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Homogeneous and Heterogeneous Pd-catalyzed Enantioselective Alkylation with C_2-symmetric Chiral Nitrogen Ligands

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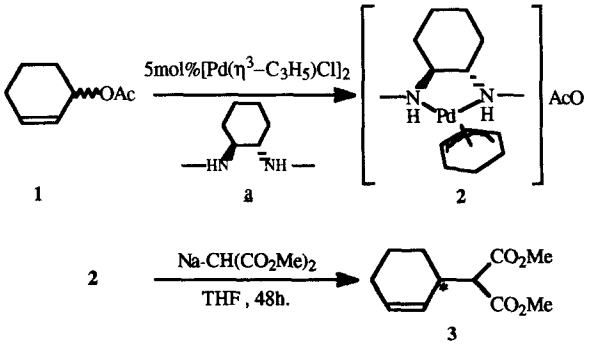
Abstract: several allylic acetates have been enantioselectively substituted by alkylation using (C_2-symmetric chiral diamine)-Pd complexes or (pseudo C_2-symmetric chiral polymer)-Pd complexes with up to 95% and 80% ee respectively.

Carbon-carbon bond formation is one of the most important challenges in organic chemistry and it is fascinating when it is enantioselectively controlled. One reaction to create a carbon-carbon bond is the allylic substitution[1] which was typically catalyzed by phosphine-Pd complexes until 1990 when Togni *et al.* [2] used (-)-sparteine as chiral inductor. Recently, Pfaltz *et al.* [3] have shown the efficiency of the neutral bidentate nitrogen ligands 1-3. High enantiomeric excesses have been obtained with phosphorus-nitrogen ligands[4]. Koga[5], Kang[6] and Tanner[7] have utilized tertiary chiral diamine ligands with σ–donor character for this reaction but the examples are still very scarce. We now report the use of several C_2-symmetric chiral primary to tertiary diamines or diamine derivatives as inducing ligands for asymmetric allylic substitution of different allylic acetates. In addition, the use of primary or secondary amine functions presents the interest for the ligand to be easily heterogenized by polyaddition to a diisocyanate or polycondensation with a diacid chloride. Heterogenization of efficient and stereoselective but rather expensive catalytic complexes is of great interest in order to make their separation easier for a more economical application[8].

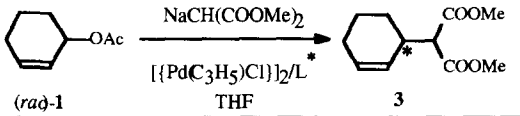
Scheme 1



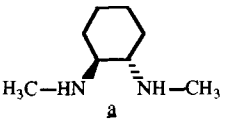
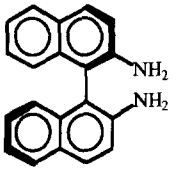
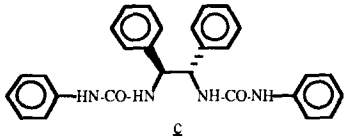
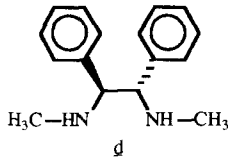
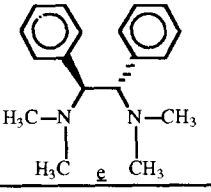
Homogeneous Palladium-Catalyzed Allylic Substitution

First we have evaluated different ligands on the substitution of the challenging cyclohex-2-enyl acetate **1**[9] in the homogeneous phase. The racemic cyclohex-2-enyl acetate **1** reacts with 5mol% of allylic palladium chloride dimer and 10mol% of the N,N'-dimethylcyclohexyldiamine a to give the π-allylpalladium complex **2** (Scheme 1). The carbonucleophile, the anion of dimethyl malonate, attacks the palladium complex **2** to give the cyclohex-2-enyldimethylmalonate **3** in a good yield and with 5% enantiomeric excess (Table 1, entry 1). The results obtained with other primary, secondary and tertiary chiral C_2-diamines are shown in Table 1. We have also tested the urea function as ligand (Table 1, entry 3) with the diurea c with the aim to prepare insoluble polymers.

Table 1. Chiral Diamines Used as Inducing Agents in the Allylic Substitution



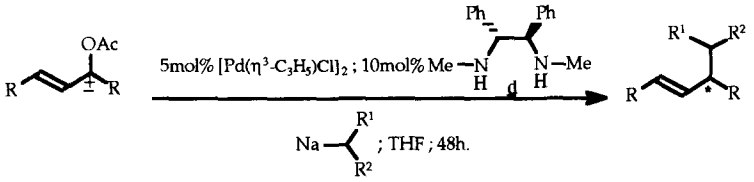
(*rac*)-**1** **3**

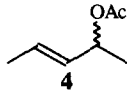
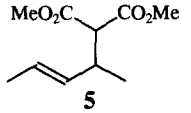
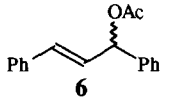
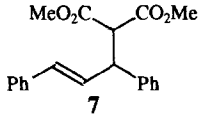
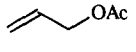
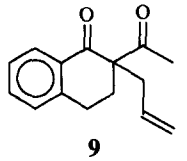
Entry	Ligand L*	Yield[a] [%]	Enantiomeric Excess[%][b] (Configuration)
1	 a	90	5 (S)
2	 b	40	2 (R)
3	 c	12[c]	7 (R)
4	 d	85	16 (S)
5	 e	83	10 (S)

a) Isolated yield after a reaction time of 48h. b) ee measured by polarimetry ($[\alpha]_D^{25}$= +105.4 (c=10, hexane))[10]. c) after a reaction time of 12 days.

Although the observed ee is low when using diurea c, this experiment shows that this type of functional group appears to be a potential ligand. The use of (R)-(+)-1,1'-binaphthyl-2,2'-diamine b (Table1, entry 2) has led to only 2% ee with 40% conversion. This lack of enantioselectivity can be explained by the absence of chirality of the nitrogen bond to the palladium. We have recently shown[11] the importance for the nitrogen to be differently substituted in hydride transfer reductions with rhodium (I) as metal. We consider that it is the case too with the palladium when ligand e, having two methyl groups on the nitrogen atom, leads to 10% ee while ligand d, differently substituted on the nitrogen atom, leads to a higher ee (Table 1, entries 4 and 5). The best result is obtained with the N,N'-dimethyl-1,2-diphenylethylenediamine d (Table1, entry 4) where a yield of 85% is achieved with 16% ee for the 2-cyclohex-2-enyl-malonic acid dimethyl ester **3**. No carbon-nitrogen bond formation due to a nucleophilic attack of the ligand is observed. We then used the diamine d as chiral inductor in the homogeneous allylic substitution of different allylic acetates. The results are reported in Table 2.

Table 2. Homogeneous Alkylation of Allylic Acetates



Entry	Acetate	Product	Yield[%]	Enantiomeric Excess [%] (Configuration)
1	 **4**	 **5**	84	47(S)[a]
2	 **6**	 **7**	90	95(S)[b]
3	 **8**	 **9**	51	30(-)[c]

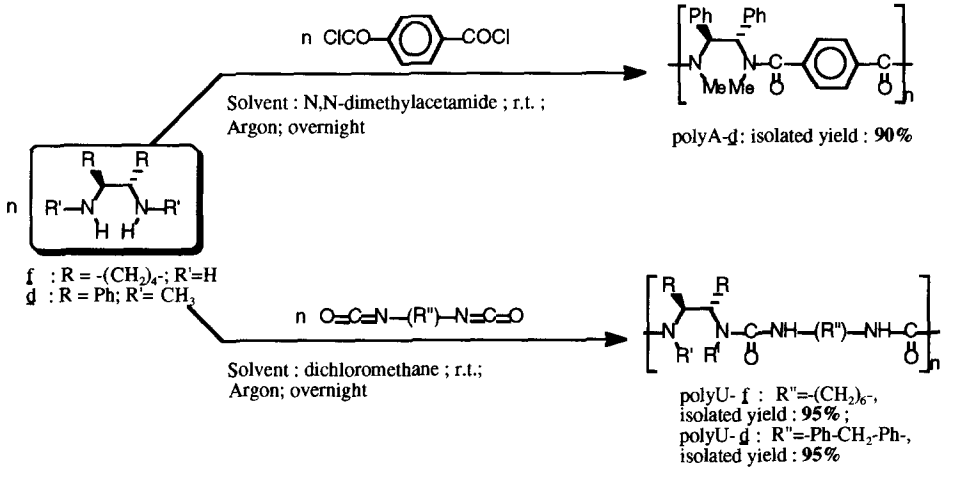
a) $[\alpha]_D^{22}$=-22.4 (c=1, $CHCl_3$)[6,12] b) ee determined by HPLC with a chiral column (ASTEC, CYCLOBOND I (β), methanol / water = 4/6) and by polarimetry ($[\alpha]_D^{20}$=-21.3 (c=1.8, $CHCl_3$))[13]. c) $[\alpha]_D^{24}$=-151.2 ($CHCl_3$)[14].

The linear aliphatic pent-3-en-2-yl acetate **4** gave the 2-(1-methyl-but-2-enyl)-malonic acid dimethyl ester **5** with a good yield and a moderate ee (Table 2, entry 1) due to the low steric effect of the methyl groups. Also, a ee of 95% is obtained with the aromatic allylic acetate **6** which leads to the 2-(1,3-diphenyl-allyl)-malonic acid dimethyl ester **7** with a good yield (Table 2, entry 2). The substitution of the allyl acetate by a prochiral carbonucleophile gave the 2-acetyl-2-allyl-1-tetralone **9** with moderate yield and ee (Table 2, entry 3).

Heterogeneous Palladium-Catalyzed Allylic Substitution

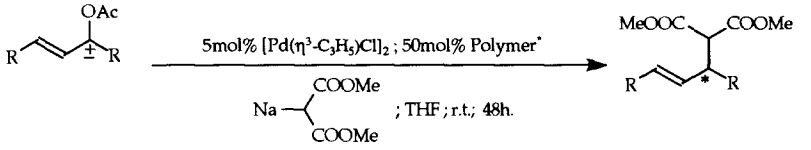
The reaction of a diamine with a diisocyanate or a diacid chloride leads respectively by polyaddition or polycondensation to an insoluble poly(urea) or poly(amide) with excellent yields(Scheme 2).

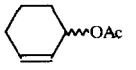
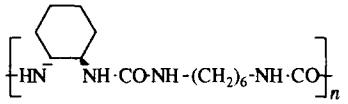
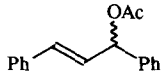
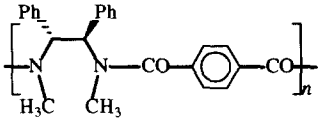
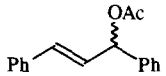
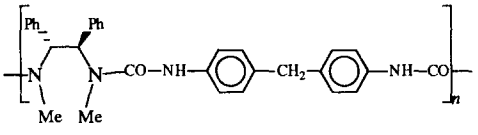
Scheme 2



Both polymerisations were realised at room temperature under an inert atmosphere of argon in *N,N*-dimethylacetamide or dichloromethane. The polymers are used in enantioselective allylic substitution as chiral inductors organic supports. The results are reported in Table 3. In cyclohex-2-enyl acetate **1** alkylation (Table1, entry 4 and Table 3, entry 1), the poly(urea) polyU-f leads to an increase of enantioselectivity from 16 to 25% with the same catalytic activity. Rigidity of the polymer backbone may have a positive effect on the enantioselective recognition on flexible substrates. We often find in the literature the reverse case where the heterogenization leads to a decrease of both activity and selectivity. Poly(amide) polyA-d gives a better ee than poly(urea) polyU-d with a lower conversion (Table 3, entries 2 and 3). In this case, both polymer catalysts are less reactive than the homogeneous one. The heterogeneous catalyst was filtered in order to be re-used. Unfortunately at the end of the allylic substitution, the palladium turns black and the recovered catalyst has no more activity unlike the heterogeneous rhodium complex we used for the hydride transfer reduction of acetophenone[15].

Table 3. Heterogeneous Alkylation of Allylic Acetates



Acetate	Polymer*	Conversion [%]	e.e.[%] (Configuration)
 1	 polyU-f	80	25(R)
 6	 polyA-d	38	80(R)
 6	 polyU-d	72	38(R)

Only a few nitrogen-ligands with σ-donor character have been used up to now for the enantioselective allylic substitution of the allylic acetate **6**[2,5,6] with 99% ee obtained by Tanner[7] with C_2-symmetric bis(aziridines). We have reported here the utilization and the efficiency of such ligands with a secondary amine function for this reaction with up to 95% ee obtained which is similar or higher to those achieved with phosphines[16]. It is also the first time, to our knowledge, that a urea function has been employed to complex a metal used in catalysis and moreover in its polymer form: we have achieved the first carbon-carbon bond formation in heterogeneous phase with enantioselective control.

EXPERIMENTAL

General. THF (*Aldrich*) was distilled from Na/benzophenone. *N,N*-dimethylacetamide 99%, chloroform 99.9%, HPLC grade: *Aldrich*; dichloromethane, HPLC grade: *Carlo erba*; *i*-PrOH: *Prolabo Normapur*, hexane 99%+, pentane 99%, dimethyl malonate 97%, 2-acetyl-1-tetralone, phenyl isocyanate 99%: *Janssen*; allyl acetate **8** 99%, 2-cyclohexen-1-ol 95%, 3-penten-2-ol 96%, 1,6-diisocyanatohexane 98%, 4,4'-methylenebis(phenyl isocyanate) 98%, (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine b 99%, (1*R*, 2*R*:)-(-)-1,2-diaminocyclohexane 98% f, (1*S*, 2*S*)-(-)-1,2-diphenylethylenediamine: *Aldrich;* terephtaloyl chloride, [{(η^3-C_3H_5)PdCl}$_2$]: *Fluka*; cyclohex-2-enyl acetate **1**, pent-3-en-2-yl acetate **4** and (E)-1,3-diphenylpropen-2-yl

acetate **6** were synthetized using literature procedures[17]. Ligands a, d and e were synthetised according to procedures already described[18]. Reactions were carried out under argon using dried glassware.TLC: silica gel 60 *Merck*, 0.2 mm, F-254, staining with iodine or under UV light. PLC: silica gel 60 *Merck*, 2 mm, F-254. Specific rotation: *Perkin-Elmer-241* polarimeter; l = 10 cm; 25°C, concentration in g/100 mL, estimated error: ±5%. Melting points were determined on a *Perkin-Elmer-DSC-7* apparatus. Infrared spectra were recorded on a *Perkin-Elmer-1720-X* spectrometer: selected bands in cm^{-1}. NMR ($CDCl_3$): spectra were recorded on a *Bruker-AM200-Fourier transform* spectrometer, δ in ppm *vs.* TMS, *J* in Hz; ^1H: 200 MHz, ^{13}C: 50 MHz.

Urea Synthesis. *(+)-(1S,2S)-N,N'-dimethyl-1,2-diphenylethylenyl-diphenyl-diurea* c. A solution of 0.5 g (2.36 mmol) of (1*S*, 2*S*)-(-)-1,2-diphenylethylenediamine in 5 mL of dichloromethane was stirred until the diamine was completely dissolved. 0.562 g (4.72 mmol) of phenyl isocyanate in 5 mL of dichloromethane were added to the solution. The reaction was exothermic. The solution was stirred overnight at room temperature. The diurea was precipited in pentane, filtered through a *Millipore* filter (vv type, pore size 0.10 μm) and washed with 200 mL of pentane. Finally, it was dried under vacuum (P=0.1 mmHg). Isolated yield: 97%. Mp 128°C. $[\alpha]^{25}_D$=+405 (c=2, $CHCl_3$). IR: 3437, 3330, 3058, 3029, 2960, 2926, 1644, 1595, 1530. ^1H-NMR: 2.78 (s, N-CH_3), 6.42 (s, N*H*), 6.52 (s, C*H*), 7.00-7.38 (m, 20H). ^{13}C NMR: 29.8 (NCH_3), 55.0 (*C*H), 119.7-139.6 (*C*arom.), 155.9 (*C*O).

Homogeneous Palladium-Catalyzed Allylic Substitution. Typical procedure: a mixture of 10 mol% of (1S,2S)-N,N'-dimethylcyclohexyldiamine a (40.5 mg, 0.285 mmol) and 5 mol% of allylic palladium chloride dimer (26 mg, 0.135 mmol) in THF (5 mL) was treated with one equivalent of racemic acetic acid cyclohex-2-enyl ester **1** (388 μL, 2.69 mmol). Then, 1.5 equivalent of sodium dimethyl malonate (4.035 mmol) freshly prepared from NaH (96.8 mg, 4.035 mmol) and dimethyl malonate (461 μL, 4.035 mmol) in THF (5 mL) is added. The reaction is monitored by GC. After a reaction time of 48 hours, the crude is treated with methanol and purified over a Pre-Coated PLC plate (SILICA GEL 60 F-254, MERCK Art.5717) by elution with a mixture of heptane and ethyl acetate (6 : 4).

(-)-(S)-cyclohex-2-enyldimethylmalonate **3.** Isolated yield: 85%. $[\alpha]^{25}_D$=-16.9 (c=10, hexane, 16% ee). ^1H-NMR: 1.30-1.43 (m, 1H), 1.51-1.62 (m, 1H), 1.66-1.83 (m, 2H), 1.96-2.02 (m, 2H), 2.84-2.93 (m, 1H), 3.29 (d, *J*=9, C*H*($COOCH_3$)$_2$), 3.75 (s, $COOCH_3$), 5.48-5.51 (m, *H*C=CH), 5.72-5.81 (m, HC=C*H*). TLC: R_f=0.39 (heptane/EtOAc 6:4).

(-)-(S)-2-(1-methyl-but-2-enyl)-malonic acid dimethyl ester **5.** Isolated yield: 84%. $[\alpha]^{25}_D$=-10.7 (c=1, $CHCl_3$, 47% ee). ^1H-NMR: 1.06 (d, *j*=6.8, 3H), 1.63 (d, *J*=6.5, 3H), 2.81-3.00 (m, 1H), 3.26 (d, *J*=9, C*H*($COOCH_3$)$_2$), 3.70 (s, $COOCH_3$), 3.72 (s, $COOCH_3$), 5.29-5.57 (m, 2H). TLC: R_f=0.46 (heptane/EtOAc 6:4).

(-)-(S)-2-(1,3-diphenyl-allyl)-malonic acid dimethyl ester **7.** Isolated yield: 90%. $[\alpha]^{25}_D$=-21.3 (c=1.8, $CHCl_3$, 95% ee (HPLC)). ^1H-NMR: 3.52 (s, $COOCH_3$), 3.72 (s, $COOCH_3$), 3.95 (d, *J*=11, C*H*($COOCH_3$)$_2$), 4.25 (dd, *J*=8.4 and *J*=11.1), 6.33 (dd, *J*=8.4 and *J*=15.8), 7.15-7.37 (m, 10H). TLC: R_f=0.43 (heptane/EtOH 13:7). HPLC: t_R=6 min (*R*), 12 min (*S*) (Astec cyclobond 1, MeOH/water 4:6, 1.5 mL/min, 250 nm).

(-)-2-acetyl-2-allyl-1-tetralone **9.** Isolated yield: 51%. $[\alpha]^{25}_D$=-45.4 (c=1.5, $CHCl_3$, 30% ee). ^1H-NMR: 2.04 (s, 3H), 1.67-2.15 (m, 1H), 2.40-3.35 (m, 3H), 2.63 (d, *J*=7, 2H), 4.95-5.20 (m, 2H), 5.34-5.91 (m, 1H), 7.00-7.53 (m, 3H), 8.01(dd, *J*=2 and *J*=8, 1H). TLC: R_f=0.44 (heptane/EtOAc 9:1).

Poly(amide) synthesis. *polyA*-d. A solution of 1 g (4.16 mmol) of diamine d in 5 mL of *N,N*dimethylacetamide was stirred until the diamine was completely dissolved. 760 mg (3.75 mmol) of terephtaloyl chloride in 5 mL of *N,N*dimethylacetamide were added to the solution which clouded after a few minutes. The solution was stirred overnight at room temperature. Poly(amide) was precipitated in 150 mL of distilled water. It was filtered through a fibrous glass frit, washed with 50 mL of distilled water and twice with 50 mL of *i*-PrOH. Finally, it was dried at 50°C overnight in a vacuum oven (P=15 mmHg). 1.33 g (96%) of a white powder was obtained. *Analytical Data*: Mp 280°C. IR: 3058, 3034, 3006, 2935, 1717, 1601, 1507, 1456, 1407, 1351, 1282, 1090, 762, 702.

Poly(ureas) synthesis. *polyU*-f. A solution of 1 g (8.76 mmol) of diamine f in 20 mL of dichloromethane was stirred until the diamine was completely dissolved. 1.473 g (8.76 mmol) of 1,6-diisocyanatohexane in 5 mL of dichloromethane were added to the solution. The reaction was exothermic. A white precipitate appeared after a few minutes. The solution was stirred overnight at room temperature. The polymer was filtered through a *Millipore* filter (vv type, pore size 0.10 μm) and washed with 200 mL of dichloromethane. Finally, it was dried at 50°C overnight in a vacuum oven (P=15 mmHg). 2.35 g (95%) of poly(urea) polyU-f is obtained as a white powder. *Analytical Data*: Mp 250°C. $[\alpha]^{25}_{D}$=-56.6 (c=5, CF_3COOH). IR: 3346, 2929, 2856, 1636. Inherent viscosity η_{inh}=0.414 (25°C, c=1 g/dL, CF_3COOH).

polyU-d. Isolated yield: 95%. Mp 254°C. $[\alpha]^{25}_{D}$=+330 (c=5, CF_3COOH). IR: 3332, 3062, 3030, 2930, 2857, 1652. Inherent viscosity η_{inh}=0.147 (25°C, c=1 g/dL, CF_3COOH).

Heterogeneous Palladium-Catalyzed Allylic Substitution. Typical procedure: a mixture of 214 mg (0.625 mmol) of chiral polymer and allylic palladium chloride dimer (11.4 mg, 0.0312 mmol) in THF (5 mL) was stirred for 20 min. Then 157.7 mg (0.625 mmol) of 1,3-diphenyl-2-propen-1-yl acetate **6** is added. 1.5 equivalent of sodium dimethyl malonate (0.938 mmol) freshly prepared from NaH (22.5 mg, 0.938 mmol) and 124 mg of dimethyl malonate (107 μL, 0.938 mmol) in THF (5 mL) is added. The reaction is monitored by GC. After a reaction time of 48 hours, the crude is treated with methanol and purified over a Pre-Coated PLC plate (SILICA GEL 60 F-254, MERCK Art.5717) by elution with a mixture of heptane and ethyl acetate (6 : 4).

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