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Asymmetric α-Allylation of Aldehydes with Alkynes by Integrating Chiral Hydridopalladium and Enamine Catalysis

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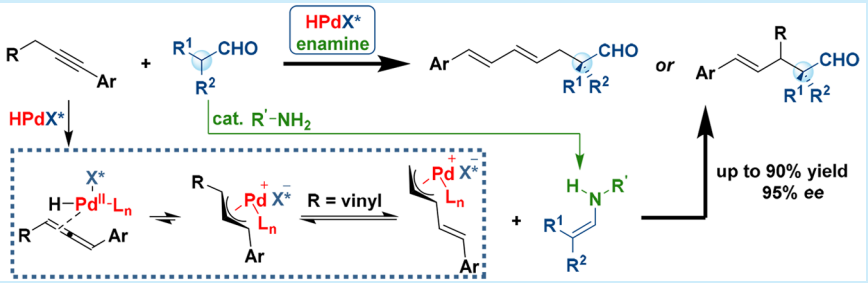
Supporting Information

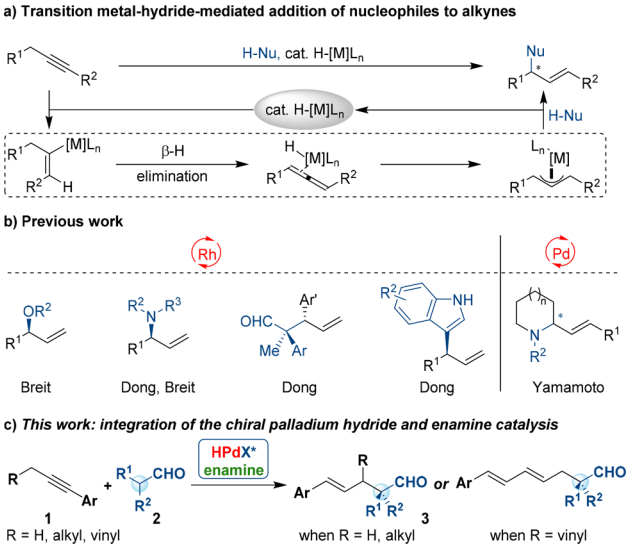


ABSTRACT: A palladium-catalyzed asymmetric α-allylation of aldehydes with alkynes has been established by integrating the catalysis of enamine and chiral hydridopalladium complex that is reversibly formed from the oxidative addition of Pd(0) to chiral phosphoric acid. The ternary catalyst system, consisting of an achiral palladium complex, a primary amine, and a chiral phosphoric acid allows the reaction to tolerate a wide scope of α,α-disubstituted aldehydes and alkynes, affording the corresponding allylation products in high yields and with excellent levels of enantioselectivity.

The discovery of completely atom-economic chemical reactions has been a long-standing research target in modern synthetic organic chemistry.[1] The transition-metal-catalyzed allylic substitution reaction[2] has been one of the most fundamentally important transformations,[3] with widespread applications to the synthesis of pharmacologically important molecules.[4] However, the general requirement of high oxidation state allylic precursors, along with the generation of stoichiometric amounts of waste, poses constant constraints on the synthetic efficiency. In recent decades, transition-metal hydride-mediated addition of nucleophiles to alkynes[5] has been a versatile alternative to generate allylmetal complexes, allowing the creation of atom-economic allylic substitution reactions for building structural complexity from easily accessible starting materials (Scheme 1a). With the use of chiral phosphine ligands, Rh-catalyzed enantioselective allylic substitution transformations of alkynes for the formation of C−O,[6] C−N,[7] and C−C[8] bonds have been successfully developed by Breit and Dong. However, only Pd-catalyzed enantioselective intramolecular allylic amination reactions have been reported, based on palladium hydride-mediated addition to the carbon−carbon triple bond (Scheme 1b).[9] Herein, we will report an asymmetric α-allylation of aldehydes with alkynes by integrating the chiral hydridopalladium complex and enamine catalysis (Scheme 1c).

Trost revealed that the palladium(0) complex is able to undergo oxidative addition to acetic acid to generate a hydridopalladium complex,[10] which then reacts with acetylenes to form electrophilic π-allylpalladium complexes.[11] Inspired by

Scheme 1. Transition-Metal-Catalyzed Asymmetric Allylic Functionalization by Using Alkynes as Allylic Precursors



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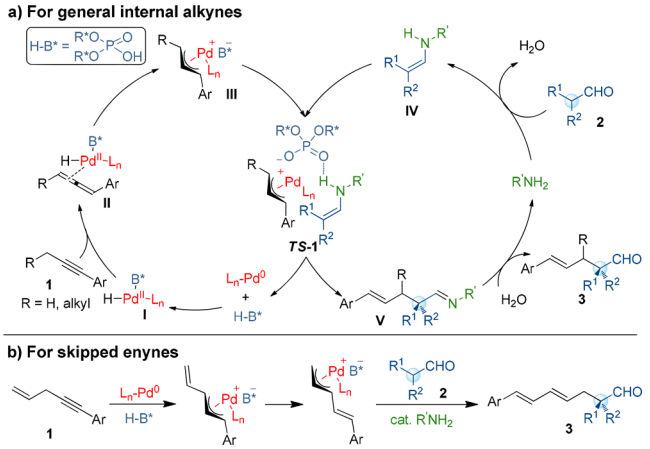
these elegant precedents, we discerned that a chiral hydridopalladium phosphate **I** would be generated from palladium(0) complex and a chiral phosphoric acid and then might isomerize an alkyne to an allene **II**. Subsequently, another hydropalladation between the allene **II** with the chiral hydridopalladium **I** may proceed to form a chiral π-allylpalladium phosphate species **III**. As indicated by previous asymmetric counteranion-directed catalysis[12,13] and our own study on the oxidative coupling of an enolizable aldehyde and a terminal alkene by using a triple catalytic system,[14] the enamine **IV** reversibly generated from the aldehyde and the amine catalyst would undergo asymmetric allylic substitution with chiral π-allylpalladium phosphate **III** via the transition state **TS-1**[12] to give a coupling product **V** stereoselectively, which finally undergoes the hydrolysis to furnish the allylation product **3** and regenerates the amine catalyst (Scheme 2a). As such, the

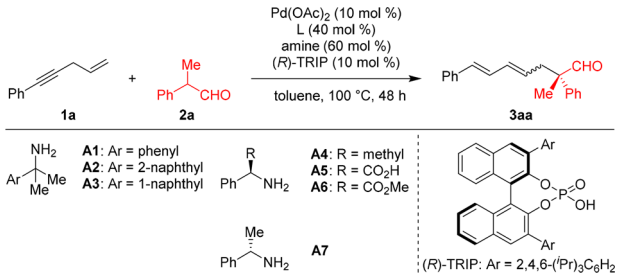
Scheme 2. Mechanistic Rationale for the Asymmetric Allylation of Enolizable Aldehydes with Alkynes by Integrating the Catalysis of Enamine and Hydridopalladium Phosphate, Reversibly Formed from Palladium(0) and Chiral Phosphoric Acid



multiple catalyst system[12,14,15] of palladium, a primary amine, and a chiral phosphoric acid[16] would enable the asymmetric α-allylation of aldehydes with alkynes by integrating the catalytic activity of enamine and chiral hydridopalladium phosphate (Scheme 2).

Because of the synthetic versatility and prevalence of conjugated dienes in biologically relevant molecules,[17] a skipped enyne[18] **1a** was selected as a model substrate for the hypothesis (Scheme 2b). The preliminary study was evaluated by the treatment of pent-4-en-1-yn-1-ylbenzene (**1a**) and 2-phenylpropanal (**2a**) in the presence of $Pd(OAc)_2$ (10 mol %), PPh_3 (40 mol %), achiral amine **A1** (60 mol %), and (*R*)-TRIP (10 mol %) at 100 °C, affording the desired allylation product **3aa** in 55% yield, 9:1 *E*/*Z* and with good enantiomeric excess (Table 1, entry 1). Fine tuning of the aryl group of the achiral amine significantly improved the yield and enantioselectivity (Table 1, entries 2 and 3). In consideration of the obvious impact of the amine catalyst on the reaction performance, other chiral amines were investigated. However, a variety of amine catalysts provided allylation product **3aa** in moderate to low yield and with significantly reduced enantioselectivity (Table 1, entries 4–7). The examination of various phosphine ligands revealed that the pattern of phosphine ligands could dramatically influence the electronic and steric feature of the

Table 1. Optimization of Reaction Conditions[a]



entry	L	amine (A)	yield[b] (%)	*E*:*Z*[c]	ee[d] (%)
1	PPh_3	**A1**	55	9:1	83
2	PPh_3	**A2**	60	9:1	86
3	PPh_3	**A3**	80	10:1	92
4	PPh_3	**A4**	56	5:1	56
5	PPh_3	**A5**	36	4:1	35
6	PPh_3	**A6**	20	6:1	44
7	PPh_3	**A7**	46	6:1	64
8	PCy_3	**A3**	75	2:1	2
9	xantphos	**A3**	50	12:1	89
10	dppf	**A3**	36	5:1	87
11	(*S*)-BINAP	**A3**	trace		
12	dppe	**A3**	trace		
13[e]		**A3**	75	10:1	94
14[e,f]		**A3**	80 (73)[g]	10:1	94
15[f,h]		**A3**	63	9:1	91
16[f,i]		**A3**	7		

[a]Reaction conditions: unless indicated otherwise, the reaction of **1a** (0.20 mmol), **2a** (0.40 mmol), $Pd(OAc)_2$ (10 mol %), **L** (40 mol %), **A** (60 mol %), and (*R*)-TRIP (10 mol %) was carried out in toluene (2 mL) for 48 h at 100 °C. [b]Yield was determined by ^{1}H NMR analysis of the crude reaction mixture by using trimethylbenzene-1,3,5-tricarboxylate as an internal standard. [c]The *E*/*Z* was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]The ee value was determined by HPLC, and the absolute configuration was assigned by comparing the optical rotation with the literature value. [e]10 mol % $Pd(PPh_3)_4$ was used. [f]80 mol % **A3** and 0.6 mmol **2a** was used. [g]Isolated yield. [h]7.5 mol % $Pd(PPh_3)_4$ and 7.5 mol % (*R*)-TRIP were used. [i]5 mol % $Pd(PPh_3)_4$ and 5 mol % (*R*)-TRIP were used.

π-allyl-Pd phosphate moiety in the transition state and thereby could alter the reactivity and stereoselectivity.[3b,c] For instance, an electron-rich alkylphosphine resulted in a similar yield but with much diminished *E*/*Z* and enantioselectivity (Table 1, entry 8). Notably, a clear effect of diphosphine ligand bite angles on the reaction was observed,[19] and the wider bite angle was beneficial to the reactivity and the control of alkene geometry. Xantphos (Table 1, entry 9, bite angle = 108°) could smoothly give **3aa** in 50% yield, 12:1 *E*/*Z* and 89% ee, and dppf (bite angle = 99°) also afforded **3aa** with reduced yield and *E*/*Z* selectivity (Table 1, entry 10), yet only trace amount of product **3aa** was obtained when either BINAP (bite angle = 93°) or dppe (bite angle = 86°) was used (Table 1, entries 11 and 12). The absence of achiral counteranion, such as acetate, could further improve the enantioselectivity (Table 1, entry 13). A slightly improved yield with maintained stereoselectivity was obtained by increasing the stoichiometry of the aldehyde **2a** and in the presence of 80 mol % of amine catalyst **A3** (Table 1, entry 14). However, much diminished results were observed when 7.5 mol % $Pd(PPh_3)_4$ and 7.5 mol % (*R*)-TRIP were used (Table 1, entry 15), and almost trace amounts of product were obtained at an even lower catalyst loading (Table 1, entry 16).

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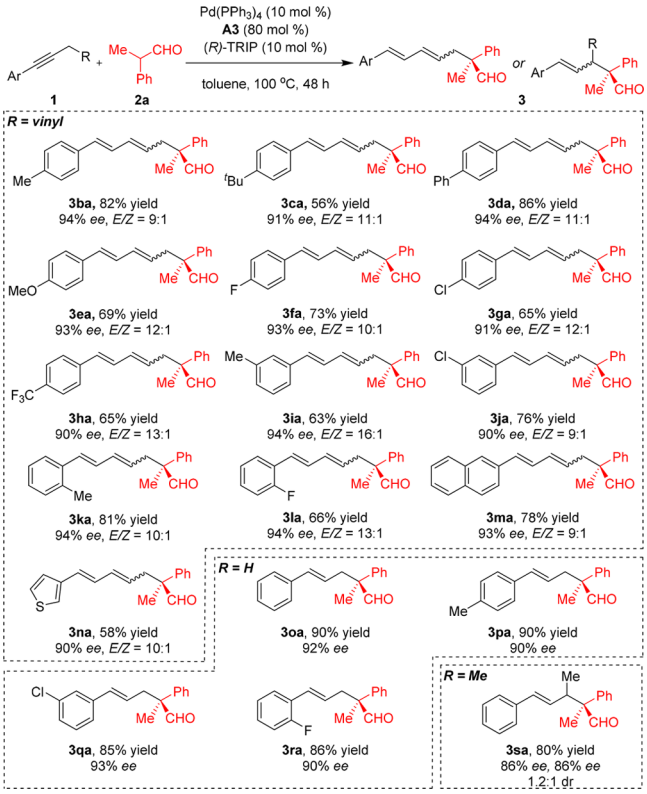
Having established the optimized conditions, the substrate scope for alkynes was explored next (Scheme 3). A wide scope

Scheme 3. Scope, with Respect to Alkynes[a]

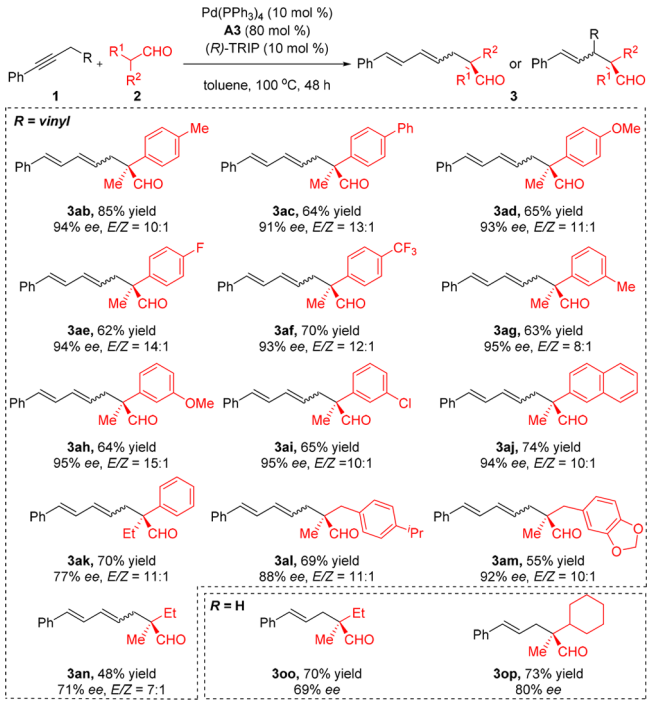


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), $Pd(PPh_3)_4$ (10 mol %), (*R*)-TRIP (10 mol %), **A3** (80 mol %), toluene (2 mL), 48 h at 100 °C, under N_2. The yield was determined after separation by silica gel chromatography. The *ee* value was determined by HPLC. The *E*/*Z* was determined by ^{1}H NMR analysis of the crude reaction mixture.

of phenyl-substituted skipped enynes (**1b**−**1l**) bearing both electron-donating and electron-withdrawing groups at the *para*-, *meta*-, and *ortho*-position of the phenyl moiety gave the desired allylation products in moderate to good yields and with excellent *E*/*Z* and enantioselectivities. In addition, skipped enynes with aromatic and heteroaromatic substituents, including 2-naphthlalene (**1m**) and 3-thiophene (**1n**), could be tolerated to undergo efficient and stereoselective allylation. Moreover, a series of 1-arylpropynes (**1o**−**1r**) were also able to participate in the asymmetric allylation reaction, providing the allylation product with excellent yields and enantioselectivities. Moreover, 1-phenyl-1-butyne (**1s**) afforded comparable yield and enantioselectivity to the 1-arylpropynes, albeit with unsatisfactory diastereoselectivity.

The generality for α,α-disubstituted aldehydes then was examined under the optimized reaction conditions (see Scheme 4). Significantly, the protocol was amenable to a wide range of enolizable aldehydes. In addition to the α-methyl-substituted 2-arylacetaldehyde (**2b**−**2j**), the reaction was tolerant of both electron-donating and electron-withdrawing substituents at different positions of the aryl moiety. The α-ethyl-substituted aldehyde (**2k**) underwent the reaction to give a good yield, but with only acceptable enantioselectivity. Remarkably, a series of aliphatic aldehydes were also suitable coupling partners for the

Scheme 4. Scope, with Respect to Aldehydes[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $Pd(PPh_3)_4$ (10 mol %), (*R*)-TRIP (10 mol %), **A3** (80 mol %), toluene (2 mL), 48 h at 100 °C, under N_2. Yield was determined after separation by silica gel chromatography. The ee value was determined by HPLC. The *E*/*Z* was determined by ^{1}H NMR analysis of the crude reaction mixture.

stereoselective allylation. For example, commercially available substances such as cyclamen aldehyde (**2l**) and helional (**2m**) were able to undergo stereoselective coupling with skipped enyne **1a**, giving chiral α,α-disubstituted aldehydes in good yields and with excellent levels of enantioselectivity. It was noteworthy that simple 2-ethylpropanal (**2n**) and 2-cyclohexyl propanal (**2o**) also afforded the corresponding products in moderate to good yields and with good enantioselectivities.

Notably, a gram-scale reaction of **1a** and **2a** was successful and afforded α-quaternary aldehyde **3aa** in 76% yield, 10:1 *E*/*Z* and 94% ee. After the condensation with 4-methoxybenzylamine and followed by reduction with $LiAlH_4$,[20] the aldehyde **3aa** was converted to a secondary amine **4** in excellent yield and maintained enantioselectivity. Alternatively, under the conditions of Pinnick oxidation,[21] the aldehyde **3aa** was transformed to a carboxylic acid, which underwent methylation with (trimethylsilyl)diazomethane ($TMSCH_2N_2$) to yield the corresponding ester **5**. On the other hand, α-quaternary nitrile **6** was accessed by sequential treatment of **3aa** with hydroxylamine hydrochloride and CDI (1,1′-carbonyldiimidazole). Furthermore, a chiral tetrahydropyran **7** could also be furnished in excellent yield via the reduction and a gold-catalyzed intramolecular cyclization, despite having low diastereoselectivity. (A derivation of chiral aldehydes is given in Scheme 5.)

In conclusion, we have established a palladium-catalyzed atom-economic asymmetric α-allylation of aldehydes with alkynes by using a ternary catalyst system of achiral palladium(0) complex, primary amine, and chiral phosphoric acid to integrate enamine and chiral hydridopalladium phosphate catalysis. The protocol enables a wide range of alkynes and enolizable aldehydes to give a diverse spectrum of

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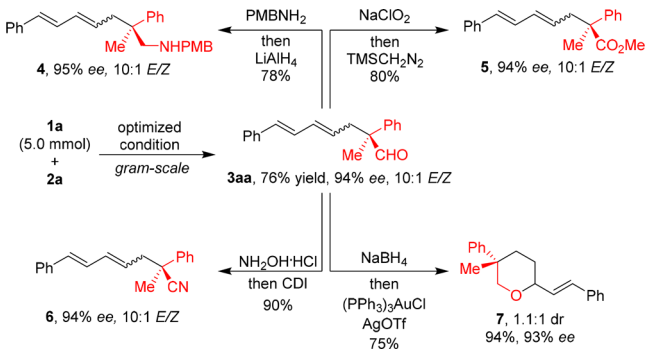
Scheme 5. Derivatization of Chiral Aldehydes



chiral α-quaternary aldehydes in high yields and with high levels of enantioselectivity. Moreover, the chiral α-quaternary aldehydes can serve as a platform molecule for the synthesis of an array of important synthetic intermediates, which highlights the potential applications in target-directed synthesis. More importantly, this work suggests a general strategy to create asymmetric allylic alkylation reactions with alkynes by trapping chiral π-allylpalladium phosphates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00740.

Complete experimental procedures and characterization data for the prepared compounds (PDF)

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Notes

The authors declare no competing financial interest.

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