Heterogeneous Pd-Catalyzed Asymmetric Allylic Substitution Using Resin-Supported Trost-Type Bisphosphane Ligands**

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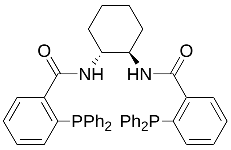
For economic, environmental, and social reasons, the trend towards the application of optically pure compounds is undoubtedly increasing. Among the various methods to produce single enantiomers, asymmetric catalysis is one of the most attractive from the atom-economic point of view of.[1] Over the last thirty years, numerous catalytic reactions allowing the enantioselective formation of C–H, C–C, C–O, C–N, and other bonds have been discovered. A number of homogeneous chiral catalysts have gained wide acceptance owing to their efficiency and selectivity, and some of them are even used on an industrial scale.[2] However, in spite of the huge amount of work devoted to this subject in both academic and industrial fields, the contribution of asymmetric catalysis in the overall production of chiral chemicals is much lower than originally expected. One of the major drawbacks of homogeneous catalysis is the need for separating the relatively expensive catalysts from the reaction mixture at the end of the process. One of the most promising solutions to this problem seems to be the anchoring of effective soluble catalytic systems to an insoluble matrix, ideally without any reduction of catalytic performance with respect to the homogeneous phase.[3]



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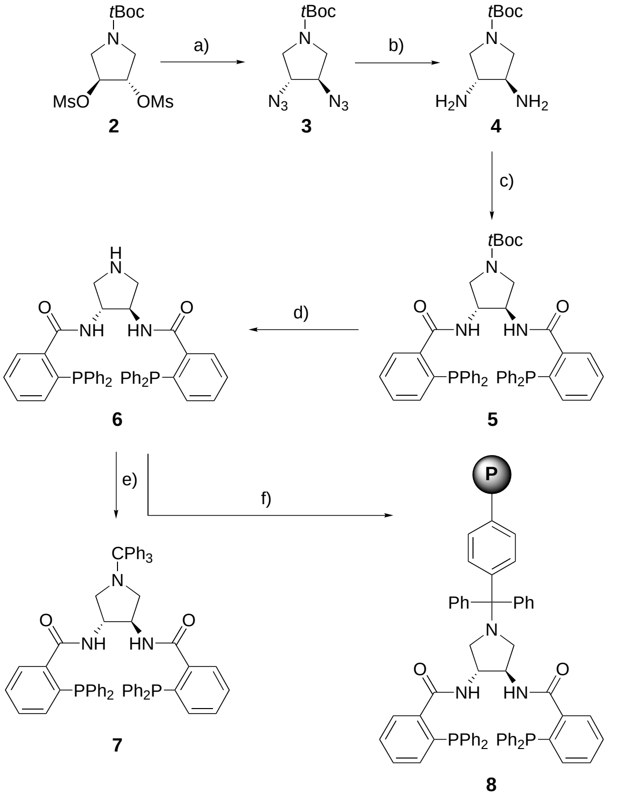
In our continuing effort to develop efficient heterogeneous chiral catalysts,[4] we became interested in the immobilization of Trost-type bisphosphane ligands such as **1**, which have proven to be extremely useful in palladium(0)-catalyzed asymmetric allylic substitutions.[5] In spite of the versatility of this class of chiral ligands, the catalytic system provides relatively low turnover numbers and frequencies, and both ligand **1** itself and palladium are quite expensive. Thus, it would be highly desirable to develop heterogeneous analogues that could be readily recovered from the reaction mixture and offer the possibility of reusing both components. Surprisingly, to the best of our knowledge, there has been no report so far on the use of a heterogeneous analogue of ligand **1** for asymmetric allylic substitutions.[6]

We present here the supported bisphosphane ligands **8a** and **8b**, which are polymeric analogues of the Trost-type ligand **1** and exhibit excellent activity and enantioselectivity (up to 99% *ee*) in Pd-catalyzed desymmetrization reactions. These ligands can be reused for consecutive reactions without any further addition of a Pd source. The immobilized ligands **8** were designed with the following criteria: 1) The molecular structure of the monomeric moiety should mimic precisely the optimum structure of ligand **1**; 2) the monomeric moiety should be attached by a single flexible linkage to the polymer support to minimize detrimental changes in the conformational preference of the reactant–catalyst intermediates; and 3) the morphology of the resin should be such that no limitation on mass transfer arises, with all active sites freely accessible.

The polymeric ligands **8** and their homogeneous analogue **7** were synthesized by the route depicted in Scheme 1. The



● **8a** : Polystyrene-based resin (0.152 mmol g^{-1})
8b : JandaJEL (0.174 mmol g^{-1})

Scheme 1. Synthesis of the polymer-bound ligands **8**. a) NaN_3, DMF, 85°C, 24 h, 78%; b) 10% Pd/C, H_2 (50 psi), MeOH, 99%; c) DPPBA, DCC, DMAP, CH_2Cl_2, RT, 24 h, 70%; d) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C→RT, 1 h, 98%; e) trityl chloride, Et_3N, DMAP, CH_2Cl_2, RT, 1 h, 96%; f) polymer-bound triphenylchloromethane (cross-linked with 1% DVB) for **8a** or JandaJEL trityl chloride for **8b**, Et_3N, DMAP, CH_2Cl_2, RT, 14 h. Boc = *tert*-butoxycarbonyl, DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, DPPBA = 2-diphenylphosphanylbenzoic acid, DVB = divinylbenzene, Ms = methanesulfonyl.

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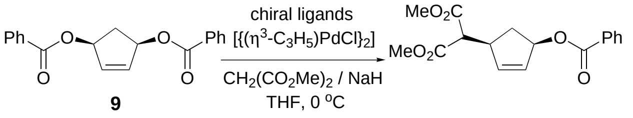
catalytic reduction of *N*-*t*Boc-(3*R*,4*R*)-3,4-diazidopyrrolidine (**3**), which was obtained by azide substitution of *N*-Boc-(3*S*,4*S*)-3,4-bis(methanesulfonyloxy)pyrrolidine (**2**),[7] followed by reaction of the resulting diaminopyrrolidine **4** with 2-diphenylphosphanylbenzoic acid (DPPBA) in the presence of dicyclohexylcarbodiimide (DCC) afforded the monomeric moiety **5**. After deprotection[8] of the *t*Boc group of **5** with $BF_3 \cdot Et_2O$ in CH_2Cl_2, the resulting monomeric ligand **6** was allowed to react with polystyrene-based trityl chloride resin[9] and JandaJEL trityl chloride[10] in the presence of triethylamine in dichloromethane to give the pale yellow polymeric ligands **8a** and **8b**, respectively. The trityl chloride is relatively inert to the formation of the phosphonium salt during the anchoring of **6** to the polymer support. The polymeric chloride moieties that remained were capped with methoxy groups[11] (see the Experimental Section). Nitrogen analysis of **8a** and **8b** indicated that 0.152 and 0.174 $mmol\,g^{-1}$ of the monomeric moiety **6** were incorporated, respectively. To compare the catalytic efficiency in homogeneous and heterogeneous reactions, the homogeneous analogue **7** was also prepared by the reaction of **6** with trityl chloride.[12]

The catalytic efficiency of the polymeric ligands **8** was examined with the Pd-catalyzed desymmetrization[13] of *cis*-1,4-bis(benzoyloxy)cyclopent-2-ene (**9**) with dimethylmalonate nucleophile (Table 1) and the intramolecular cyclization of biscarbamate **10** (Table 2). The catalytic activity and enantioselectivity of the monomeric analogue **7** was first investigated as a control experiment. We were pleased to find that this ligand showed high activity and enantioselectivity (up to 99% *ee*) in the Pd-catalyzed desymmetrization reactions of **9** and **10** (entry 1, Tables 1 and 2). This result indicates that the homochiral pyrrolidine diamine moiety is an appropriate chiral scaffold for the catalyst.

Table 1. Results of the Pd-catalyzed desymmetrization of **9** with dimethylmalonate nucleophile.[a]

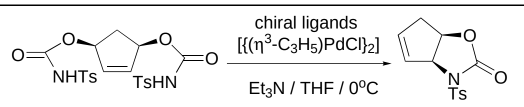


Entry	Ligand	Time	Yield [%][b]	*ee* [%][c]	Config.
1	**7**	1 h	98	98	1*S*,4*R*
2	**8a**	15 h	73	84	1*S*,4*R*
3	**8b**	30 min	98	96	1*S*,4*R*

[a] All reactions were carried out on a 0.2-mmol scale based on substrate **9** at 0 °C. The molar ratio of $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$:ligand:**9**:NaH(95%):dimethylmalonate was 0.025:0.15:1:1.8:1.5. [b] Yields of isolated product. [c] Determined by HPLC using Chiralcel OJ column with *i*PrOH/hexane (15/85), flow rate: 1.0 $mL\,min^{-1}$; elution times: 15.8 min (1*S*,4*R*), 21.5 min (1*R*,4*S*).

With these results in hand, we turned to studying polymer-bound **8a** and **8b**. The activity and enantioselectivity of the polystyrene-based catalyst **8a** (entry 2, Tables 1 and 2) were slightly lower than those obtained with **7**. However, the JandaJEL-based catalyst **8b** (entry 3, Tables 1 and 2) was nearly as effective (up to 99% *ee*) as **7**. The JandaJEL resin is a polystyrene resin containing flexible tetrahydrofuran-derived cross-linkers, and is therefore reported to swell much better than Merrifield resin.[14] This characteristic of the JandaJEL support is envisaged to give the bulky ligand greater degrees of freedom and, as a result, to act more like a homogeneous catalyst.

Table 2. Results of the Pd-catalyzed intramolecular cyclization of biscarbamate **10**.[a]



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Entry	Ligand	Time [min]	Yield [%][b]	*ee* [%][c]	Config.
1	**7**	20	99	99	1*S*,4*R*
2	**8a**	30	98	97.5	1*S*,4*R*
3	**8b**	20	99	99	1*S*,4*R*
4[d]	**8b**	20	99	98.2	1*S*,4*R*
5[d]	**8b**	40	99	97.7	1*S*,4*R*
6[d]	**8b**	60	99	97.1	1*S*,4*R*
7[d]	**8b**	180	95	94.7	1*S*,4*R*

[a] All reactions were carried out on a 0.2-mmol scale based on biscarbamate **10** at 0 °C. The molar ratio of $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$:ligand:**10**:$NEt_3$ was 0.025:0.075:1:1; Ts = *p*-toluenesulfonyl. [b] Yields of isolated product. [c] Determined by HPLC using Chiralpak AD column with *i*PrOH/heptane (15/85), flow rate: 1.0 $mL\,min^{-1}$; elution times: 24.4 min (1*S*,4*R*), 27.3 min (1*R*,4*S*). [d] The reaction was carried out with the **8b**–Pd complex recovered from the previous run without further addition of $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$.

After the successful first run of the intramolecular cyclization of **10** (entry 3, Table 2), the reaction mixture was filtered off under an argon atmosphere and the catalyst–resin complex was rinsed with dry THF (3 × 5 mL). The ^{31}P NMR spectrum of the recovered orange resin showed a signal at $\delta = +26.0$ ppm (85% H_3PO_4 external reference). This remarkable downfield shift indicates that the phosphanyl group of **8b** in the recovered resin is coordinated to palladium. Finally, the recovered Pd complex of **8b** was subjected to further catalytic reactions without any further addition of a Pd source. The recovered catalyst could be recycled with only a slight loss in activity and enantioselectivity (from 99% *ee* in the first run to 94.7% *ee* in the fifth run; entries 3–7, Table 2). These results demonstrate that in addition to highly facilitated workup procedures, the JandaJEL-bound catalyst **8b** offers the advantage of easy recovery and reutilization in consecutive heterogeneous asymmetric desymmetrization reactions.

In summary, we have prepared a promising class of polymer-bound chiral ligands for heterogeneous asymmetric allylic substitution reactions. In particular, the JandaJEL-bound ligand **8b** exhibited excellent activity and enantioselectivity in Pd-catalyzed asymmetric desymmetrizations. To the best of our knowledge, this is the first successful work on heterogeneous asymmetric desymmetrization reactions in which Trost-type ligands were used. Studies to optimize the reaction conditions for continuous processing are currently in progress.

Experimental Section

8b: Compound **6** (288.7 mg, 0.426 mmol) and Et_3N (89 μL, 0.639 mmol) were added to a suspension of polymer-bound triphenylchloromethane (JandaJEL; 2.0 g, 1.42 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred at ambient temperature for 14 h under a nitrogen atmosphere. The resin was filtered and washed with CH_2Cl_2 (160 mL), water (150 mL), and methanol (200 mL) and then dried under vacuum. To cap the unchanged chloride moieties with methoxy groups, the resin was stirred for 15 min in CH_2Cl_2/methanol (1/1, v/v; 15 mL) containing an excess of Et_3N (383 µL, 2.75 mmol). The resin was filtered and washed with CH_2Cl_2 (50 mL), water (150 mL), and methanol (200 mL). To remove any traces of unchanged chiral monomer **6** in the resin, **8b** was then continuously extracted in a Soxhlet device with THF for 24 h and dried under vacuum. Solid-state ^{31}P NMR (85 % H_3PO_4 external reference): $\delta = -11.6$ ppm (br s).

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[12] Physical data for **7**: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.15$–2.21 (m, 1 H), 2.75–2.81 (m, 1 H), 3.78–3.83 (m, 1 H), 6.24 (d, $J = 4.4$ Hz, 1 H), 6.89–6.93 (m, 1 H), 7.16–7.36 (m, 18 H), 7.43 (d, $J = 7.5$ Hz, 3 H), 7.54–7.58 ppm (m, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 51.93$, 55.50, 74.89, 126.73, 128.06, 128.35, 128. 41, 128.97, 129.00, 129.06, 129.09, 129.19, 129.27, 129.73, 130.66, 134.17, 134.25, 134.44, 134.51, 136.49, 136.77, 137.50, 137.60, 137.65, 137.75, 141.07, 141.40, 142.57, 169.76 ppm; ^{31}P NMR (121 MHz, $CDCl_3$, 85 % H_3PO_4 as external reference): $\delta = -9.6$ ppm.

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Noncovalent Chemistry of Nitrous Oxide: Interactions with Secondary *cis* Amides in Solution**

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The environmental impact of nitrous oxide (N_2O) is enormous. As one of the most abundant components of the atmosphere, N_2O plays a critical role in the destruction of the ozone layer and contributes to the greenhouse effect.[1] Emission of N_2O into the atmosphere has already reached 13 million tons and is constantly growing. The widespread use of nitrogen-containing fertilizers and the industrial manufacture of nylon are critical contributors to this amount. The major natural suppliers of N_2O are enzyme-supported nitrification/denitrification processes in soils in which this gas is the key intermediate.[2] N_2O is also involved in a number of biochemical processes, especially related to anesthesia.[3] Together with O_2 and CO, N_2O belongs to the family of blood gases.

The chemistry of N_2O is limited, although it is considered to be a reliable and nontoxic source of oxygen for catalysis.[4] It is commonly known as a noncoordinating gas and as a very poor ligand. Although several metal complexes react with N_2O, $[Ru(NH_3)_5(N_2O)]^{2+}$ is the *only* characterized complex to date.[5]

The rules governing reversible interactions between N_2O and various receptor sites, which usually precede the covalent fixation and are also responsible for the biochemical action, are still poorly understood. We report herein the previously unnoticed noncovalent interactions between secondary amides and N_2O in apolar solutions. N_2O frequently circulates in biological fluids,[2,3] and its rather weak dipole–dipole interactions with hydrophobic fragments of proteins has been noticed.[6] At the same time, the possibility of its involvement in hydrogen bonding with proteins and enzymes has been routinely ignored.

Hydrogen bonding is one of the most important forces in Nature and is responsible for self-assembly and enzyme selectivity.[7] In chemistry, it has been used in the design of effective receptors for polar neutral molecules and anions in the gas phase, in solution, and in the solid state.[8] Molecules of gases are known to form hydrogen bonds in the gas phase. Among the typical examples are the adducts of acidic HF, HCl, HBr, and HCN with N_2, CO, CO_2, and OCS,[9] and weak PhOH···Ar (N_2, CO) molecular clusters.[10] At the same time,

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