An outstanding palladium system containing a C_2-symmetrical phosphite ligand for enantioselective allylic substitution processes

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The use of efficient Pd systems bearing C_2-symmetric chiral diphosphite ligands derived from carbohydrates in asymmetric allylic substitution reactions is described here, reaching TOFs > 22 000 h^{-1} in allylic alkylation and *ca.* 400 h^{-1} in allylic amination, giving excellent enantioselectivities (ee > 99%) and kinetic resolution of the racemic substrate.

Palladium-catalysed asymmetric allylic substitution is a versatile and widely used process for the enantioselective formation of carbon–carbon and carbon–heteroatom bonds. Over the past decade, high enantiomeric excesses have been achieved for these reactions, mainly using phosphorus and nitrogen based ligands.[1] However, these systems are generally hampered by low reaction rates.[1] In enantioselective allylic substitution reactions, the use of catalysts containing C_1- and C_2-symmetric diphosphite ligands was proved to be efficient.[2] In particular, C_1-diphosphites lead to highly active catalysts (TOF > 3000 h^{-1}) yielding enantioselectivities up to >99%.[2b]

Although allylic substitution reactions have been widely studied, relatively few catalysts have been reported for kinetic resolution.[3,4]

Here, we report the first use of C_2-symmetric chiral diphosphite ligands **1** and **2** (Fig. 1) in asymmetric allylic alkylation and allylic amination reactions using *rac*-1,3-diphenyl-3-acetoxyprop-1-ene, *rac*-**I** as the substrate with evidence for kinetic resolution at low Pd concentrations.

Initially, the Pd-catalysed asymmetric allylic alkylation using dimethyl malonate as a base and *rac*-1,3-diphenyl-3-acetoxyprop-1-ene, *rac*-**I**, as the substrate was investigated with the ligand **1**. The results are collected in Table 1. At low substrate to palladium ratio (entry 1), total conversion was achieved in 10 minutes with 98% ee. Similar results were obtained using the isolated complex [Pd(η^3-C_3H_5)(**1**)]PF_6 as the catalytic precursor (entry 2).† When the substrate/palladium ratio was increased to 5000, 34% conversion was obtained after 5 min of reaction (entry 3, TOF = 20 400 h^{-1}); and after 1 h, 89% conversion was achieved (entry 4, TOF = 4450 h^{-1}). In both cases, excellent asymmetric induction was achieved (ee ≥ 96%). To the best of our knowledge, this is the highest TOF value reported for an asymmetric allylic alkylation reaction. Interestingly, the monitored reaction (analyses at up to 2 h of reaction) using a substrate to palladium ratio of 10 000 gave a constant substrate conversion of 55% (entries 5–7) with a TOF = 22 000 h^{-1} after 15 minutes of reaction. The ee of the product **II** was 98% and optically pure (*S*)-**I** remained for the unreacted substrate. To demonstrate the difference in reactivity between both substrate enantiomers, the resulting reaction mixture

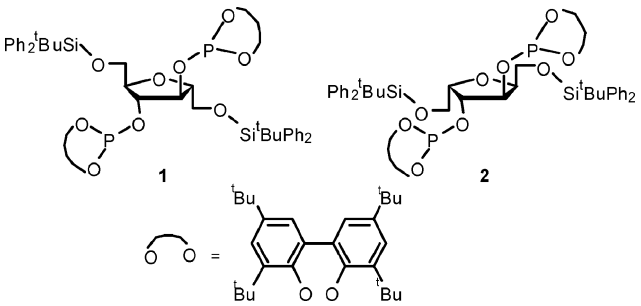
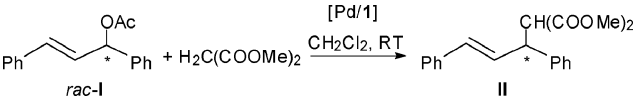


Fig. 1 Chiral diphosphite ligands, **1** and **2**.

Table 1 Pd-catalysed asymmetric allylic alkylation with **1**[a]



Entry	Pd/**1**/*rac*-**I**	Time (min)	Conv. (%)[b]	Ee(**I**) (%)[c]	Ee(**II**) (%)[c]
1	1/1.25/50	10	100	—	98 (*S*)
2[d]	1/1.25/100	30	100	—	98 (*S*)
3	1/1.25/5000	5	34	nd	96 (*S*)
4	1/1.25/5000	60	89	nd	96 (*S*)
5	1/1.25/10000	15	55	99 (*S*)	98 (*S*)
6	1/1.25/10000	30	55	99 (*S*)	98 (*S*)
7	1/1.25/10000	120	55	99 (*S*)	98 (*S*)
8[e]	1/1.25/10000	15	0	—	—
9[e]	1/1.25/10000	1440	20	0	>98 (*S*)

[a] Reaction conditions: 1 mmol of substrate, 3 mmol of dimethyl malonate, 3 mmol of *N*,*O*-bis(trimethylsilyl)acetamide (BSA); Pd/**1** = 0.5 [Pd(μ-Cl)(η^3-C_3H_5)]$_2$ + 1.25 eq. of **1**, a pinch of KOAc in 4 mL of CH_2Cl_2 at room temperature. [b] Conversion determined by ^{1}H NMR analysis. [c] Enantiomeric excess determined by HPLC on a Chiracel-OJ column. Absolute configuration, in parentheses, determined by optical rotation.[5] [d] Catalyst precursor = [Pd(η^3-C_3H_5)(**1**)]PF_6. [e] Mixture of **I** and **II** obtained from entry 7 used as substrate.

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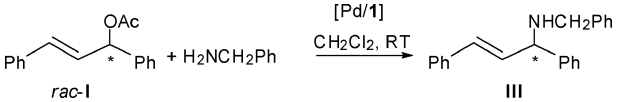
Table 2 Pd-catalysed asymmetric allylic amination with chiral ligand **1**[a]



rac-**I** **III**

Entry	Pd/**1**/*rac*-**I**	Time (h)	Conv.[b] (%)	Ee(**I**)[c] (%)	Ee(**III**)[c] (%)	k(*R*-**I**)/k(*S*-**I**)[d]
1	1/1.25/50	1	100	—	98 (*R*)	—
2	1/1.25/2500	1	16	16 (*S*)	>99 (*R*)	13.4
3	1/1.25/2500	2	26	31 (*S*)	>99 (*R*)	21.6
4	1/1.25/2500	4	40	58 (*S*)	>99 (*R*)	25.8
5	1/1.25/2500	7	55	87 (*S*)	>99 (*R*)	16.4
6	1/1.25/2500	24	60	93 (*S*)	99 (*R*)	13.8

[a] Reaction conditions: 1 mmol of substrate, 1 mmol of benzylamine; Pd/**1** = 0.5 $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ + 1.25 eq. of **1**, in 4 mL of CH_2Cl_2 at room temperature. [b] Conversion determined by ^1H NMR analysis. [c] Enantiomeric excess determined by HPLC on a Chiracel-OD column. Absolute configuration, in parentheses, determined by optical rotation.[5] [d] k_R/k_S = ln[(1 − C/100)(1 − ee/100)]/ln[(1 − C/100)(1 + ee/100)] with C and ee corresponding to the substrate **I**.[7]

containing the enantiopure (*S*)-1,3-diphenyl-3-acetoxyprop-1-ene, (*S*)-**I**, was re-used as the substrate under the same catalytic conditions (entries 8 and 9). After 24 h of reaction, only 20% conversion was observed. This fact evidences that the reaction rate for the transformation of the (*S*)-**I** is more than 100 times slower than that of the corresponding (*R*)-**I** enantiomer, confirming the efficient kinetic resolution that occurred under these conditions.

The same catalytic system was also evaluated in the Pd-catalysed allylic amination using benzylamine as the nucleophile (Table 2). At low substrate to Pd ratio (entry 1), the reaction was completed in 1 h with excellent ee (98%). When this ratio was increased to 2500 (entries 2–5), evidence for kinetic resolution was again observed. Indeed, the ee of the product **III** was constant throughout the reaction ($\geq$ 99%) while that corresponding to the substrate **I** was increasing as the reaction went on (entries 2–6), to reach 93% after 24 h with a substrate conversion of 60% (entry 6). The ratio of the reaction rates for the enantiomers (*R*)-**I** and (*S*)-**I** was found to vary between *ca.* 8 and 26. Concerning the activity, the turn over frequency of the reaction achieves 400 h^{-1} at 16% conversion (entry 2) and *ca.* 250 h^{-1} for a substrate conversion of 40% (entry 4). To the best of our knowledge, this is the highest activity reported for this asymmetric allylic amination process with such high enantioselectivity.

In addition, both the amount and the nature of the nucleophile modify the rate of the allylic substitution. When a large excess of dimethyl malonate in relation to the substrate (*rac*-**I**/dimethyl malonate/BSA = 1/20/20) was used, the catalytic activity dropped significantly (9% conversion *versus* 89% obtained for *rac*-**I**/dimethyl malonate/BSA = 1/3/3 (entry 4, Table 1)). Moreover, this effect was even more remarkable for the allylic amination. Only a moderate excess of benzylamine (*rac*-**I**/benzylamine = 1/3) led to a 15% conversion in comparison with 55% for *rac*-**I**/benzylamine = 1/1 (entry 5, Table 2). This effect could be explained by the slow decomposition of ligand **1** in the presence of a large excess of nucleophile and base, as observed by ^{31}P NMR spectroscopy.

Interestingly, the significant difference in activity for both allylic substitution reactions using identical substrate to nucleophile ratio clearly indicates that the kinetics of the reaction highly depends on the nature of the nucleophile used. These results suggest that the nucleophile not only participates in the selectivity-determining step but could also be involved in the decomposition of the ligand, which competes with the catalytic reaction.

To investigate the effect of the environment around the phosphite moieties, we have also used ligand **2** showing opposite configuration at the C2 and C5 carbon atoms. Surprisingly, very low conversions in the allylic alkylation were obtained with this catalytic system (less than 5% conversion after 1 h of reaction using *rac*-**I**/Pd = 50), independently if the catalyst precursor was the preformed complex $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{2})]PF_6$† or whether it was generated *in situ*. Such a remarkable remote effect was previously reported for ligands **1** and **2** and their diphosphinite analogues in other transition metal catalysed processes.[6] The increased steric hindrance induced by this ligand could explain these observations.

In conclusion, our preliminary results in asymmetric allylic substitution reactions using diphosphite ligands with C_2-symmetry show that the catalytic system containing ligand **1** is highly active, showing the highest turn over frequency values reported for asymmetric allylic alkylation (TOF = 22 000 h^{-1}) and allylic amination (TOF = 400 h^{-1}) processes with excellent ee values for the substituted products, **II** and **III** (up to >98%). Moreover, the effect of the substrate/nucleophile ratio in the activity of these reactions points to a poison effect of the good donor nucleophiles. Furthermore, the results obtained with ligand **2** clearly show that small changes in the ligand structure can drastically affect the catalytic activity. Further kinetic and mechanistic studies are currently on-going and will be reported at a later stage.

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Notes and references

† **Synthesis of complexes $[Pd(\eta^3\text{-}C_3H_5)(1)]PF_6$ and $[Pd(\eta^3\text{-}C_3H_5)(2)]PF_6$.** In a purged Schlenk tube, 9 mg (0.025 mmol) of $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$ and 75 mg (0.05 mmol) of ligand (**1** or **2**) were dissolved in 5 mL of

distilled dichloromethane. The solution was stirred for 30 min at room temperature and 15 mg of NH_4PF_6 (0.09 mmol) dissolved in 1 mL of dichloromethane was then added. After 24 h of stirring, washings with degassed water were carried out (4 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered off and the solvent removed under reduced pressure. The pale yellow solid obtained was washed with diethyl ether (3 × 5 mL) and dried under reduced pressure. Yields: **1**: 83%; yield of **2**: 85%. High resolution LC/ESI-TOF/MS: *m*/*z* (100%) = 1663.7945 ($[M - PF_6]^+$) for both complexes.

[Pd(η^3-C$_3$H$_5$)(1)]PF$_6$: NMR ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.0–7.6 (m, Ph), 5.66 (t, 1H, CH), 5.59 (t, 1H, CH), 5.26 (m, 1H, CH), 4.27 (br s, 2H), 3.98 (br s, 2H), 3.71 (d, 2H), 3.33 (d, 2H), 1.45 (s, 18H), 1.40 (s, 18H), 1.32 (s, 18H), 1.25 (s, 18H), 0.95 (s, 18H); ^{31}P ($CDCl_3$, 101.3 MHz, 298 K) 138.77 ppm (s), −150.9 ppm (PF_6).

[Pd(η^3-C$_3$H$_5$)(2)]PF$_6$: NMR ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 7.2–7.6 (m, Ph), 5.65 (br s, 1H, CH), 5.53 (br s, 1H, CH), 5.02 (m, 1H, CH), 4,61 (br s, 2H), 4.68 (br s, 2H), 3.79 (m, 2H), 3.76 (m, 2H), 1.46 (s, 18H), 1.37 (s, 18H), 1.33 (s, 18H), 1.26 (s, 18H), 0.95 (s, 18H); ^{31}P ($CDCl_3$, 101.3 MHz, 298 K) 140.32 ppm (s), −161.3 ppm (PF_6).

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