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Pd-Catalyzed Asymmetric Hydroalkylation of 1,3-Dienes: Access to Unnatural α-Amino Acid Derivatives Containing Vicinal Quaternary and Tertiary Stereogenic Centers

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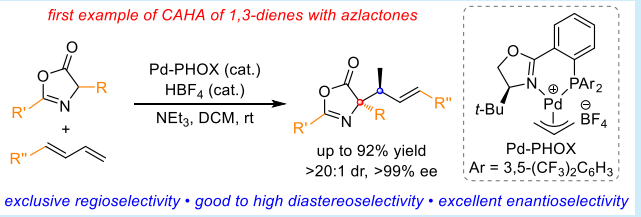
Supporting Information

ABSTRACT: Pd-phosphinooxazoline (Pd-PHOX)-catalyzed asymmetric hydroalkylation of 1,3-dienes with azlactones was successfully developed for the first time, affording various enantioenriched α-quaternary α-amino acid derivatives bearing contiguous quaternary and tertiary stereogenic centers in good yields with exclusive regioselectivity and excellent stereoselective control (up to 92% yield, >20:1 dr, and >99% ee). The scale-up catalytic asymmetric hydroalkylation was performed well without loss of reactivity and stereoselectivities, which exhibited great potential application. The synthetic utility of the current methodology was demonstrated through product transformations to access other biologically important compounds such as chiral β-amino alcohol and α-quaternary cyclic α-amino acid derivatives.



Optically active unnatural α-quaternary α-amino acids (α-AAs) and derivatives have captured great attention, which could be attributed to their advantages as versatile building blocks for the synthesis of unnatural peptides, and they play an important role in medicinal chemistry.[1] In addition, they have been identified as prevalent substructures in a large number of other chiral molecules with biological activities.[2] The remarkable importance of chiral unnatural quaternary α-amino acids has caused an increasing interest to develop efficient methodologies for the asymmetric construction of these valuable compounds. However, the preparation of chiral α-quaternary α-amino acid and derivatives, especially α-quaternary α-amino acid containing vicinal tertiary and quaternary stereocenters, has been one of the major and challenging targets in the field of asymmetric catalytic synthesis.

Azlactones have been extensively explored and emerged as important kinds of valuable synthons for the construction of chiral quaternary α-amino acids in the past decades.[3] Various synthetic strategies have been developed[4−11] such as asymmetric alkylations,[4] conjugate additions,[5] Mannich-type reactions,[6] cycloadditions,[7] and allylic alkylations.[8−10] Among them, transition-metal-catalyzed allylic alkylations of azlactones have proven to be powerful synthetic methodologies which are mainly involved allylic alcohols, activated derivatives,[8] and allenes[9] as π-allyl fragment sources, and also most recently in elegant work documented by Gong and coworkers with 1,4-dienes via C−H activation strategy.[10] Since Takahashi reported the first example of catalytic intermolecular diene hydroalkylation promoted by a Pd catalyst in early 1970s,[11] conjugated 1,3-dienes have become attractive synthons in asymmetric hydrofunctionalization,[12] which is initiated by a migratory insertion of in situ-generated transition-metal hydride (M-H) to deliver an electrophilic π-allyl metal intermediate followed by a nucleophilic attack. However, asymmetric hydroalkylation of 1,3-dienes with carbon-based nucleophiles is rarely explored, especially for the construction of multiple stereogenic centers.[13] To the best of our knowledge, there is only one racemic example on the hydroalkylation of 1,3-dienes with azlactones, that is, (CDC)−Rh-catalyzed hydroalkylation of 1,3-dienes with azlactones developed by Meek and coworkers to generate α,α-disubstituted allylic amino acid products containing vicinal tertiary and quaternary stereocenters in good yields with high diastereoselectivities (Scheme 1, top).[14] Most recently, Malcolmson and coworkers reported a pioneering asymmetric addition of carbon-based nucleophiles to 1,3-dienes catalyzed by a Pd-phosphinooxazoline (Pd-PHOX) complex with high enantioselectivities.[12f,g] However, only moderate diastereoselectivity was observed with the examined prochiral nucleophiles. Encouraged by these achievements and in continuation of our efforts on asymmetric synthesis of unnatural α-AAs,[15] we herein reported the first Pd-catalyzed asymmetric hydroalkylation of 1,3-dienes with various prochiral azlactones, which led to a wide range of chiral α-quaternary α-amino acid derivatives containing vicinal quaternary and tertiary stereo-

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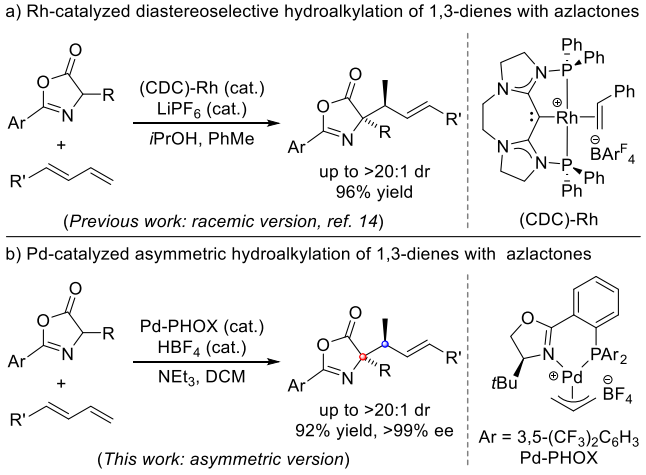
Scheme 1. Synthesis of Quaternary α-Amino Acid Derivatives Containing Vicinal Tertiary and Quaternary Stereocenters via Hydroalkylation of 1,3-Dienes with Azlactones

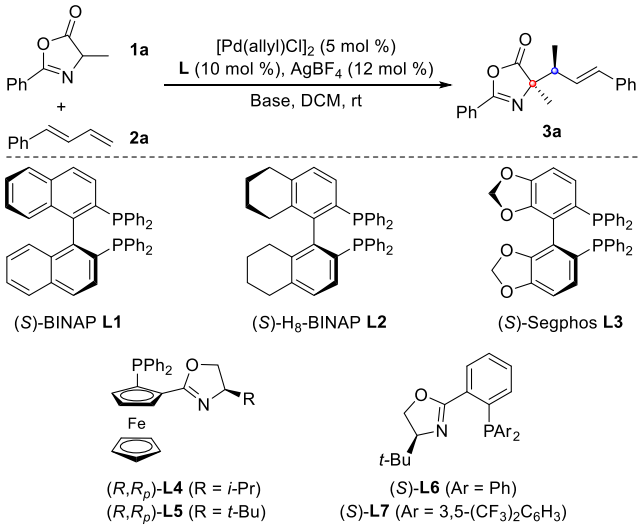


genic centers in good yields with exclusive regioselectivity, high diastereoselectivities, and excellent enantioselectivities (Scheme 1, bottom).

Initially, we investigated the asymmetric induction of commercially available chiral ligands in the Pd-catalyzed hydroalkylation with alanine derived azlactone **1a** and 1-phenylbutadiene **2a** as the model substrates in the presence of 5 mol % of $[Pd(allyl)Cl]_2$, NEt_3, and $AgBF_4$ in CH_2Cl_2 at room temperature. As shown in Table 1, some axially chiral bisphosphine ligands such as (*S*)-BINAP **L1**, (*S*)-H_8–BINAP **L2**, and (*S*)-Segphos **L3** provided the desired hydroalkylation product **3a** in moderate to good yields with exclusive regioselectivity albeit with poor stereoselectivities (56–89% yields, 3.5:1–3.8:1 dr, 37–48% ee, Table 1, entries 1–3). The planar chiral P,N-ligands **L4** and **L5** provided the corresponding product **3a** in acceptable yields with moderate diastereoselectivities and good to excellent enantioselectivities, and chiral ligand **L5** containing a *tert*-butyl group with steric hindrance displayed higher efficiency (4:1–6:1 dr, 84–96% ee, Table 1, entries 4 and 5). Then, two other P,N-ligands **L6** and **L7** containing *tert*-butyl groups were then applied; promising stereocontrol results were obtained to give product **3a** in moderate yields with excellent diastereoselectivities and enantioselectivities, and ligand **L7** with two trifluoromethyl groups on the phenyl ring proved to be the best choice (67–70% yields, 10:1–12:1 dr, 94–95% ee, Table 1, entries 6 and 7). Subsequently, other organic bases, including *N*,*N*-diisopropylethylamine (DIPEA) and 1,4-diazabicyclo[2.2.2]-octane (DABCO), were examined in this asymmetric transformation. Although the diastereoselectivities were improved, unsatisfactory reactivities were detected with reduced yields (43–50% yields, 14:1 dr, 94–95% ee, Table 1, entries 8 and 9). Fortunately, when Brønsted acid $HBF_4{\cdot}Et_2O$ was added, the yield was greatly improved to 92% with maintained stereoselectivity control, which could be ascribed to accelerating the formation of key Pd-π-allyl species[12g] (Table 1, entry 10).

Having established the optimized reaction conditions, we explored the substrate scope generality of this Pd-catalyzed asymmetric hydroalkylation of 1-phenylbutadiene **2a** with a variety of azlactones. As shown in Table 2, with the performed

Table 1. Initial Test and Reaction Optimization[a]



entry	ligand	base	yield (%)[b]	dr[c]	ee (%)[d]
1	**L1**	NEt_3	56	3.8:1	48
2	**L2**	NEt_3	60	3.5:1	47
3	**L3**	NEt_3	89	3.8:1	37
4	**L4**	NEt_3	46	4:1	84
5	**L5**	NEt_3	46	6:1	96
6	**L6**	NEt_3	67	10:1	94
7	**L7**	NEt_3	70	12:1	95
8	**L7**	DIPEA	43	14:1	94
9	**L7**	DABCO	50	14:1	95
10[e]	**L7**	NEt_3	92	12:1	95

[a]All reactions were carried on with 0.15 mmol **1a**, 0.1 mmol **2a**, base (3 equiv), and $AgBF_4$ (12 mol %) in 2 mL of DCM, 18–24 h. [b]Isolated yield. [c]dr was determined by the crude ^1H NMR. [d]ee was determined by HPLC analysis. [e]With 10 mol % of $HBF_4{\cdot}Et_2O$ as the additive.

Pd-**L7** complex, a series of alkyl substituents with different steric hindrances at the C4 position of azlactones was first explored, which showed good compatibility in this reaction system. The azlactones with methyl (**1a**), ethyl (**1b**), benzyl (**1c**), *iso*-butyl (**1d**), and allyl (**1e**) group underwent the reactions smoothly to afford the desired products (**3a–3e**) in good yields with exclusive regioselectivity and good to excellent diastereoselectivities and enantioselectivities (75–92% yields, 10:1 to >20:1 dr, 93 to >99% ee, Table 2, entries 1–5). Remarkably, valine derived azlactone (**1f**) with sterically bulky *iso*-propyl group worked well in this transformation, which is a challenging substrate in the bismetallic catalytic system (entry 6).[13] In addition, the substrates with different substituted groups at the C2 position were further investigated. We found that the electric properties and positions of the substituents on the aryl ring have little influence on the reactivities and stereoselectivities. The substrates containing electron-rich (**1g–1h**, **1k**) or electron-deficient (**1i–1j**, **1l–1m**) substituents on the phenyl ring at different positions have proved to be good reaction partners, affording the corresponding products (**3g–3m**) with excellent results (75–90% yields, 10:1–19:1 dr and 94–98% ee, Table 2, entries 7–13). In addition, azlactones (**1n–1o**) with phenyl group at the C4 position were also tested, and the desired products (**3n–3o**) were obtained in good yields and excellent enantioselectivities,

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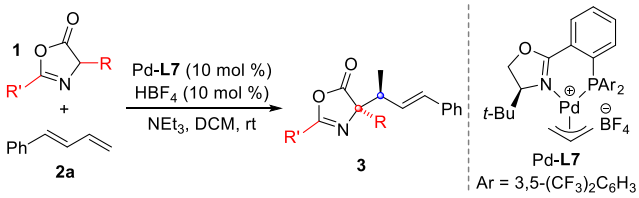
Table 2. Substrate Scope of Azlactones[a]



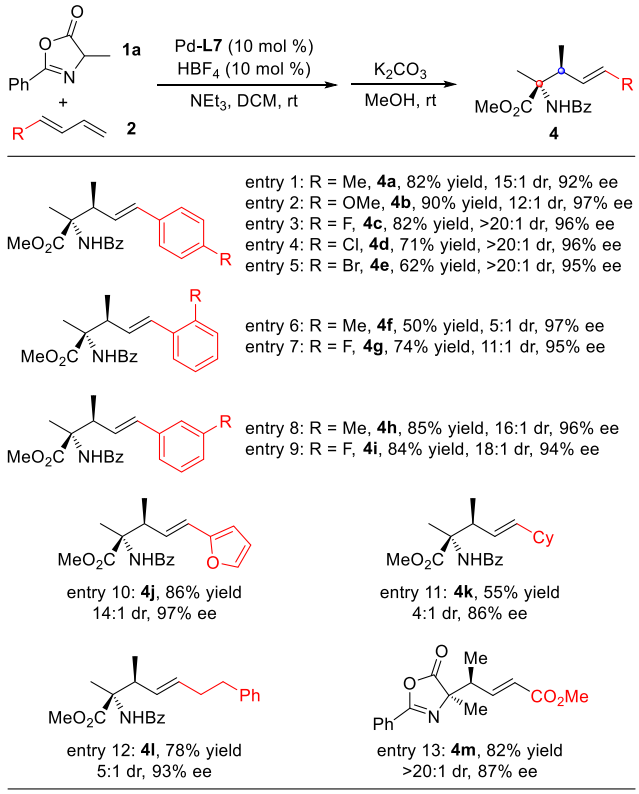
entry	R	R′	3	yield (%)[b]	dr[c]	ee (%)[d]
1	Me	Ph	**3a**	92	12:1	95
2[e]	Et	Ph	**3b**	85	>20:1	>99
3[f]	Bn	Ph	**3c**	82	10:1	95
4[f]	^{i}Bu	Ph	**3d**	80	>20:1	93
5[f]	allyl	Ph	**3e**	75	10:1	99
6[f]	^{i}Pr	Ph	**3f**	54	>20:1	97
7	Me	*p*-MeC$_6$H$_4$	**3g**	89	15:1	96
8[e]	Me	*p*-MeOC$_6$H$_4$	**3h**	90	13:1	98
9	Me	*p*-FC$_6$H$_4$	**3i**	87	19:1	95
10	Me	*p*-ClC$_6$H$_4$	**3j**	80	19:1	95
11	Me	*m*-MeC$_6$H$_4$	**3k**	78	10:1	95
12[e]	Me	*m*-FC$_6$H$_4$	**3l**	86	19:1	95
13	Me	*o*-FC$_6$H$_4$	**3m**	75	15:1	94
14[f]	Ph	Me	**3n**	70	4.3:1	95
15[f]	Ph	Ph	**3o**	85	1.2:1	87

[a]All reactions were carried on with 0.15 mmol **1**, 0.1 mmol **2a**, Pd-**L7** catalyst (10 mol %), NEt$_3$ (3 equiv), and HBF$_4$·Et$_2$O (10 mol %) in 2 mL of DCM, 18−24 h. [b]Isolated yield. [c]dr was determined by crude ^{1}H NMR. [d]ee was determined by HPLC analysis. [e]DABCO was used as the base. [f]Ee was determined after alcoholysis with K$_2$CO$_3$/MeOH to facilitate HPLC analysis.

albeit with moderate diastereoselectivities (70−85% yields, 1.2:1−4.3:1 dr and 87−95% ee, Table 2, entries 14 and 15).

Promoted by these experimental results, we then evaluated various 1,3-dienes for further substrate scope study. A wide range of diversified 1,3-dienes was well-tolerated. To facilitate HPLC analysis of ee values, the corresponding products were subsequently alcoholyzed to deliver quaternary α-amino acid derivatives containing adjacent tertiary and quaternary stereocenters in good yields with exclusive regioselectivity and good to excellent stereoselectivities (50−90% yields, 4:1 to >20:1 dr, 86−97% ee). Various aryl substituted 1,3-dienes bearing electron-donating or electron-withdrawing groups worked well in this transformation (Table 3, entries 1−9). In addition, we also examined the position of substituted group on the phenyl ring, whether it is at the *ortho*-, *meta*-, or *para*-position; these reactions were performed smoothly to provide the desired products in good yields with excellent stereoselectivities. Moreover, the heteroaromatic substrate (*E*)-2-(buta-1,3-dien-1-yl)furan (**2j**) was suitable to work in this reaction system, affording the expected product (**4j**) with 86% yield, 14:1 dr, and 97% ee (Table 3, entry 10). To be noted, the alkyl substrates (*E*)-buta-1,3-dien-1-ylcyclohexane (**2k**) and (*E*)-hexa-3,5-dien-1-ylbenzene (**2l**) also facilitated the reactions with 1,3-oxazol-5(4*H*)-one (**1a**) efficiently, which led to the corresponding products (**4k** and **4l**) with good to excellent results (55−78% yields, 4:1−5:1 dr, 86−93% ee, Table 3, entries 11 and 12). The methyl (*E*)-penta-2,4-dienoate **2m**, the functionalized 1,3-diene bearing electron-withdrawing ester group, was also tolerated in this Pd-catalyzed asymmetric hydroalkylation, and the desired product **4m** was obtained with good yield, high diastereoselectivity and excellent enantioselectivity (82% yield, > 20:1 dr, 87% ee, Table 3, entry 13).

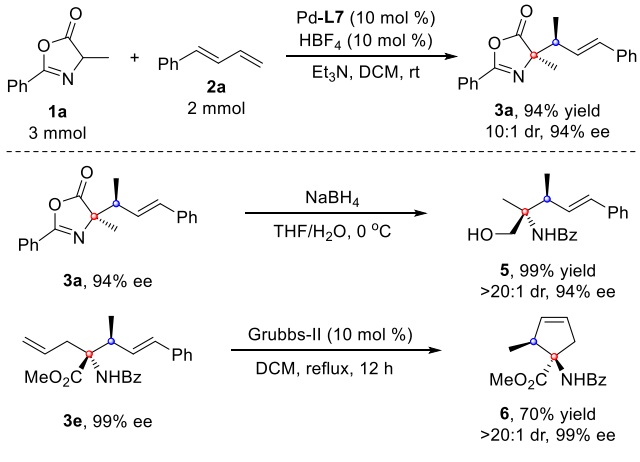
Table 3. Substrate Scope of 1,3-Dienes[a]



[a]All reactions were carried on with 0.15 mmol **1a**, 0.1 mmol **2**, Pd-**L7** catalyst (10 mol %), NEt$_3$ (3 equiv), and HBF$_4$·Et$_2$O (10 mol %) in 2 mL of DCM, 18−24 h. Yield is isolated yield. dr was determined by crude ^{1}H NMR, and ee was determined by HPLC analysis.

To demonstrate the synthetic utility of the current methodology, a scale-up asymmetric catalytic hydroalkylation reaction between azlactone **1a** and 1-phenylbutadiene **2a** was performed under the standard conditions, and **3a** was readily obtained in comparable yields without loss of enantioselectivity, as shown in Scheme 2 (top). The enantioenriched hydroalkylation product obtained herein can be converted into synthetically useful chiral compounds in a facile manner.

Scheme 2. Scale-up and Synthetic Transformations



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For example, reduction of **3a** with $NaBH_4$ furnished β-amino alcohol derivative **5** in nearly quantitative yield without decrease of enantioselectivity.[16] In addition, the hydroalkylation/alcoholysis product **3e** containing two vinyl groups was readily converted to α-quaternary cyclic α-amino acid derivative **6** in 70% yield and without loss of stereoselectivity via intramolecular ring closing metathesis,[17] which is a synthetically useful building block in medicinal chemistry[18] (Scheme 2, bottom).

In summary, we successfully developed the first Pd-catalyzed asymmetric hydroalkylation of 1,3-dienes with azlactones. A series of chiral α-quaternary α-amino acid derivatives bearing vicinal tertiary and quaternary stereogenic centers was obtained in good yields, exclusive regioselectivity, and good to excellent stereoselective control. This protocol can be proceeded well in scale-up version, and the desired products were easily converted to other important molecules such as chiral β-amino alcohol and α-quaternary cyclic α-amino acid derivative. Further investigations on detailed mechanism of the current Pd-catalyzed asymmetric hydroalkylation are in progress in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04341.

General procedures, synthetic transformations, proposed catalytic cycle, references, and NMR and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

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