ORGANIC LETTERS

2003
Vol. 5, No. 8
1197−1200

Remarkable Dendritic Effect in the Polymer-Supported Catalysis of the Heck Arylation of Olefins

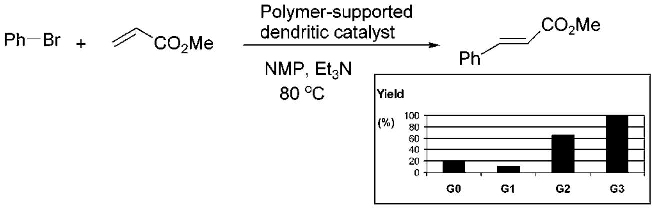
Adi Dahan and Moshe Portnoy*

School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences,
Tel Aviv University, 69978 Tel Aviv, Israel

portnoy@post.tau.ac.il

Received January 7, 2003

ABSTRACT



Phosphine–palladium complexes, immobilized on polystyrene, demonstrated a remarkable increase in catalytic activity and selectivity in the Heck reaction upon the introduction of a dendritic spacer between the support and phosphine. For some reactions an up to 5-fold increase in yield is observed.

Immobilization of analogues of homogeneous catalysts via covalent attachment to a support is one of the possible ways to prepare well-defined heterogeneous catalytic systems, a task of great economic and environmental importance.[1] Unfortunately, along with the advantages of the heterogeneous catalysts, a substantial decrease in activity and selectivity is frequently observed. Herein we report results suggesting that one possible way to overcome these drawbacks is the introduction of a dendritic template between the support and catalyst. Our study of the intermolecular Heck reaction with supported dendritic catalysts reveals a remarkable positive dendritic effect on the catalysis.

Soluble dendrimers with peripherally attached catalytic units were applied to a variety of reactions.[2,3] Surprisingly, only a few efforts were devoted to the investigation of catalysis on dendronized insoluble supports.[4] In two of these reports, a positive dendritic influence was apparent.[4b,f] Alper and co-workers investigated the Heck reaction using the silica-bound PAMAM-bis(diphenylphosphinomethyl)amine catalytic system (PAMAM = polyamidoamine dendron), but the ineffective palladium complexation to the dendritic ligands prevented conclusive investigation of the dendritic effect in this reaction.[4d]

Heck olefin arylation, one of the most widely used reactions in synthetic organic chemistry, was successfully accomplished in solution with aryl iodides, bromides, and even chlorides, using a variety of catalytic systems.[5,6] Heteroge-

---

[1] (a) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217. (b) McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275. (c) de Miguel, Y. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4213. (d) de Miguel, Y. R.; Brulé, E.; Margue, R. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3085.

[2] (a) Oosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1828. (b) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991. (c) van Heerbeek, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Rev.* **2002**, *102*, 3717.

[3] For positive dendritic effects in solution, see: (a) Lee, J.-J.; Ford, W. T.; Moore, J. A.; Li, X. *Macromolecules* **1994**, *27*, 4632. (b) Breinbauer, R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 3604. (c) Ropartz, L.; Morris, R. E.; Foster, D. F.; Cole-Hamilton, D. J. *Chem. Commun.* **2001**, 361. (d) Francavilla, C.; Drake, M. D.; Bright, F. V.; Detty, M. R. *J. Am. Chem. Soc.* **2001**, *123*, 52.

[4] (a) Bourque, S. C.; Maltais, F.; Xiao, W.-J.; Tardif, D.; Alper, H.; Arya, P.; Manzer, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 3035. (b) Bourque, S. C.; Alper, H.; Manzer, L. E.; Arya, P. *J. Am. Chem. Soc.* **2000**, *122*, 956. (c) Arya, P.; Rao, N. V.; Singkhonrat, J.; Alper, H.; Bourque, S. C.; Manzer, L. E. *J. Org. Chem.* **2000**, *65*, 1881. (d) Alper, H.; Arya, P.; Bourque, S. C.; Jefferson, G. R.; Manzer, L. E. *Can. J. Chem.* **2000**, *78*, 920. (e) Antebi, S.; Arya, P.; Manzer, L. E.; Alper, H. *J. Org. Chem.* **2002**, *67*, 6623. (f) Chung, Y.-M.; Rhee, H.-K. *Chem. Commun.* **2002**, 238.

[5] Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

10.1021/ol0340181 CCC: $25.00

neous catalysis, however, was performed almost entirely with iodides or electron-deficient bromides,[7,8] mainly using metal palladium adsorbed on an inorganic support.[9] It is notable that although in solution phosphines are the most popular ligands for Heck catalysis, on solid support only a few phosphorus-based systems have been reported.[10] The reactivities of these systems were limited to iodides, and only the fundamental study by Hallberg and co-workers exposed the need for multiple phosphine ligation to Pd as a tool for effective bromoarene olefination with a supported catalyst.[11] Unfortunately, such coordination modes result in severe cross-linking of the polymer, which frequently has a negative effect on the catalytic activity. With this notion in mind, we found it imperative to investigate catalytic systems that are based on ligands derived from dendronized polymeric support.

Looking for an alternative to the potentially coordinating amide-type linkage, mostly used in the backbone of the dendritic templates prepared on solid support,[4,12] we recently developed an alternative, efficient route to poly(aryl benzyl ether) dendronized polystyrene resins **G1**−**G3** (Figure 1).[13,14]

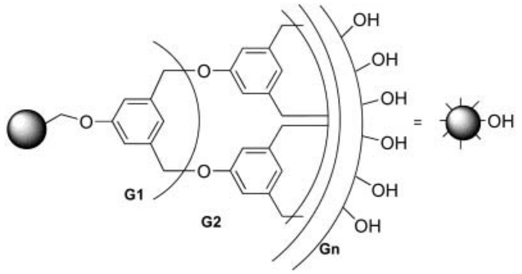
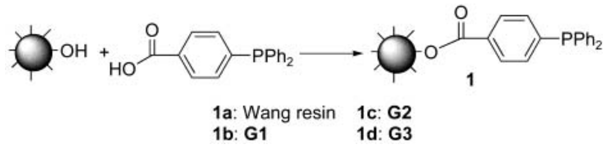


Figure 1. Dendronized support (**Gn**).

Ligands **1a**−**1d** (Scheme 1) that are based on such support have already been used for the study of the Co-catalyzed intramolecular Pauson−Khand reaction, demonstrating a positive dendritic effect on the catalysis.[15]

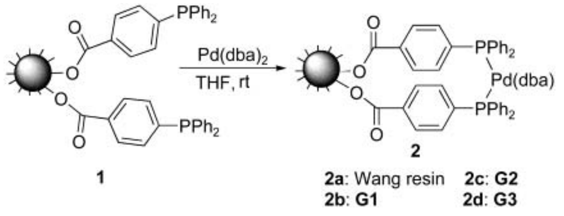
Scheme 1[a]



[a] Reagents and conditions: DIC, DMAP, DMF.

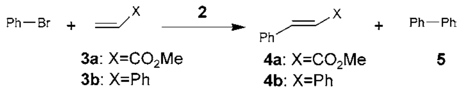
Incubation of resins **1** with Pd(dba)$_2$ in deoxygenated THF at room temperature for 4 h yielded reddish brown resins **2a**−**2d** (Scheme 2).[16] Gel-phase ^{31}P NMR demonstrated quantitative complexation of the phosphines with Pd. ^{1}H NMR spectra of the TFA-cleaved solutions of **2a**−**2d** revealed that, for each two phosphine groups, one molecule of dibenzylideneacetone is present. Thus, the most probable structure of the Pd complexes on the supports is (phosphine)$_2$-Pd(dba), and accordingly, the loading of the active catalyst on support was calculated.[17]

Scheme 2. Complexation of **1** with Pd(dba)$_2$



The reaction of bromobenzene with methyl acrylate, chosen as a model for the Heck reaction with catalysts **2a**−**2d**, was performed under two different temperature regimes: at 120 °C for 14 h and at 80 °C for 72 h (Scheme 3). In some experiments, the bromobenzene homocoupling byproduct, biphenyl **5**, is obtained. The results of the model reaction, summarized in Table 1, demonstrate a remarkable improvement in the catalyst performance upon dendronization of the support. Although at 120 °C, the conversions of the dendronized resins is only marginally better than that of

Scheme 3. Heck Reaction with **2** as Catalyst



---

(6) For polyamine-based soluble dendritic catalyst for this reaction, see: (a) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1526. (b) Reetz, M. T. *Top. Catal.* **1997**, *4*, 187.

(7) (a) Kivaho, J.; Hanaoka, T.; Kubota, Y.; Sugi, Y. *J. Mol. Catal. A* **1995**, *101*, 25. (b) Zhao, F.; Bhanage, B. M.; Shirai, M.; Arai, M. *Chem. Eur. J.* **2000**, *6*, 843. (c) Biffis, A.; Zecca, M.; Basato, M. *Eur. J. Inorg. Chem.* **2001**, 1131. (d) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139. (e) Zhao, F.; Shirai, M.; Ikushima, Y. Arai, M. *J. Mol. Catal. A* **2002**, *180*, 211.

(8) For rare examples of supported systems capable of unactivated bromoarene olefination, see: (a) Buchmeiser, M. R.; Wurst, K. *J. Am. Chem. Soc.* **1999**, *121*, 11101. (b) Schwarz, J.; Böhm, V. P. W.; Gardiner, M. G.; Grosche, M.; Herrman, W. A.; Hieringer, W.; Raudaschl-Sieber, G. *Chem. Eur. J.* **2000**, *6*, 1773. (c) Dell'Anna, M. M.; Mastrorilli, P.; Muscio, F.; Nobile, C. F.; Surranna, G. P. *Eur. J. Inorg. Chem.* **2002**, 1094.

(9) For rare metal palladium catalysts capable of unactivated bromoarene olefination, see: (a) Köhler, K.; Wagner, M.; Djakovitch, L. *Catal. Today* **2001**, *66*, 105 and references therein. (b) Mehnert, C. P.; Ying, T. Y. *Chem. Commun.* **1997**, 2215. (c) Köhler, K.; Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J. *Chem. Eur. J.* **2002**, *8*, 622.

(10) (a) Wang, P.-W.; Fox, M. A. *J. Org. Chem.* **1994**, *59*, 5358. (b) Villemin, D.; Jaffrès, P. A.; Nechab, B.; Courivaud, F. *Tetrahedron Lett.* **1997**, *38*, 6581. (c) Riegel, N.; Darcel, C.; Stéphan, O.; Jugé, S. *J. Organomet. Chem.* **1998**, *567*, 219.

(11) Andersson, C.-M.; Karabelas, K.; Hallberg, A.; Andersson, C. *J. Org. Chem.* **1985**, *50*, 3891.

(12) (a) Lebreton, S.; Monaghan, S.; Bradley, M. *Aldrichim. Acta* **2001**, *34*, 75. (b) Klein Gebbink, R. J. M.; Kruithof, C. A.; van Klink, G. P. M.; van Koten, G. *Rev. Mol. Biol.* **2002**, *90*, 183.

(13) Dahan, A.; Portnoy, M. *Macromolecules* **2003**, *36*, 1034.

(14) For first route to such dendrons on polymer see: Basso, A.; Evans, B.; Pegg, N.; Bradley, M. *Chem. Commun.* **2001**, 697.

(15) Dahan, A.; Portnoy, M. *Chem. Commun.* **2002**, 2700.

(16) Loading of phosphine groups: **1a**, 0.89 mmol/g; **1b**, 0.82 mmol/g; **1c**, 1.12 mmol/g; **1d**, 0.70 mmol/g

Table 1. Heck Reaction of Methyl Acrylate (**3a**)[a]

entry	catalyst	conversion (%)	yield of **4a** (%)	selectivity (**4a**:**5**)
1	**2a**[b]	95	75	3.8
2	**2b**[b]	100	81	4.3
3	**2c**[b]	100	86	6.1
4	**2d**[b]	100	97	32
5	**2a**[c]	20	18	9.0
6	**2b**[c]	11	11	22
7	**2c**[c]	66	66	>130
8	**2d**[c]	100	100	>200
9	**6**[c,d]	84	82	41

[a] Using 0.5 mmol of bromobenzene, 0.6 mmol of methyl acrylate, 0.65 mmol of triethylamine, and **2** (0.0125 mmol of Pd) in 1 mL of *N*-methylpyrrolidone (NMP). [b] At 120 °C, 14 h. [c] At 80 °C, 72 h. [d] **6**: Pd(dba)$_2$ + 2 *p*-MeO$_2$CC$_6$H$_4$PPh$_2$.

Table 2. Heck Reaction of Styrene (**3b**)[a]

catalyst	conversion (%)	yield of **4b** (%)	selectivity (**4b**:**5**)
2a[b]	100	66	1.9
2b[b]	100	67	2.0
2c[b]	100	68	2.1
2d[b]	100	91	10
2a[c]	99	67	2.0
2b[c]	73	56	3.3
2c[c]	100	81	4.3
2d[c]	100	89	8.1

[a] Using 0.5 mmol of bromobenzene, 0.6 mmol of styrene, 0.65 mmol of triethylamine, and **2** (0.0125 mmol of Pd) in 1 mL of NMP. [b] At 120 °C, 14 h. [c] At 80 °C, 72 h.

Scheme 4. Heck Reaction of Butyl Vinyl Ether with **2** as Catalyst

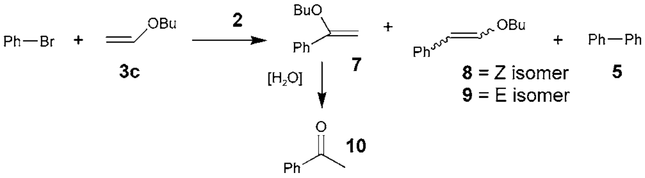


Table 3. Heck Reaction of Butyl Vinyl Ether (**3c**)[a]

catalyst	conversion (%)	yield (**7** + **8** + **9**, %)	selectivity ([**7** + **8** + **9**]:**5**)
2a[b]	100	58	1.4
2b[b]	100	58	1.4
2c[b]	100	75	3.0
2d[b]	100	83	4.9
2a[c]	55	46	5.1
2b[c]	49	41	5.1
2c[c]	54	46	5.8
2d[c]	77	72	14

[a] Using 0.5 mmol of bromobenzene, 0.6 mmol of butyl vinyl ether, 0.65 mmol of triethylamine, and **2** (0.0125 mmol of Pd) in 1 mL of NMP. [b] At 120 °C, 14 h. [c] At 80 °C, 72 h.

the catalyst derived from the Wang resin (**2a**), the selectivity of the formation of the Heck versus the homocoupling product consistently improves from **2a** to **2d** (an 8-fold increase is achieved, entries 1 and 4). This increase in selectivity is reflected in the substantially higher yield reached using the third-generation-derived **2d** as compared with its nondendronized analogue.

The difference in the reactivity within the **2a**−**2d** series of catalysts is even more dramatic at 80 °C (Table 1, entries 5−8). The second- and third-generation-derived catalysts are superior to their nondendronized analogue in all parameters. Although there is a notable decrease in the activity of **2b**, as compared with that of **2a**, the activity increases significantly for **2c** and even further for **2d**, rendering for the latter a quantitative conversion. The selectivity of the catalysis is also significantly improved upon the increase of the dendron generation and, for **2c** and **2d**, no biphenyl is observed. Notably, the conversion and selectivity achieved with **2d** are markedly *higher* than those obtained with **6**, the nondendritic homogeneous analogue of ligands **2a**−**2d**, prepared in situ from Pd(dba)$_2$ and the methyl ester of the 4-(diphenylphosphino)benzoic acid (entries 8 and 9).[18]

When styrene is examined as a substrate, the trends in activity and selectivity of the catalysts are very similar to those of methyl acrylate (Table 2), although the magnitude of the effect is somewhat smaller.

To determine whether the observed effects are limited only to the electron-deficient olefinic substrates, we examined the performance of **2a**−**2d** in the Heck reaction with butyl vinyl ether as a substrate (Scheme 4, Table 3).

For this substrate, the regioselectivity and stereoselectivity are important issues, as three products—*cis*- and *trans*-1,2-disubstituted **8** and **9** as well as 1,1-disubstituted **7** (undergoing partial hydrolysis to acetophenone (**10**))—are formed. The trends observed for the conversion to Heck products (**7**−**9**) and selectivity toward these products (versus **5**) are very similar to those obtained for substrates **3a** and **3b**. At both temperatures, **2d** is clearly superior to **2a**. According to the regio- and stereoselectivity data, summarized in Table 4, the proportion of the α-arylated product **7** increases as the generation number of the polymer template increases. The decrease in the ratio *β*-arylation/α-arylation for butyl vinyl ether can be attributed to the higher portion of the olefin insertion occurring through cationic intermediates (enforcing α-arylation) versus neutral intermediates (yielding mixtures of α- and *β*-arylated enol ethers).[19] This change in the distribution between the two alternative catalytic pathways may result from the more polar environment of the catalytic units in higher generation catalysts. Alternatively, or additionally, the reason for this change may be associated with

---

(17) Loading of palladium: **2a**, 0.38 mmol/g; **2b**, 0.36 mmol/g; **2c**, 0.47 mmol/g; **2d**, 0.31 mmol/g

(18) Although monodentate phosphine is used for preparation of **6**, the minimal chelate size on dendronized resins is 20 atoms and thus chelate effects are not likely to be responsible for the observed phenomenon.

(19) Cabri, W.; Candian, I. *Acc. Chem. Res.* **1995**, *28*, 2.

Table 4. Regio- and Stereoselectivity in Heck Reaction of Butyl Vinyl Ether (**3c**)

catalyst	yield of β-arylation (**8** + **9**, %)	yield of α-arylation (**7** + **10**, %)	regio-selectivity ([**8** + **9**]/[**7** + **10**])	stereo-selectivity **9**/ **8**[c]
2a[a]	33	25	1.3	2.4
2b[a]	31	27	1.2	2.6
2c[a]	40	35	1.1	3.0
2d[a]	42	41	1.0	3.0
2a[b]	37	9	4.1	2.6
2b[b]	30	10	3.0	2.6
2c[b]	29	17	1.7	2.8
2d[b]	44	28	1.6	3.0

[a] At 120 °C, 14 h. [b] At 80 °C, 72 h. [c] Determined by ^{1}H NMR.

the increased *local* loading of phosphines in higher generation dendrons.

Precipitation of metallic palladium occurs during the reaction, and thus the possibilities of the catalysis being performed by Pd metal nanoparticles, stabilized inside the dendritic matrix,[20] or the dendritic effect being merely the reflection of a reduced decomposition rate of the higher generation-derived complexes[21] cannot be ruled out at this stage of the research.

However, some preliminary experimental data may point to the higher intrinsic reactivity of the higher-generation-derived complexes as the source of the effect. First, the ratio between products **9** (trans) and **8** (cis) in the reaction of **3c** (Table 4), which is known to be sensitive to the nature of the catalyst,[22] is more characteristic of the phosphine−palladium catalysts. Additionally, when we performed the reaction of **3a** at 80 °C for 14 h, it exhibited a more pronounced positive dendritic effect than that of the aforementioned 3-day experiments.

In conclusion, the novel supported dendron-based catalysts were successfully employed in the Heck reaction of bromobenzene. The systems we prepared exhibit a truly remarkable positive dendritic effect, demonstrating superiority even over their homogeneous nondendritic analogue, although more work has to be done in order to fully elucidate the origins of the effect, improve the catalyst stability, and further increase its activity. The proposed architecture demonstrates a promising solution toward boosting the activity and selectivity of supported catalytic systems.

Acknowledgment. This research was partially supported by a grant from the Ministry of Science, Israel.

Supporting Information Available: General procedures for complexation and for catalysis. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0340181

---

[20] Zhao, M.; Crooks, R. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 364.

[21] As observed in ref 6a.

[22] According to ref 11, phosphine−Pd complexes as catalysts yield a ca. 2.5:1 ratio, while the “naked” Pd catalysts form 1:1 product mixtures.