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Chiral Counteranions in Asymmetric Transition-Metal Catalysis: Highly Enantioselective Pd/Brønsted Acid-Catalyzed Direct α-Allylation of Aldehydes

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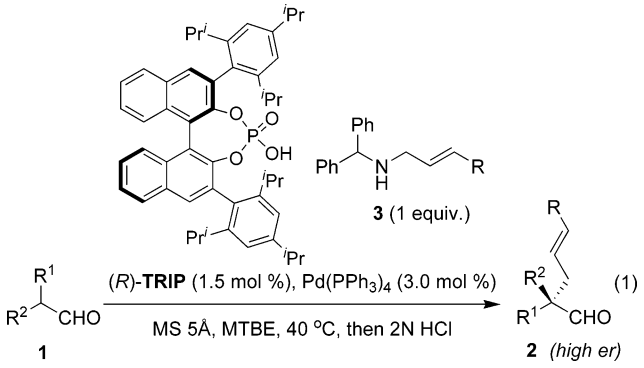
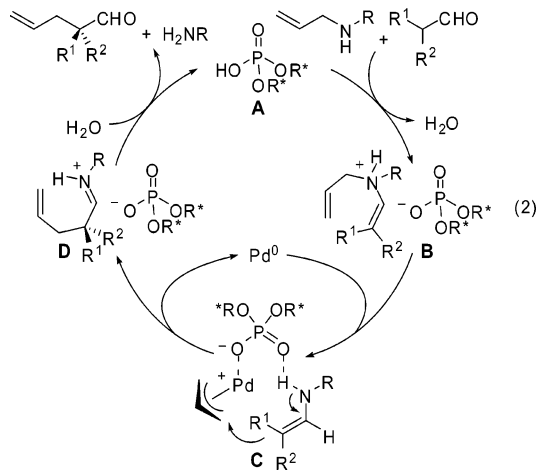
Inspired by recent pioneering contributions on the use of chiral phosphoric acid catalysts[1] and our own studies in asymmetric aminocatalysis,[2] we have recently developed the concept of asymmetric counteranion directed catalysis (ACDC).[3] Accordingly, reactions that proceed via cationic intermediates can be conducted highly enantioselectively when a chiral counteranion is introduced into the catalyst.[4] As proof of principle, we have developed efficient asymmetric transfer hydrogenations of α,β-unsaturated carbonyl compounds that are catalyzed by salts consisting of an achiral ammonium ion and a chiral phosphate counteranion.[3,5] We reasoned that this concept could be applied not only to purely organic catalysts, but to organometallic systems as well. Here we describe an example in the area of Pd-catalysis: We found that the combination of a Pd(0) catalyst with a chiral phosphoric acid can mediate highly enantioselective Tsuji−Trost-type α-allylations[6] of branched aldehydes with an allyl amine (eq 1). These reactions proceed via well-established cationic π-allyl Pd(II) complexes and our reaction is the first enantioselective version[7] where the enantiodifferentiation is achieved by introducing a chiral counteranion/anionic ligand rather than a more commonly used neutral ligand.[8]



The enantioselective construction of all-carbon quaternary stereogenic centers is a challenging task in organic synthesis owing to the involved steric repulsion between the carbon substituents.[9] Asymmetric alkylations of α-branched carbonyl compounds[10] constitute an attractive solution to this problem, and the palladium-catalyzed asymmetric allylic alkylation has proven particularly useful. However, the α-allylation of α-branched aldehydes and ketones still remains a considerable challenge. While a few direct[11] and several preformed enolate-based methods[12,13] are known for ketone substrates, catalytic asymmetric α-allylations of α-branched aldehydes are unknown. Córdova et al. described a combination of Pd and enamine catalysis for the direct α-allylation of carbonyl compounds.[14] Recently, MacMillan and co-workers reported an enantioselective aminocatalytic direct α-allylation of aldehydes applying the newly developed SOMO activation concept.[15] However, in both the above cases the formation of quaternary stereogenic centers has not been described.

In 1985 Murahashi et al. reported a Pd(0)-catalyzed direct α-allylation of carbonyl compounds in which *N*-benzyl allylamine was used as the allylating reagent.[16] This reaction was found to proceed only in the presence of an acid cocatalyst. We envisioned a catalytic cycle for an asymmetric version of this reaction involving a chiral phosphoric acid cocatalyst **A** (eq 2). Accordingly, an initial condensation of a secondary allylamine with the aldehyde should lead to an enamonium phosphate salt **B**, which upon reaction with Pd(0) leads to a cationic π-allyl-Pd-complex, an enamine, and the chiral phosphate counteranion. This assembly **C** may lead to the α-allylated iminium ion **D** via the nucleophilic attack of the enamine onto the π-allyl-Pd-complex in the coordination sphere of the phosphate anion. This species may not be considered solely as a chiral counteranion in this hypothetical catalytic cycle but rather a chiral anionic ligand for palladium, effectively inducing asymmetry in the critical carbon−carbon bond-forming step.



Initial experiments revealed the validity of our hypothesis and chiral phosphoric acids were indeed capable of inducing asymmetry in the Pd-catalyzed α-allylation of 2-phenyl propinonaldehyde **1a** with *N*-benzyl allyl amine.[17] After optimizing the reaction conditions (see Supporting Information), which included solvent, temperature, and allylamine as well as phosphoric acid cocatalyst structure, good yields and high enantioselectivity were achieved, and the preliminary scope of the reaction was investigated (Table 1). The improved conditions involved treating an aldehyde **1** with *N*-benzhydryl allyl amine (**3**) as the allylating species in the presence of a phosphoric acid cocatalyst (TRIP) (1.5 mol %) and $Pd(PPh_3)_4$ (3 mol %) in methyl *tert*-butyl ether (MTBE) containing molecular sieves (5Å). Our reaction requires both TRIP *and* Pd.

Differently substituted phenyl as well as the 2-naphthyl and 2-thiophenyl derived aldehydes afforded the allylated products in

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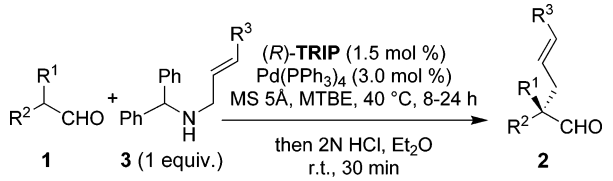
Table 1. Preliminary Scope of the Catalytic Asymmetric α-Allylation of Aldehydes

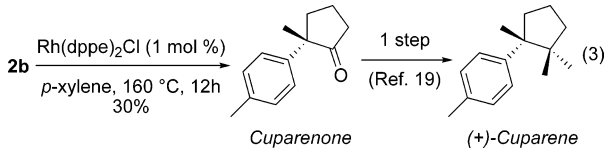


entry	R^1	R^2	R^3		yield (%)	er[a]
1	Me	Ph	H	**2a**	85	98.5:1.5
2	Me	4-Me-C_6H_4	H	**2b**	89	97:3
3	Me	3-Me-C_6H_4	H	**2c**	84	98:2
4	Me	3-F-C_6H_4	H	**2d**	85	98:2
5[b]	Me	2-F-C_6H_4	H	**2e**	74	97:3
6	Me	4-*i*-Bu-C_6H_4	H	**2f**	76	97.5:2.5
7	Me	2-naph	H	**2g**	71	97:3
8	Me	2-thiophenyl	H	**2h**	80	93:7
9			H	**2i**	45	95:5
10[c]	Me	*c*-hex	H	**2j**	65	85:15
11[d,e]	Me	Ph	Me	**2k**	40	96:4
12[d,e]	Me	Ph	Ph	**2l**	82	91:9

[a] From GC or HPLC. [b] Reaction run at 50 °C. [c] Reaction run at 110 °C in toluene. [d] Reaction run at 60 °C. [e] Reaction run for 72 h.

good yields (71−89%) and enantiomeric ratios (93:7 to >98:2) (entries 1−8).[18] The allylated product of 2,3-dihydro-1-indanone derived aldehyde (**2i**) was obtained in high er but in moderate yield (entry 9). 2-Alkylpropionaldehydes can also be used but rather harsh reaction conditions are necessary, and the enantioselectivity obtained so far is only moderate (entry 10). Substitution at the 3-position of the allyl group has also been investigated; 3-methyl and 3-phenyl substituted products were obtained in 96:4 and 91:9 er respectively (entries 11, 12).

A short application of our method in a formal synthesis of (+)-cuparene has also been developed. Rh-catalyzed hydroacylation of aldehyde **2b** gave cuparenone, which can be converted into cuparene via Reetz dimethylation (eq 3).[19]



In conclusion, we have developed a highly enantioselective α-allylation of α-branched aldehydes that creates all-carbon quaternary stereogenic centers. This reaction represents the first example of a catalytic enantioselective α-allylation of α-branched aldehydes. The phosphoric acid cocatalyst (TRIP) plays a dual catalytic role: as Brønsted acid it acts as the proton source while the resulting conjugate base functions as the counteranion/ligand for the cationic π-allyl-Pd-intermediate. To our knowledge, this is the first time that a chiral anionic ligand is applied for achieving asymmetric induction in a palladium-catalyzed allylic alkylation reaction. We are aware of the implications of our results for other transition metal-catalyzed reactions and continue to explore ACDC as a powerful new strategy for asymmetric catalysis.

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Supporting Information Available: Experimental procedures, compound characterization, NMR-spectra, and HPLC and GC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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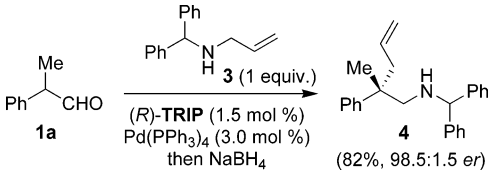
(17) For example, if aldehyde **1a**, *N*-benzyl allyl amine, $Pd(PPh_3)$ (3 mol %), and (*R*)-TRIP (1.5 mol %) were reacted at 40 °C, full conversion to α-allylated aldehyde **2a** in 89:11 er was obtained.
(18) The initial reaction product is the corresponding imine as confirmed by GC−MS. Consequently, if the reaction of aldehyde **1a** is worked up with $NaBH_4$ rather than by acidic hydrolysis, the corresponding amine is obtained:



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