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Enantioselective allylic substitution on Pd/Al_2O_3 modified by chiral diphosphines

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Abstract

The allylic substitution of (*E*)-1,3-diphenylallyl acetate (**1a**) with dimethyl malonate was investigated on Pd/Al_2O_3 modified by (*R*)- and (*S*)-BINAP, (*S*,*S*)-Chiraphos, (*R*)-C_3-Tunephos, and (*R*)-Solphos. Stable performance of Pd/Al_2O_3 required its reduction in hydrogen before the allylic substitution reaction, which was carried out under Ar. The enantioselectivity of the Pd/Al_2O_3-BINAP system [58–60% ee to (*S*)-**2**] was independent of the reaction temperature (60 and 120 °C), and only 300 ppm BINAP related to **1a** was required. According to UV–vis analysis, only a small fraction of BINAP was adsorbed on Pd/Al_2O_3. At 120 °C, full conversion and 94% chemoselectivity were achieved in 6 h. For comparison, analogous soluble Pd–BINAP complexes were poorly efficient and afforded low ee to the opposite enantiomer of the product at 60 °C or above. Electron microscopy could detect no restructuring of Pd in Pd/Al_2O_3 during the reaction. Surprisingly, the addition of BINAP induced a significant rate acceleration (by a factor of almost 7 at 60 °C) and also improved the chemoselectivity of Pd/Al_2O_3. Among the diphosphine ligands tested, (*R*)-Solphos was the most effective (67% ee). An important advantage of the Pd/Al_2O_3–BINAP system is that it can transform not only the allyl acetate **1a**, but also the corresponding allyl alcohol **1b** without the application of any additive.

Keywords: Asymmetric; Allylic substitution; Palladium/alumina; Chiral modification; Diphosphines; BINAP; Rate acceleration

1. Introduction

Allylic substitution is a versatile reaction for the formation of new carbon–carbon and carbon-heteroatom bonds. After Tsuji reported the reaction of nucleophiles with π-allylpalladium chloride [1], Trost reported the first example of an asymmetric allylic substitution reaction in the 1970s [2]. Since then, the reaction has been investigated thoroughly, and numerous novel chiral catalysts have been developed that allow high yield and enantioselectivity [3–6]. A widely used test reaction is the allylic substitution of (*E*)-1,3-diphenylallyl acetate (**1a**, Scheme 1) with dimethyl malonate. Depending on the ligands and reaction conditions, >90% ee and good yields can be achieved. The reaction is usually carried out at room temperature in THF or CH_2Cl_2, and the nucleophile is added in the form of its salt or generated in situ by *N*,*O*-bis(trimethylsilyl)acetamide (BSA). The nucleophile has a large influence on the performance of the Pd–BINAP system; for example, 80% yield and 30% ee were achieved in 44 h when the sodium salt of dimethyl malonate was used in THF [7]. When the nucleophile was generated in situ in CD_2Cl_2, the yield (85%) and particularly the enantioselectivity (90%) increased, but the reaction time also doubled [8].

Intrigued by the well-known technical advantages of heterogeneous catalysts, Jansat et al. attempted the enantioselective allylic substitution of **1a** with Pd nanoparticles modified with a chiral diphosphite ligand [9]. The modifier, which had been synthesized in four steps, afforded excellent enantioselectivity (97% ee). Interestingly, it was not possible to increase the conversion beyond 61% even after a prolonged reaction time of 168 h. Instead, a high kinetic resolution (89%) was observed for the substrate. More recently, allylic substitution of **1a** with diethyl malonate (instead of dimethyl malonate) as a nucleophile was catalyzed with a Pd/C–(*R*)-BINAP system [10]. The reaction in water at 70 °C afforded an ee of 80% but a yield of only 21% after 12 h reaction time. Interestingly, the absolute config-

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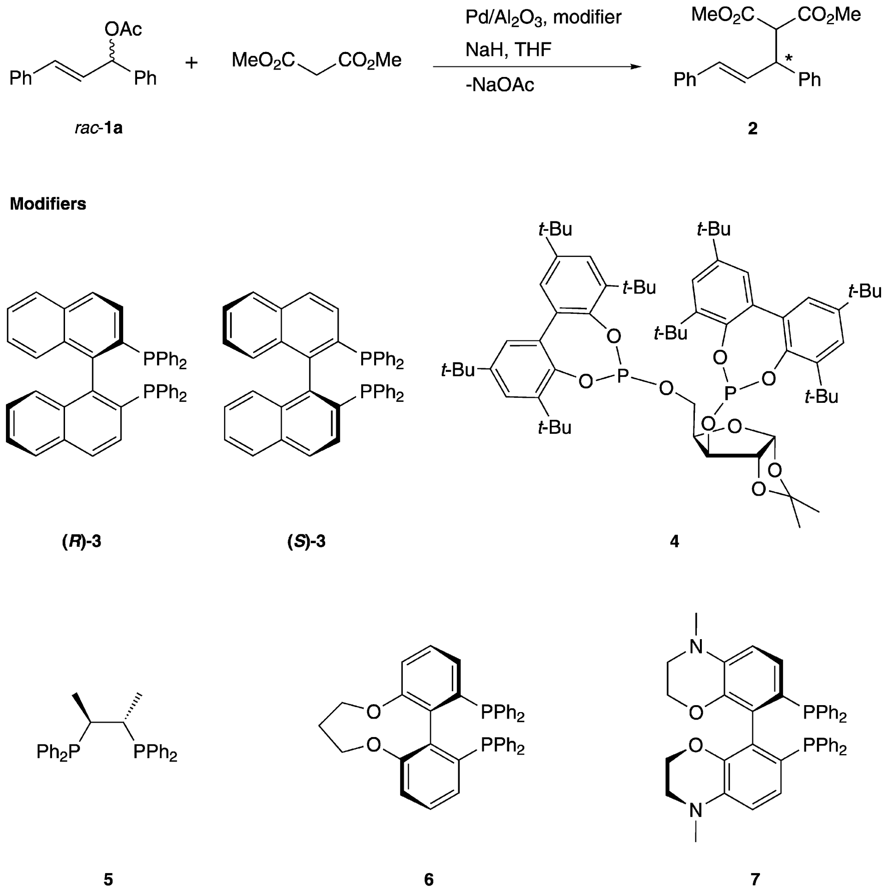

Scheme 1. Pd-catalyzed allylic substitution of **1a** with dimethyl malonate and the structure of chiral modifiers.

uration of the product was (*R*), not (*S*) as is usually observed for (*R*)-BINAP.

Considering these heterogeneous catalysts from a broader perspective, enantioselective reactions on chirally modified (supported) Pd metal are well known. With only a few exceptions [11–13], research has focused on the hydrogenation of C=C bonds [14–22], using mainly cinchona and vinca alkaloids and their simple derivatives as modifiers. A fundamental deviation from the homogeneous metal–ligand systems is that on the metal surface, the substrate cannot interact with the same metal atom that is blocked by the chiral modifier due to steric limitations; this deviation is expected to lead to different reaction characteristics and mechanisms.

Here we report the allylic substitution of **1a** using a conventional Pd/Al_2O_3 catalyst modified with various chiral biphosphines (Scheme 1). A detailed analysis of the reaction revealed some unprecedented characteristics of this chirally modified Pd catalyst.

2. Experimental

2.1. Materials

(*E*)-1,3-diphenylallyl acetate (*rac*-**1a**) was synthesized from (*E*)-1,3-diphenylprop-2-en-1-ol (*rac*-**1b**, $\geqslant$98%, Fluka) as described previously [23]. The diphosphite ligand **4** was prepared by reacting the corresponding diol [24] with 2 equivalents of 4,4′,6,6′-tetra-*t*-butyl-2,2′-bisphenoxyphosphorus chloride [25] in the presence of a base [26]. All synthesized compounds were purified by column chromatography. The structures of **1a** and **4** were confirmed by ^1H and ^{13}C NMR. Ligand **4** was also characterized by HR-MALDI-MS. The purity (>99%) of **1a** was confirmed by GC. Tetrahydrofuran (THF, 99.99%, Acros) was dried and stored over activated molecular sieve (water content: 0.012 wt%). $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ ($\geqslant$98%, Fluka), $Pd(OAc)_2$ (>99%, Merck), (*R*)-(+)- and (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene ((*R*)- and (*S*)-BINAP ((*R*)-and (*S*)-**3**), puriss., Fluka), (2*S*,3*S*)-(−)-bis(diphenylphosphino)butane ((*S*,*S*)-Chiraphos (**5**), Aldrich), (*R*)-(6,6′-*O*-(1,3-propylene)-oxylbiphenyl-2,2′-diyl)bis(diphenyl)-phosphine ((*R*)-C_3-Tunephos (**6**), Aldrich), (*R*)-7,7′-bis(diphenylphosphino)-3,3′,4,4′-tetrahydro-4,4′-dimethyl-8,8′-bi-(2H-1,4-benzoxazine) ((*R*)-Solphos (**7**), >97%, Aldrich), dimetyl malonate (>99%, Aldrich), *N*,*O*-bis(trimetylsilyl) acetamide (BSA, 95%, Acros), and NaH (60% dispersion in mineral oil, Fluka) were used without further purification. The 5 wt% Pd/Al_2O_3 (No. 40692) catalyst was purchased from Engelhard.

2.2. Catalytic experiments

The commercial 5 wt% Pd/Al_2O_3 catalyst was stored in air and prereduced in solution or in gas phase before use. For the pretreatment in solution, the catalyst was stirred in 5 ml of THF