

Investigation of the origin and synthetic application of the pseudodilution effect for Pd-catalyzed macrocyclisations in concentrated solutions with immobilized catalysts†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 4750Received 16th May 2013,
Accepted 18th June 2013

DOI: 10.1039/c3ob41020j

www.rsc.org/obc

Elisabeth Brehm^{a,b} and Rolf Breinbauer^{*a,b,c}

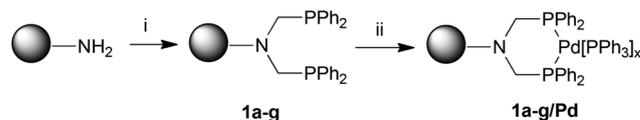
Immobilized Pd-complexes allowed macrocyclisations via the Tsuji–Trost-reaction in concentrated solutions. Systematic studies suggest that the origin of this pseudodilution effect is neither film diffusion nor gel diffusion, but the reduction in conformational freedom of intermediates and intramolecular pre-nucleophile activation. In contrast a pseudodilution effect could not be observed for Sonogashira- and Suzuki-macrocyclisations.

The conformational restriction caused by the macrocyclic nature of many natural products and several drug molecules is believed to be of superior importance for their biological activity.¹ The synthesis of such macrocyclic structures is a challenging task as any cyclisation reaction of a difunctional substrate has to compete with concurring intermolecular oligomerization reactions.² According to the high dilution principle of Ziegler and Ruggli, concentrations of 10⁻³ M or less are applied to favor intramolecular reactions.³ In 1982 Trost and Warner reported a stunning observation: with a polymer-bound metal complex macrocyclisations via Pd-catalyzed allylation of vinyloxydes succeeded in good yields at 0.1–0.5 M concentrations, while using a homogeneous variant of the catalyst at the same concentrations delivered only oligomerization products.⁴ Besides another report of Tsuji–Trost allylation,⁵ the only other examples of a similar effect have been documented for macrocyclisations via Stille-coupling⁶ and Cu-catalyzed Huisgen-cycloaddition.⁷ The dramatic improvements in macrocyclisation products using an immobilized catalyst have been interpreted as originating from a pseudodilution effect. This effect is well documented in solid phase synthesis for immobilized substrates at low substrate

loadings, which favors intramolecular reactions through site isolation.⁸ We report now a systematic investigation to study several parameters which might be involved in the performance of immobilized catalysts. In particular we were interested in the following questions: (1) How general is this effect? Can it be extended to other metal-catalyzed reactions? (2) Is the substrate transport to and across the catalyst-bead an influencing factor?⁹ (3) Do other resin properties (loading, flexibility, hydrophilicity/hydrophobicity) of the polymer support play a role?¹⁰

One prerequisite for our studies was a reliable access for well characterized polymer bound phosphine ligands. A limitation of previous studies which have relied on polystyrene (PS) phosphine is that this ligand is not only difficult to prepare but due to its monodentate it might lead to several different catalytically active species. We identified the bis(phosphinomethyl)amine moiety¹¹ as a convenient and suitable ligand unit for our purposes, as it can be easily made from readily accessible H₂N-functionalized resins in quantitative yield.¹² The bidentate ligand should warrant more defined Pd-coordination, which through the chelating effect should also diminish leaching. We synthesized a series of polymer-supported bis(phosphinomethyl)amine ligands **1a–1g**, in which we varied loading, cross linking, bead size and hydrophilicity of the support (Scheme 1, Table 1). All polymer ligands were characterized by ³¹P-NMR showing only a single signal for the P(III)-species. The ligands were converted to the Pd-complexes **1a–g/Pd** by stirring the resin with Pd[PPh₃]₄ followed by extensive washing.

For a first series of experiments in the Tsuji–Trost-macrocyclisation we needed a suitable substrate which can be



Scheme 1 Synthesis of immobilized phosphine ligands **1a–g** and the conversion to the corresponding Pd-complexes. (i) (1) Ph₂PH, HCHO, MeOH, 60 °C, (2) resin, toluene, 105 °C, 2d; (ii) Pd[PPh₃]₄.

^aMax-Planck-Institute of Molecular Physiology, Otto-Hahn-Str. 11, D-44227 Dortmund, Germany

^bFachbereich Chemie, Technische Universität Dortmund, Otto-Hahn-Str. 6, D-44227 Dortmund, Germany

^cInstitute of Organic Chemistry, Graz University of Technology, Stremayrgasse 9, A-8010 Graz, Austria. E-mail: breinbauer@tugraz.at; Fax: +43 316 873 32402; Tel: +43 316 873 32400

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ob41020j



Table 1 Properties of immobilized phosphine ligands **1a–g**

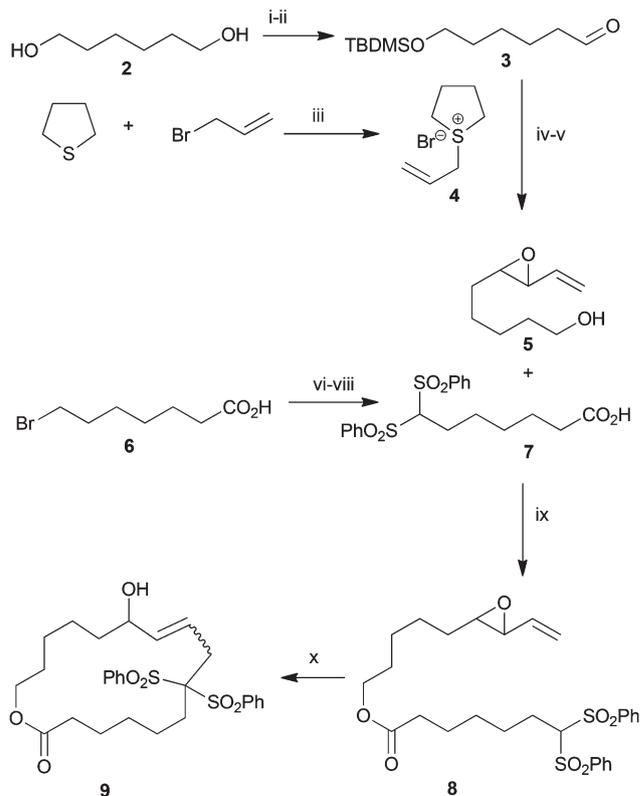
Entry	1	Type ^a	Size [mesh]	DVB [%]	Loading ^b [mmol g ⁻¹]
1	a	PS	200–400	1	0.77
2	b	PS	100–200	1	0.59
3	c	PS	70–90	1	0.79
4	d	PS	70–100	1	0.72
5	e	PS	~120	1	0.29
6	f	Tentagel	~20	1	0.68
7	g	PS	~100	High	0.90

^a For more details about the resins see ESI. ^b Loading with respect to NH₂-groups.

synthesized in a convergent manner and would give ready access to differently sized analogs. Similar to the methodology reported before, substrate **8** was prepared from vinyl epoxide **5**, which resulted from a reaction of sulfur ylide **4** with aldehyde **3**.¹³ After silyl deprotection, alcohol intermediate **5** was esterified with carboxylic acid **7** to furnish cyclisation substrate **8** in 21% overall yield for the 6 step synthesis in the longest linear sequence. Adapting the conditions of Fürstner and Weintritt established for their total synthesis of roseophilin,⁵ we achieved the Tsuji–Trost-macrocyclisation (10% Pd[PPh₃]₄, 20% dppe, THF, reflux, 0.0015 M) of **8** to form 17-membered lactone **9** in 64% yield (Scheme 2).

In order to evaluate the performance of polymer-supported catalysts for the same macrocyclisation of **8**, we used catalyst **1a/Pd** as a standard, as it featured the most popular resin properties (PS, 1% DVB, 200–400 mesh) used in solid phase organic synthesis. Using 10% **1a/Pd** under reflux conditions in THF, we varied the substrate concentration from 0.002 to 0.2 M (Fig. 1). To our delight, we could observe that immobilized catalyst **1a/Pd** produced macrocycle **9** even at the high concentration of 0.2 M in good yields (45%), confirming the previously reported effect of catalyst immobilization in Tsuji–Trost-cyclizations. The best yields were observed at 0.04 M (63%) (Fig. 1).

We used the concentration of 0.04 M for the next experiment in which we varied the reaction temperature. While at RT the yield decreased to 59% yield, at 50 °C it improved to 67%. As these experiments had confirmed that the immobilization effect was also valid for our substrate, we were considering the hypothesis that diffusion through the laminar layer surrounding the bead (film diffusion) resp. diffusion inside the bead (pore/gel diffusion) might be rate limiting. In such a scenario a locally lower substrate concentration inside the bead would be created, potentially equivalent to high dilution concentrations.^{9,14} In order to validate this hypothesis, we performed two sets of experiments. To test for potential film diffusion at first, we varied the stirring rate of the magnetic stirrer, which should influence the thickness of the laminar film layer around the beads. No influence of film diffusion could be detected, as the yields for a reaction at 0.022 M remained almost indistinguishable at the highest stirring rate (52%) from the one where no stirring was applied (51%) and values in between. Secondly, we screened our set of Pd-catalysts



Scheme 2 Synthesis of cyclisation substrate **8**. (i) NaH, TBDMSCl, 67%; (ii) (COCl)₂, DMSO, Et₃N, DCM, –78 °C to rt, 88%; (iii) MeOH–H₂O (9/1); (iv) **3**, DCM–10 M NaOH (1/1), –20 °C to rt, 1 h, 80%; (v) NH₄F, MeOH, reflux, 8 h, 65%; (vi) MeOH, H₂SO₄, 89%; (vii) (PhSO₂)₂CH₂, NaH, DMF, 81%; (viii) LiOH, THF–MeOH–H₂O (3/3/1), quant.; (ix) EDC, DMAP, DCM, RT, 12 h, 68%; (x) 10% Pd[PPh₃]₄, 20% dppe, syringe pump, 0.0015 M, THF, reflux, 64%.

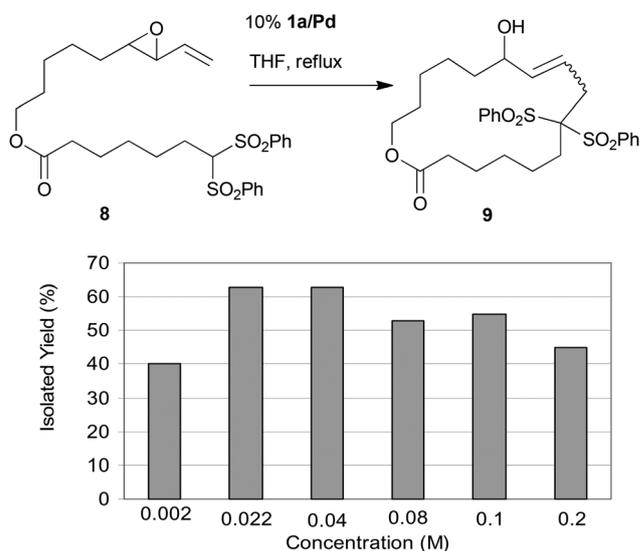
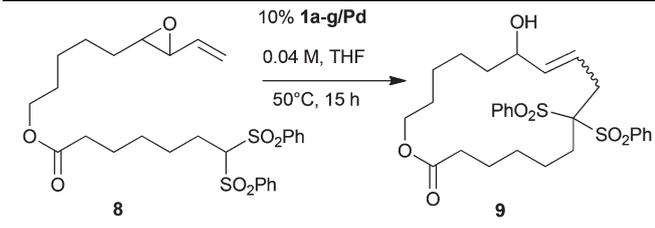


Fig. 1 Influence of the substrate concentration on the product yield for the macrocyclisation of substrate **8** with immobilized catalyst **1a/Pd**.

produced from polymer-supported phosphine resins **1a–g** featuring different bead sizes and degrees of cross linking (Table 2).



Table 2 Macrocyclisation yields for substrate **8** with immobilized Pd-catalysts **1a-g/Pd**


Entry	Catalyst	Size [mesh]	9 Yield [%]
1	1a/Pd	200–400	67
2	1b/Pd	100–200	67
3	1c/Pd	70–90	59
4	1d/Pd	70–100	62
6	1e/Pd	~120	70
7	1f/Pd	~20	51
8	1g/Pd	~100	44

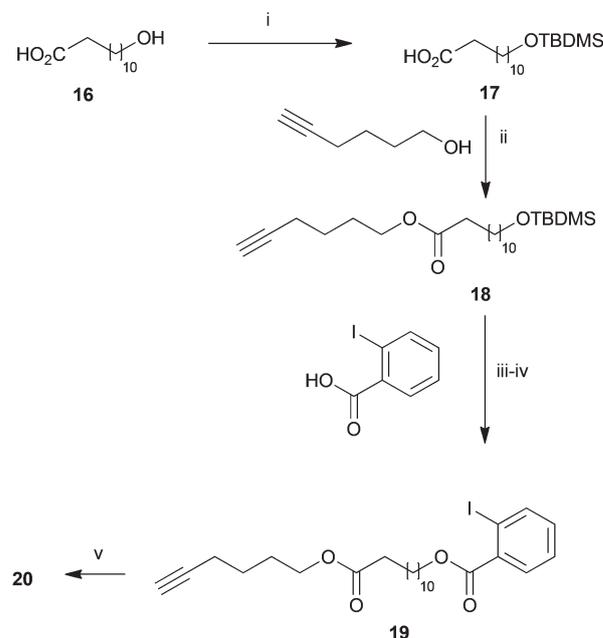
When comparing the similarly structured catalysts **1a/Pd**, **1b/Pd**, **1c/Pd**, **1d/Pd**, which differ primarily in their bead size, consistently good yields (59–67%) could be observed. Catalyst **1e/Pd**, which is in bead size similar to catalyst **1b/Pd** but has only half its loading, performs equally well (70%). As the larger beads (**1c** and **1d**) exhibited similar or slightly diminished yields, the hypothesis that pore/gel diffusion might have any (or even a positive) effect on macrocycle yields is not supported. For comparison, the homogeneous catalyst Pd[PPh₃]₄ gave under otherwise identical conditions only 29% yield of **9**. A resin which significantly performed differently, in this case worse than others, was catalyst **1g** made from a highly cross-linked resin, which does not swell in solvents. Interestingly, Tentagel-derived catalyst **1f** which is most distinct from all other resins in terms of bead size, ligand flexibility, loading and hydrophilicity performed quite well with test substrate **8**. From these two series of experiments we conclude that we have no evidence that limitation of substrate transport to and across the beads has an influence on macrocyclisation yields for the Pd-catalyzed Tsuji–Trost-macrocyclisation of our test substrate. To explore other substrates we limited our investigations to three catalysts: our standard catalyst **1a/Pd**, its close analog **1b/Pd**, and Tentagel-derived catalyst **1f/Pd**, and compared them with the homogeneous catalyst Pd[PPh₃]₄.

When comparing catalyst performance, it can be seen that **1a/Pd** and **1b/Pd** gave consistently good yields also for other substrates, whereas the Tentagel-based catalyst **1f/Pd** gave results similar to the homogeneous catalyst with the previously investigated standard substrate **8** as an exception. The almost congruent behaviour between homogeneous and Tentagel-immobilized catalysts matches well the perception that Tentagel-resin through its long and flexible spacer units emulates solution-phase behaviour, which has been used advantageously for several applications.¹⁵ Together these data led us to conclude that the observed effect, that catalyst immobilization on cross-linked polystyrene resins leads to improved yields for Tsuji–Trost-cyclisations, can be explained by two

factors: (a) a pseudodilution effect, which results from the intermittent immobilization of the substrate as a Pd-allyl complex within a polymeric bead, thereby restricting the conformational reach of its reactive ends, and (b) the special case of the internal base activation mechanism *via* intramolecular deprotonation of the pre-nucleophile by the alkoxide resulting from vinyl epoxide opening by the Pd-catalyst, which positions the nucleophile in close proximity to the electrophilic Pd-allyl complex (Fig. 3).⁴

We next set out to explore if the catalyst-immobilization effect can be extended to other Pd-catalyzed transformations. In particular, we were interested in the Sonogashira- and Suzuki-macrocyclisations. Despite its frequent application in synthesis these macrocyclisation reactions have not been performed with immobilized Pd catalysts yet. For the Sonogashira-macrocyclisation¹⁶ a set of eleven different substrates was synthesized, which would result in 14- to 25-membered rings. The synthetic strategy is based on the modular assembly of terminal alkyne building blocks with various iodoarenes. As an example the synthesis of **19** is described in Scheme 3 (for all other substrates see ESI†) (Table 3, Fig. 2).

12-Hydroxy undecanoic acid (**16**) was silyl-protected allowing the esterification with 5-hexyn-1-ol to produce ester **18**. Fluoride-mediated deprotection of the TBDMS-group quantitatively furnished the free alcohol which underwent carbodiimide-mediated esterification with 2-iodo benzoic acid to produce macrocyclisation substrate **19** in 34% yield for the entire four step synthetic sequence. The homogeneous catalyst Pd[PPh₃]₄ and the standard polymer supported catalyst **1a/Pd** were compared at 0.04 M substrate concentration for the



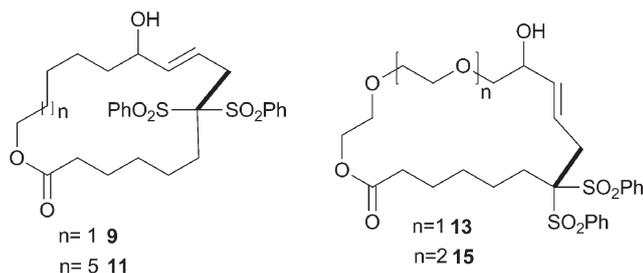
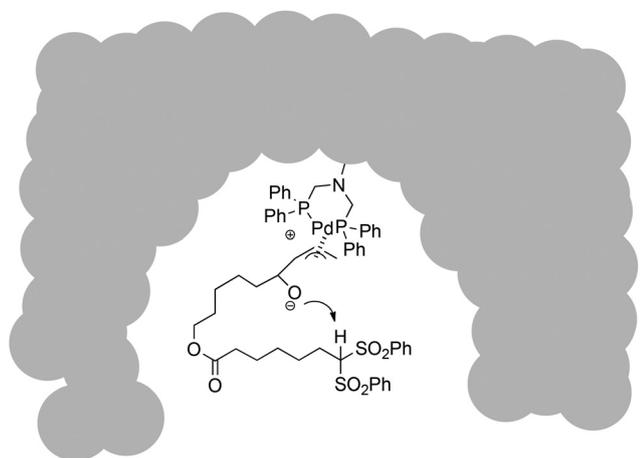
Scheme 3 Synthesis of Sonogashira-cyclisation substrate **19**. (i) TBMSCl, imidazole, 50%; (ii) EDC, DMAP, 83%; (iii) NH₄F, quant.; (iv) 2-iodobenzoic acid, EDC, DMAP, 83%; (v) 20% Pd[PPh₃]₄, 20% CuI, 0.04 M, 1,4-dioxane–piperidine (2/1), 60 °C, 15 h, 22%.



Table 3 Tsuji–Trost-macrocyclisation yields with immobilized Pd-catalysts **1a,b**, **f**/**Pd**

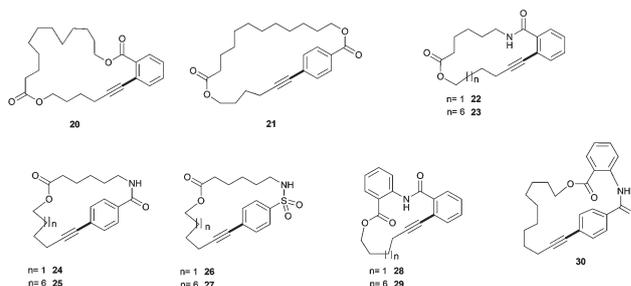
Entry	Catalyst	17-Ring 9	19-Ring 13	21-Ring 11	22-Ring 15
1	1a / Pd	67%	33% ^a	46%	53%
2	1b / Pd	67%	48%	47%	26%
3	1g / Pd	51%	28%	35%	19%
4	Pd [PPh ₃] ₄	29%	31%	34%	29%

Conditions: 10% **1**/**Pd**, 50 °C, 0.04 M, THF, 15 h.^a At 80% conversion.

**Fig. 2** Tsuji–Trost-macrocyclisation products. The bond formed in the cyclisation step is indicated in bold.**Fig. 3** Mechanistic proposal for intramolecular cyclization at the active site within a catalyst bead.

transformation of **19** to cyclisation product **20**. Both catalysts produced the 23-membered ring in 22% yield. In order to gain a more representative view of the Sonogashira-macrocyclisation, more substrates were investigated to produce the macrocycles depicted in Fig. 4 (Table 4).

The experimental results allow two important conclusions: (1) due to the conformational constraints imposed by the large number of sp²- and sp-hybridized carbon atoms in our substrates the yield depends strongly on the particular substrate ranging from 0% for highly constrained rings **24** and **28** (entries 5 and 9) up to 50% (entry 3) for product **22**, which is less constrained. (2) The yields from the reactions with the immobilized catalyst and the homogeneous reaction are very similar with only slight variations. We interpret these data that

**Fig. 4** Sonogashira-macrocyclisation products. The bond formed in the cyclisation step is indicated in bold.**Table 4** Comparison between homogeneous catalyst and immobilized catalyst for the Sonogashira-macrocyclisation

Entry	Product	Ring size	Yield with Pd [PPh ₃] ₄	Yield with 1a / Pd
1	20	23	22%	22%
2	21	25	—	25%
3	22	17	40%	50%
4	23	22	29%	27%
5	24	19	0%	0%
6	25	24	9%	13%
7	26	19	6%	12%
8	27	24	40%	38%
9	28	14	0%	0%
10	29	19	35%	33%
11	30	21	14%	14%

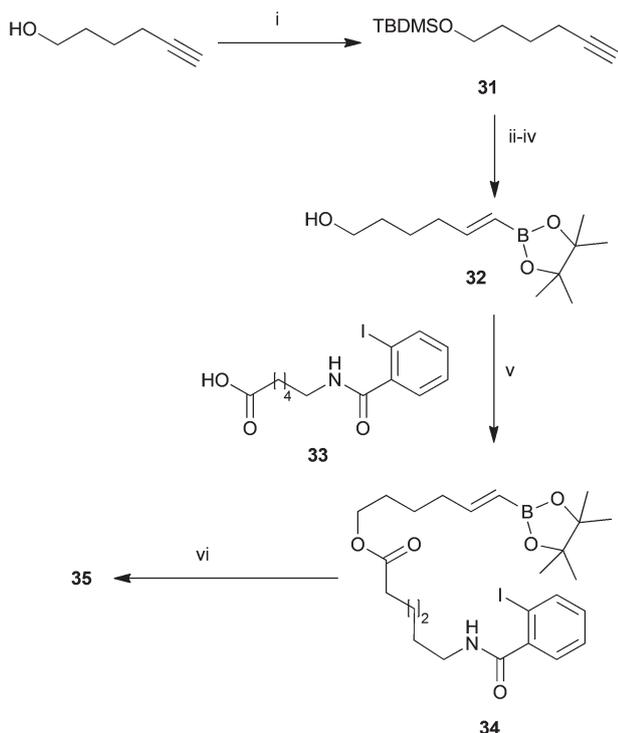
Conditions: 20% catalyst, 20% CuI, 0.04 M, 1,4-dioxane/piperidine (2/1), 60 °C, 15 h.

we cannot observe a catalyst immobilization effect for the Sonogashira-macrocyclisation of the investigated substrates. Apparently, the pseudodilution effect stemming from the transient immobilization of a reaction intermediate as it would occur during oxidative addition of the substrate is not sufficient to produce an improved cyclisation yield for the Sonogashira reaction.

The Suzuki-reaction has achieved considerable attention for macrocyclisations.¹⁷ However, to the best of our knowledge no efforts have been made to explore the use of immobilized catalysts in the context of this transformation. For substrate synthesis we had to adapt our modular synthetic strategy, as a direct transformation of our alkyne substrates for Sonogashira-macrocyclisations *via* hydroboration failed because of substrate decomposition. Our preferred synthetic route is illustrated for substrate **34** in Scheme 4 (for all other Suzuki substrates, see ESI†).

Alkynol **31** was converted *via* hydroboration by catecholborane followed by *in situ* hydrolysis and transesterification to vinyl pinacol boron ester **32**. This intermediate underwent carbodiimide-mediated esterification with carboxylic acid **33** to furnish cyclisation substrate **34** in 33% yield for the five-step reaction sequence. All in all, we had six substrates in hand which upon Suzuki-reaction would form 17- to 24-membered rings (Fig. 5, Table 5).





Scheme 4 Synthesis of Suzuki-macrocyclisation substrate **34**. (i) TBDMSCl, Et₃N, DMAP, DCM, overnight, quant.; (ii) catecholborane, 75 °C, 6 h; (iii) H₂O, 1 h, then CH₂O, 1 h, then pinacol, overnight; (iv) NH₄F, MeOH, 6 h, 49% (3 steps); (v) DIC, DMAP, DCM, overnight, 68%; (vi) 10% Pd[PPh₃]₄, 0.04 M DME–H₂O–DMF (7/3/2), 2 eq. Cs₂CO₃, 80 °C, 15 h, 60%.

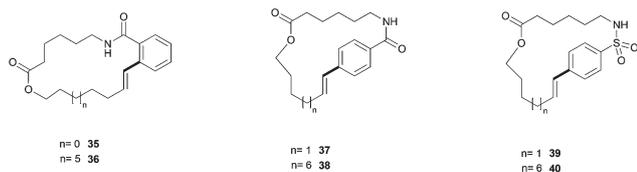


Fig. 5 Suzuki-macrocyclisation products. The bond formed in the cyclisation step is indicated in bold.

Table 5 Comparison between homogeneous catalyst and immobilized catalyst for the Suzuki-macrocyclisation

Entry	Product	Ring size	Yield with Pd[PPh ₃] ₄	Yield with 1a /Pd
1	35	17	60%	41%
2	36	22	57%	58%
3	37	19	0%	0%
4	38	24	61%	47%
5	39	19	22%	30%
6	40	26	0%	0%

Conditions: 10% Pd[PPh₃]₄, 0.04 M DME–H₂O–DMF (7/3/2), 2 eq. Cs₂CO₃, 80 °C, 15 h.

When performing the cyclisations with immobilized catalyst **1a**/Pd and homogeneous catalyst Pd[PPh₃]₄ at 0.04 M substrate concentration, we again saw a great substrate dependence originating from the conformational strain of the

formed compounds. Importantly, we also observed again a largely coherent efficiency between heterogeneous and homogeneous catalysts, showing better yields with the homogeneous catalyst for substrates **35** (entry 1) and **38** (entry 4), which led us to conclude that no substrate immobilization effect can be observed for the Suzuki-macrocyclisation of our tested substrates.

In conclusion, we have achieved the macrocyclisation of suitable substrates *via* Tsuji–Trost-macrocyclisation, and for the first time the Sonogashira-macrocyclisation and Suzuki-macrocyclisation using polymer-bound Pd-complexes.¹⁸ Our study has revealed that the catalyst-immobilization effect is not of general applicability to Pd-catalyzed macrocyclisations. For a set of eleven Sonogashira- and six Suzuki-macrocyclisation substrates we could not observe any evidence for such an effect. However, we could consistently see such an effect for Pd-catalyzed Tsuji–Trost-allylation of vinyloxydes. In contrast to previous intermolecular alkylation reactions catalyzed by solid-supported phase transfer catalysts,⁹ we could show that for the intramolecular Tsuji–Trost-allylation, substrate transport to and across the resin beads does not play a major role. Instead we believe that the combination of restricted freedom of the intermittently immobilized substrate and the idiosyncratic intramolecular activation mechanism through the formation of an alcoholate base and subsequent deprotonation of the pre-nucleophile plays an important role in this reaction. The flexibility of Tentagel resins does obscure the immobilization effect. It remains to be seen that other macrocyclisation reactions can be designed in which the effect of catalyst immobilization will allow macrocyclisations even in concentrated solutions,¹⁹ as has now been well exemplified for the intramolecular Tsuji–Trost-allylation with vinyloxyde substrates.

Notes and references

- 1 Leading reviews: (a) E. M. Driggers, S. P. Hale, J. Lee and N. K. Terrett, *Nat. Rev. Drug Discovery*, 2008, **7**, 608–624; (b) C. M. Madsen and M. H. Clausen, *Eur. J. Org. Chem.*, 2011, 3107–3115; (c) A. Isidro-Llobet, T. Murillo, P. Bello, A. Cilibrizzi, J. T. Hodgkinson, W. R. J. D. Galloway, A. Bender, M. Welch and D. R. Spring, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 6793–6798; (d) C. J. White and A. K. Yudin, *Nat. Chem.*, 2011, **3**, 509–524; and leading original works: (e) Y.-k. Kim, M. A. Arai, T. Arai, J. O. Lamenza, E. F. Dean III, N. Patterson, P. A. Clemons and S. L. Schreiber, *J. Am. Chem. Soc.*, 2004, **126**, 14740–14745; (f) M. T. Burger and P. A. Bartlett, *J. Am. Chem. Soc.*, 1997, **119**, 12697–12698.
- 2 Reviews: (a) B. Dietrich, P. Viout and J.-M. Lehn, *Macrocyclic Chemistry*, VCH, Weinheim, 1992; (b) Q. Meng and M. Hesse, *Top. Curr. Chem.*, 1991, **161**, 107–176; (c) C. J. Roxburgh, *Tetrahedron*, 1995, **51**, 9767–9822.
- 3 Reviews: (a) P. Knops, N. Sendhoff, H.-B. Meikelburger and F. Vögtle, *Top. Curr. Chem.*, 1991, **161**, 1–36; (b) K. Ziegler,



- Methoden der Organischen Chemie (Houben-Weyl)*, 4th edn, 1955, Vol. 4/II, pp. 729–822.
- 4 (a) B. M. Trost and R. W. Warner, *J. Am. Chem. Soc.*, 1982, **104**, 6112–6114; (b) B. M. Trost and R. W. Warner, *J. Am. Chem. Soc.*, 1983, **105**, 5940–5942; (c) B. M. Trost, *Angew. Chem., Int. Ed.*, 1999, **28**, 2817–2825.
- 5 A. Fürstner and H. Weintritt, *J. Am. Chem. Soc.*, 1998, **120**, 2817–2825.
- 6 J. K. Stille, H. Su, D. H. Hill, P. Schneider, M. Tanaka, D. L. Morrison and L. S. Hegedus, *Organometallics*, 1991, **10**, 1993–2000.
- 7 A. R. Kelly, J. Wei, S. Kesavan, J.-C. Marie, N. Windmon, D. W. Young and L. A. Marcaurelle, *Org. Lett.*, 2009, **11**, 2257–2260.
- 8 (a) M. Fridkin, A. Patchornik and E. Katchalski, *J. Am. Chem. Soc.*, 1965, **87**, 4646–4648; (b) S. Mazur and P. Jayalekshmy, *J. Am. Chem. Soc.*, 1979, **101**, 677–683; (c) J. Rebek Jr. and J. E. Trend, *J. Am. Chem. Soc.*, 1979, **101**, 737; (d) H. Franzyk, M. K. Christensen, R. M. Jorgensen, M. Meldal, H. Cordes, S. Mouritsen and K. Bock, *Bioorg. Med. Chem.*, 1997, **5**, 21–40; (e) C. Herb and M. E. Maier, *J. Org. Chem.*, 2003, **68**, 8129–8135; (f) E. Gonthier and R. Breinbauer, *Mol. Diversity*, 2005, **9**, 51–62.
- 9 The influence of transport processes on intermolecular reactions on beads has been demonstrated before, see: (a) S. L. Regen and J. J. Besse, *J. Am. Chem. Soc.*, 1979, **101**, 4059–4063; (b) M. Tomoi and W. T. Ford, *J. Am. Chem. Soc.*, 1980, **102**, 7140–7141; (c) M. Tomoi and W. T. Ford, *J. Am. Chem. Soc.*, 1981, **103**, 3821–3828; (d) M. Tomoi and W. T. Ford, *J. Am. Chem. Soc.*, 1981, **103**, 3828–3837; (e) B. Kim, P. Kirszensztejn and S. L. Regen, *J. Am. Chem. Soc.*, 1983, **105**, 1567–1571.
- 10 For studies on diffusion and reactivity phenomena on polymeric beads, see: (a) W. Li, X. Xiao and A. W. Czarnik, *J. Comb. Chem.*, 1999, **1**, 127–129; (b) A. R. Vaino and K. D. Janda, *J. Comb. Chem.*, 2000, **2**, 579–596; (c) J. Rademann, M. Barth, R. Brock, H.-J. Egelhaaf and G. Jung, *Chem.–Eur. J.*, 2001, **7**, 3884–3889; (d) T. Groth, M. Grotli and M. Meldal, *J. Comb. Chem.*, 2001, **3**, 461–468; (e) J. Kress, R. Zanaletti, A. Rose, J. G. Frey, W. S. Brocklesby and M. Bradley, *J. Comb. Chem.*, 2003, **5**, 28–32.
- 11 (a) A. M. LaPointe, *J. Comb. Chem.*, 1999, **1**, 101–104; (b) M. T. Reetz, G. Lohmer and R. Schwickardi, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1526–1529; (c) M. T. Reetz and S. R. Waldvogel, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 865–867.
- 12 (a) Y. Uozumi and Y. Nakami, *Org. Lett.*, 2002, **4**, 2997–3000; (b) E. Gonthier and R. Breinbauer, *Synthesis*, 2003, 1049–1051; (c) M. Westhus, E. Gonthier, D. Brohm and R. Breinbauer, *Tetrahedron Lett.*, 2004, **45**, 3141–3142.
- 13 M. Rosenberger, C. Newkom and E. R. Aig, *J. Am. Chem. Soc.*, 1983, **105**, 3656–3661.
- 14 For authoritative reviews about diffusion phenomena in heterogeneous catalysis, see: (a) G. Emig and R. Dittmeyer, in *Handbook of Heterogeneous Catalysis*, ed. G. Ertl, H. Knözinger and J. Weitkamp, VCH, Weinheim, 1997, pp. 1209–1252; (b) M. Baerns, H. Hofmann and A. Renken, *Chemische Reaktionstechnik*, 2, Aufl. Thieme, Stuttgart, 1992; (c) F. Kapteijn and J. A. Moulijn, in *Handbook of Heterogeneous Catalysis*, ed. G. Ertl, H. Knözinger and J. Weitkamp, VCH, Weinheim, 1997, 1359–1376; (d) R. J. Madon and M. Boudart, *Ind. Eng. Chem. Fundam.*, 1982, **21**, 438–447.
- 15 See for example: (a) K. Kuramochi, T. Haruyama, R. Takeuchi, T. Sunoki, M. Watanabe, M. Oshige, S. Kobayashi, K. Sakaguchi and F. Sugawara, *Bioconjugate Chem.*, 2005, **16**, 97–104; (b) B. Lehr, H.-J. Egelhaaf, H. Fritz, W. Rapp, E. Bayer and D. Oelkrug, *Macromolecules*, 1996, **29**, 7931–7936; (c) P. Wright, D. Lloyd, W. Rapp and A. Andrus, *Tetrahedron Lett.*, 1993, **34**, 3373–3376.
- 16 For selected examples of Sonogashira-macrocyclisations, see: (a) M. Schmittel and H. Ammon, *Synlett*, 1999, 750–752; (b) A. C. Spivey, J. McKendrick, R. Srikanan and B. A. Helm, *J. Org. Chem.*, 2003, **68**, 1843–1851; (c) T. Harada, S.-I. Matsui, T. M. T. Tuyet, M. Hatsuda, S. Ueda, A. Oku and M. Shiro, *Tetrahedron: Asymmetry*, 2003, **14**, 3879–3884; (d) S. Odermatt, J. L. Alonso-Gomez, P. Seiler, M. M. Cid and F. Diederich, *Angew. Chem., Int. Ed.*, 2005, **44**, 5074–5078; (e) J. Krauss, D. Unterreitmeier, C. Neudert and F. Bracher, *Arch. Pharm.*, 2005, **338**, 605–608; (f) V. Balraju, D. S. Reddy, M. Periasamy and J. Iqbal, *J. Org. Chem.*, 2005, **70**, 9626–9628; (g) J. Sakamoto and D. A. Schlüter, *Eur. J. Org. Chem.*, 2007, 2700–2712; (h) G. Chen, L. Wang, D. W. Thompson and Y. Zhao, *Org. Lett.*, 2008, **10**, 657–660.
- 17 For selected examples of Suzuki-macrocyclisations, see: (a) R. Ostaszewski, W. Verboom and D. N. Reinhoudt, *Synlett*, 1992, 354–356; (b) W. Li and K. Burgess, *Tetrahedron Lett.*, 1999, **40**, 6527–6530; (c) N. C. Kallan and R. L. Halcomb, *Org. Lett.*, 2000, **2**, 2687–2690; (d) V. Lobregat, G. Alcaraz, H. Bienayme and M. Vaultier, *Chem. Commun.*, 2001, 817–818; (e) J. D. White, R. Hanselmann, R. W. Jackson, W. J. Porter, J. Ohba, T. W. Tille and S. Wang, *J. Org. Chem.*, 2001, **66**, 5217–5231; (f) M. Bauer and M. E. Maier, *Org. Lett.*, 2002, **4**, 2205–2208; (g) J. T. Njardarson, K. Biswas and S. J. Danishefsky, *Chem. Commun.*, 2002, 2759–2761; (h) P. J. Mohr and R. L. Halcomb, *J. Am. Chem. Soc.*, 2003, **125**, 1712–1713; (i) G. A. Molander and F. Dehmel, *J. Am. Chem. Soc.*, 2004, **126**, 10313–10318; (j) T. Esumi, M. Wada, E. Mizushima, N. Sato, M. Kodama, Y. Asakawa and Y. Fukuyama, *Tetrahedron Lett.*, 2004, **45**, 6941–6945; (k) B. Wu, Q. Liu and G. A. Sulikowski, *Angew. Chem., Int. Ed.*, 2004, **43**, 6673–6675; (l) D. Deng, B. Wang, A. J. Augatis and N. I. Totah, *Tetrahedron Lett.*, 2007, **48**, 4605–4607; (m) J. M. W. Chan and T. M. Swager, *Tetrahedron Lett.*, 2008, **49**, 4912–4914; (n) M. Tortosa, N. A. Yakelis and W. R. Roush, *J. Org. Chem.*, 2008, **73**, 9657–9667; (o) A. B. Smith, M. A. Foley, S. Dong and A. Orbin, *J. Org. Chem.*, 2009, **74**, 5987–6001; (p) Z. Wang, M. Bois-Choussy, Y. Jia and J. Zhu, *Angew. Chem., Int. Ed.*, 2010, **49**, 2018–2022; (q) J. Dufour,



- L. Neuville and J. Zhu, *Chem.–Eur. J.*, 2010, **16**, 10523–10534; (r) W. Huang, M. Wang, C. Du, Y. Chen, R. Qin, L. Su, C. Zhang, Z. Liu, C. Li and Z. Bo, *Chem.–Eur. J.*, 2011, **17**, 440–444; (s) A. Afonso, L. Feliu and M. Planas, *Tetrahedron*, 2011, **67**, 2238–2245; (t) M. Dieckmann, M. Kretschmer, P. Li, S. Rudolph, D. Herkommer and D. Menche, *Angew. Chem., Int. Ed.*, 2012, **51**, 5667–5670; (u) F.-M. Meyer, J. C. Collins, B. Borin, J. Bradow, S. Liras, C. Limberakis, A. M. Mathiowetz, L. Philippe, D. Price, K. Song and K. James, *J. Org. Chem.*, 2012, **77**, 3099–3114.
- 18 Reviews about the synthesis and application of polymer-bound Pd complexes: (a) N. E. Leadbeater, *Curr. Med. Chem.*, 2002, **9**, 2147; (b) N. End and K. U. Schöning, *Top. Curr. Chem.*, 2004, **242**, 241; (c) Y. Uozumi, *Top. Curr. Chem.*, 2004, **242**, 77–112; (d) M. Guino and K. K. Hii, *Chem. Soc. Rev.*, 2007, **36**, 608–617; (e) L. Yin and J. Liebscher, *Chem. Rev.*, 2007, **107**, 133–173; (f) A. Molnar, *Chem. Rev.*, 2011, **111**, 2251–2320; (g) A. C. Albeniz and N. Carrera, *Eur. J. Inorg. Chem.*, 2011, 2347–2360.
- 19 Recently, the ring closing metathesis with Ru-complexes immobilized in silica nanopores has been reported to occur with improved yields for macrocyclisation products: J. E. Jee, J. L. Cheong, J. Lim, C. Chen, S. H. Hong and S. S. Lee, *J. Org. Chem.*, 2013, **78**, 3048–3056.

