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A third generation chiral phosphorus-containing dendrimer as ligand in Pd-catalyzed asymmetric allylic alkylation

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Abstract—The synthesis of a third generation phosphorus-containing dendrimer possessing 24 chiral iminophosphine end groups derived from (2*S*)-2-amino-1-(diphenylphosphinyl)-3-methylbutane is described. In situ complexation of this dendrimer by $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ affords a catalyst, which is used in asymmetric allylic alkylations of *rac*-(*E*)-diphenyl-2-propenyl acetate and pivalate. The percentage of conversion, the yield of isolated 2-(1,3-diphenylallyl)-malonic acid dimethyl ester, and its enantiomeric excess have been measured in each case, and were found to be good to very good (ee from 90% to 95%). Furthermore, the dendritic catalyst can be recovered and reused at least two times, with almost the same efficiency.

Dendrimers constitute an outstanding new field of researches in chemistry,[1] which produces about one thousand publications each year since the last three years. The remarkable development of this subject is both due to the so aesthetic structure of these well defined hyperbranched macromolecules, and to their numerous properties in diverse fields such as new materials,[2] biology[3] and catalysis.[4] The latter application has been recognized very early,[5] and a large number of dendritic catalysts have been synthesized and studied since these pioneering works. Dendrimers bearing catalytic units as end groups can combine both the best features of homogeneous and heterogeneous catalysts, since they are both easily soluble and easily recoverable by precipitation or filtration through a membrane.

A variety of phosphine complexes as end groups have attracted much attention in the field of dendritic catalysts,[6] but few of them have found application in asymmetric catalysis to date.[7] We are interested since a long time in the synthesis of phosphorus-containing dendrimers[8] bearing phosphine complexes as end groups,[9] and we have shown previously, the use of some of them as catalysts in Knoevenagel condensations, Stille couplings and Michael additions.[10] In most cases, a slightly positive dendritic effect was observed. We have shown also in the case of a diastereoselective Michael addition that the ratio of diastereoisomers was the same using a monomeric catalyst or dendritic catalysts, showing that both activity and selectivity features were preserved in the dendrimer.

These first results encouraged us to tackle the field of enantioselective catalysis. For this purpose, we decided to use P,N-ligands.[11] We choose (2*S*)-2-amino-1-(diphenylphosphinyl)-3-methylbutane **2**[12] as P,N-iminophosphine ligand, synthesized according to a previously described procedure.[13] The condensation reaction was first carried out with *p*-methoxybenzaldehyde to afford the model compound **3** ($MeO\text{–}C_6H_4CH{=}N\text{–}CH(iPr)\text{-}CH_2PPh_2$). The same type of condensation reaction was then conducted with 24 equiv of compound **2** and 1 equiv of the third generation of the dendrimer **1-G$_3$**. The reaction proceeds gently overnight at room temperature to yield the chiral dendrimer **3-G$_3$** isolated in 88% yield after work up as a white powder, very sensitive to oxidation (Scheme 1). The reaction of all the end groups is shown by the disappearance of the signals corresponding to the aldehydes in ^{1}H NMR, ^{13}C NMR and IR spectrometries (diastereotopy is observed for the expected signals in ^{13}C NMR).[14]

Having in hand this chiral dendrimer, we decided to use it in asymmetric allylic alkylations. Even if this field is not as thoroughly developed as catalysis involving transfer of oxygen or of molecular hydrogen, the synthetic

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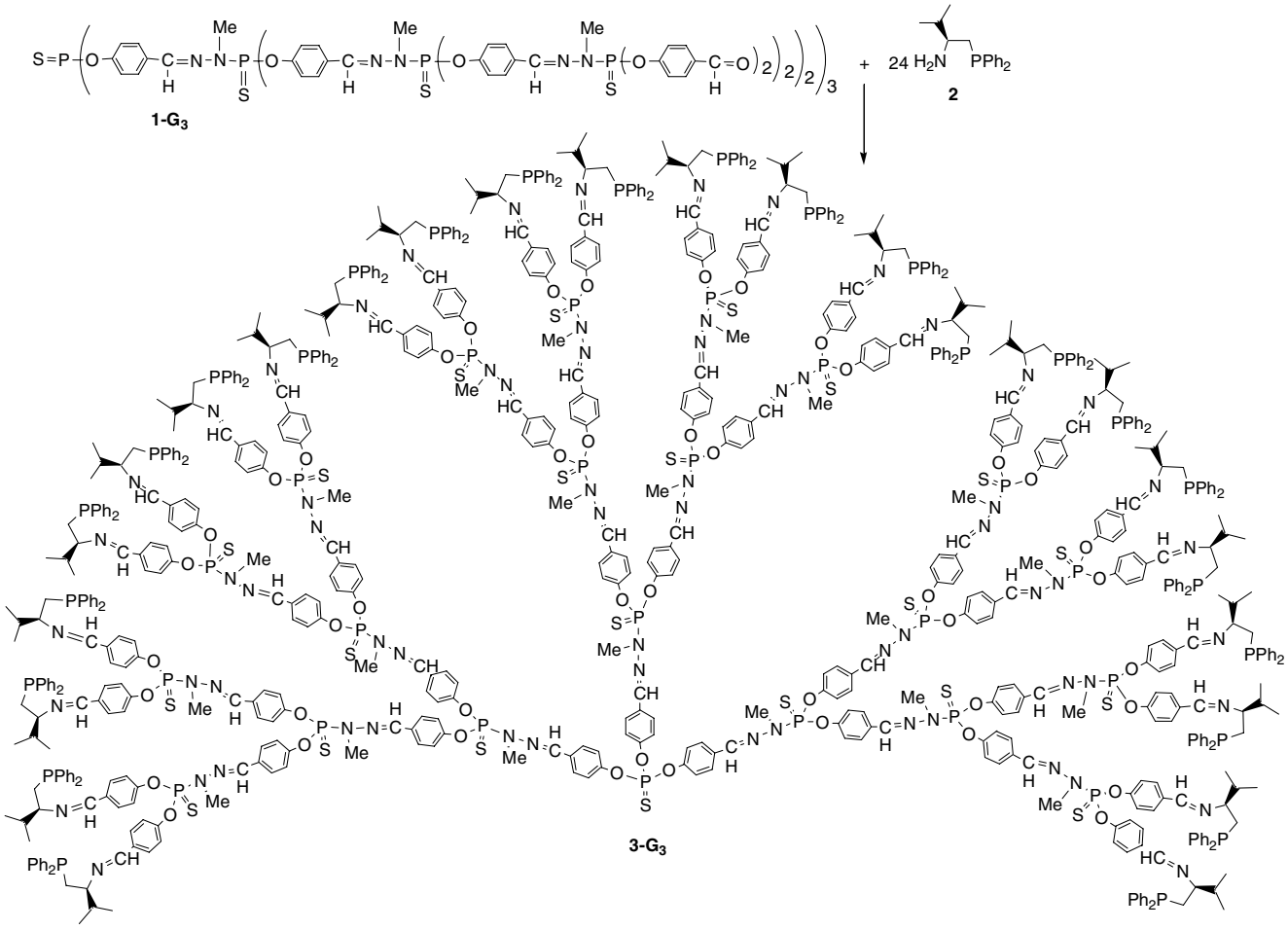


Scheme 1. Synthesis of the chiral dendrimer **3-G$_3$**.

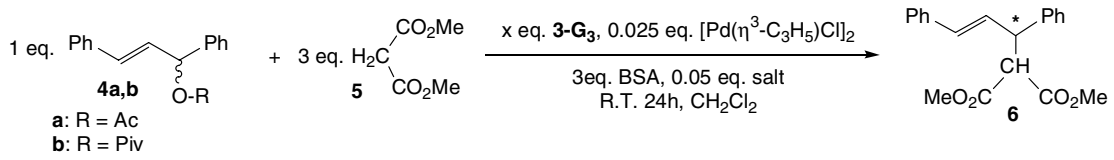
utility of allylic alkylations has been soundly demonstrated,[15] in particular for their usefulness in total synthesis.[16] Furthermore, monomeric iminophosphine ligands derived from compound **2** have already been used in Pd-catalyzed allylic alkylations.[12,13b,17]

The conditions we used are derived from the Trost and Murphy's procedure[18] and are shown in Table 1. Experiments were carried out either with *rac*-(*E*)-diphenyl-2-propenyl acetate (**4a**) or pivalate (**4b**), using *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as base and either LiOAc or KOAc as catalyst to produce the nucleophile from dimethylmalonate **5**. The palladium catalyst is synthesized in situ, by mixing **3-G$_3$** with [Pd(η^3-C_3H_5)Cl]$_2$ in CH_2Cl_2 with a stoichiometry of either one Pd per each P,N-end group of **3-G$_3$**, or one Pd per two P,N-end groups. This mixture is immediately added via canula to the solution containing all the other reagents and reactives. In all cases, the ratio **4a**,**b**/Pd is 1/0.05. An analogous experiment has been carried out with the model compound **3**, used instead of **3-G$_3$**. In all cases, the percentage of conversion was determined by ^{1}H NMR, by integration of the signals corresponding to the methyl groups of **5** and **6**. It was found always of 100% after 24 h. In order to determine if 24 h are really needed to go to completion, we measured the rate of conversion in CH_2Cl_2, also by ^{1}H NMR; the result is plotted in Figure 1 (black squares) for the conversion of **4a**, in the presence of KOAc.

Et_2O is added to the reaction mixture when the reaction has gone to completion, to precipitate an orange powder, whereas 2-(1,3-diphenylallyl)-malonic acid dimethyl ester **6** remains in solution. It is isolated in very good to excellent yields, as previously described,[19] by chromatography.[20] The enantiomeric excess of **6** is determined by ^{1}H NMR in $CDCl_3$ using europium tris[3-(heptafluopropylhydroxymethylene)-(+)-camphorate] as NMR shift reagent, by integration of the methyl groups. The ee is good to very good in all cases, as could be expected for electron donating groups located at the *para* position on the arylimino group.[17a,b] The absolute configuration (*R*) is determined by optical rotation.[17c]

Generally, the main interest of dendritic catalysts is that they can be easily recovered by precipitation. The orange powder isolated by precipitation as indicated above is in fact the dendritic catalyst. This powder is recovered and reused in a catalytic experiment, in the same conditions than described previously, using this orange powder instead of the mixture [**3-G$_3$**–Pd]. The catalytic reaction is also monitored by ^{1}H NMR (Fig. 1, grey rhombus), and goes also to completion after 24 h. However, a slight decrease of the ee is

Table 1.



Entry	Experiment	R	Salt	*x*	N,P/Pd[a]	Conversion (%)	Yield (%)	ee (*R*)
1	1	CH_3CO	KOAc	0.00208	0.05/0.05	100	97	90
2	1st reuse	CH_3CO	KOAc			100	95	82
3	2nd reuse	CH_3CO	KOAc			92	89	82
4	2	CH_3CO	KOAc	0.00208	0.05/0.05	100	97	89
5	3	CH_3CO	KOAc	0.00208	0.05/0.05	98	92	88
6	4	CH_3CO	LiOAc	0.00417	0.1/0.05	100	96	91
7	1st reuse	CH_3CO	LiOAc			100	94	85
8	2nd reuse	CH_3CO	LiOAc			98	92	84
9	5	$(CH_3)_3CCO$	LiOAc	0.00417	0.1/0.05	100	95	95
10	1st reuse	$(CH_3)_3CCO$	LiOAc			97	92	94
11	2nd reuse	$(CH_3)_3CCO$	LiOAc			90	87	92
12	6	$(CH_3)_3CCO$	LiOAc	0.00417	0.1/0.05	100	96	92
13	7	$(CH_3)_3CCO$	LiOAc	0.00417	0.1/0.05	98	93	90
14	**3** instead of **3-G$_3$**	CH_3CO	KOAc	0.05	0.05/0.05	100	92	80

[a] N,P/Pd: ratio iminophosphine end group per metal.

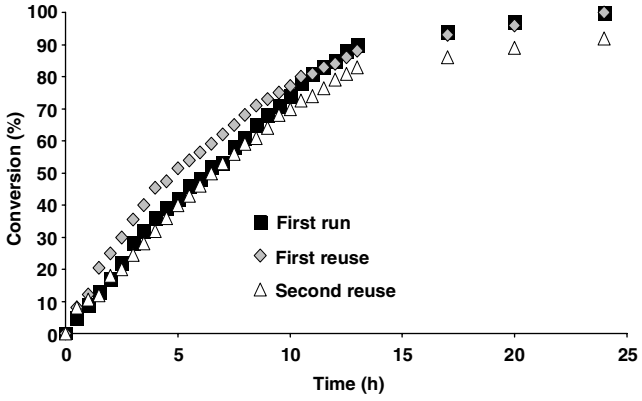


Figure 1. Allylic alkylation of **4a** induced by the catalyst [**3-G$_3$**–Pd] measured by ^{1}H NMR (integration of Me groups of **5** and **6**).

observed (Table 1, entry 2). The procedure of recovery of the catalyst used previously is applied again, and the catalyst (orange powder) is used again in a third experiment (Fig. 1, black and white triangles). In this case, the percentage of conversion is slightly lower (Table 1, entry 3), and the ee is identical to what was obtained in the first reuse.

In order to check both the reproducibility of the first experiment and the stability of dendrimer **3-G$_3$** with time, two other experiments have been carried out several months later, exactly in the same conditions than for the first experiment. The results obtained show a very good reproducibility and the stability of the dendrimer (kept at −15 °C) (Table 1, entries 1, 4 and 5).

An experiment has been carried out with the monomer **3** (Table 1, entry 14) instead of the dendrimer **3-G$_3$**, using exactly the conditions already used in entries 1, 4 and 5. The results concerning the percentage of conversion and yield are analogous, but the enantiomeric excess is slightly lower with the monomer. Furthermore, it is impossible to recover and to reuse the monomeric catalyst [**3**–Pd], contrarily to [**3-G$_3$**–Pd].

New experiments have been carried out with the dendrimer **3-G$_3$** to try to enhance the enantiomeric excess, by changing several parameters. First, LiOAc is used instead of KOAc, and the amount of dendrimer is increased twice, for the same amount of palladium (Table 1, entry 6). Practically no difference is observed, compared to the first series of experiments. We also tried to reuse twice the dendritic catalyst; a slightly better result is observed in the third run of this series (Table 1, entry 8), compared to the third run of the first series (entry 3).

Another slight improvement of the enantiomeric excess is observed when the pivalate derivative **4b** is used instead of the acetate **4a**. The best ee value is obtained in this case (95%) (Table 1, entry 9). A first reuse, then a second reuse are carried out as described previously. The rate of these catalyses (first to third runs) were also monitored by ^{1}H NMR; the data are not shown, but they are very similar to those obtained in Figure 1. The reproducibility of this experiment with time has been also checked for this series of experiments (entries 12 and 13). The reproducibility remains very good, even if a slightly lower enantiomeric excess is measured, compared to the first experiment of this series.

In conclusion, dendrimer **3-G$_3$** appears as one of the best P,N-ligand usable for palladium-mediated asymmetric allylic substitutions, in terms of percentage of conversion, yield in isolated products, and enantiomeric excess. Furthermore, contrarily to monomeric catalysts, it can be easily recovered and reused at least two times, with practically the same efficiency.

Acknowledgements

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14. NMR data for dendrimer **3-G$_3$**; the lower case number of atoms corresponds to the generation, the upper case of C refers to the O–Ar groups (O–C^1): ^{31}P {^{1}H} NMR ($CDCl_3$): −20.4 (s, PPh_2), 52.7 (s, P_0), 62.3 (s, P_3), 62.7 (s, P_2), 62.9 (s, P_1); ^{1}H NMR ($CDCl_3$): 0.86 (br s, 144H, CH_3C), 1.89 (m, 24H, $CHMe_3$), 2.42 (m, 48H, CH_2), 2.97 (m, 24H, $CHCH_2$), 3.30 (m, 63H, NCH_3), 7.0–8.0 (m, 465H, $C_6H_4CH{=}N$, C_6H_5). ^{13}C (J_{mod}) NMR (THF-d_8): 18.5 and 20.2 (2s, CH_3–C), 33.3 (br d, $^2J_{CP} = 12.5$ Hz, $CH_3NP_{1,2,3}$), 34.1 (d, $^1J_{CP} = 13.5$ Hz, CH_2P), 35.0 (d, $^3J_{CP} = 9.0$ Hz, $CHCH_3$), 75.3 (d, $^2J_{CP} = 11.0$ Hz, CH–N), 122.3 (d, $^3J_{CP} = 4.3$ Hz, C_3^2), 122.8 (br s, C_0^2, C_1^2, C_2^2), 129.0 (s, C_0^3, C_1^3, C_2^3, C_3^3), 129.1 (s, *p*-C_6H_5), 129.2 (s, C_3^4), 129.3 (d, $^3J_{CP} = 5$ Hz, *m*-C_6H_5), 130.4 (br s, C_0^4, C_1^4, C_2^4), 133.6 and 134.1 (2 d, $^1J_{CP} = 15.0$ Hz, *i*-C_6H_5), 140.2 and 140.5 (2 d, $^2J_{CP} = 19.0$ Hz, *o*-C_6H_5), 140.6 (br m, CH=N–N), 152.6 (br m, C_0^1, C_1^1, C_2^1), 153.3 (d, $^2J_{CP} = 7.0$ Hz, C_3^1), 159.6 (s, $CH{=}N$–C). Anal. Calcd for $C_{744}H_{768}N_{66}O_{45}P_{46}S_{22}$ (13485): C, 66.27; H, 5.74; N, 6.86. Found: C, 66.13; H, 5.68; N, 6.80. ^{31}P {^{1}H} NMR ($CDCl_3$) of the complex [**3-G$_3$**+12[Pd(η^3-C_3H_5)Cl]$_2$]: 32.0 (s, $PdPPh_2$), 52.6 (s, P_0), 62.3 (s, P_3), 62.6 (s, P_2), 62.8 (s, P_1).
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20. In a typical experiment, a solution of **3-G$_3$** (0.002 or 0.004 mmol) and [Pd(η^3-C_3H_5)Cl]$_2$ (0.025 mmol) in CH_2Cl_2 was immediately added to a solution of **4a**,**b** (1 mmol), **6** (3 mmol), BSA (3 mmol), and KOAc or LiOAc (0.05 mmol) in CH_2Cl_2, and stirred for 24 h. Then Et_2O is added to precipitate an orange powder (the dendritic catalyst), which can be reused after filtration in a new catalytic experiment. The remaining solution is washed with saturated NH_4Cl in water; the organic phase is dried over $MgSO_4$, concentrated and purified by column chromatography (pentane–AcOEt, 3:1 as eluent), to afford **6**.