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Palladium(0)-Catalyzed Rearrangement of Allyl Enol Ethers to Form Chiral Quaternary Carbon Centers via Asymmetric Allylic Alkylation

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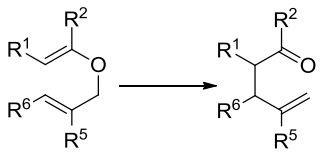
ABSTRACT

Herein we report the first palladium(0)-catalyzed asymmetric allylic alkylation (AAA) of allyl enol ether via π-allylpalladium intermediate using Trost chiral diphosphine. This unprecedented reaction produced very rare α-aryl quaternary aldehydes with multi-functional groups. The main novelty in the chemistry demonstrates that enol ethers can be used as precursors for π-allylpalladium intermediates, an observation that is certainly rare and to the best of our knowledge, perhaps without prior precedent. Chiral ligand (R,R)-L3 was found to be optimal in this Pd-AAA reaction and provided good to excellent yield (80-95%) and enantioselectivity (70-90%) with a range of analogs.

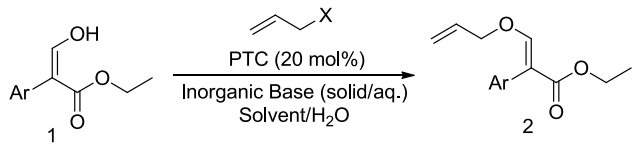
Introduction

Ever since the first example of [3,3]-sigmatropic rearrangement of an allyl enol ether was reported by Claisen in 1912,[1] this reaction has been developed into one of the most powerful C-C bond forming methods (Scheme 1).[2] There are numerous methods to carry out the Claisen rearrangement and related [3,3]-sigmatropic rearrangements enantioselectively by using chiral reagents.[3] Overman *et al.* reported the first catalytic enantioselective [3,3]-sigmatropic rearrangement for allyl-imidates using a Pd(II) asymmetric catalyst.[4] Yamamoto *et al.* used chiral Lewis acids based on Al(III) for the enantioselective Claisen rearrangement of acyclic, aliphatic allyl vinyl ethers.[5] However, 1-2 equivalents of the chiral Lewis acid are required and the scope of the reactions are limited to selective substrates. Recently the Kozlowski group described Cu(II)- and Pd(II)-catalyzed enantioselective Claisen rearrangement of allyloxy- and propargyloxy-indoles to quaternary oxindoles and spirocyclic lactones with excellent yield and enatioselectivity.[6]



Scheme 1. The Claisen rearrangement of an allyl enol ether subsrates

We developed a new procedure of synthesizing arylhydroxyacrylates from simple aromatic aldehydes and ethyl diazoacetate (EDA) in the presence of a Brønsted acid or iron Lewis acid. We also found out that these substrates are very useful precursors for the synthesis of indoles[8] and furans[9]. Most importantly, the presence of prochiral carbon centers in these compounds allow us to synthesize chiral all-carbon quaternary stereocenters.[10]



PTC = Bu_4NX; X = Cl, Br, I; Solvent = toluene, DCM, THF
Inorganic bases = KOH, NaOH

Scheme 2. Phase transfer catalyzed reaction of ethyl 2-aryl-3-hydroxyacrylates **1** provided mostly O-allylated product **2**.

In order to synthesize all-carbon quaternary centers first we investigated the allylation reactions of hydroxyacrylates with allyl halides, as electrophilic counterparts, in bases such as solid or aqueous KOH and NaOH using achiral Bu_4NI or Bu_4NBr as the phase transfer catalyst (PTC). All of the reactions provided exclusively *O*-allylation product **2** (Scheme 2).[11] Reactions carried out in the absence of a PTC resulted in very low yields of product. The NMR studies (NOESY experiment) showed *E*-stereochemistry of the double bond of *O*-allylated product, presumably due to minimization of dipoles in an approximate anti-parallel orientation between the oxygen of the allyl vinyl

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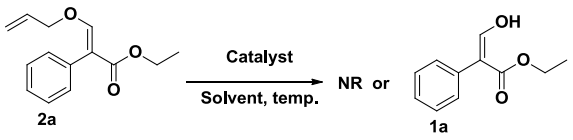
ether and the carbonyl oxygen of the ester. The *O*-allylation is more favored because of the high degree of conjugation present in the acrylate **1** is preserved during *O*-allylation, and it is disrupted in *C*-allylation. Later, we observed the *O*-allylated compound, allyl enol ether **2** undergoes the thermal Claisen rearrangement reactions to provide all carbon quaternary aldehydes in good yields.[11]

Results and discussion

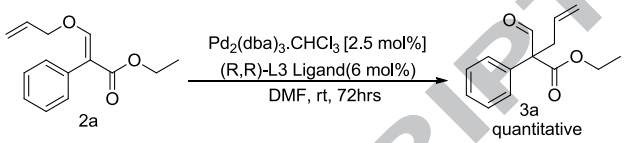
Encouraged by the results from the thermal Claisen rearrangement, we then turned our attention to the asymmetric variant using chiral catalysts. In order to identify the desired catalyst, allyl enol ether **2a** as a test substrate**,** different chiral Lewis acids[3-6] along with some achiral Lewis acids have been investigated. The results are summarized in Table 1. In this study, we found that our catalytic rearrangement reaction resulted either in no product being formed or, for stronger achiral Lewis acids (entries 4 and 6), cleavage of the bond between the enolic oxygen and the allylic carbon was occurred. Only low yields of product have been observed (29% C-alkylated) for the Claisen rearrangement with the [Cu(box)](SbF6)2 metal complex at elevated temperature (60 °C) (entry 11).

Table 1. Attempted Claisen rearrangement with Lewis acids.



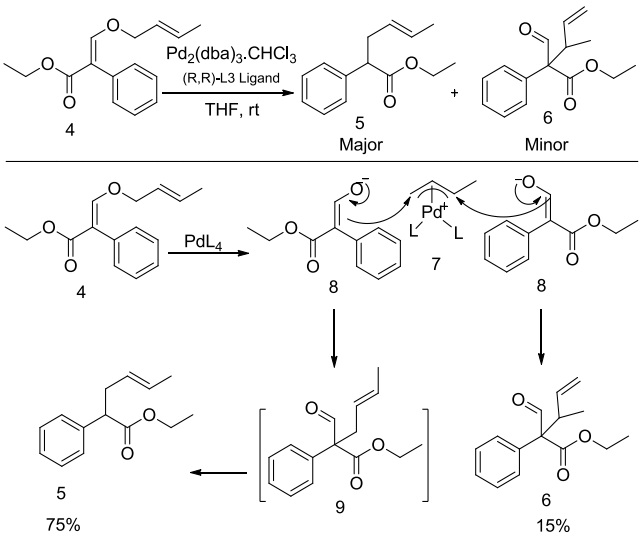
entry	catalyst	ligand	product	T (°C)
1	$Zn(OTf)_2$	BOX	-	rt
2	$Zn(SbF_6)_2$	BOX	-	rt
3	$Ni(SbF_6)_2$	BINAP	-	rt
4	$PdCl_2(CH_3CN)_2$	-	1+2	rt
5	$Pd(dppf)Cl_2$ $.CH_2Cl_2$	-	-	rt to 50
6	$BF_3{\cdot}OEt_2$	-	1+2	rt
7	$Fe(SbF_6)_2$	PyBox	-	rt
8	$[Rh(COD)Cl]_2$	(*R,R*)-L3	-	50
9	$(Cp^*RhCl_2)_2$	-	-	rt to 50
10	$Cu(SbF_6)_2$	BOX	-	rt
11	$Cu(SbF_6)_2$	BOX	3a (29%)	60

To our surprise, during investigation, we observed that allyl enol ether **2a** did go through a Pd(0)-catalyzed rearrangement to give quantitative yield of the *α*-aryl quaternary aldehyde **3a** (Scheme 3). As a Pd(0) source both $Pd(PPh_3)_4$ and $Pd_2(dba)_3.CHCl_3$ were equally found to be effective in the catalytic transformation. To understand the mechanism of this arrangement, we investigated the reaction of the *O*-crotylated compound **4** in the presence of Pd(0) (Scheme 4). The compound **4** was synthesized from arylhydroxyacrylate **1** and crotyl bromide using the same procedure which was used for the preparation of compound **2**. Reaction of the *O*-crotyl compound **4** catalyzed by Pd(0) generated both the decarbonylated product **5** and the quaternary aldehyde **6** in 75% and 15% yields, respectively (Scheme 4). However, when the reaction was refluxed in DMF, the compound **4** exclusively produced Claisen product **6**. Based on these observations whereas both **5** and **6** were detected as products, it is likely that the Pd(0)-catalyzed reaction of **4** is proceeding through a mechanism other than a Claisen rearrangement.



Scheme 3. Pd(0) catalyzed rearrangement of allyl enol ether **2a**.

In this palladium-catalyzed mechanism, we believe that the strong nucleophilicity of Pd(0) and the stability of aryl acrylate anion **8** are the driving forces for the formation of Pd-allyl complex **7** from **4** (Scheme 4). The nucleophilic attack by the acrylate anion **8** to *π*-allyl complex **7** could occur at symmetrical and asymmetrical ends,[12] providing compounds **9** and **6**. Compound **9** subsequently undergoes decarbonylation under the reaction condition to form compound **5**. A similar process such as an allylic alkylation rather than a Claisen rearrangement is occurring in Pd(0)-catalyzed reaction of compound **2** in the formation of **3**.



Scheme 4. Proposed mechanism of Pd(0) catalyzed reaction of (*Z*)-ethyl 3-((*E*)-but-2-en-1-yloxy)-2-phenylacrylate **4**.

Later, we directed our study to the asymmetric variant of this Pd(0)-catalyzed allylic alkylation. To optimize the reaction conditions for high asymmetric induction, we first attempted investigating the effects of systematic variations of the ligand, solvent, and temperature on enantiodiscrimination. For our ligand screening, we selected *C2* symmetric Trost diphenylphosphino benzoic acid (DPPBA) ligands and phosphinooxazolines (PHOX) ligands, which are well known for Pd(0)-catalyzed asymmetric allylic alkylation reactions (Figure 1). It was demonstrated from our studies that *C2* symmetric Trost ligands (*R,R*)-L3, (*R,R*)-L4 are more effective in enantiodiscrimination than the PHOX type ligand (*S*)-L2.

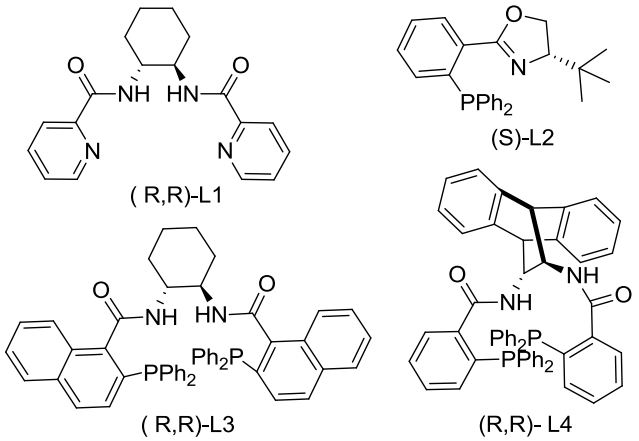
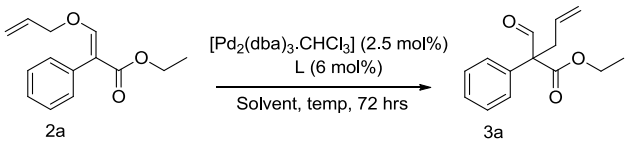


Figure 1. Chiral ligands used for the optimization

Among the Trost ligands, DACH-napthyl Trost ligand, (R,R)-L3 is the most effective. The highest level of enantioselectivity were observed with the use of (R,R)-L3 (Table 2, entry 9 and 10) and ANDEN-phenyl Trost (R,R)-L4 gave only 30% ee (Table 2, entry 16) whereas with DACH-pyridyl ligand (R,R)-L1 there was no reaction at all (Table 2, entry 1, and 2). Other ligands such as phosphinooxazoline (PHOX), bis(oxaziline) (BOX), and (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) (BINAP) did not yield product at all and sometimes they were found less active in the transformation, and in all cases they failed to induce any enantioselectivity. After ligand screening, the effect of temperature on reaction rate and enantioselectivity was investigated. We did reaction by varying temperature from room temperature to -78 °C. Our results showed that temperature also has a profound effect in both yield and %ee. The reaction was found to work best between -10 °C and -20 °C. We observed that reaction at room temperature or at 0 °C, rate of the reaction were faster but resulted in reduced enantioselectivity (Table 2, entries 3, 5, 13, and 15). At lower temperature (i.e., -40 °C or -78 °C) there were no reactions at all (Table 2, entries 11 and 12). We investigated the best yield as well as best enantiomeric excess at -20 °C (Table 2, entry 9).

Finally, we explored the reaction in different solvents. It was mentioned that nonpolar aprotic solvents gave higher yields and %ee of the product.[13] During our observation of solvent screening it was also revealed that nonpolar aprotic solvents gave higher yields and % ee of the product (Table 2, entry 6) and at lower temperature it was more effective (Table 2, entry 8). But with the help of polar protic solvent such as methanol, it provided higher yield and higher enantiomeric excess. Experimental results showed solvent polarity played a major role in the reaction rate and enantioselectivity; for instance, under similar reaction condition the %ee in mixed solvent toluene:hexane (1:1) was 65% (Table 2, entry 8), whereas in the toluene:methanol (20:1), the %ee jumped to 83% (Table 2, entry 9). The ideal solvent polarity, toluene:methanol (20:1), afforded us with maximum yield and enantioselectivity for our parent system comes from mixed solvent. We believe a plausible explanation for this lies in the solubility and complex formation of ligand and metal. In our reaction pathway acrylate and palladium complex ion were formed, so nonpolar solvents help to dissolve the ligand slowly to form the metal complex, and the polar solvents has better interaction with the substrate enolate in a 'tight ion pair' formation for a longer period of time over the course of the reaction which were found in the reaction mechanism.

Table 2. Selected optimization studies[a]

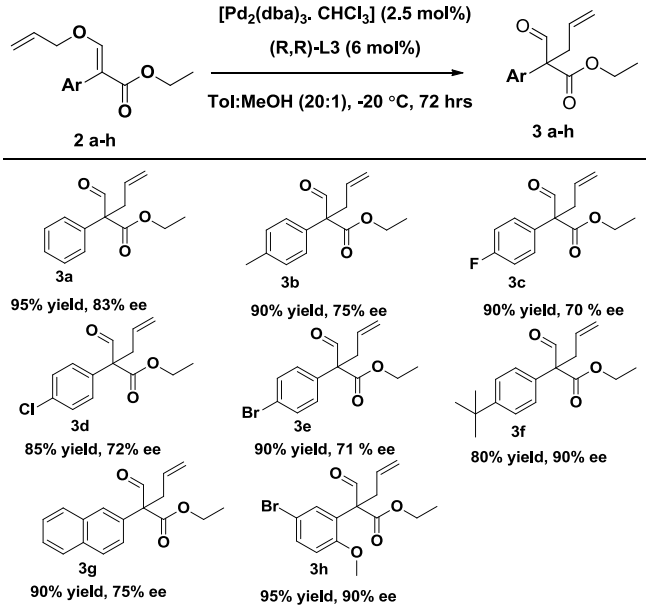


entry	ligand	solvent	T[b] (°C)	conv.[c] (%)	ee[d] (%)
1	(*R*,*R*)-**L1**	CH_2Cl_2	rt	0	0
2	(*R*,*R*)-**L1**	Tol:Hex (1:1)	-20	0	0
3	(*S*)-**L2**	Tol:Hex (1:1)	rt	>99	20
4	(*S*)-**L2**	Tol:Hex (1:1)	-20	>99	0
5	(*R*,*R*)-**L3**	Tol:Hex (1:1)	rt	>99	30
6	(*R*,*R*)-**L3**	Toluene	-20	90	50
7	(*R*,*R*)-**L3**	THF	-20	90	33
8	(*R*,*R*)-**L3**	Tol:Hex (1:1)	-20	90	65
9	(*R*,*R*)-L3	Tol : MeOH (20:1)	-20	95	83
10	(*R*,*R*)-**L3**	Tol : EtOH (30:1)	-20	80	75
11	(*R*,*R*)-**L3**	Tol : MeOH (30:1)	-40	0	0
12	(*R*,*R*)-**L3**	Tol : MeOH (30:1)	-78	0	0
13	(*R*,*R*)-**L3**	CH_2Cl_2	rt	>99	Rac.
14	(*R*,*R*)-**L3**	ACN	0	>99	Rac.
15	(*R*,*R*)-**L3**	DMSO	rt	>99	20
16	(*R*,*R*)-**L4**	Tol:Hex (1:1)	-20	70	0
17	(*R*,*R*)-**L4**	CH_2Cl_2	rt	>99	30

[a]The reaction was performed with 2a (0.25 mmol) in solvent (5.0 mL). [b]Optimized temperature for the best ee value and conversion. [c]Determined by analysis of the reaction mixture by ^{1}H NMR spectroscopy. [d]Determined by HPLC analysis by using a chiral stationary phase.

In order to determine the scope of this rearrangement reaction, a number of analogs were subjected to the newly optimized reaction conditions (Table 3). In general, good to excellent yields (80%-95%) and enantioselectivities (70-90%) were obtained. Studies showed that electron donating substituents (**3f, 3h**) appreciably affect the yields and enantioselectivities. These groups make the acrylate ion electron rich and help to attack π-allyl complex **7 to** get higher yields and enantioselectivities (with an exception of 3b**)** compare with electron withdrawing substituents (**3c-e**). Surprisingly, the sterically bulky and hence theoretically more challenging napthyl analog (**3g**) provided high yield (90%) and good enantioselectivity (75% ee) as well.

Table 3. Scope of the optimized Pd-catalyzed intramolecular AAA reactions 3a-h[a].



[a]All reactions were performed on 0.25 mmol scale in solvent (5.0 mL). The yields shown are those of the isolated products, and the %ee values were determined by HPLC analysis using a chiral stationary phase.

Conclusion

In summary, we have developed palladium(0)-catalyzed asymmetric allylic alkylation (AAA) of allyl enol ethers via π-allylpalladium intermediate using Trost chiral diphosphine ligand. In this process, syntheses of *α*-aryl quaternary aldehydes[14] were achieved in high yields and moderate to high enantioselectivies. To the best of our knowledge, we believe this is the first example of allyl enol ethers rearrangement to create chiral *α*-aryl quaternary aldehydes via AAA catalyzed by Pd(0). Synthetic methodologies to access compounds containing *α*-aryl groups to the quaternary carbon stereocenters are still rare. The increasing appearance of these all-carbon *α*-aryl quaternary stereocenters[14,15,16] in a growing number of biologically active natural products and pharmaceutical agents[17] make this important motif very demanding.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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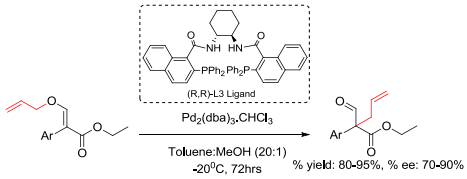

Highlights

- The first palladium(0)-catalyzed allylic alkylation of enol ether.
- Development of catalytic and enantioselective reaction via π-allyl complex.
- Quaternary aldehydes with multiple functional groups were enantioselectively prepared.