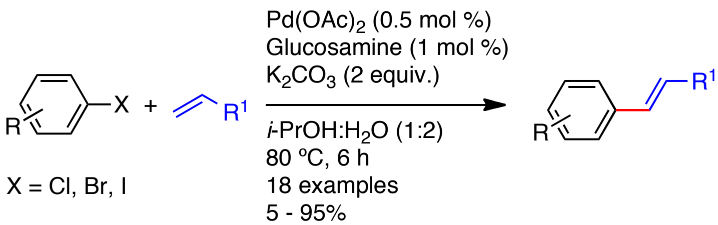
D-glucosamine has also been successfully employed as a ligand in iron-catalyzed Grignard cross-coupling reactions of vinylic **10** and allylic bromides **11** (Scheme 4). Phenyl- or benzylmagnesium bromides **9** were reacted with bromides **10** or **11** in the presence of iron(II) acetylacetonate (5 mol %) and D-glucosamine hydrochloride (5 mol %). Triethylamine (5 mol %) was added to deprotonate the ligand and thus increase its solubility in THF.[32] Moderate yields of substituted alkenes **12** were obtained from allylic bromides **10**, and good yields of the sp^3-hybridized products **13** were obtained from alkenyl bromides **11.**

Scheme 4.



D-glucosamine was shown to improve the yield in palladium-catalyzed Mizoroki–Heck reactions of aryl halides (Scheme 5).[33] Aryl halides **14** were reacted with activated alkenes **15** (1.2 equiv.) in the presence of palladium(II) acetate (0.5 mol %), D-glucosamine (1 mol %) and potassium carbonate (2.0 equiv.). Aryl iodides and bromides afforded good to excellent conversion to stilbenes **16** with unsubstituted and *para*-substituted electron withdrawing groups. Conversion was moderate when the arene was substituted at the *ortho* position. Aryl chlorides **14** reacted, albeit with low conversion (5-25%).

Scheme 5.

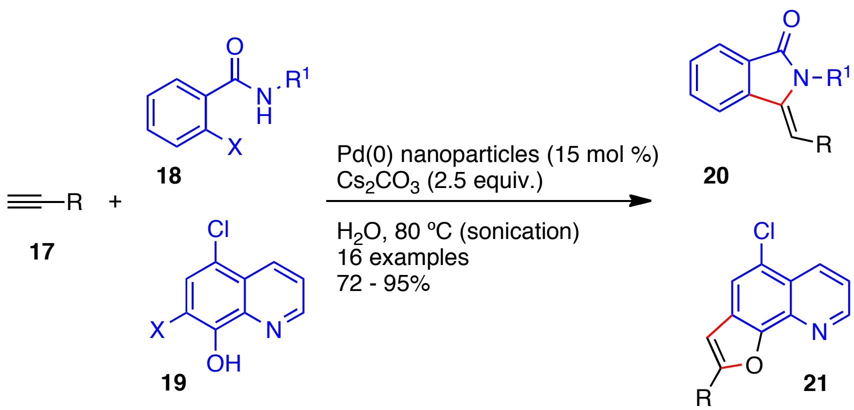


Monosaccharides for nanoparticle formation

One of the most common uses of monosaccharides in organic transformations are as reductants for the formation of metal nanoparticles, in which the sugar serves to reduce the metal in the presence of a template.[34,35,36,37,38,39,40,41,42,43,44,45] Monosaccharides, glucose in particular, have also been used as supports for metal nanoparticles.[46,47,48,49] In some cases, the monosaccharides act as both the stabilizer for the metal nanoparticles as well as the reducing agent.[50,51,52,53,54] Alternatively, additional reducing agents can be added to the mixture of sugar and metal if required. For example, monodispersed colloidal carbon spheres have been synthesized by a two-step hydrothermal approach under mild conditions by Sun *et a*l.[55] In this work, separating the nucleation and growth steps allowed for a narrow size distribution with diameters ranging from 160-400 nm. Interestingly, the size distribution decreased with an increasing concentration of glucose. D-glucose has also been used as the metal nanoparticle support. In this case palladium(0) nanoparticles were synthesized by the reduction of $H_2[PdCl_4]$ or $[Pd(NH_3)_4Cl_2]Cl_2$ in the presence of excess hydroxylamine and D-glucose under ambient, aqueous conditions.[56] Characterization of the palladium nanoparticles revealed magnetization differences depending on the oxidation state of the palladium precursor. TEM analysis revealed that when starting from the Pd(II) complex, the nanoparticles were an average size of 6 nm and polydispersed, while starting from the Pd(IV) complex formed nanoparticles with an average size of 8 nm that were mainly monodispersed. In 2004 Sun and Li reported the synthesis of colloidal carbon spheres starting from glucose, which underwent subsequent functionalization due to the reactive surface present.[57] For example, the FTIR spectrum revealed the existence of carbonyl and hydroxyl groups which maintained the hydrophilicity of the carbon spheres. Colloidal carbon spheres were prepared from aqueous glucose by hydrothermal synthesis, undergoing aromatization and carbonization to form 200 nm carbon spheres at 160 ºC in 3.5 hours, and 1500 nm at 180 ºC in 10 hours. Under reflux, palladium(0) nanoparticles were loaded onto the surface, covering the carbon spheres with a uniform shell of 10-20 nm palladium. In related methodology, Zhang *et al*. described the preparation of highly dispersed, narrow diameter palladium nanoparticles on carbon spheres via *in situ* reduction.[58] Precise control of the dispersity and size of the palladium(0) nanoparticles was possible by careful adjustment of the reaction conditions (temperature, time, pH and ratio of palladium(0) to carbon spheres). Homogenously distributed, small diameter (7.7 nm) palladium crystals were prepared on carbon spheres at pH 7.0 in ethanol at 70 ºC.

The isolated metal nanoparticles have subsequently been used in a number of important catalytic processes. For example Sen *et al*. recently reported a palladium(0) nanoparticle catalyzed domino Sonogashira-cyclization reaction to synthesize various isoindolinones **20** and furoquinolines **21** in good yields (Scheme 6).[59] Palladium(0) nanoparticles were prepared by the procedure of Sarkar *et al*. in which $H_2[PdCl_4]$ was reduced in the presence of hydroxylamine and D-glucose under aqueous conditions.[56] Following the reaction, the catalyst could be recovered in high yield and a recycling study showed only a gradual decrease in activity for up to five subsequent reactions before significant loss of yield was observed.

Scheme 6.

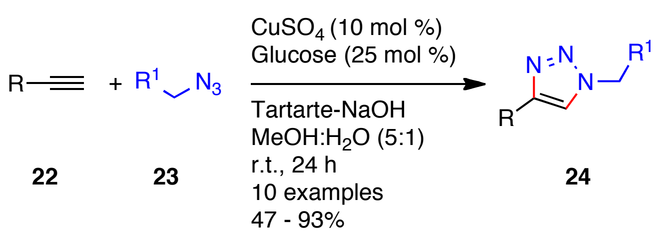


17 18 19 20 21

Monosaccharides as reductants in chemical processes

Monosaccharides can also be added to organic transformations to act as reductants for chemical process that occur in the absence of catalyst[60,61] or to reduce a metal pre-catalyst to the necessary oxidation state *in situ* so that the reaction can proceed. This concept has been employed for a variety of reactions such as dehalogenations,[62] reductions[63,64,65,66] and coupling processes. Glucose can also be used for the *in situ* formation of the active metal catalyst. For example, Cuevas-Yañez *et al.* showed that addition of 25 mol % of glucose to the reaction mixture resulted in an increased yield of the desired triazoles **24** from alkynes **22** and azides **23** under copper-catalyzed click reaction conditions (Scheme 7).[67]

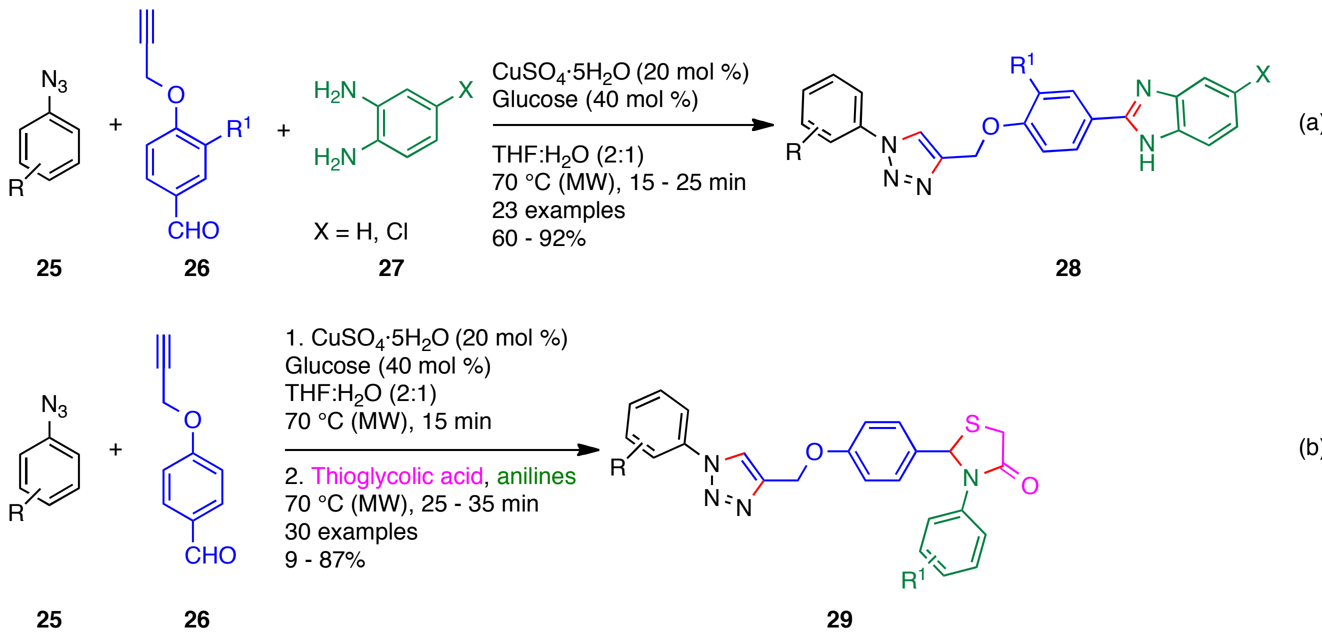
Scheme 7.



22 **23** **24**

In related work, Singh *et al.* showed that it was beneficial to add glucose to copper-catalyzed click reactions[68] that were part of multicomponent coupling reactions under microwave conditions (Scheme 8). Thus, the three component reaction of phenylazides **25**, 4-(prop-2-yn-1-yloxy)benzaldehydes **26**, and 1,2-diaminobenzenes **27** afforded the triazole adducts **28** in good yields (Scheme 8a).[69] Additionally, a four component process resulted in the efficient formation of 3-phenyl-2-[4-{(1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy}phenyl]thiazolidin-4-ones **29** from readily available starting materials (Scheme 8b)[70]. In both cases, the glucose is purported to reduce the copper to the catalytically active species. Related work by Wan *et al.* demonstrated that copper – glucose systems catalyzed the three component reactions of phenols, acyl chlorides and Wittig reagents to form β-aryloxy acrylates.[71] Furthermore, Guchhait *et al.* developed a novel A^3-coupling methods for the synthesis of *N*-fused imidazoles using a copper(II) sulfate – glucose catalyst.[72] This methodology was subsequently harnessed by Iyer *et al.* for the synthesis of luminescent imidazo[1,2-*a*]pyridines.[73]

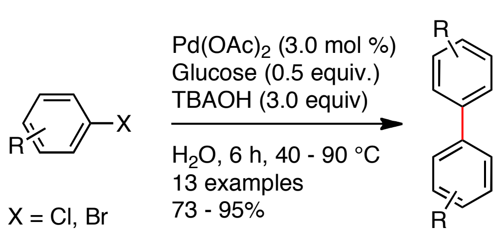
Scheme 8.



Monosaccharides for the *in situ* formation/stabilization of catalysts

One of the most important advances in this area is the ability to form catalytically active metal nanoparticles *in situ* from unmodified reducing sugars and subsequently recycle the catalyst. Traditionally, bio-derived metal catalysts need to be synthesized and isolated prior to reaction, and are frequently difficult to recycle following the reaction, which can increase the amount of time, chemical waste and expense of the overall process.[74,75,76,77,78,79,80,81] Building upon the work in nanoparticle formation from reducing sugars, and the use of reducing sugars as reductants in catalytic processes, Nacci *et al.* recently disclosed an Ullman type homo-coupling of aryl halides catalyzed by *in situ* generated palladium(0) nanoparticles (Scheme 9).[82] Thus the homo-coupling of bromo- and chloroarenes **30** in the presence of glucose (0.5 equiv.), palladium(II) acetate (3 mol %) and tetrabutylammonium hydroxide (3.0 equiv.) afforded the desired biaryls **31** in good yield. In this process, the glucose is believed to both reduce the palladium(II) acetate to the catalytically active palladium(0) species, as well as stabilize the *in situ* formed catalyst through the formation of nanoparticles. In contrast to other related reports (*vide infra*), exogenous capping agents were used in this study. TEM analysis was used to confirm the formation of nanoparticles, which had an average particle size around 15 nm, and XPS was used to show that the palladium in the isolated nanoparticles was in the zero oxidation state. A recycling study demonstrated that the catalytic solution was active for 3 cycles, but the yield decreased precipitously thereafter.

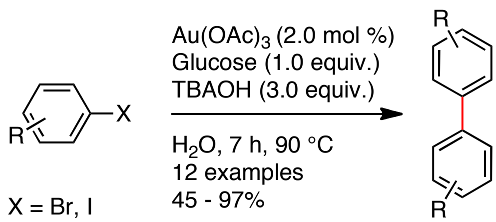
Scheme 9.



30 **31**

Nacci *et al.* also showed that an Ullman type homo-coupling of haloarenes **32** to give the corresponding biaryls **33** could be facilitated by gold nanoparticles formed *in situ* from the reduction of gold(III) acetate (2 mol %) with a stoichiometric amount of glucose (Scheme 10).[83] This catalytic system was active for bromo- and iodo-substituted arenes **32**, as well as alkenes. The less reactive aryl chlorides were found to be unreactive under the reaction conditions. It was also found that the ionic liquid tetrabutylammonium acetate (TBAA) was a competent solvent and base for the reaction, which could substitute for water. Interestingly, the nanoparticles formed in the ionic liquid were much larger than those formed in water (circa 2 nm *vs*. 20 nm respectively) and in general resulted in a decreased yield compared to the aqueous conditions. Unfortunately, attempts at recycling these catalysts showed a similar poor performance to the palladium system discussed above (*cf.* Scheme 9).

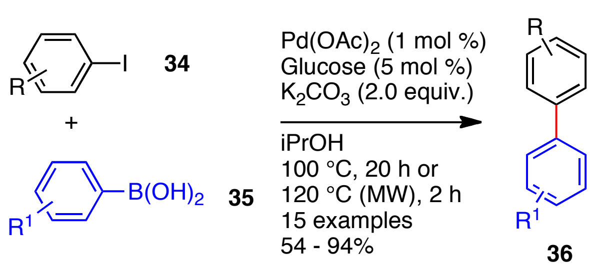
Scheme 10.



32 **33**

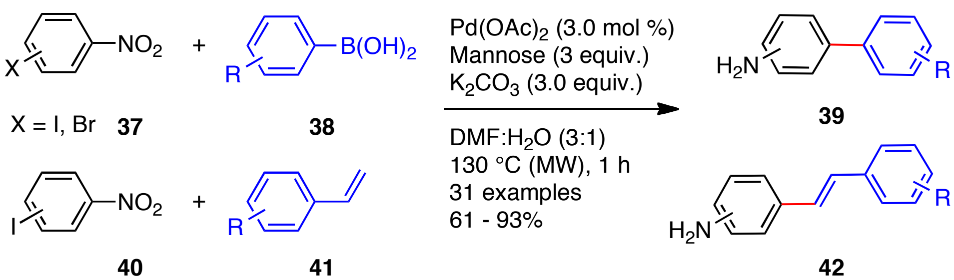
Recently we disclosed methods for the use of glucose derived palladium(0) nanoparticles as *in situ* formed catalysts for Suzuki-Miyaura cross-coupling reactions in the green solvent isopropanol (Scheme 11).[84] The cross-coupling of aryl iodides **34** and aryl boronic acids **35** in the presence of palladium(II) acetate (1 mol %) and glucose (5 mol %) gave the desired biaryls **36** in moderate to good yields under either thermal or microwave heating conditions. In contrast to the reports of Nacci *et al.*, only a small amount of glucose was required and no capping agents were employed. EF-TEM analysis of the *in situ* formed nanoparticles showed that the palladium was surrounded by a hydrophilic, hydroxylated shell. The hydrophilic/polar nature of the nanoparticles allowed for their facile removal from the cross-coupled product. ICP-MS analysis showed a 65% decrease in the amount of metal incorporated into the final compounds compared to reactions that did not contain glucose. Interestingly, Jiang and Fossey *et al.* have found that monosaccharides bind to boronic acid to form the less reactive boronate ester. They used the retardation of the Suzuki-Miyaura homo-coupling reaction to develop fluorescent sensors for glucose detection.[85,86]

Scheme 11.



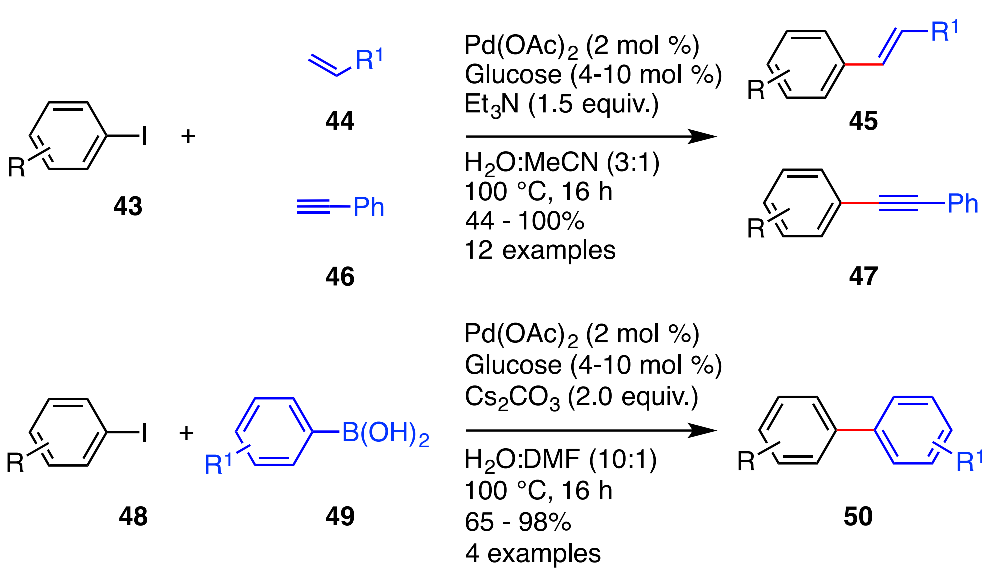
Subsequently, Jain *et al*. described the use of reducing sugars in palladium mediated cross-coupling reactions, in which the metal was catalyzing multiple, mechanistically distinct steps; auto-tandem catalysis[87,88] (Scheme 12).[89] After screening nine difference reducing sugars, they found that the addition of mannose (3 equiv.) gave the desired cross-coupled products of Suzuki-Miyaura and Mizoroki–Heck reactions, whilst concurrently reducing the nitro functionality to an aniline. For example, reaction of halo-nitrobenzenes **37** with arylboronic acids **38** in aqueous DMF at 130 °C (microwave) gave the coupled biaryl anilines **39** in moderate to excellent yields. Similarly, the reaction of iodo-nitrobenzenes **40** with styrenes **41** under the same reaction conditions afforded substituted amino-stilbenes **42** in good to excellent yields. It is unclear from the analysis conducted by the researchers whether the mannose is simply acting as a ligand and source of hydrogen under the reaction conditions, or if it is also stabilizing *in situ* formed nanoparticles.

Scheme 12.



Building upon our work discussed above, we recently reported the use of glucose-derived nanoparticles for the Mizoroki–Heck, Sonogashira and Suzuki-Miyaura cross-coupling reactions in aqueous solvents (Scheme 13).[90] The reaction of aryl halides **43** with alkenes **44** or alkynes **46** proceeded in moderate to excellent yields to afford stilbenes **45** or substituted alkynes **47**, respectively. The palladium(0) nanoparticle catalysts were formed *in situ* from palladium(II) acetate (2 mol %) via the addition of glucose (4-10 mol %) to the reaction. In addition, a Suzuki-Miyaura protocol for the synthesis of biaryls **50** in aqueous DMF was developed using the same *in situ* derived palladium(0) nanoparticles. Importantly, this protocol was also viable for aryl bromides. In contrast to the study by Jian *et al.*,[74] the nitro functionality was not reduced in any of the three cross-coupling reactions that were investigated. This is possibly due to the relatively small amount of glucose that was added to the reaction (*cf.* Scheme 12). EF-TEM analysis of the *in situ* formed nanoparticles confirmed that the palladium was surrounded by a hydrophilic, hydroxylated shell. The nature of this shell allowed for the facile partitioning of the catalyst between the aqueous and organic phases, which enabled catalyst recycling for up to four cycles without significant loss of activity.

Scheme 13.



Conclusion

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Sara H. Kyne,[†*] and Jason E. Camp[‡*]

The importance of the addition of monosaccharides to metal-catalyzed processes in organic chemistry has expanded rapidly in recent years. These bio-renewable materials can be used for a number of important processes including as ligands for a metal catalyst, to provide the appropriate reduction potential for a chemical process, and as a reducing agent for the formation and stabilization of catalytically active metal nanoparticles. These recent developments in the field will provide the basis for further rapid advancements. Looking forward, catalytic processes in which the reducing potential of renewable sugars is harnessed for the generation, stabilization and turnover of catalytically active metal nanoparticles, sugar-powered catalysis, will be developed. These processes have the potential to make existing protocols greener in terms of time, expense and cost to the environment, as well as allowing for the development of novel metal-catalyzed processes that are currently not possible. Additionally, the inherent chirality of the monosaccharides will be harnessed in order to develop catalytic access to enantiomerically enriched products. In conclusion, the addition of monosaccharides to metal-catalyzed processes has resulted in a number of important new methods that allow access to the small molecules on which we have all come to rely. It is expected that innovative new applications will be developed that build on this exciting research.

Biographies

Sara H. Kyne obtained her PhD from The University of Melbourne (Australia) under the supervision of Prof. Carl H. Schiesser in the area of physical-organic intramolecular radical chemistry. She then undertook a postdoctoral position with Prof. Jonathan M. Percy (University of Strathclyde, UK) and a Marie Curie Intra European Fellowship with Prof. Louis Fensterbank (Université Pierre et Marie Curie, France). She is currently a lecturer at the University of Lincoln working on the development of sustainable catalysis and radical methodology.

Jason E. Camp obtained his PhD from The Pennsylvania State University under the supervision of Prof. Steven Weinreb working on the total synthesis of the chartellamide and chartelline family of marine natural products. He then was a postdoctoral fellow working with Prof. Donald Craig (Imperial College London) before obtaining lectureships at the University of Nottingham and Queen Mary University of London. He is currently a senior lecturer at the University of Huddersfield working on the development of novel auto-tandem catalysis methods as well as sugar-powered catalysis protocols.

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