

Synthesis and Application of Phosphorus Dendrimer Immobilized Azabis(oxazolines)

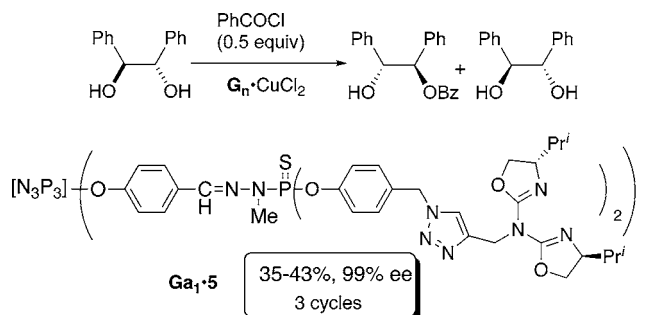
Anja Gissibl,^{†‡} Clément Padié,^{†‡} Markus Hager,^{†‡} Florian Jaroschik,^{†‡}
Ramesh Rasappan,[†] Erick Cuevas-Yañez,[†] Cédric-Olivier Turrin,[‡]
Anne-Marie Caminade,[‡] Jean-Pierre Majoral,^{*,‡} and Oliver Reiser^{*,†}

Institut für Organische Chemie, Universität Regensburg, Universitätsstrasse 31,
93053 Regensburg, Germany, and Laboratoire de Chimie de Coordination du CNRS,
205 route de Narbonne, 31077 Toulouse cedex 4, France

oliver.reiser@chemie.uni-regensburg.de; majoral@lcc-toulouse.fr

Received May 15, 2007

ABSTRACT



Phosphorus dendrimer immobilized azabis(oxazoline) ligands can be efficiently synthesized up to the third generation with 48 ligand molecules being attached to the periphery using click chemistry. The so-assembled macromolecules were evaluated in copper(II)-catalyzed asymmetric benzoylations, showing good yields and enantioselectivities. Moreover, the copper(II)-catalysts could be readily recovered and reused in several cycles. The globular structure of the dendritic ligands seems to prevent interference of the triazole moieties in the catalysis, contrasting MeOPEG or polystyrene bound ligands of the same type.

Azasemicorrins¹ and bis(oxazolines)^{1,2} have proven to be privileged classes of chiral ligands, being able to form complexes with a broad variety of metals that are able to catalyze a great number of reactions with unparalleled enantioselectivity. Owing to the success of bis(oxazoline) ligands, more recently their immobilization on various supports has been intensively studied.³ As a general trend it

is observed that bis(oxazolines) grafted on soluble supports such as poly(ethylene glycole) behaved similarly to their non-immobilized counterparts; however, an efficient recovery is often problematic and requires large amounts of solvents from which the catalysts can be precipitated. On the other hand, immobilization of bis(oxazoline) ligands on heterogeneous supports such as polystyrenes allows efficient recovery by simple filtration; however, selectivities and especially yields are often drastically reduced. Azabis-(oxazolines)⁴ have proved to be especially suitable ligands for attachment onto supports owing to their strong binding

[†] Universität Regensburg.

[‡] Laboratoire de Chimie de Coordination du CNRS.

(1) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.

(2) (a) Lowenthal, R.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (b) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (c) Corey, E. J.; Imai, N.; Zhang, H. Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. For recent reviews see: (d) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151. (e) Desimoni, G.; Faita, G.; Jorgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.

(3) Rechavi, D.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 3467.

(4) (a) Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045. (b) Werner, H.; Vicha, R.; Gissibl, A.; Reiser, O. *J. Org. Chem.* **2003**, *68*, 10166. (c) Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005**, *7*, 2325. (d) Werner, H.; Herreras, C. I.; Glos, M.; Gissibl, A.; Fraile, J. M.; Perez, I.; Mayoral, J. A.; Reiser, O. *Adv. Synth. Catal.* **2006**, *348*, 125.

to metals and therefore greatly reduced leaching when they are used in repeating cycles in catalyses.⁵

Dendrimers might offer an attractive alternative for the immobilization of catalysts, combining homogeneity but also ease of recovery owing to their solubility properties and, moreover, offer the additional potential for continuous processes through confining them by size exclusion in a membrane reactor. However, the defined build-up of dendrimers is often laborious and low yielding because of purification problems.

We report here that phosphorus dendrimers, which can be reliably constructed up to eight generations (1536 terminal functional groups) with high purity⁶ are excellent cores for dendrimer bound azabis(oxazoline) ligands.⁷ Moreover, we demonstrate that the copper-catalyzed⁸ azide-alkyne cycloaddition⁹ (CuAAC) reaction can be used as a superior immobilization strategy to ligate aza(bisoxazoline) ligands onto such dendrimers.¹⁰

We initially wanted to make use of the high reactivity of P(S)Cl₂ groups with phenols to attach dendrimers **G**₁–**G**₃ (Figure 1) to azabis(oxazoline) ligands being modified by a

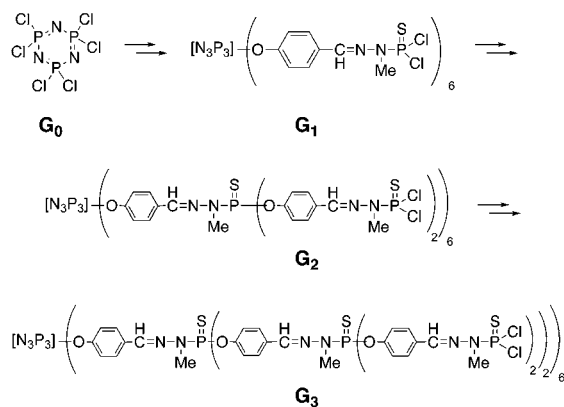


Figure 1. Dendrimers generation **G**₀–**G**₃ with P(S)Cl₂-end groups.

suitable phenolic linker (Scheme 1). Benzylation of the central nitrogen of azabis(oxazoline) **1** generally works well,⁴ however, such a connection with a 4-hydroxybenzyl group

(5) (a) Fraile, J. M.; García, J. I.; Harmer, M. A.; Herreras, C. I.; Mayoral, J. A.; Reiser, O.; Werner, H. *J. Mater. Chem.* **2002**, *12*, 3290. (b) Fraile, J. M.; García, J. I.; Herreras, C. I.; Mayoral, J. A.; Reiser, O.; Socuéllamos, A.; Werner, H. *Chem.–Eur. J.* **2004**, *10*, 2997. (c) Fraile, J. M.; García, J. I.; Herreras, C. I.; Mayoral, J. A.; Reiser, O.; Vaultier, M. *Tetrahedron Lett.* **2004**, *45*, 6765.

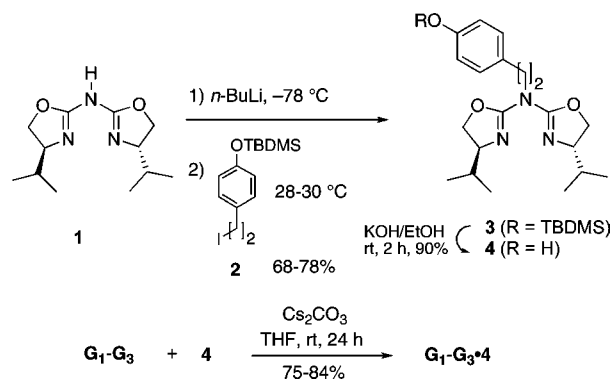
(6) (a) Caminade, A.-M.; Majoral, J.-P. *Acc. Chem. Res.* **2004**, *37*, 341. (b) Launay, N.; Caminade, A.-M.; Majoral, J.-P. *J. Organomet. Chem.* **1997**, *529*, 51.

(7) Achiral dendritic bis(oxazoline)copper(II) catalysts have been reported: Chow, H.-F.; Mak, C. C. *J. Org. Chem.* **1997**, *62*, 5116.

(8) (a) Tornøe, C. W.; Meldal, M. In *American Peptide Symposium*; Lebl, M., Houghten, R. A., Eds.; American Peptide Society and Kluwer Academic Publishers: San Diego, CA, 2001, p 263. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (d) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192. (e) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.

(9) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613.

Scheme 1. Synthesis of Azabis(oxazoline)-Containing Dendrimers **G**₁–**G**₃•**4**



proved to be highly labile and therefore not suitable. A stable linkage with a phenol moiety was achieved with the synthesis of **4**; however, the reaction between **1** and **2** was extremely sensitive to the reaction temperature, resulting in little conversion below 25 °C and substantial decomposition above 35 °C, which made the scale-up of this reaction difficult.

Nevertheless, **4** proved to be an excellent building block for the ligation with **G**₁–**G**₃, giving rise to dendrimers with 12 (**G**₁•**4**) (Figure 2), 24 (**G**₂•**4**), and 48 (**G**₃•**4**) azabis(oxazoline) ligands on the periphery.

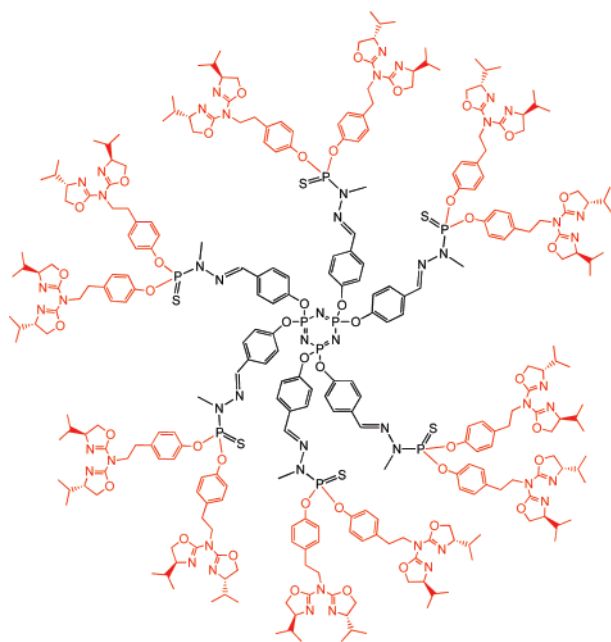
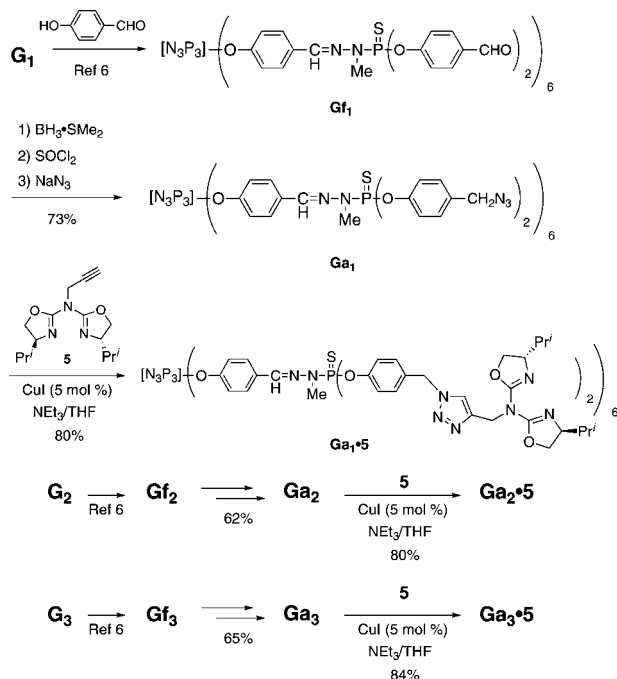


Figure 2. Formula of **G**₁•**4**.

We recently demonstrated that the copper-catalyzed alkyne azide cycloaddition (CuAAC) allows an effective ligation of catalysts and reagents to organic supports.^{4c,11} Applying this concept to P,S-dendrimers and having already azabis(oxazolines) with propargylic linkers in hand required the

synthesis of P,S-dendritic building blocks with a terminal azide functionality (Scheme 2). This seemingly simple task

Scheme 2. Ligation of P,S-Dendrimers and Azabis(oxazolines) by the Copper-Catalyzed Azide–Alkyne Cycloaddition



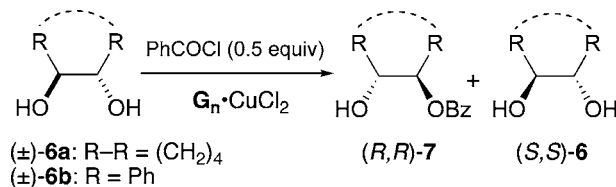
was more problematic than anticipated, since, for example, direct coupling of **G₁** with *p*-hydroxybenzyl azide or 3-azidopropan-1-amine failed, most likely because of a cross reactivity of the dichlorophosphine with the azide group. Since the reaction of **G₀**–**G₃** with *p*-hydroxybenzaldehyde is well established as part of the dendrimer build-up, we envisioned to use the formyl-containing derivatives⁶ **Gf₁**–**Gf₃** as the starting point for P,S-dendrimers with a terminal azide functionality.

Indeed, **Gf₁**–**Gf₃** could be converted with high yields to the azides **Ga₁**–**Ga₃** by reduction of the aldehyde to the corresponding alcohol, followed by chlorination with thionyl chloride and final chloride azide exchange. Ligation of **Ga₁**–**Ga₃** using 1.2 equiv of **5** for each azide group proceeded with excellent efficiency in the presence of 5 mol % CuI¹² to give **Ga₁·5**–**Ga₃·5** by precipitation with pentane from the reaction mixture. **Ga₃·5** turned out to be only scarcely soluble in organic solvents, making its characterization

difficult. Nevertheless, the conversion of **Ga₃** could be judged by the complete disappearance of the azide band at 2098 cm^{−1} in the IR spectrum.

To evaluate the new ligands for metal catalysis, we chose the copper(II)-catalyzed asymmetric benzoylation of diols (Table 1) pioneered by Matsumura and co-workers.¹³ From

Table 1. Copper(II) Catalyzed Asymmetric Benzoylation of Diols with Dendrimer Bound Azabis(oxazoline) Ligands^a



entry	substrate	ligand	cycle	yield ^b 7 %	selectivity 7 %ee
1	6a	1	1	45	70
2	6a	3	1	35	80
3	6a	G₁·4	1	34	78
4	6a	G₁·4	1	34	76
5	6a	G₂·4	1	41	80
6	6a	G₂·4	2	32	73
7	6a	G₂·4	3	36	54
8	6a	G₃·4	1	40	73
9	6a	Ga₁·5	1	31 ^c	73 ^c
10	6a	Ga₁·5	2	30 ^c	82 ^c
11	6a	Ga₁·5	3	34 ^c	85 ^c
12	6a	Ga₂·5	1	28 ^c	86 ^c
13	6a	Ga₂·5	2	32 ^c	80 ^c
14	6a	Ga₂·5	3	35 ^c	82 ^c
15	6a	Ga₃·5	1	30	33
16	6a	Ga₃·5	2	18	38
17	6a	Ga₃·5	3	27	34
18	6b	Ga₁·5	1	35 ^c	99 ^c
19	6b	Ga₁·5	2	43 ^c	99 ^c
20	6b	Ga₁·5	3	41 ^c	99 ^c
21	6b	Ga₂·5	1	36 ^c	99 ^c
22	6b	Ga₂·5	2	45 ^c	99 ^c
23	6b	Ga₂·5	3	41 ^c	95 ^c
24	6b	Ga₃·5	1	39	83
25	6b	Ga₃·5	2	38	85
26	6b	Ga₃·5	3	28	23

^a Reagents and Conditions: 5 mol % CuCl₂, 5 mol % ligand **1** or **3** or 10^{−3} to 10^{−2} mol % (5 mol % end groups) dendritic ligands, 1.0 equiv **6**, 0.5 equiv PhCOCl, CH₂Cl₂, 3 h, 0 °C. ^b Isolated yield based on **6** (maximum theoretical yield 50%). ^c Average of two runs.

the two different series of dendritic azabox ligands compared, the copper complexes of the **Ga_n·5** series proved to be superior to the **G_n·4** series with respect to recoverability: the former could be precipitated much more easily from hexanes than the latter, most likely because of the very polar triazole moieties present. In fact, **Ga₃·5** was already difficult to apply in the benzoylation reactions because of its low solubility in organic solvents, making **Ga₁·5** and **Ga₂·5** the ligands of

(10) Synthesis of functional dendrimers using click chemistry: (a) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928. (b) Wu, P.; Malkoch, M.; Hunt, J. N.; Vestberg, R.; Kaltgrad, E.; Finn, M. G.; Fokin, V. V.; Sharpless, K. B.; Hawker, C. J. *Chem. Commun.* **2005**, 5775. (c) Kehat, T.; Portnoy, M. *Chem. Commun.*, published online 2007, <http://dx.doi.org/10.1039/b703016a>.

(11) (a) Gheorghe, A.; Matsuno, A.; Reiser, O. *Adv. Synth. Catal.* **2006**, *348*, 1016. (b) Gheorghe, A.; Cuevas-Yanez, E.; Horn, J.; Bannwarth, W.; Narsaiiah, B.; Reiser, O. *Synlett* **2006**, 2767.

(12) Löber, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett.* **2003**, *5*, 1753.

(13) Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052.

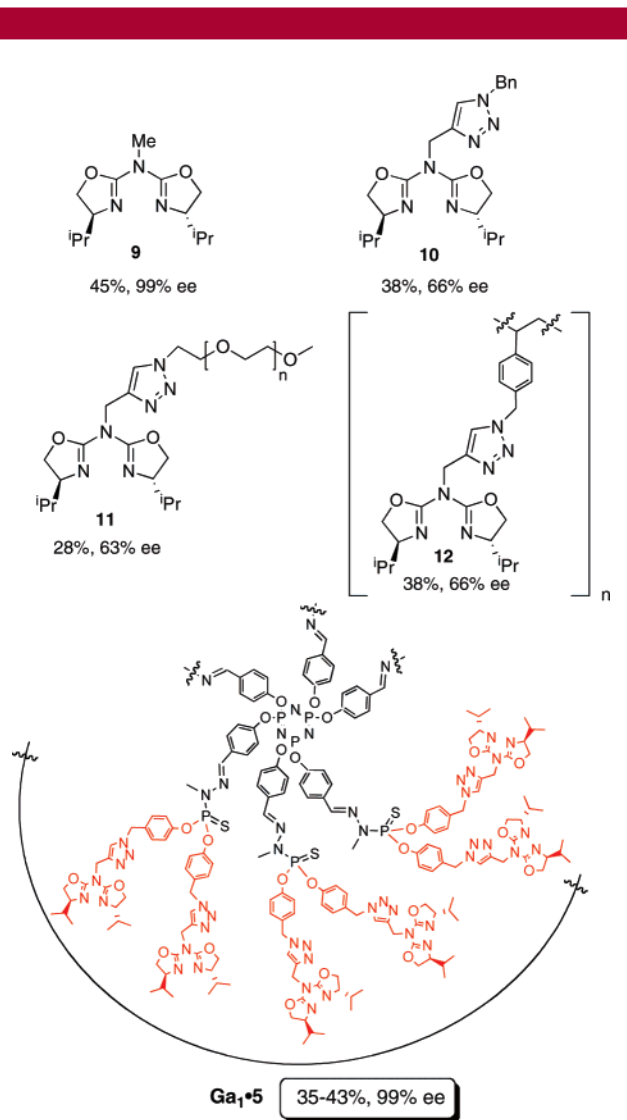


Figure 3. Comparison of ligands for the benzoylation of **6b**. For reaction conditions see Table 1.

choice for the title transformation. Notably, the recovered complexes could be reused without further addition of copper salt, pointing again to the good binding affinity of azabox ligands to metals that minimizes leaching in contrast to the corresponding bis(oxazoline) ligands.⁵

Quite strikingly, the dendritic catalysts could rival or even exceed the parent metal–ligand complexes with respect to selectivity (Figure 3). While with **9** high enantioselectivity in the copper(II)-catalyzed benzoylation of **6b** was achieved, the triazole modified ligand **10^{dc}** alone, bound to MEOPEG **11^{dc}** or polystyrene **12**, gave much inferior results. This can be attributed to the ability of the achiral triazole moiety to coordinate with copper,¹⁴ therefore competing with the chiral oxazoline moieties for the metal. In contrast, both **Ga₁•5** and **Ga₂•5** gave excellent selectivity, each being used in three repetitive runs without a loss of performance (Table 1, entries 18–23). Obviously, the triazole moieties do not interfere with the catalysis, which could be an indication that owing to the globular structure of the dendrimers only the azabox end groups are exposed enough to coordinate with copper and/or to consequently perform the catalysis.

In conclusion, we have developed a facile method for the synthesis of dendrimer bound azabis(oxazoline) ligands using copper-catalyzed azide-alkyne cycloaddition. Depending on the generation, the dendritic ligands seem to be promising in metal-catalyzed processes, as was demonstrated for the copper(II)-catalyzed benzoylation. A special advantage seems to be the globular structure of the dendritic ligands which prevents interference of the triazole moieties in the catalysis, contrasting immobilized azabis(oxazolines) being attached in an analogous fashion to linear polymers.

Acknowledgment. This work was supported by the DAAD (Procope travel grants (C.P., A.G., M.H.) and fellowships for R.R. and E.C.), the International Doktorandenkolleg NANOCAT (Elitenetzwerk Bayern), the Fonds der Chemischen Industrie, and through generous chemical gifts by Degussa Rexim, Degussa AG.

Supporting Information Available: Experimental procedures, spectroscopical data, and copies of ¹H and ¹³C spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL071128P

(14) (a) Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. *Org. Lett.* **2006**, *8*, 6099. (b) For a related observation on the addition of zincorganyls to aldehydes see: Bastero, A.; Font, D.; Pericas, M. A. *J. Org. Chem.* **2007**, *72*, 2460.