Triple Catalysis

DOI: 10.1002/anie.201103263

Direct Asymmetric α-Allylation of Aldehydes with Simple Allylic Alcohols Enabled by the Concerted Action of Three Different Catalysts**

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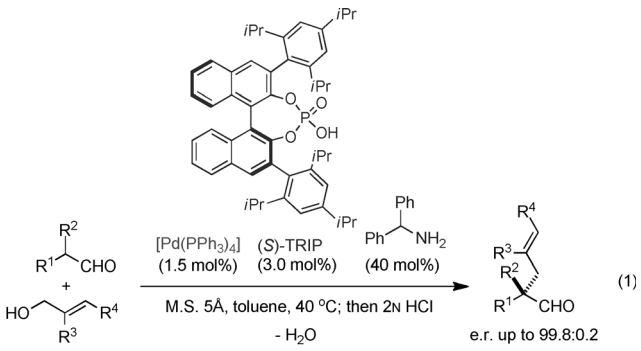
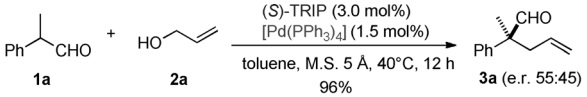
Tsuji–Trost allylations are Pd^0-catalyzed reactions in which diverse nucleophiles are allylated with allylic alcohol derivatives such as allylic acetates.[1] Asymmetric catalysis of these reactions is commonly achieved by the use of chiral neutral ligands.[1,2] We have recently described a different approach that is based on the use of chiral counteranions, which are introduced to the reaction in catalytic amounts.[3,4] We discovered an asymmetric α-allylation of α-branched aldehydes using benzhydryl allyl amine as the allylating reagent and a combination of $[Pd(PPh_3)_4]$ and the chiral Brønsted acid TRIP as catalysts.[4a] Herein, we report the first example of a highly enantioselective α-allylation of aldehydes with simple allylic alcohols [Eq. (1)]. This reaction is catalyzed by the concerted action of three different species, $[Pd(PPh_3)_4]$, benzhydryl amine, and TRIP, and constitutes another example of asymmetric counteranion-directed catalysis (ACDC).[4]



(1)

While great progress in the asymmetric catalysis of Tsuji–Trost-type allylations has been made in recent years, the direct use of allylic alcohols as allylating reagents is extremely rare[5] and even entirely unprecedented with carbonyl nucleophiles.[6,7] Continuing our studies on the use of chiral counteranions in asymmetric Pd catalysis,[4a] we recently became interested in further simplifying and potentially improving our previous protocol by directly utilizing simple allylic alcohols rather than benzhydryl allyl amines, which have to be synthesized individually in a separate step.

In our previous allylation studies, we have suggested that our reaction involves the generation of the equivalent of a π-allyl-Pd-TRIP ion pair as the critical intermediate, which reacts with an enamine generated from the released benzhydryl amine and the aldehyde. We reasoned that the same π-allyl-Pd complex should also be generable from allylic alcohol and the combined action of TRIP and $[Pd(PPh_3)_4]$. Indeed, very recently we have shown that a simple achiral Brønsted acid and $[Pd(PPh_3)_4]$ constitutes a powerful catalyst pair for nonasymmetric α-allylations of aldehydes,[8] suggesting that the concentration and nucleophilicity of the aldehyde-derived enol is sufficient for the reaction to occur. This transformation proceeds via a mass-spectrometrically detectable π-allyl-Pd intermediate and not through a Claisen mechanism,[6a,b] and no reaction occurs in the absence of Pd. However, while we were delighted to find that TRIP and $[Pd(PPh_3)_4]$ indeed readily catalyze the α-allylation of hydratropic aldehyde (2-phenylpropanal, **1a**) with allylic alcohol (**2a**), the enantiomeric ratio of product **3a** was disappointingly minuscule [Eq. (2)].



(2)

We hypothesized that the low enantioselectivity can be attributed to the fact that both *E*- and *Z*-enol isomers are generated under our reaction conditions but lead to opposite enantiomeric products (Figure 1). In our previous and highly enantioselective variant, a benzhydryl amine derived enamine was invoked, of which we expect the preferred *E* isomer to predominantly engage in the transition state. Consequently,

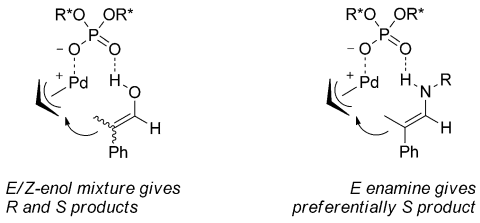


Figure 1. Developing a working hypothesis.

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[**] We thank A. Lee for kindly donating several racemic aldehydes and M. W. Alachraf for MS studies. Generous funding by the Max Planck Society is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103263.

our initial result immediately suggested a solution to the enantioselectivity problem of the aldehyde α-allylation with allylic alcohols: If an amine would be added as the third catalyst, the resulting enamine, because of its higher nucleophilicity, could potentially outperform the corresponding enol in the allylation, and provide the product with high enantioselectivity (Figure 1).

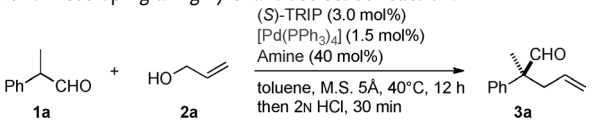
Indeed, this hypothesis served as the guideline of our initial screening experiments. Accordingly, a mixture of substrates **1a** and **2a** was treated with a catalytic amount of $[Pd(PPh_3)_4]$ (1.5 mol%) and (*S*)-TRIP (3.0 mol%) at 40°C for 12 h in the presence or absence of different amines to give aldehyde **3a** in varying yields and enantioselectivities (Table 1). Gratifyingly, adding 40 mol% of different amines to the reaction mixture dramatically increased the enantioselectivity. For example, with amine **A1**, an e.r. of 88:12 was obtained (Table 1, entry 2). As expected from our previous studies, of the different amines (Table 1, entries 2–6), benzhydryl amine **A5** gave the best result and afforded product **3a** in 97% yield and with an excellent enantioselectivity of 97:3 e.r. (Table 1, entry 6). It is noteworthy that 40 mol% of amine **A5** is necessary to ensure high enantioselectivity. Reducing the amount of the cocatalyst leads to lower yield and enantioselectivity (Table 1, entry 7). This seems to mainly result from product inhibition leading to the corresponding benzhydryl imine of **3a**, which undergoes relatively slow hydrolysis under the reaction conditions. In fact, acidic workup of the reaction is required to ensure complete hydrolysis of this imine.

Having established optimized conditions for the asymmetric α-allylation of aldehydes with allylic alcohol, we next examined the scope and limitations of our new reaction. As shown in Table 2, the reaction is quite general and tolerates α-methyl-branched aromatic aldehydes bearing electron-donating and electron-withdrawing groups at different positions. Treating various aldehydes (**1a–i**) with allylic alcohol (**2a**, 2 equiv) in the presence of $[Pd(PPh_3)_4]$ (1.5 mol%), (*S*)-TRIP (3.0 mol%), **A5** (40 mol%), and 5 Å molecular sieves at 40°C in toluene for 12 h readily furnished the corresponding α-allylated aldehydes **3a–i** in 94–98% yields and excellent enantioselectivities (up to e.r. 99.8:0.2; Table 2, entries 1–9). In comparison, our previous protocol gave similar enantioselectivities but slightly lower yields.[4a] For the α-ethyl-substituted substrate **1j** slightly higher catalyst loading was required to obtain the corresponding product **3j** in 77% yield and 81:19 e.r. Remarkably, while aliphatic aldehydes failed to give reasonable conversion with this protocol, we found that when aldehyde **1k** was treated with $[Pd(PPh_3)_4]$, (*S*)-TRIP, and 80 mol% of (*S*)-1-phenylethylamine instead of benzhydryl amine (**A5**) at 110°C, the allylated product **3k** was obtained smoothly and in high yield and promising enantioselectivity (Table 2, entry 11).

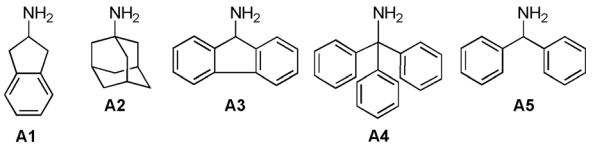
Importantly, we were pleased to find that our new method can be easily extended to a range of substituted allylic alcohols (Table 3). Accordingly, treating aldehyde **1a** with four different substituted allylic alcohols (**2b–e**) readily furnishes the desired products **3l–o** in excellent enantioselectivities (up to 99.3:0.7).

We currently propose the mechanism of our reaction to involve three intertwined catalytic cycles (Figure 2). First, there is an enamine catalytic cycle, in which the aldehyde is activated via an enamine formed with the primary amine catalyst **A5**. The enamine is allylated by the π-allyl-Pd-phosphate via an intermediate that involves all three catalysts and leads to the formation of the product imine and the regeneration of Pd^0 and TRIP. Imine hydrolysis then gives the final product. The π-allyl-Pd-phosphate is generated in the

Table 1: Developing a highly enantioselective reaction.[a]



1a 2a 3a

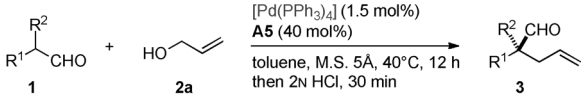


A1 A2 A3 A4 A5

Entry	Amine	Conv. [%][b]	e.r.[d]
1	–	96	55:45
2	**A1**	83	88:12
3	**A2**	94	92.5:7.5
4	**A3**	>99 (96)[c]	91:9
5	**A4**	19	55:45
6	**A5**	>99 (97)[c]	97:3
7[e]	**A5**	88	92:8

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[Pd(PPh_3)_4]$ (1.5 mol%), (*S*)-TRIP (3.0 mol%), amine (40 mol%), M.S. 5 Å (100 mg), toluene (1.0 mL), 40°C, 12 h. [b] Determined by GC–MS or ^{1}H NMR spectroscopy. [c] Yield of isolated product in parenthesis. [d] Determined by HPLC after reduction to the alcohol with $NaBH_4$. [e] 30 mol% of **A5** used.

Table 2: Asymmetric α-allylation of different aldehydes.[a]

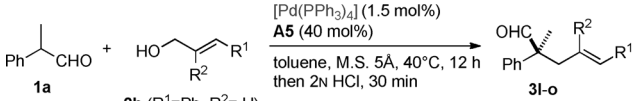


1 2a 3

Entry	R^1	R^2	Prod.	Yield [%][b]	e.r.[f]
1	C_6H_5	Me	**3a**	97	97:3
2	4-MeO-C_6H_4	Me	**3b**	95	97:3
3	4-Me-C_6H_4	Me	**3c**	94	99.8:0.2
4	3-Me-C_6H_4	Me	**3d**	94	96:4
5	4-Ph-C_6H_4	Me	**3e**	98	96:4
6	4-Cl-C_6H_4	Me	**3f**	98	95:5
7[c]	2-F-C_6H_4	Me	**3g**	94	96:4
8	3-F-C_6H_4	Me	**3h**	97	96:4
9	6-MeO-2-naph	Me	**3i**	96	96:4
10[d]	C_6H_5	Et	**3j**	77	81:19
11[d,e]	Cyclohexyl	Me	**3k**	90	84.5:15.5

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[Pd(PPh_3)_4]$ (1.5 mol%), (*S*)-TRIP (3.0 mol%), **A5** (40 mol%), M.S. 5 Å (100 mg), toluene (1.0 mL), 40°C, 12 h. [b] Isolated product. [c] For 24 h. [d] $[Pd(PPh_3)_4]$ (5.0 mol%), (*S*)-TRIP (10 mol%), **A5** (80 mol%), 72 h. [e] 80 mol% of (*S*)-1-phenylethylamine instead of **A5**, 110°C, 24 h. [f] Determined by HPLC after reduction to the alcohol with $NaBH_4$, or by GC with a chiral stationary phase.

Table 3: Asymmetric α-allylation with diverse allylic alcohols.[a]



Entry	Product		Yield [%][f]	e.r.[g]
1[b,c]	$R^1 = Ph$, $R^2 = H$	**3 l**	96	94:6
2[b]	$R^1 = H$, $R^2 = Ph$	**3 m**	96	99.3:0.7
3[d]	$R^1 = Me$, $R^2 = H$	**3 n**	66	96:4
4[e]	$R^1 = H$, $R^2 = Me$	**3 o**	95	94:6

[a] Reaction conditions: **1** (0.2 mmol), **2 a** (0.4 mmol), $[Pd(PPh_3)_4]$ (1.5 mol%), (*S*)-TRIP (3.0 mol%), **A5** (40 mol%), M.S. 5 Å (100 mg), toluene (1.0 mL), 40°C, 12 h. [b] 0.21 mmol of **2**. [c] 60 mol% of **A5**, 24 h. [d] $[Pd(PPh_3)_4]$ (3.0 mol%), (*S*)-TRIP (6.0 mol%). [e] $[Pd(PPh_3)_4]$ (5.0 mol%), (*S*)-TRIP (10 mol%), 60 h. [f] Yield of isolated product. [g] Determined by HPLC after reduction to the alcohol with $NaBH_4$.

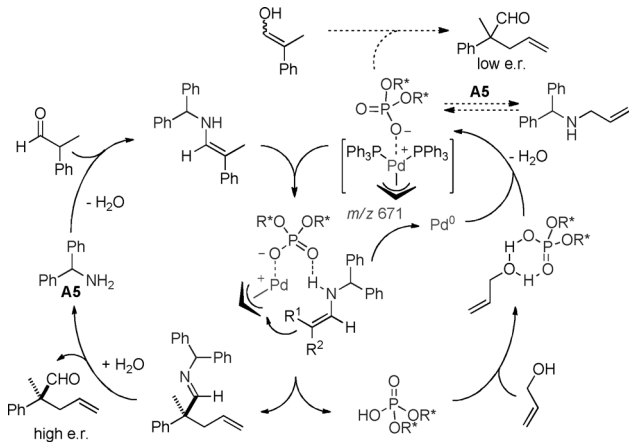


Figure 2. Proposed mechanism for the α-allylation of aldehydes.

second catalytic cycle involving the oxidative addition of Pd^0 into the activated allylic alcohol.[9] This intermediate may also react with benzhydryl amine itself, leading to benzhydryl allyl amine. However, this reaction should be reversible and is therefore likely inconsequential. The third catalytic cycle describes the Brønsted acid catalysis by TRIP, which activates the allylic alcohol for Pd insertion.

As suggested above, we suspect the high enantioselectivity to arise from an ACDC complex that involves all three catalysts: the amine, which engages in the formation of a configurationally defined *E* enamine, Pd^{II}, and the chiral counteranion. Hydrolysis of the initial imine product is relatively slow, leading to product inhibition and the requirement of a relatively high loading of the amine catalyst to ensure an enamine pathway that is faster than the competing enol pathway. Our suggested mechanism is supported by MS studies, in which we could detect the π-allyl-Pd cation (*m*/*z* 671). We could also detect the enamine intermediate and the product-derived imine (see the Supporting Information). That an alternative Claisen rearrangement mechanism is not operative has been shown by experiments using a deuterated allylic alcohol ($CH_2{=}CHCD_2OH$), which leads to the product mixture expected from a π-allyl-Pd-mechanism (see the Supporting Information).[6a]

In summary, we have developed the first highly enantioselective direct α-allylation of α-branched aldehydes with allylic alcohols. Effective asymmetric induction is realized through the incorporation of a chiral anion within the activated complex following an ACDC strategy. Our reaction efficiently creates all-carbon quaternary stereogenic centers in a single step from readily available precursors. Most importantly, simple allylic alcohols can be used directly and do not require derivatization in an additional chemical step.

Received: May 12, 2011
Revised: June 7, 2011
Published online: September 13, 2011

Keywords: allylation · allylic alcohol · chiral counteranions · palladium · phosphates

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