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An iminophosphine dendrimeric ligand and its evaluation in the Heck reaction

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Abstract—DAB-*dendr*-$(NH_2)_{32}$ has been modified to produce two novel dendrimeric *P*,*N*-ligands, DAB-*dendr*-$[1,2\text{-}(N{=}CHC_6H_4PPh_2)]_{32}$ and DAB-*dendr*-$[1,2\text{-}(NHCH_2C_6H_4PPh_2)]_{32}$. These were both found to activate electron rich aryl bromides in the Heck reaction. The reactions seem to proceed better in a novel solvent system consisting of an equimolar mixture of a tertiary amine with acetic acid. A marked dependence of the conversion on the [equivalents of dendrimeric ligand]/[Pd] ratio has been observed with conversion decreasing as the ratio of dendrimer equivalents to Pd increases. This phenomenon is attributed to interactions of the arms bearing the metal with neighboring ones within the dendrimer. © 2003 Published by Elsevier Science Ltd.

Dendrimeric ligands in general,[1] and dendrimers bearing a multitude of *P*-centers, either at the core or on the periphery, in particular, have found rather wide application in catalysis.[2] The reason for this is that these types of ligands may present certain important advantages in catalysis as compared to their monomeric counterparts. Dendrimeric ligands possess persistent shapes and sizes and these properties provide the conditions for the recoverability of the catalyst by nanofiltration.[3] Another advantage of dendrimeric ligands stems from the accurately defined microenvironment of the catalytic site, i.e. a metal-coordination site with constrained geometry, which may result in enhanced selectivity and/or catalytic efficiency.[1] It has been pointed out that dendrimers may be characterized as 'unimolecular' micelles[4] and it is perhaps possible to attribute to this characteristic their special behavior, manifested as *positive* and *negative dendritic effects*, i.e. enhanced and diminished catalytic activities, respectively, which have been noted in many instances.[5]

The commercial availability of DAB dendrimers has prompted researchers to devise schemes by which a desired functionality is attached at the peripheral amino groups of the dendrimer. The best example of this type of dendrimeric ligand, bearing *P*-centers on the periphery, is 'Reetz's dendritic phosphine',[2l,m,6] DAB-*dendr*-$[N(CH_2PPh_2)_2]_{16}$.

Following this trend we wish in this letter to report the synthesis of the iminophosphine, DAB-*dendr*-$[1,2\text{-}(N{=}CHC_6H_4PPh_2)]_{32}$, '*DAB-32-imiphos*', and the corresponding aminophosphine, DAB-*dendr*-$[1,2\text{-}(NHCH_2C_6H_4PPh_2)]_{32}$, '*DAB-32-amiphos*', i.e. two dendrimeric *P*,*N*-ligands. In addition, we report on the evaluation of these novel dendrimeric ligands in the Heck reaction.

The synthesis of the dendrimeric iminophosphine was carried out by stirring a mixture of DAB-*dendr*-$(NH_2)_{32}$ and an excess of 2-diphenylphosphinobenzaldehyde in a mixture of absolute ethanol and methylene chloride under argon and in the presence of sodium carbonate (Scheme 1) aiming towards DAB-*dendr*-$[1,2\text{-}N{=}CHC_6H_4PPh_2]_{32}$. Indeed, this procedure[7] afforded a product with 100% coverage as shown by a combination of NMR spectroscopy and residual primary amine-group analysis.[8] It is worth mentioning that this method, even without exclusion of air, gave a product with little phosphine oxidation. In contrast, the formic acid catalyzed method without exclusion of air resulted in a product with substantial phosphine oxidation. Sodium borohydride-reduction of the iminophosphine afforded the corresponding aminophosphine.

Keywords: dendrimer; catalysis; Heck reaction; phosphine; palladium complex.

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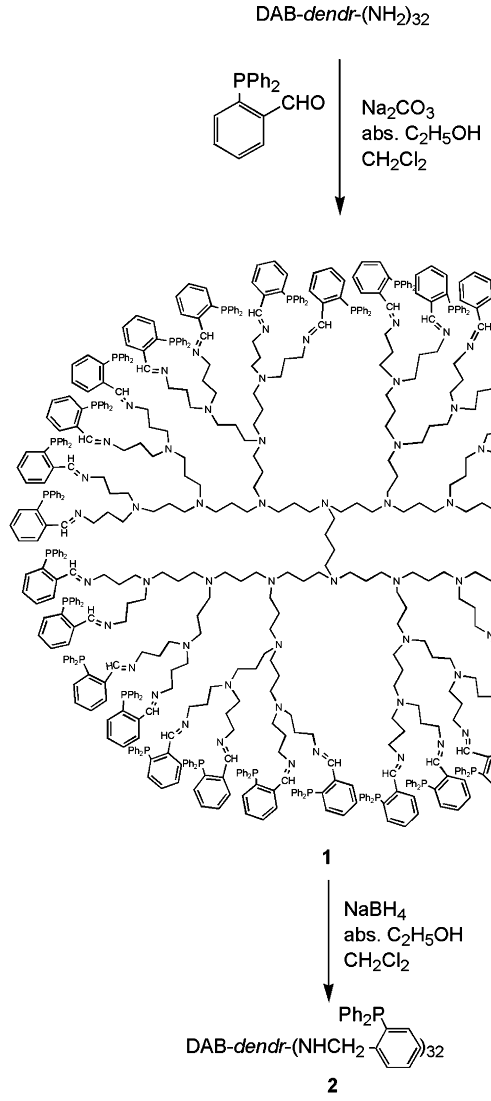


Scheme 1.

In the case of the iminophosphine, one has to take into consideration the possibility of *syn* and *anti* isomerism. Actually, in the iminic-proton region of the NMR spectrum only one significant resonance is observed at 8.82 ppm and, for steric reasons and from previously reported data for simpler iminophosphines,[9] we assign this to the *anti* conformation. An extremely low intensity resonance is observed at ca. 8.9 ppm and this could be assigned to the *syn* isomer but may also be due to an occluded impurity.

Bearing in mind the early work on the effect of excess phosphine, which results in a deceleration of the catalytic reaction,[10] we chose to examine whether the dendritic polyphosphine behaves as an assembly of 'independent' phosphine moieties or as a molecular entity with 32 equivalent coordination sites with some sort of 'tripodal'[11] or even 'multipodal' interaction between neighboring 'arms', i.e. in the case that an intradendrimer fluxionality is operable. In such a case one could reasonably expect that a strong interaction between the arm(s) bearing the catalytic metal with neighboring ones could markedly affect the catalytic activity.

More specifically, the dendrimeric iminophosphine ligand was employed in the Pd-catalyzed reaction between aryl bromides,[12] especially *p*-anisyl bromide, and styrene and its performance compared with the catalytic efficacy of simple iminophosphines of varying steric requirements, **3**, **4** (Fig. 1). We also examined the effect of solvent on the same reaction. In this respect, we tested a rather novel reaction medium, i.e. an equimolar mixture of acetic acid and a tertiary amine. Relevant to the present work is a recent report on an analogous dendrimeric iminophosphine ligand and its application in the catalytic Stille coupling reaction.[13] Our results on the coupling of *p*-anisyl bromide with styrene are summarized in Table 1.

Palladium acetate, 1%, in the presence of 3 equivalents of *DAB-32-imiphos* and lithium acetate and an equimolar mixture of tributylamine and acetic acid as solvent (temperature 130°C, time 15.5 h) converted bromobenzene completely to a mixture of ca. 90% *trans*-stilbene and ca. 10% isomers. However, at 100°C, and otherwise under the same conditions, the conversion was only 4%.

Table 1. Heck coupling of *p*-anisyl bromide with styrene. Temperature 130°C, reaction time 23 h, catalyst system Pd(OAc)$_2$-*DAB-32-imiphos*[a]

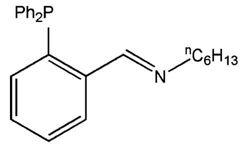
Entry	mol% Pd	[L]/[Pd]	Solvent	Base	Conversion (%)[b]	Product (%)[c]
1	1	1:1	Bu$_3$N–AcOH	LiOAc	66	57
2	1	11:1	Bu$_3$N–AcOH	LiOAc	55	55
3	1	15:1	Bu$_3$N–AcOH	LiOAc	1	0.6
4	2	2:1	Bu$_3$N–AcOH	LiOAc	88	83
5	2	2:1	Bu$_3$N–AcOH	NaOAc	88	85
6	2	2:1	Bu$_3$N–AcOH	None	92	87
7	2	2:1	TMEDA–AcOH	None	93	92 (77)
8	2	2:1	Bu$_3$N	None	0	0
9	2	2:1	AcOH[d]	NaOAc	6	4
10	2	2:1	DMF	NaOAc	72	71

[a] General conditions: 5 mmol of each reactant, solvent 3.0 mL, argon atmosphere.

[b] Determined by GC.

[c] *trans*-4-Methoxystilbene, in parentheses isolated yield.

[d] In the presence of paraformaldehyde.



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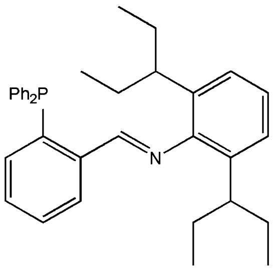

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Figure 1.

With the electron-rich bromide, *p*-anisyl bromide with 2% $Pd(OAc)_2$ and a ratio $[L]/[Pd]=2$, (L in equivalents, i.e. $12218/32=381.81$ where mol. wt. of $L=12218$) the conversion ranged from 88 to 92% at 130°C in 23 h, the solvent being an equimolar mixture of Bu_3N–AcOH.[14] A 93% conversion was also realized by using as solvent an equimolar mixture of TMEDA and acetic acid (entries 4–7). These results should be contrasted with the 0 and 6% conversions in tributylamine alone or acetic acid alone, respectively, containing NaOAc and paraformaldehyde as the reducing agent[15] (entries 8 and 9). Even the widely used solvent and base conditions of DMF and NaOAc gave only a 72% conversion. Therefore, the equimolar mixture of TMEDA or tributylamine, and perhaps other tertiary amines, and acetic acid appears to be superior to DMF. It appears reasonable to assume that the R_3N–AcOH solvent system behaves like an ionic liquid.[16] The data indicate that, in the reaction medium R_3N–AcOH, addition of either lithium or sodium acetate does not improve the conversion (cf. entries 4 and 5 with entries 6 and 7). In fact, regioselectivity appears to be better in the absence of inorganic base, particularly so in TMEDA–AcOH (Entry 7).

Variation of the [L]/[Pd] ratio revealed an interesting trend. The conversion dropped dramatically as the ratio increased. Namely, for the ratios 4:1, 11:1 and 15:1, conversions were 65, 55 and 1%, respectively (entries 1–3). This implies that there is a rather strong *inter-arm* interaction within the dendrimer to which the metal is coordinated, preventing the substrate from competing for a coordination site on the metal.[17]

For comparison purposes, we employed the iminophosphines **3** and **4**. The corresponding conversions were 16 and 85% under otherwise the same conditions. The efficacy of the iminophosphine ligand **4** can be readily attributed to the steric crowding around the imine nitrogen. It therefore appears that the *DAB-32-imiphos* functions as a ligand of great steric demand. It should be pointed out, however, that given the thermal instability of DAB-*dendr*-$(NH_2)_{32}$, the *DAB-32-imiphos* ligand most probably undergoes degradation under the reaction conditions and the extensive formation of *Pd black* indicates that this could, perhaps, be the case. The catalytic system is therefore not recoverable. Also nothing can be said with certainty about the actual catalytic species. A possibility is that this involves a cyclopalladated compound resulting from the intact dendrimeric ligand or a fragment thereof. In any case, the ligand must be sterically demanding, judging from the results with the simple iminophosphines **3** and **4** (Fig. 1).[18]

The dendrimeric aminophosphine ligand, *DAB-32-amiphos*, gave a 78% conversion, which is somewhat lower than that obtained with the *DAB-32-imiphos* ligand.

In conclusion DAB-*dendr*-$(NH_2)_{32}$ has been modified to produce two novel dendrimeric *P*,*N*-ligands, DAB-*dendr*-$[1,2\text{-}(N{=}CHC_6H_4PPh_2)]_{32}$ and DAB-*dendr*-$[1,2\text{-}(NHCH_2C_6H_4PPh_2)]_{32}$, which were both found to activate electron rich aryl bromides in the Heck reaction. The reaction seems to proceed better in a novel solvent, i.e. an equimolar mixture of a tertiary amine and acetic acid. A marked dependence of the conversion on the [equivalents of dendrimeric ligand]/[Pd] ratio has been observed; the higher the ratio the lower the conversion, which becomes zero for ratios greater than 15. This phenomenon is attributed to a rather strong interaction of the arm bearing the metal with neighboring ones within the dendrimer.

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References

1. (a) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991; (b) Oostrom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1828.
2. (a) Ropartz, L.; Morris, R. E.; Foster, D. F.; Cole-Hamilton, D. J. *Chem. Commun.* **2001**, 361; (b) Oosterom, G. E.; van Haaren, R. J.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Commun.* **1999**, 1119; (c) De Groot, D.; Emmerink, P. G.; Coucke, C.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Inorg. Chem. Commun.* **2000**, *3*, 711; (d) Brinkmann, N.; Giebel, D.; Lohmer, G.; Reetz, M. T.; Kragl, U. *J. Catal.* **1999**, *183*, 163; (e) Arya, P.; Panda, G.; Rao, N. V.; Alper, H.; Bourque, S. C.; Manzer, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 2889; (f) Arya, P.; Rao, N. V.; Singkhonrat, J.; Alper, H.; Bourque, S. C.; Manzer, L. E. *J. Org. Chem.* **2000**, *65*, 1881; (g) Bourque, S. C.; Maltais, F.; Xiao, W. J.; Tardif, O.; Alper, H.; Manzer, L. E.; Arya, P. *J. Am. Chem. Soc.* **1999**, *121*, 3035; (h) Alper, H.; Arya, P.; Bourque, C. S.; Jefferson, G. R.; Manzer, L. E. *Can. J. Chem.* **2000**, *78*, 920; (i) Fan, Q.-H.; Chen, X.-M.; Jiang, D.-Z.; Xi, F.; Chan, A. S. C. *Chem. Commun.* **2000**, 789; (j) Petrucci-Samija, M.; Guillemette, V.; Dasgupta, M.; Kakkar, A. K. *J. Am.*

Chem. Soc. **1999**, *121*, 1968; (k) Gong, A.; Fan, Q.; Chen, Y.; Liu, C.; Xi, F. *J. Mol. Catal.* **2000**, *159*, 225; (l) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1526; (m) Mizugaki, T.; Ooe, M.; Ebitani, K.; Kaneda, K. *J. Mol. Catal. A* **1999**, *145*, 329; (n) Mizugaki, T.; Murata, M.; Ooe, M.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **2002**, 52.

3. Hovestad, N. J.; Eggeling, E. B.; Heidbüchel, H. J.; Jastrzebski, J. T. B. H.; Kragl, U.; Keim, W.; Vogt, D.; van Koten, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1655.
4. (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules: Concepts, Syntheses and Perspectives*; VCH: New York, 1996; (b) Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665; (c) Piotti, M. E.; Rivere, F., Jr.; Bond, R.; Hawker, C. J.; Fréchet, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 9471.
5. For positive dendritic effects, see: (a) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 707; (b) Oosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1828; (c) Brunner, H. *J. Organomet. Chem.* **1995**, *500*, 39; (d) Breinbauer, R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 3604; (e) Butz, T.; Murer, P.; Seebach, D. *Polym. Pater. Sci. Eng.* **1997**, *77*, 132; (f) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 92; (g) Francavilla, C.; Drake, M. D.; Bright, F. V.; Detty, M. R. *J. Am. Chem. Soc.* **2001**, *123*, 57; for negative dendritic effects, see: (h) Peerlings, H. W. I.; Meijer, E. W. *Chem. Eur. J.* **1997**, *3*, 1563; (i) Kleij, A. W.; Gossage, R. A.; Jastrzebski, J. T. B. H.; Boersma, J.; van Koten, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 176.
6. Alonso, E.; Astruc, D. *J. Am. Chem. Soc.* **2000**, *122*, 3222.
7. A mixture of 0.5 g of DAB-*dendr*-$(NH_2)_{32}$, 2.6 g of *o*-diphenylphosphinobenzaldehyde (free of phosphine oxide by ^{31}P NMR), 3.5 g of sodium carbonate 25 mL of absolute ethanol and 25 mL of methylene chloride were degassed and stirred for seven days under an atmosphere or argon. After dilution with 100 mL of CH_2Cl_2, the mixture was freed from sodium carbonate by filtration and the filtrate was washed with water, dried over sodium sulfate and evaporated on a rotary evaporator at a temperature below 40°C. The residue was persistently triturated with 2×25 mL of acetone to remove excess phosphinobenzaldehyde and dried on a rotary evaporator at room temperature. A solid foam was formed which was broken up into an off-white fluffy solid. This material, after further drying under a vacuum of 0.02 mbar for 8 h at room temperature, was analyzed for residual primary amine groups[8] and by NMR. The former indicated 0.2 residual primary amino groups per mol of dendrimer. Therefore, the dendimer was $(31.8/32)\times100=99.4\%$ covered, practically *monodispersed*, thus confirming the NMR analysis, which indicated 100% coverage. ^1H NMR ($CDCl_3$): δ 1.53 (br.s.), 2.26 (br.s.), 2.36 (br.s.), 3.39 (br.s.), 6.82 (s), 7.22 (s), 7.91 (s), 8.82 (s), 8.9 (vw. s); ^{31}P NMR ($CDCl_3$): δ −13.82 (major: *anti*), −11.62 (minor: *syn* or occluded starting *o*-diphenylphosphinobenzaldehyde).
8. Udenfriend, S.; Stein, S.; Böhlen, P.; Dairman, W.; Leimgruber, W.; Weigele, M. *Science* **1972**, *178*, 871.
9. Antonaroli, S.; Crociani, B. *J. Organomet. Chem.* **1998**, *560*, 137.
10. Frohning, C. D.; Kohlpainter, C. W. In *Applied Homogeneous Catalysis with Organometallic Compounds*, Cornils, B.; Herrmann, W. A., Eds.; VCH, Weinheim, 1996; Vol. 1, Chapter 2.1
11. Peori, M. B.; Kakkar, A. K. *Organometallics* **2002**, *22*, 1788.
12. Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449.
13. Koprowski, M.; Sebastián, R.-M.; Maraval, V.; Zablocka, M.; Cadierno, V.; Donnadieu, B.; Igau, A.; Caminade, A.-M.; Majoral, J.-P. *J. Am. Chem. Soc.* **2002**, *21*, 4680.
14. This mixture forms two layers at room temperature, which coalesce at temperatures roughly above 50°C.
15. Formaldehyde in this solvent system most probably exists in the form of CH_3COOCH_2OH.
16. Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *107*, 2941.
17. Beletskaya, I. P.; Cheprakov, A. *Chem. Rev.* **2000**, *100*, 3066.
18. The syntheses of the iminophosphines, **3** and **4**, were carried out by reaction of 2-diphenylphosphinobenzaldehyde with *n*-hexylamine and 2,6-bis(3-pentyl)aniline (see Ref. 19), respectively, in methanol in the presence of a catalytic quantity of formic acid.
19. Steele, B. R.; Micha-Screttas, M.; Screttas, C. G. *Appl. Organomet. Chem.* **2002**, *16*, 501.