


Forcing a *cis*-Product by Matrix Imprinting: Heck Reaction Catalyzed by Palladium Acetate Entrapped within *cis*-Imprinted Sol-Gel Derived Silicates

Dmitry Tselikhovsky,^a Dikla Pessing,^a David Avnir,^{a,*} and Jochanan Blum^{a,*}

^a Institute of Chemistry, The Hebrew University, Jerusalem 91904, Israel
Fax: (+972)-2-651-3832; e-mail: jblum@chem.ch.huji.ac.il or david@chem.ch.huji.ac.il

Received: September 23, 2008; Published online: December 8, 2008

 Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.200800590>.

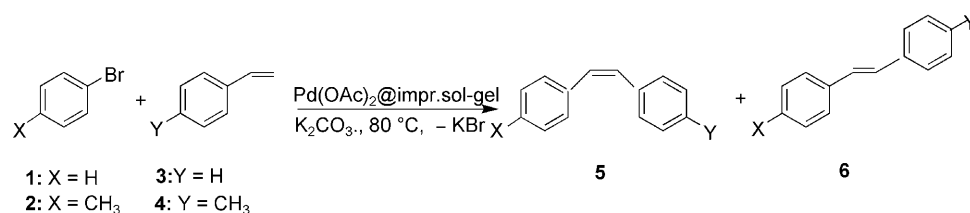
Abstract: While the Heck coupling of aryl bromides with styrenes by palladium acetate entrapped within octylated silica sol-gel forms almost entirely *trans*-stilbenes, the catalysis by the palladium compound within the *cis*-pre-imprinted support gives stilbenes that are substantially enriched by *cis*-oriented isomers. Although the ceramic support is completely freed from the imprint prior to the coupling process, *cis*-stilbenes are formed with similar selectivities upon recycling of the catalyst systems for at least four consecutive runs.

Keywords: C–C coupling reactions; heterogeneous catalysis; imprinting; sol-gel process; stereoselectivity

An ongoing challenge in organic chemistry is how to force a reaction to result in enrichment with a less favored isomer. In double bond synthetic chemistry, the challenge has been to control the *cis* to *trans* isomers ratio. There are several conceptually distinct ways for direct interconversion of *cis* and *trans* isomers which have been thoroughly studied and reviewed.^[1] One is the thermal-chemical interconversion of the isomers and the other is based on photochemical means. Other notable methods are the stereoselective (*syn* and *anti*) oxidative additions to the double bond followed by selective reductive eliminations, selective cleavage of epoxides, thiirans and related heterocycles^[1] as well as the application of a variety of organometallic catalysts with spatial structurally demanding ligands.^[2] In this communication we demonstrate a new approach that changes the regular stereochemical course of a catalytic reaction into an energetically less favored direction by imprinting the matrix with a template shaped as the desired *product*. The specific reac-

tion with which we demonstrate this approach is the palladium acetate-catalyzed Heck coupling^[3,4] of a bromoarene and a styrene derivative in an aqueous microemulsion.^[5] This reaction has led to hardly any *cis* products when carried out in solution,^[3,4] and to no *cis* products at all under heterogeneous sol-gel conditions.^[5] We found that we could force this reaction to yield considerable amounts of *cis*-stilbenes – typically *cis:trans* ratios of 1:1, and up to 8.5:1 – by imprinting the matrix within which the catalyst is embedded with *cis*-stilbenes. It should be noted that in the voluminous literature on imprinting of either oxides or polymers since the early 1930s,^[6] we could not locate a *cis*-directing imprinting study.^[7] Other shape selective imprints for synthesis and catalysis are of course known, mainly in the context of “foot-printing” and other types of surface and thin layer catalytic operations.^[8–10] Only very little had been achieved in attempted shape selective catalysis using bulk imprinted sol-gel materials.^[11]

When a 4:1 mixture of tetramethoxysilane (TMOS), octyl(triethoxy)silane (OTEOS) and palladium acetate was treated with *cis*-stilbene during the hydrolysis and polycondensation of the silanes, followed by extraction of 96–98% of the imprint from the resulting ceramic sol-gel material with CH₂Cl₂, (see Experimental Section) the aforementioned Heck reaction of microemulsified bromobenzene and styrene in water resulted in 86% of *cis*-stilbene. Carrying out the same reaction with the non-imprinted matrix afforded >99% of *trans*-stilbene. In yet another important blank test reaction, when the template compound was *trans*-stilbene the coupling reaction gave exclusively the *trans*-stilbene. At 80 °C the encaged Pd(OAc)₂ could be recycled with only a small decrease in the selectivity. The conversion in the first four runs remained quantitative and the respective yields of *cis*-stilbene were 86, 83, 81 and 72%. Thus, after the fourth run we have isolated more than 3.2

Table 1. Heck coupling of bromoarenes with styrene derivatives by Pd(OAc)₂ entrapped within imprinted hydrophobicized silica sol-gel.^[a]

Entry	Imprint	Reactants Bromide Alkene		Time [h]	Conversion [%] ^[b]	Products [relative yield, %] ^[b]
1	5, X = Y = H	1	3	4	> 99	5, X = Y = H (86); 6, X = Y = H (14)
2	5, X = H, Y = CH ₃	1	4	24	99	5, X = H, Y = CH ₃ (49); 6, X = H, Y = CH ₃ (51)
3	5, X = CH ₃ , Y = H	2	3	24	99	5, X = H, Y = CH ₃ (50); 6, X = H, Y = CH ₃ (50)
4	5, X = Y = CH ₃	2	4	24	30	5, X = Y = CH ₃ (48); 6, X = Y = CH ₃ (52)
5	5, X = Y = CH ₃	1	3	24	98	5, X = Y = H (25); 6, X = Y = H (75)

^[a] Reaction conditions: Pd(OAc)₂ (30 mg, 0.134 mmol) entrapped within hydrophobicized sol-gel as described in the Experimental Section. The substrates (1.34 mmol of each) were 0.8 wt% of a microemulsion containing 89.3 wt% water, 3.3 wt% SDS, 6.6 wt% 1-PrOH, and K₂CO₃ (2 mmol); 80 °C.

^[b] In the first run.

times the amount of *cis*-stilbene used as imprint. This excludes unequivocally any possibility that the isolated product originates from the template molecules. The temperature of 80 °C was found to be optimal for the recycling, as well as, for the formation of the maximal *cis*-oriented product.

In analogy to the imprinting of the sol-gel with *cis*-stilbene, we imprinted the support also with *cis*-4-methyl- and with *cis*-4,4'-dimethylstilbene. After removal of the imprint the matrices were used in the Heck coupling reactions that led to the corresponding mono- and dimethylated stilbenes. As noted in our previous paper,^[5] both methylated bromobenzenes and methylated styrenes react much slower than the unsubstituted substrates. Nevertheless, with extension of the reaction time, substantial amounts of the *cis*-oriented stilbenes have been formed (see Table 1), and here too the immobilized catalyst could be recovered and recycled after completion of the couplings (4 runs were investigated in each case).

Although we do not know yet the reason for the selectivity in the Heck coupling in the presence of the imprinted sol-gel support, we assume that the template molecules leave after their extraction cavities that resemble in shape and size the transition state required for the generation of the *cis*-stilbenes. It seems that the key reaction intermediates are able to accommodate themselves within the cavity, break down, and release the *cis*-enriched products [*cf.*, the transition state analogue (TSA) concept frequently used to rationalize the selectivity caused by imprinting^[11a,11b,12]]. It is remarkable that larger cavities may host also reaction intermediates that are of smaller size, but then the lack of adequate fitness causes a drop in selectivity.

Thus, the lower *cis* to *trans* ratio obtained when the imprint was *cis*-4,4'-dimethylstilbene and the substrates bromobenzene and styrene may be explained by the formation of considerable extra space within the cavities, permitting the formation of the *trans* isomer. Under such conditions the selectivity drops sharply upon recycling. In entry 5, the second run gave only 10% of *cis*- and 90% of *trans*-stilbene. As to the opposite situation, attempts to interact substrates that were expected to form with Pd(OAc)₂ a larger complex than the dimensions of the proposed cavity, gave no reaction. In any event, in none of these experiments were we able to trace *cis*-4,4'-dimethylstilbene that might have been left from the imprinted molecules. Finally, the selective formation of *cis*-stilbene takes place also in non-aqueous solvents, albeit in a lower yield. For example, in dry benzene (and in the presence of Et₃N instead of K₂CO₃) the relative yields under comparable conditions were 20% of *cis*-stilbene and 79% of the *trans*-isomer. The reaction in benzene did not require hydrophobicization of the silica sol-gel support.

In summary, we provide the first example of the use of imprinting to convert a reaction which forms solely or mainly the *trans* isomer into a reaction that is substantially *cis*-enriched, up to becoming the main product. As *cis-trans* stereochemical control is a routine need in synthetic routes, and as the imprinting of sol-gel materials provide chemically inert, stable matrices, we believe that the approach described here will find further usage in catalysis and organic synthesis.

Experimental Section

Entrapment of Palladium Acetate within Imprinted Hydrophobicized Sol-Gel Matrices

A solution of octyltriethoxysilane (2.1 mL, 6.68 mmol; OTEOS) in EtOH (5.6 mL) was hydrolyzed by magnetic stirring for 24 h at 25°C with triply distilled water (0.4 mL; TDW). Separately a mixture of tetramethoxysilane (3.6 mL, 24.2 mmol; TMOS), MeOH (2.4 mL) and TDW (2 mL) was stirred for 10 min at 25°C and then admixed with a solution of palladium acetate (30 mg, 0.134 mmol) in dichloromethane (4 mL). To this mixture was added the hydrolyzed OTEOS solution as well as the imprint compound (1.32–1.34 mmol, 241 mg of *cis*-stilbene, 257 mg of *cis*-4-methylstilbene, or 276 mg of *cis*-4,4'-dimethylstilbene). The stirring was continued for as long as possible. The gelation was completed with 15–17 h. The gel was then dried for 24 h at 80°C and 0.5 Torr. The imprint material was extracted with boiling CH₂Cl₂ (several portions of 25 mL were employed until the dried extract accounts at least for 96% of the original imprint). The residual ceramic material was redried until constant weight was achieved. In order to assure that no metal leached during the extraction the final matrix was subjected to ICP analysis and tested (after concentration) for possible catalytic activity. All these tests gave negative results.

For comparison and for studies in organic solvents, samples of imprinted non-hydrophobicized sol-gel entrapped Pd(OAc)₂, which did not include the OTESOS, were prepared.

The Catalytic Coupling Reactions

Typically, a microemulsion was prepared by mixing the bromoarene and the styrene derivative (1.34 mmol of each), together with TDW (89.3 wt%), SDS (3.3 wt%), 1-propanol (6.6 wt%) at 25°C, for 10 min. The immobilized catalyst [containing 30 mg of Pd(OAc)₂ and solid K₂CO₃ (280 mg, 2 mmol)] was mixed with the microemulsion and heated with stirring at 80°C. After 24 h (4 h when the starting compounds were bromobenzene and styrene) the reaction mixture was cooled to room temperature and NaCl (2 g) was added. This caused phase separation. The organic layer was separated, diluted with ether (25 mL), dried on MgSO₄, concentrated, and the products were analyzed both by NMR and GC by comparison with authentic samples of *cis*-stilbene, *cis*-4-methylstilbene^[13] or *cis*-4,4'-dimethylstilbene^[14] prepared according to literature procedures. The results are summarized in Table 1. Comparative experiments in benzene were carried out with Et₃N (2 mmol) instead of with K₂CO₃.

The used immobilized catalyst was washed and sonicated at first for 10 min with water (2×25 mL) dried and then with CH₂Cl₂ (3×10 mL) and redried at room temperature at 0.5 Torr for 12 h before its application in another catalytic cycle.

Acknowledgements

We gratefully acknowledge the financial support of this study by the Israel Science Foundation (ISF) through Grant No. 296/06.

References

- [1] a) E. L. Eliel, S. H. Wilen, N. Mander, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, **1994**, pp 574–590, and references cited therein; b) P. E. Sonnet, *Tetrahedron* **1980**, *36*, 557–604.
- [2] See, e.g.: G. P. F. van Strijdonck, M. D. K. Boele, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **1999**, 1073–1076.
- [3] R. F. Heck, *Org. React.* **1982**, *27*, 345–390.
- [4] See, e.g.: *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: A. de Meijere, F. Diedrich), Wiley-VCH, Weinheim, **2004**.
- [5] D. Tsvetikhovskiy, J. Blum, *Eur. J. Org. Chem.* **2008**, 2417–2422.
- [6] a) M. W. Polyakov, *Zhur. Fiz. Khim.* **1931**, *2*, 799–805; b) S. Mudd *J. Immunol.* **1932**, *23*, 423–427; c) L. Pauling, *J. Am. Chem. Soc.* **1940**, *62*, 2643–2657; d) L. Pauling, D. H. Campbell *J. Exper. Med.* **1942**, *76*, 211–220; e) F. H. Dickey, *Proc. Natl. Acad. Sci. USA* **1949**, *35*, 227–229.
- [7] For a recent comprehensive review see: C. Alexander, H. S. Anderson, L. I. Anderson, R. I. Ansell, N. Kirsch, I. A. Nicholls, J. O'Mahony, M. J. Whitcombe, *J. Mol. Recognit.* **2006**, *19*, 106–180.
- [8] K. Morihara, S. Kurihara, J. Suzuki, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3991–3998.
- [9] See also: a) G. Wulff, *Chem. Rev.* **2002**, *102*, 1–27; b) A. P. Wight, M. E. Davis, *Chem. Rev.* **2002**, *102*, 3589–3614; c) M. E. Díaz-García, R. B. Laíño, *Microchim. Acta* **2005**, *149* 19–36; and references cited therein.
- [10] a) S. Fireman-Shores, I. Popov, D. Avnir, S. Marx, *J. Am. Chem. Soc.* **2005**, *127*, 2650–2655; b) S. Fireman-Shores, S. Marx, D. Avnir, *J. Mater. Chem.* **2007**, *17*, 536–544.
- [11] Reports on selective catalysis on silicon dioxide with substrate specific cavities later proved to be in dispute. See: a) J. Heilmann, W. F. Maier, *Angew. Chem.* **1994**, *106*, 491–493; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 471–473; b) J. Heilmann, W. F. Maier, *Z. Naturforsch. B* **1995**, *50*, 460–468; c) W. R. Ahmed, M. E. Davis, *Catal. Lett.* **1996**, *40*, 109–114; d) W. F. Maier, W. Ben-Mustapha, *Catal. Lett.* **1997**, *46*, 137–140.
- [12] See, e.g.: K. Ohkubuto, K. Sawakuma, T. Sagawa, *J. Mol. Catal. A: Chem.* **2001**, *165*, 1–7, and references cited therein.
- [13] H. Shi, B. Xu, *J. Org. Chem.* **2002**, *67*, 294–297.
- [14] Y. Obora, H. Moriya, M. Tokunaga, Y. Tsuji, *Chem. Commun.* **2003**, 2820–2821.