Enantioselective Allylation

Enantioselective Catalytic Allylation of Carbonyl Groups by Umpolung of π-Allyl Palladium Complexes**

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Dedicated to Luisa Beghi

The development of catalytic asymmetric C–C bond-forming reactions remains one of the main challenges in organic chemistry. Transformations mediated by transition-metal complexes with properly designed ligands have enabled this challenging synthetic goal to be achieved, often with remarkable results.[1] Among the transition-metal-catalyzed reactions known to form C–C bonds, the palladium-catalyzed allylic substitution developed by Trost and Tsuji stands out as one of the most valuable synthetic tools available.[2] In this reaction the key stage is the formation of a π-allyl palladium complex that can act both as an electrophilic and a nucleophilic species because of the ambiphilic nature of the metal-coordinated allylic ligand. Nucleophilic displacement across the π-allyl palladium complex has been extensively used in organic synthesis, particularly as its asymmetric variant—widely known as the asymmetric allylic alkylation (AAA), a strategically powerful option for the preparation of complex molecules such as natural products. On the other hand, nucleophilic metal-coordinated allylic moieties obtained from the so-called Umpolung of π-allyl palladium complexes have recently provided a versatile allylation method for aldehydes and ketones.[3] Of the various routes that utilize this Umpolung, the transmetalation of a π-allyl palladium complex with diethylzinc, according to the Tamaru protocol, has recently attracted attention. Here a putative allyl zinc species is delivered as an active allylating agent to a carbonyl electrophile.[3]

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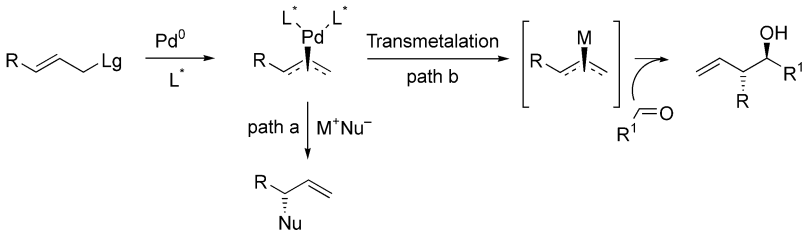
However, while impressive strides in asymmetric induction have been made in palladium-catalyzed AAA (Scheme 1, path a), to our knowledge the enantioselective allylation of carbonyl compounds by the Umpolung of π-allyl palladium complexes (Scheme 1, path b) has not been reported in the literature.



Scheme 1. Allylation of carbonyl compounds by Umpolung of π-allyl palladium complexes. Lg = leaving group.

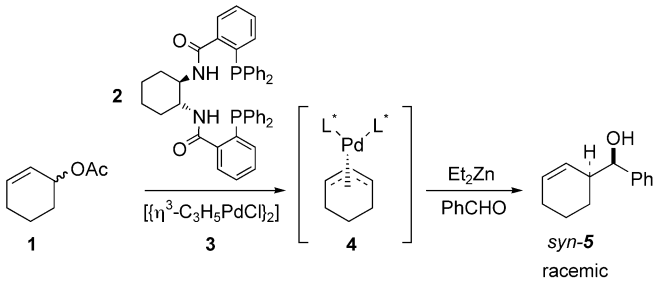
Here we report the first example of a catalytic asymmetric aldehyde addition of an allyl zinc reagent generated from an allyl ester and diethylzinc in the presence of a catalytic amount of a Pd complex and a chiral monophosphane.

Initial studies have dealt with the reaction of cyclohexenyl acetate **1** in the presence of 5 mol% of ligand (*R*,*R*)-**2**, 2.5 mol% of Pd complex **3** and 2.4 equivalents of diethylzinc (Scheme 2). According to Trost and Lee,[4] **2** emerges as the ligand of choice for the highly enantioselective allylic alkylation of cyclohexenyl acetate through intermediacy of π-allyl palladium complex **4**. In their work dealing with the palladium-catalyzed nucleophilic allylation of aldehydes, Tamaru et al. assumed that a reactive σ-allyl zinc species is stereospecifically generated with retention of configuration from the intermediate π-allyl palladium complex. Moreover, the Pd-catalyzed and Zn-mediated allylation of benzaldehyde with various cyclohexenyl moieties was shown to occur with high diastereoselectivity.[5]

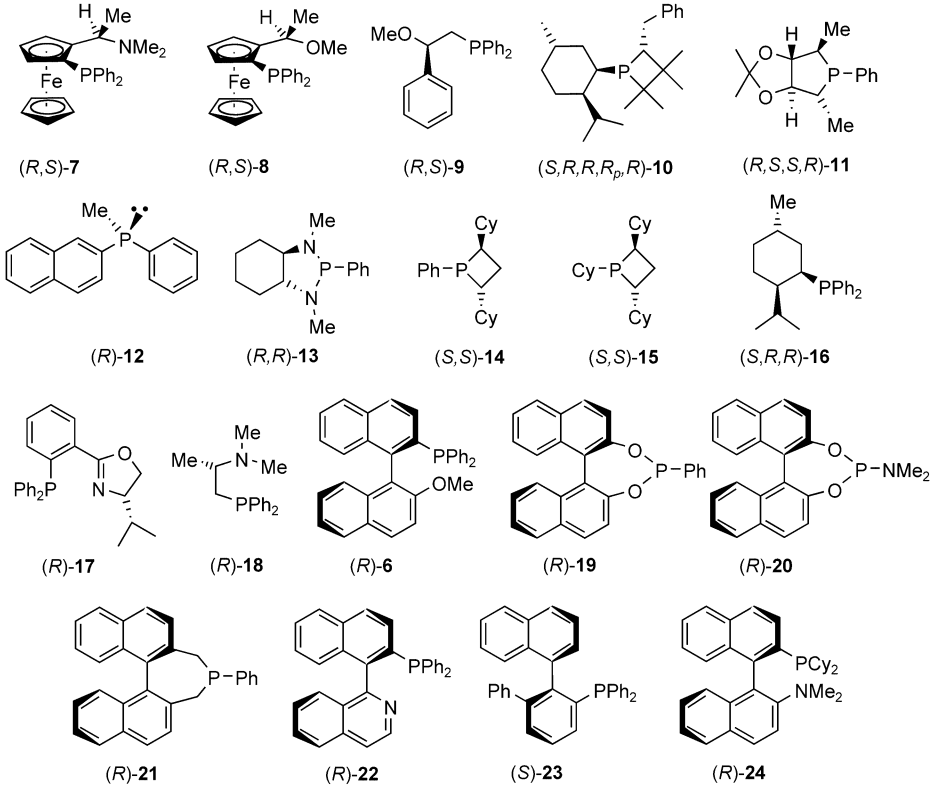
From these observations, we wondered whether the chiral information encoded in complex **4** could be transferred into the transmetalated Zn complex and then eventually into the final alcohol adduct. In a preliminary attempt, the expected homoallylic alcohol **5** was indeed obtained as a single *syn* diastereoisomer in a satisfying 70% yield, but as a racemic mixture.

The loss of the chiral information in complex **4** was assumed to happen at the transmetalation step, hence closer attention to the Pd–Zn exchange mechanism was demanded. While the diethylzinc-mediated Umpolung mechanism needs further elucidation, preliminary studies suggest transmetalation occurs after transfer of an ethyl group from the Zn to the Pd center, followed by elimination of diethylpalladium.[6]

The stereochemical discrimination that determines the enantioenrichment in the product may arise from the asymmetric induction exerted on the conjectural transient allyl zinc species by the chiral space where the ethyl transfer occurs. Whereas diphosphanyl ligand **2** was designed by Trost and Bunt for asymmetric induction on electrophilic π-allylic moieties reacting with soft nucleophiles through an outer-sphere mechanism,[7] chiral monophosphanes, such as Hayashi's (*R*)-2-(diphenylphosphanyl)-2′-methoxy-1,1′-binaphthyl ((*R*)-MOP **6**) or ferrocenylphosphane (*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-diphenylphosphanylferroceneethylamine] (PPFA, **7**; Scheme 3), fared as the most efficient ligands when hard nucleophiles attacked the metal center of the π-allyl palladium complex to be and were subsequently relayed onto the electrophile (inner-sphere mechanism).[8] If the



Scheme 2. Allylation of benzaldehyde with cylohexenyl acetate **1** in the presence of chiral biphosphane ligand **2**.



Scheme 3. A list of chiral monodentate ligands. Cy = cyclohexyl.

stereochemical discrimination occurs during the transfer of a "hard" ethyl group[7a] from the Zn to the Pd center in a inner-sphere fashion, asymmetric induction may be achieved by employing chiral monophosphanes. Our expectations were met by replacement of diphosphane **2** with monophosphane (*R*)-**6**. The *syn* addition product (3*S*,1′*R*)-**5** was obtained in 22% *ee* and 68% yield.

The absolute configuration of the adduct was assigned by comparson of the rotation with that of an identical compound from the literature,[9] the *ee* value was determined by chiral high-performance liquid chromatography (HPLC). Enhancement of the *ee* value was pursued using parallel synthesis—a particularly convenient technique when few mechanistic data are available.[10] A pool of chiral monophosphane ligands (Scheme 3) was screened against the reaction given in Scheme 2.[11] Nineteen ligands were selected because of their different electronic properties at the phosphorus center, and of the Tolman's cone angles (Scheme 3).[12] All reactions were carried out using acetate **1** and benzaldehyde in a 1.2:1 ratio, 2.4 equivalents of diethylzinc, 2.5 mol% of Pd complex **3**, and 10 mol% of the chiral ligand in THF (0.2 M with respect to benzaldehyde) at 4°C. The metal and ligand were premixed at room temperature in THF (1 mL) for 0.5 h, diluted with THF, and then cooled to 0°C.

Benzaldehyde, **1** and diethylzinc were sequentially added in a parallel synthesizer, and the mixture stirred under argon at 4°C (see Supporting Information). After quenching with NH_4Cl and simple work-up, the crude products were analyzed by high-resolution gas chromatography (HRGC) for chemical yields, and by chiral HPLC for their *ee* values (Figure 1).

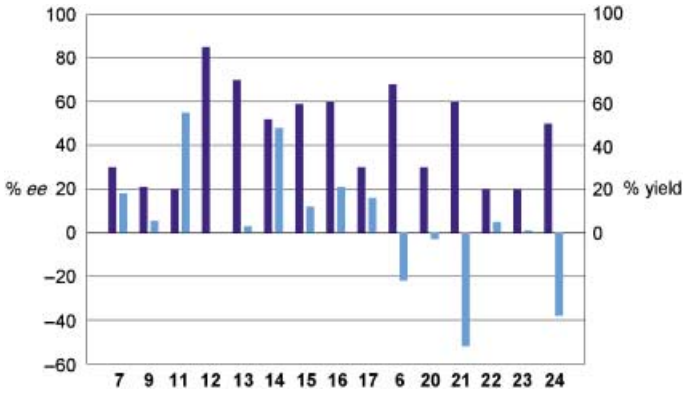
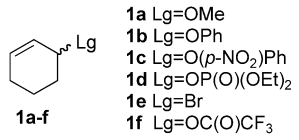


Figure 1. Results of allylation of cyclohexenyl acetate **1** with a selection of chiral ligands. Key: blue, yield as measured by high-resolution gas chromatography (HRGC); azure, percent enantiomeric excess as measured by chiral high-performance liquid chromatography (Kromasil CHI-DMB, heptane/*tert*-butylmethyl ether 98:2).

Employment of phosphanes **8**, **10**, and **18** as well as phosphonite **19** did not bring about any reaction, while the monophosphane **12** resulted in formation of **5** in 85% yield, albeit as a racemate. The best performing ligand was the phosphepine (*R*)-**21**, which provided the addition product (3*S*,1′*R*)-**5** in 60% yield and a promising 52% *ee*.

Ligand (*R*)-**21** was thenexamined further in a second screening so that the influence of the leaving group (Scheme 4), the palladium source and other reaction parameters on stereoselectivity could be determined (Figure 2).



Scheme 4. Cyclohexenyl derivatives employed in a second screening.[13]

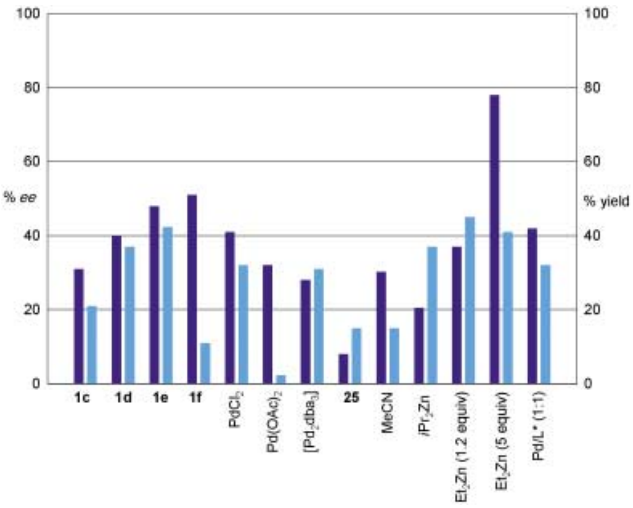


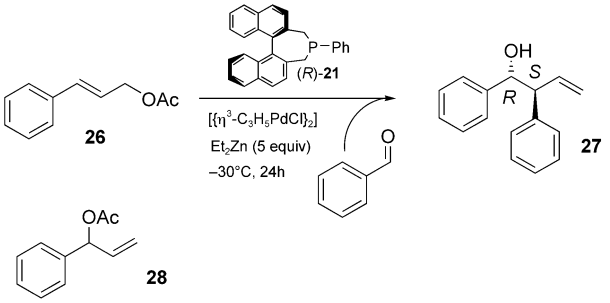
Figure 2. Results of allylation using phosphepine (*R*)-**21** with a selection of leaving groups on the cyclohexenyl moiety, Pd sources, Umpolung reagents (R_2Zn), Pd/ligand ratio and solvents. Key: blue, yield as measured by HRGC; azure, percent enantiomeric excess as measured by chiral high-performance liquid chromatography (Kromasil CHI-DMB, heptane/*tert*-butylmethyl ether 98:2).

The results revealed that the leaving group had a dramatic effect on the enantioselectivity. The greater the ease with which the leaving group can ionize and depart from the allylic unit, the lower the *ee* value. Notably, trifluoroacetate **1f** afforded **5** in the highest yield, but only in 10% *ee*. To the best of our knowledge such a relationship between enantioselectivity in Pd-catalyzed AAAs and the nature of the leaving group has not been the subject of systematic studies published to date. In addition, we observed no addition products with ethers **1a** and **b**, despite them being reported to effect the allylation of benzaldehyde through Umpolung in good yields.[6a]

Variation of the solvent caused a detrimental effect both on the yield and enantioselectivity. A 1:1 mixture of DMF/THF, CH_2Cl_2, and MeCN all gave worse results than THF. $PdCl_2$, $Pd(OAc)_2$, $[Pd_2(dba)_3]$ (dba = *trans*,*trans*-dibenzylideneacetone), and the chloride-free allyl palladium complex $[Pd(\eta^3\text{-}C_3H_5)(MeCN)_2]OTf$ (**25**; Tf = trifluoromethanesulfonyl) were investigated as the palladium source,[14] but with unsatisfactory results (Figure 2).

A change in the Pd/ligand ratio from 1:2 to 1:1 decreased the yield (42%) and *ee* value (32%), as did the reduction in the amount of diethylzinc to 1.2 equivalents (addition product **5** was obtained in 37% yield and 45% *ee*; Figure 2). Conversely, an increase in the amount of diethylzinc to 5 equivalents boosted the reaction rate and yield, with the allylation now being completed in 6 h at 4°C (instead of 24 h as required with 2.4 equivalents of diethylzinc at 4°C) in a 78% yield. Replacement of the ethyl group on the Zn center with the more sterically demanding isopropyl group did not affect the *ee* value (37%), but the yield was reduced to 21%. Finally, lowering the reaction temperature to −30°C and using 5 equivalents of Et_2Zn showed little effect on substrate **1**, whereas the trifluoroacetate **1f** product **5** was isolated with an *ee* value that was more than tripled (up to 38% from 11%).

Achiral cinnamyl acetate (**26**) performed even better as a substrate, with a faster and more stereoselective reaction being observed. Addition product (1*R*,2*S*)-*anti*-**27** was obtained in a 77% yield and 60% *ee* (Scheme 5) under our



Scheme 5. Allylation of benzaldehyde with cinnamyl acetate **26** as the substrate.

standard conditions with 5 equivalents of diethylzinc at 4°C.[15] The *ee* value gratifyingly climbed to 70% at −30°C (24 h, 70% yield). Isomeric racemic allyl acetate **28**, which is expected to originate the same intermediate π-allyl palladium complex as **26**, gave rise to (1*R*,2*S*)-*anti*-**27** in a 49% yield, while the *ee* value plummeted to 15%. This reduction in enantioselectivity is not unexpected in view of the possible intervention of memory effects, as amply investigated by Lloyd-Jones et al.[16]

In summary, we have documented the first catalytic asymmetric aldehyde allylation by Umpolung of a π-allyl palladium complex mediated by diethylzinc, which afforded products in satisfactory yields with *ee* values up to 70%.

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Keywords: allylation · asymmetric synthesis · enantioselectivity · ligand design · Umpolung

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[11] With the exception of compounds **4**, **10**, **14**, and **15**, ligands of Scheme 3 were prepared according to literature procedures, as detailed in the Supporting Information.

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