Palladium N-Heterocyclic Carbene Precatalyst Site Isolated in the Core of a Star Polymer
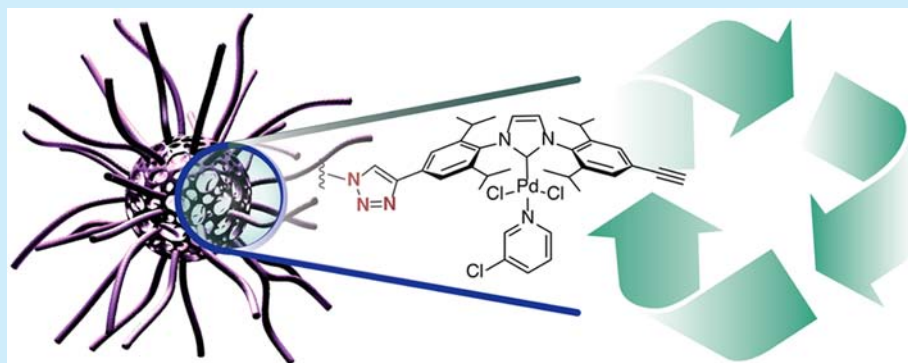
Konstantin V. Bukhryakov,[†,‡] Clément Mugemana,[†,‡] Khanh B. Vu,[†] and Valentin O. Rodionov*,[†]

[†]KAUST Catalysis Center and Division of Physical Sciences and Engineering, King Abdullah University of Science and Technology, Thuwal 23955-6900, Kingdom of Saudi Arabia

S *Supporting Information*

ABSTRACT: An approach for supporting a Pd–NHC complex on a soluble star polymer with nanoscale dimensions is described. The resulting star polymer catalyst exhibits excellent activity in cross-coupling reactions, is stable in air and moisture, and is easily recoverable and recyclable. These properties are distinct and unattainable with the small-molecule version of the same catalyst.

Transition-metal-catalyzed cross-coupling reactions, especially Pd-catalyzed ones, are one of the more powerful and important strategies for creating C–C and C–heteroatom bonds.[1] Many homogeneous and heterogeneous forms of Pd have been used in cross-coupling catalysis.[2–5]

Heterogeneous and supported forms of Pd are stable and easy to recycle and separate from reaction products. However, the nature of the active sites of heterogeneous catalysts is often uncertain.[6] Some of the nominally heterogeneous Pd catalysts operate by a homogeneous "catch-and-release" mechanism,[4] which can lead to metal leaching and undesirable evolution of the catalyst morphology.[7,8] In contrast, molecular Pd catalysts and precatalysts have well-defined structures, and their properties are amenable to rational design.[9] The specific activity of such catalysts can be higher than that of heterogeneous counterparts. However, recycling and reuse of homogeneous catalysts is not trivial.[2]

Metal complexes immobilized on nanoscale supports could offer the advantages of both homogeneous and heterogeneous catalysts: well-defined structures, readily accessible catalytic sites, and recyclability.[10] Nature's metalloenzymes operate on this very principle. Chemist-designed, enzyme-inspired nanoscale catalysts have been the focus of intensive investigation,[11,12] and a number of successful designs have emerged.[13–16] Among the nanoscale catalyst supports, branched constructs such as dendrimers and star polymers are unique in that they can be designed to approximate some of the key features of natural biopolymers.[17–19] To date, striking

examples of organocatalysis with these macromolecules have been more prevalent than examples of metal-complex catalysis, in part due to the difficulties involved in tethering of elusive transition metal ions to carbon- and heteroatom-based supports.

Here, we describe a Pd precatalyst system confined in the core of a star polymer through a strongly binding, bulky N-heterocyclic carbene (NHC) ligand. The NHC functionality is incorporated into the macromolecule via a reliable and tolerant copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction.[20,21] The resulting Pd–NHC star polymer is competent in catalyzing Heck and Stille reactions and is highly stable to air and moisture. As the Pd centers are site-isolated due to the core–shell polymer topology, the propensity of Pd to aggregate and form nanoparticles (NPs) is strongly inhibited. The polymer catalyst can be recycled multiple times without a loss of activity. This degree of site isolation is not attainable with a more traditional cross-linked Merrifield-type resin.

We prepared the star polymer support through an adaptation of a previously described arm-first strategy.[22] Linear polystyrene macroinitiator **P1** with $M_n \sim 9700$ g/mol and narrow polydispersity was synthesized via nitroxide-mediated controlled radical polymerization (NMP).[23] **P1** was used to copolymerize divinylbenzene (DVB) and chloromethylstyrene

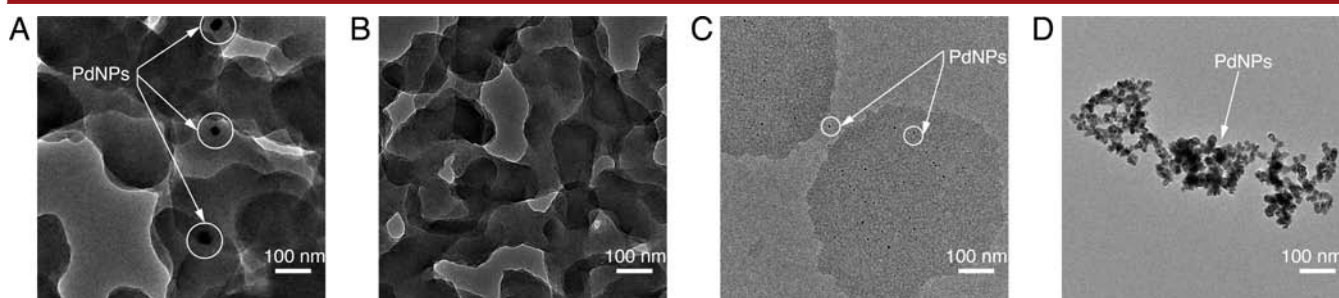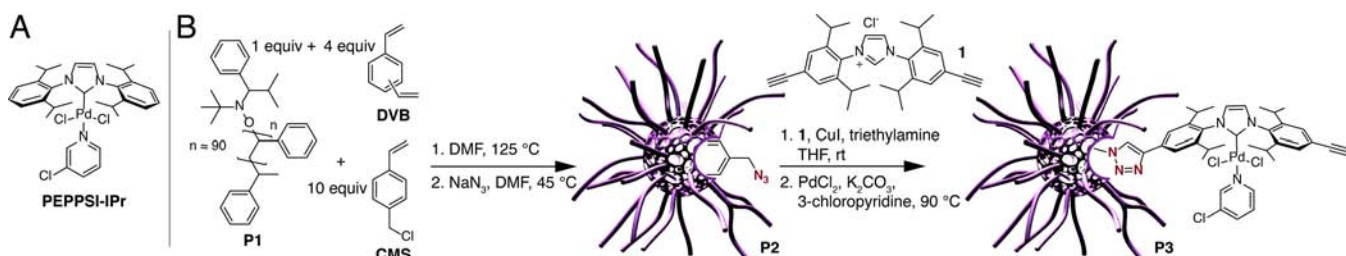**Scheme 1. Synthesis of the Pd−NHC Star Polymer Catalyst**

Figure 1. TEM images of (A) as-prepared polymer **P3**; (B) Hg-treated polymer P3; (C) Hg-treated polymer P3 after a Stille reaction; (D) reaction mixture for a Stille coupling catalyzed by PEPPSI-IPr in a microwave reactor.

Table 1. Cross-Coupling Reactions with Pd−NHC Polymer Catalysts

entry	ArI	olefin	product	Pd, mol %[a]	base	solvent	temp	time, h	yield, %[b]
1[e]	PhI	(n-Bu)₃Sn⌁COOEt	⌁COOEt	2	none	DMF	100 °C	0.5	90
2[c,e]	PhI	(n-Bu)₃Sn⌁COOEt	⌁COOEt	1	none	DMF	100 °C	0.5	90
3	PhI	⌁COOMe	⌁COOMe	1	K₂CO₃	DMF	120 °C	1	99
4	PhI	⌁CN	⌁CN	1	TEA	DMF	120 °C	0.5	99
5	p-NO₂PhI	⌁O	O₂N⌁O	1	NaHCO₃	DMF	50 °C	16	60
6	Ph-I	(n-Bu)₃Sn⌁O	⌁O	1	none	DMF	rt	19	99
7	p-NO₂PhI	(n-Bu)₃Sn⌁O	O₂N⌁O	1	none	DMF	rt	2	99
8	PhI	(n-Bu)₃Sn⌁COOEt	⌁COOEt	1	none	THF	60 °C	16	77
9	PhI	(n-Bu)₃Sn⌁COOEt	⌁COOEt	0.1	none	THF	rt	72	62
10[d,e]	PhI	(n-Bu)₃Sn⌁COOEt	⌁COOEt	8	none	DMF	100 °C	0.5	80

[a]Includes both Pd NPs and NHC-Pd. [b]Isolated yield. [c]Pd−NHC polymer treated with Hg. [d]Pd−NHC on Merrifield resin. [e]Performed in a microwave reactor.

(CMS) with a 1:4:10 macroinitiator/DVB/CMS ratio (Scheme 1 B). The resulting star polymer was conveniently separated from excess **P1** by fractional precipitation in benzene/methanol. Following that, the star polymer was treated with NaN₃ in DMF, which resulted in quantitative transformation of core chloride functionalities to azides. The azide content of the resulting star polymer **P2** was 0.57 mmol/g. The star polymer species thus prepared had an average hydrodynamic diameter of

~12 nm in DMF, as determined by dynamic light scattering (DLS). The M_w of the polymer, as determined by static light scattering, was found to be ~3.0 × 10⁵ g/mol, corresponding to ~25−30 arms per star.

NHCs are a privileged class of ligands in homogeneous catalysis.[24,25] In Pd-catalyzed cross-couplings, NHCs facilitate both the initial oxidative addition and the final reductive elimination steps of the catalytic cycle. Furthermore, the strong

Pd−NHC bond keeps the metal attached to the ligand even under vigorous reaction conditions, making NHCs attractive for immobilizing transition metals.[26−30] However, the sensitivity of the NHC moieties has so far limited their incorporation into any complex macromolecular architectures.

One of the most commonly used and versatile Pd−NHC precatalysts is PEPPSI-IPr introduced by Organ[31] (Scheme 1 A). We prepared compound **1**, a "clickable" version of PEPPSI NHC ligand precursor, and coupled it to the azide-functionalized star polymer **P2** using an established CuAAC protocol (Scheme 1 B).[16] The reaction progress was conveniently monitored by the disappearance of the characteristic azide absorption band (2097 cm^{-1}) in the IR spectrum of the polymer. As **1** features two alkyne groups, it is possible that some of them remained unreacted. While we could not observe any discernible signals of free alkyne groups in the NMR and IR spectra of the polymer, we assume at least some free alkynes remained in the core of the star polymer. The presence of these alkynes should not be detrimental for any of the subsequent experiments. An increase of the polymer's apparent hydrodynamic diameter to ∼18 nm was observed by DLS (Figure S31 and Table S2, SI). The comparison of intensity and volume distributions revealed that this increase was due to the formation of a limited number of larger aggregates, while the size of the majority of the population remained unchanged (Figure S32 and Table S2, SI). The NHC precursor polymer was converted to its Pd complex via a reaction with PdCl$_2$ and 3-chloropyridine, closely following the protocol established for PEPPSI.[31] This step led to a further increase in the apparent DLS hydrodynamic diameter to ∼47 nm (Figures S31 and S32, SI). We attribute this increase to the higher functionalization of the polymer cores, as well as to the appearance of large Pd NPs (see below). The star polymer fully retained its dispersibility through the CuAAC and Pd metalation steps, and the distribution of hydrodynamic diameters remained unimodal and narrow. The presence of 1,2,3-triazoles, which are relatively weakly binding monodentate ligands for late transition metals, is not expected to interfere with the formation of the NHC complexes.[32]

The Pd content in as prepared polymer **P3** was determined by ICP−OES to be 0.28 mmol/g. Transmission electron microscopy (TEM) imaging of the polymer revealed a limited number of large (∼30−40 nm) Pd NPs in the sample (Figure 1A and Figure S4, SI). To remove these, the solution of **P3** was stirred overnight with metallic mercury.[33,34] TEM images after this procedure indicated that all of the Pd NPs have been amalgamated and removed from the polymer (Figure 1B and Figures S6, SI). The Pd content of the Hg-treated star polymer was 0.15 mmol/g, corresponding to the amount of metal present as the desired Pd−NHC complex.

The as-prepared and Hg-treated Pd−NHC polymers were evaluated for the catalysis of a Stille coupling between iodobenzene and ethyl (Z)-3-(tributylstannyl)acrylate under standard microwave reactor conditions (Table 1, entries 1 and 2). No special precautions have been taken to exclude water or O$_2$. Despite the higher content of Pd in the as prepared **P3**, the yields obtained with both catalysts were identical. This suggests that the large Pd NPs do not meaningfully participate in catalysis. For all subsequent experiments, we used the as-prepared **P3** for the reasons of practicality.

It is important to note that a small number of uniformly dispersed ∼5 nm Pd NPs could be observed in the Hg-treated **P3** after the Stille reaction (Figure 1C and Figure S7, SI).

However, drastically more Pd NPs formed in the reactions catalyzed by small-molecule PEPPSI-IPr. After a Stille coupling performed under the same conditions as the reaction with **P3**, most of the PEPPSI-IPr was transformed into ∼17 nm NPs (Figure 1D and Figure S2, SI). These NPs aggregated and precipitated rapidly (Figure S10B, SI). The black precipitate could not be reused for another cycle of catalysis. The crude reaction product contained 666 ppm of Pd (and still 543 ppm Pd remained after the product was purified by flash chromatography). The typically accepted limit of Pd in pharmaceutical products is 10 ppm.[35]

We explored the recyclability of the as prepared polymer catalyst **P3** using a model Stille coupling (Table 1, entry 1). As the model reaction is incomplete after 30 min, these conditions were convenient for evaluating any changes in the activity of the catalyst. After each cycle, the mixture was filtered through a 0.2 μm PTFE membrane, and the polymer catalyst was precipitated in methanol. The precipitate was dried under high vacuum and used directly for subsequent runs. The activity and solubility of the catalyst were unchanged after at least five cycles (Figure 2). The color of the catalyst solution did not change
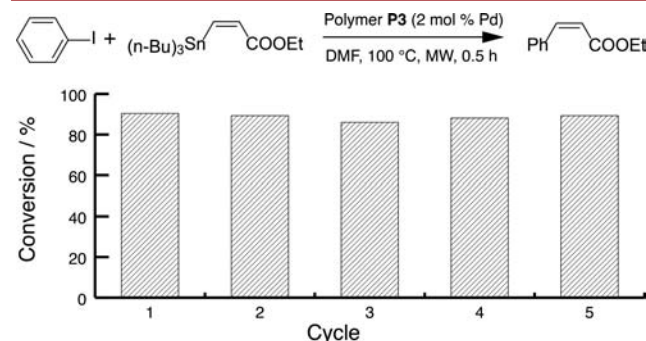

Figure 2. Recycling of Pd−NHC star polymer **P3**.

either, which suggests that the number and size of the large Pd NPs remained relatively constant (Figure S10A, SI). The workup of the reactions and catalyst recovery were facile: the five cycles were performed in less than 8 h. Recovery of a previously described polymer-supported Pd catalyst required 48 h of dialysis.[30] The reaction product were analyzed by ICP−OES to evaluate the extent of Pd leaching. After the first catalytic cycle, ∼2.8 ppm of Pd was detected before any chromatographic separation. The Pd content in the product remained stable at ∼0.7 ppm for the subsequent runs.

To evaluate the difference between the star polymer and a more traditional resin support, we coupled the NHC precursor **1** to azido-Merrifield resin (5% cross-linked). Despite the high degree of cross-linking, all the azides in the resin were reactive under our CuAAC protocol. During the metalation step, most of the Pd was transformed into large NPs (Figure S8, SI). In contrast with the star polymer, it was impossible to remove Pd NPs from the resin by Hg treatment. The resin-supported catalyst was significantly less active than the star polymer. At least four times higher Pd loading was required for comparable activity (Table 1, entries 1 and 10).

Unlike the cross-linked resin, the star polymer **P3** exhibits catalytic activity comparable to that of small-molecule PEPPSI complex[31] for a range of Still and Heck cross-couplings (Table 1). Some reactions proceeded readily at room temperature (Table 1, entries 6, 7, and 9) and with loadings of Pd down to 0.1 mol % (Table 1, entry 9). This low Pd loading would be at

the lower practical limit even for the small-molecule PEPPSI catalyst.

In conclusion, we have introduced the design and synthesis of a Pd−NHC star polymer catalyst that exhibits excellent activity in Heck and Stille reactions and is easily recycled through precipitation without loss of activity. Site isolation of Pd centers in the core of the polymer prevents the aggregation of Pd into NPs, which in turn leads to good recyclability and prevents leaching of Pd. The amount of leached Pd in the product after using the Pd−NHC polymer catalyst was 3 orders of magnitude lower than the amount found when using the commercially available PEPPSI complex. We believe that the site-isolation strategy we describe is general and applicable to other organotransition-metal catalysts.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.5b02388.

> Additional experimental details and characterization (TEM, EDX, SAED, ^{1}H and ^{13}C NMR, SEC, and DLS) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: valentin.rodionov@kaust.edu.sa. Tel: +966-12-8084592.

Author Contributions

‡K.V.B. and C.M. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062.

(2) Molnár, Á. *Chem. Rev.* **2011**, *111*, 2251.

(3) Kohler, K.; Prockl, S. S.; Kleist, W. *Curr. Org. Chem.* **2006**, *10*, 1585.

(4) Astruc, D. *Inorg. Chem.* **2007**, *46*, 1884.

(5) Astruc, D.; Lu, F.; Aranzaes, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 7852.

(6) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609.

(7) Narayanan, R.; El-Sayed, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 8340.

(8) Narayanan, R.; El-Sayed, M. A. *J. Phys. Chem. B* **2005**, *109*, 12663.

(9) DeAngelis, A.; Colacot, T. J. In *New Trends in Cross-Coupling: Theory and Applications*; Colacot, T. J., Ed.; Royal Society of Chemistry: Cambridge, 2014; p 20.

(10) Uozumi, Y. *Top. Curr. Chem.* **2004**, *242*, 77.

(11) Lu, A.; O'Reilly, R. K. *Curr. Opin. Biotechnol.* **2013**, *24*, 639.

(12) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325.

(13) Helms, B.; Guillaudeu, S.; Xie, Y.; Mcmurdo, M.; Hawker, C.; Fréchet, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6384.

(14) Huerta, E.; Stals, P. J. M.; Meijer, E. W.; Palmans, A. R. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2906.

(15) Mugemana, C.; Chen, B.-T.; Bukhryakov, K. V.; Rodionov, V. *Chem. Commun.* **2014**, *50*, 7862.

(16) Rodionov, V.; Gao, H.; Scroggins, S.; Unruh, D. A.; Avestro, A. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2010**, *132*, 2570.

(17) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74.

(18) Gao, H. *Macromol. Rapid Commun.* **2012**, *33*, 722.

(19) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991.

(20) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

(21) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(22) Bosman, A. W.; Heumann, A.; Klaerner, G.; Benoit, D.; Fréchet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2001**, *123*, 6461.

(23) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661.

(24) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314.

(25) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151.

(26) Kim, J.-H.; Kim, J.-W.; Shokouhimehr, M.; Lee, Y.-S. *J. Org. Chem.* **2005**, *70*, 6714.

(27) Kim, J.-W.; Kim, J.-H.; Lee, D.-H.; Lee, Y.-S. *Tetrahedron Lett.* **2006**, *47*, 4745.

(28) Bergbreiter, D. E.; Su, H.-L.; Koizumi, H.; Tian, J. *J. Organomet. Chem.* **2011**, *696*, 1272.

(29) He, Y.; Cai, C. *Chem. Commun.* **2011**, *47*, 12319.

(30) Karimi, B.; Akhavan, P. F. *Chem. Commun.* **2011**, *47*, 7686.

(31) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. - Eur. J.* **2006**, *12*, 4743.

(32) Suijkerbuijk, B. M. J. M.; Aerts, B. N. H.; Dijkstra, H. P.; Lutz, M.; Spek, A. L.; van Koten, G.; Klein Gebbink, R. J. M. *Dalton Trans.* **2007**, 1273.

(33) Mizuike, A.; Sakamoto, T.; Onishi, N. *Microchim. Acta* **1971**, *59*, 783.

(34) Sigeev, A. S.; Peregudov, A. S.; Cheprakov, A. V.; Beletskaya, I. P. *Adv. Synth. Catal.* **2015**, *357*, 417.

(35) *Guidelines for Elemental Impurities Q3D*; U.S. Food and Drug Administration, published online 2013. DOI: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm371025.pdf.