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Stereodivergent Synthesis of Allenes with α,β-Adjacent Central Chiralities Empowered by Synergistic Pd/Cu Catalysis

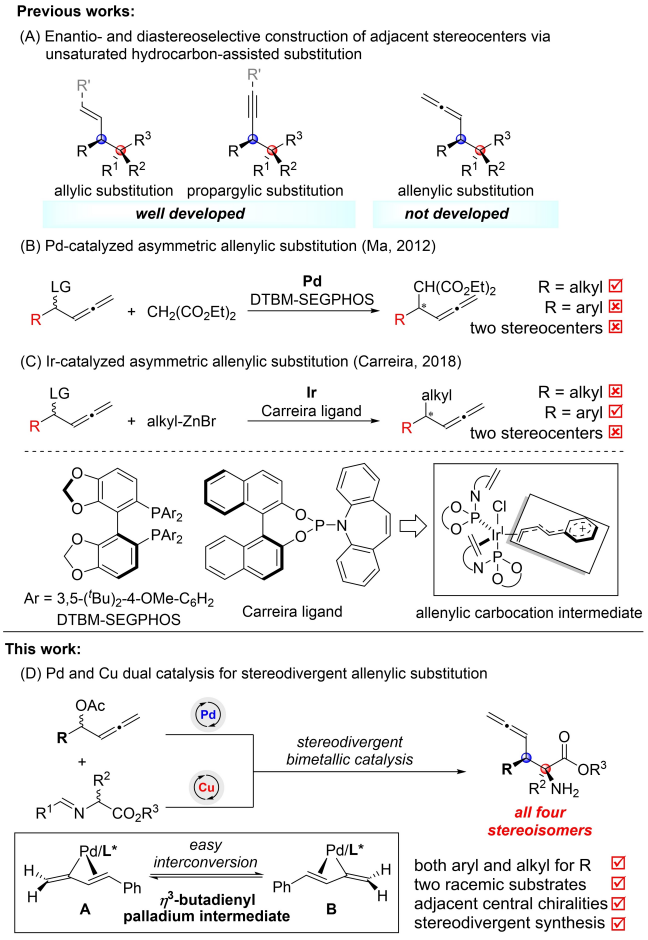
Ling Zhao, Yicong Luo, Junzhe Xiao, Xiaohong Huo, Shengming Ma, and Wanbin Zhang**

Abstract: The stereodivergent synthesis of allene compounds bearing α,β-adjacent central chiralities has been realized via the Pd/Cu-catalyzed dynamic kinetic asymmetric alkylation of racemic allenylic esters. The matched reactivity of bimetallic catalytic system enables the challenging reaction of racemic aryl-substituted allenylic acetates with sterically crowded aldimine esters smoothly under mild reaction conditions. Various chiral non-natural amino acids bearing a terminal allenyl group are easily synthesized in high yields and with excellent diastereo- and enantioselectivities (up to >20:1 dr, >99% ee). Importantly, all four stereoisomers of the product can be readily accessed by switching the configurations of the two chiral metal catalysts. Furthermore, the easy interconversion between the uncommon η^3-butadienyl palladium intermediate featuring a weak C=C/Pd coordination bond and a stable Csp^2–Pd bond is beneficial for the dynamic kinetic asymmetric transformation process (DyKAT).

Introduction

Structural motifs bearing two adjacent stereocenters widely exist in many natural products and important bioactive molecules, thus, stimulating the rapid development of their efficient synthetic methodologies.[1] Among these methodologies, transition-metal-catalyzed allylic/propargylic substitution reactions are well-established (Scheme 1A).[2,3] In consideration of the versatile reactivities of allenes[4,5] and their biological activities in drug discovery,[6] the development of an allenylic substitution for the enantio- and diastereoselective construction of allene compounds bearing adjacent stereocenters is highly desired and of current interest (Scheme 1A). However, almost no progress has been reported in this area due to challenges related to the differentiation of the allene unit and an R group of similar size, as well as the creation of the adjacent carbon stereocenters.[7–10]

In 2012, one of our co-authors developed the first metal-catalyzed asymmetric allenylic substitution for the synthesis of allenes bearing α-central chirality with excellent results using a chiral palladium complex coordinated with commer-



Scheme 1. Construction of two adjacent stereocenters with unsaturated carbon unit and transition-metal-catalyzed asymmetric allenylic substitution for the synthesis of allenes bearing α-central chirality.

[*] L. Zhao, Y. Luo, Dr. X. Huo, Prof. Dr. W. Zhang
Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, Frontiers Science Center for Transformative Molecules, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240 (China)
E-mail: wanbin@sjtu.edu.cn
Dr. J. Xiao, Prof. Dr. S. Ma
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (China)
E-mail: masm@sioc.ac.cn
Prof. Dr. S. Ma
Research Centre for Molecular Recognition and Synthesis, Department of Chemistry, Fudan University
220 Handan Lu, Shanghai 200433 (China)

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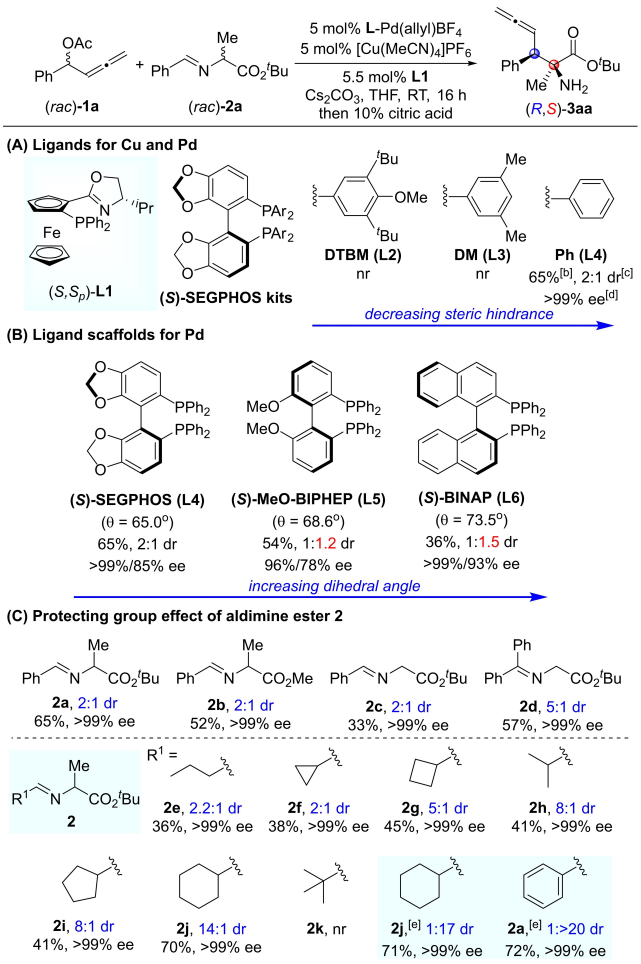
cially available DTBM-SEGPHOS (Scheme 1B).[8a] The ligand possessing electron-rich and bulky groups is indispensable for achieving high reactivity and satisfactory enantioselectivity. However, the crowded chiral environment makes the reaction sensitive to the substitution pattern of the allenylic substrates and only substrates bearing alkyl groups are suitable.[8] In 2018, Carreira and co-workers developed the first Ir-catalyzed asymmetric allenylic alkylation reaction for the synthesis of allenes bearing α-central chirality using their own phosphoramidite-olefin ligand (Scheme 1C).[9a] The mechanistic study revealed that an allenylic carbocation intermediate with η^2-coordination of the Ir center with the terminal double bond of the allene was proposed instead of the initially postulated η^3-butadienyl Ir intermediate. The carbocation needs to be stabilized by the highly delocalized system, which limits the scope of the allenylic substrates and only substrates bearing aryl groups are suitable.[9] To date, a catalytic system which is compatible with both aryl- and alkyl-substituted allenylic substrates for the synthesis of allenes bearing α-central chirality has not been reported. In addition, an apparent challenge in this area is the construction of vicinal stereocenters with racemic nucleophiles in a diastereo- and enantioselective fashion;[7] no stereodivergent method has been reported yet,[11] even though such chiral allene products have broad potential applications.

Recently, bimetallic catalysis has been proven to be highly efficient for the improvement of reactivity and precise control of stereoselectivity even for stereodivergent synthesis in several kinds of asymmetric reactions.[12,13] Therefore, we conceived that bimetallic catalysis could be used for asymmetric allenylic substitution which would be suitable for both aryl- and alkyl-substituted allenylic substrates, affording stereodivergent allene products with α,β-adjacent central chiralities. Herein, we report a Pd/Cu-catalyzed stereodivergent allenylic alkylation of both aryl- and alkyl-substituted allenylic substrates with the amino acid-derived aldimine esters. A series of non-natural chiral amino acids bearing a terminal allenyl group and a challenging quaternary carbon center could be easily synthesized in high yields and with excellent diastereo- and enantioselectivities (up to >20:1 dr, >99% ee). The mechanistic studies based on experiments and theoretical calculations suggest that the easy interconversion between the uncommon η^3-butadienyl palladium intermediates **A** and **B**, consisting of a weakly coordinating C=C/Pd coordination bond and a stable Csp^2–Pd bond, is beneficial to the DyKAT of the racemic allenylic esters (Scheme 1D).[14]

Results and Discussion

To prove our hypothesis, the racemic aryl-substituted allenylic acetate **1a** was selected as the model substrate for the asymmetric substitution with aldimine ester **2a** in the presence of a [Pd/**L***+Cu/**L***] catalytic combination (Table 1). Based on our previous studies,[8,12d,h] the use of Phosferrox (S,S_p)-**L1** for the copper catalyst and (*S*)-DTBM-SEGPHOS (**L2**) possessing electron-rich and bulky groups

Table 1: Optimization of the reaction conditions.[a]



[a] Reaction conditions: (*rac*)-**1a** (0.30 mmol, 1.5 equiv), **2a**–**2k** (0.20 mmol, 1.0 equiv), **L**-Pd(allyl)BF_4 (5 mol%), $[Cu(MeCN)_4]PF_6$ (5 mol%), (S,S_p)-**L1** (5.5 mol%), Cs_2CO_3 (1.2 equiv), THF (2 mL), 16 h. [b] Isolated yield of two diastereomers based on the starting material **2**. However, 5 mol% of nucleophiles are consumed by the **L**-Pd(allyl)BF_4. nr = no reaction. [c] Determined by ^{1}H NMR integration of the crude reaction mixtures. [d] Determined by HPLC analysis. [e] (*R*)-SEGPHOS instead of (*S*)-SEGPHOS.

for the palladium catalyst was first screened but none of the desired product was obtained. This may be due to steric incompatibility between the phenyl group of the allenylic substrate and the large steric hindrance of the DTBM-SEGPHOS ligand. Subsequently, ligands with different substitutents [(*S*)-DM-SEGPHOS (**L3**) and (*S*)-SEGPHOS (**L4**)] were applied in this reaction. To our delight, the desired product (*R*,*S*)-**3aa** was obtained in 65% yield, 2:1 dr, and >99% ee using (*S*)-SEGPHOS as the ligand for the palladium catalyst. Following this result, two other classical axially chiral ligands with different scaffolds [MeO-BIPHEP (**L5**) and BINAP (**L6**)] were explored. It is interesting to note the diastereoselectivity of the product **3aa** was reversed using both MeO-BIPHEP and BINAP as the ligands. These results indicated that: 1) the reaction yield is very sensitive to the steric environment of the chiral ligand (Table 1A); 2) the dihedral angle of the ligand scaffolds (**L4**–**L6**) also has

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an important influence on the reactivity and diastereoselectivity (Table 1B).

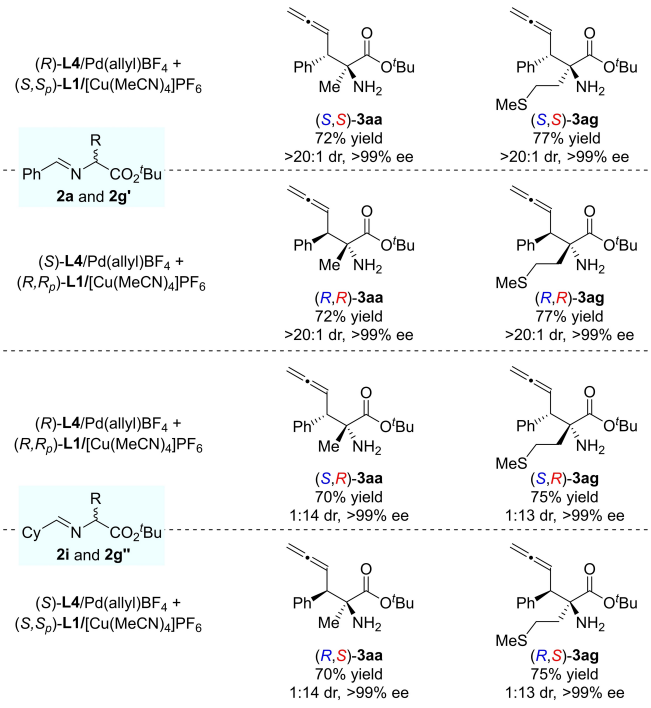
In consideration of the complex and crowded three-dimensional space of the Pd/Cu catalytic system, the ester group, α-substituent, and *N*-protecting group of the aldimine ester **2** were further explored to improve the diastereoselectivity (Table 1C). At first, aldimine methyl ester **2b** was tested. No obvious change in stereoselectivity was observed. A similar stereoselectivity with 33 % yield was obtained using the glycine-based aldimine ester **2c** as the substrate. Fortunately, benzophenone-protected glycine *tert*-butyl ester **2d** gave the corresponding products in 5:1 dr, 57 % yield, and >99 % ee. These results encouraged us to further explore various kinds of protecting groups including linear alkyl (**2e**), cyclic alkyl (**2f**–**g**, **2i**–**j**), and branched alkyl (**2h**, **2k**) moieties. Finally, cyclohexyl-protected aldimine *tert*-butyl ester **2j** gave the best results (70 % yield, 14:1 dr, and >99 % ee). To our delight, the complementary diastereomer (*S,S*)-**3aa** could be smoothly prepared in 71 % yield, 1:17 dr, and >99 % ee by using (*R*)-SEGPHOS instead of (*S*)-SEGPHOS. When the Cy protecting group was replaced by Ph, the dr value could be further increased from 17:1 to >20:1 with comparable performance in yield and enantioselectivity. In order to gain insight into the nature of the cooperative effect, control experiments were also conducted. No reaction occurred in the absence of the Pd or Cu catalysts. These results suggested that the combined use of two chiral metal catalysts appears to be essential for the reactivity and stereochemical control of this reaction.

With the optimized reaction conditions in hand, the scope of racemic aryl-substituted allenylic acetates was first explored using a combination of (S,S_p)-**L1** and (*R*)-**L4** (Table 2). A series of electron-donating and electron-withdrawing groups at varying positions on the aryl units were well tolerated, providing the desired products (*S,S*)-(**3ba**–**3ma**) in 65–78 % yield with >20:1 dr and >99 % ee. Alkyl-substituted allenylic acetates were also examined. Ethyl-, *n*-butyl-, and *n*-hexyl-substituted allenylic acetates worked well to furnish the corresponding products (**3na**–**3pa**) with the same high dr and ee values (69–71 % yield, >20:1 dr and >99 % ee). The allenylic acetates bearing synthetically useful functional groups, such as phenyl, halide, and hydroxyl moieties could successfully afford the substituted products (**3qa**–**3sa**) with >20:1 dr and >99 % ee. Furthermore, allenylic acetates derived from drug molecules such as ketoprofen, naproxen, and ibuprofen were evaluated under our Pd/Cu catalytic system. The allenylic products bearing the enantiopure quaternary amino acids (**3ta**–**3va**) were easily synthesized in moderate yields and with excellent stereoselectivities (52–57 % yield and >20:1 dr).

Next, the scope of the nucleophiles was investigated (Table 2). A variety of aldimine esters prepared from natural and non-natural amino acid derivatives were treated with (*rac*)-**1a** under the standard reaction conditions. Substrates with less bulky ester groups such as methyl and isopropyl substituents performed well to provide the products (*S,S*)-**3ab** and **3ac** smoothly with slightly lower dr values compared with (*S,S*)-**3aa** (70 % yield, 6:1 dr, >99 % ee; 73 % yield, 15:1 dr, >99 % ee, respectively). Aldimine esters with different substituents at the α-position of the ester group successfully underwent allenylation in good to high yields and with excellent diastereo- and enantioselectivities (**3ad**–**3ak**). In particular, when an aldimine ester derived from glutamic acid was used, the lactam (*S,S*)-**3ai** could be obtained through a one-pot process which included substitution, hydrolysis, and ring closure. Furthermore, a glycine-based ketimine ester was also suitable in this reaction and the desired product (*S,S*)-**3al** could be obtained in 81 % yield, 14:1 dr, and 99 % ee.

The stereodivergence of this allenylation was further evaluated by treating (*rac*)-**1a** with aldimine esters derived from alanine and methionine with four possible configuration combinations of the two chiral ligands **L1** and **L4** (Scheme 2). At first, two stereoisomers (*S,S*)- and (*R,R*)-**3aa** and **3ag** were successfully obtained using a phenyl group as the protecting group for the aldimine esters in high yields (72 % and 77 % yield) with excellent diastereoselectivities and enantioselectivities (>20:1 dr, >99 % ee). The remaining two stereoisomers (*S,R*)- and (*R,S*)-**3aa** and **3ag** could also be prepared smoothly using cyclohexyl as the protecting group for the aldimine esters by changing the configuration combinations of **L1** and **L4**. These results indicate that the Pd complex and the Cu complex synergistically exert complete control over the configurations of the stereocenters derived from the allenylic electrophile and the aldimine nucleophile, respectively.

In our previous work, the ligand DTBM-SEGPHOS, possessing electron-rich and bulky groups, is required to achieve high reactivity and satisfactory enantioselectivity in Pd-catalyzed asymmetric allenylic substitution process.[8] However, excellent stereoselectivities and high yields were



Scheme 2. Stereodivergent synthesis.

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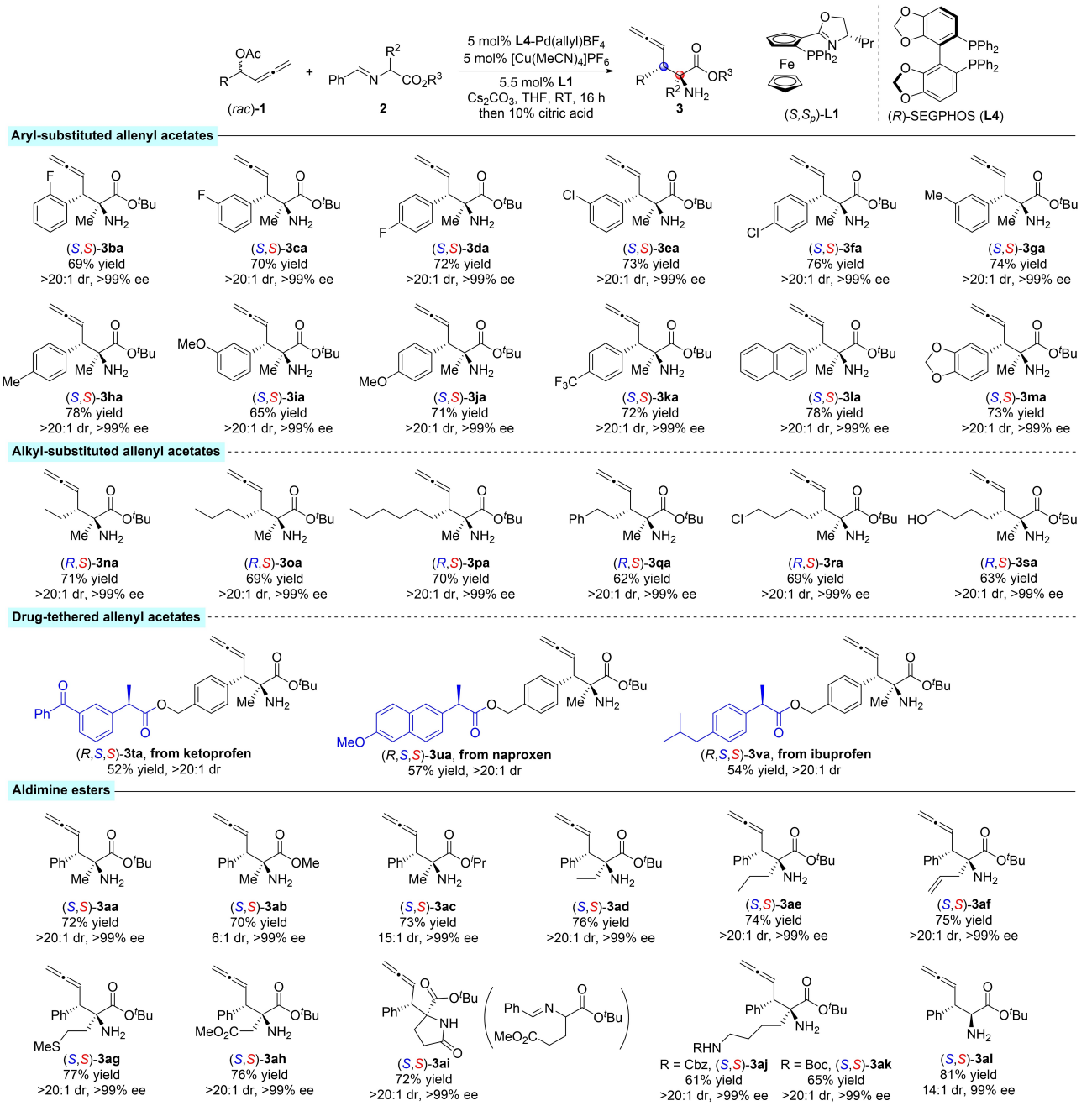
Table 2: Scope of the aryl- and alkyl-substituted allenylic acetates and aldimine esters.[a]



[a] Reaction conditions: **1** (0.30 mmol, 1.5 equiv), **2** (0.20 mmol, 1.0 equiv), (*R*)-**L4**-Pd(allyl)BF_4 (5 mol%), $[Cu(MeCN)_4]PF_6$ (5 mol%), (S,S_p)-**L1** (5.5 mol%), Cs_2CO_3 (1.2 equiv), THF (2 mL), 16 h. Isolated yield of all products based on the starting material **2**.

also obtained for most examples using the Pd/(*R*)-SEGPHOS catalyst in combination with the Cu/**L1** catalyst (> 20:1 dr even obtained as a single diastereomer, > 99% ee). Accordingly, we were curious of the specific role of the chiral Cu catalyst in the Pd-catalyzed asymmetric allenylic substitution (Table 3). Several control experiments were first conducted. None of the desired products were obtained for either aryl- and alkyl-substituted allenylic substrates **1a** and **1p** when Pd/(*R*)-SEGPHOS was used as the only catalyst (entries 2 and 3). An increase in basicity by employing NaH in place of Cs_2CO_3 resulted in the desired product being obtained in only 26% yield with 1:1 dr and 82%/81% ee (entry 4). By using [Pd/**L4**+Cu/dppf] instead of [Pd/**L4**+Cu/**L1**], the desired product was obtained in 37% yield with 2.5:1 dr and 66%/14% ee (entry 5). It can be concluded that the chiral copper catalyst could not only improve the reactivity, even for the reaction of the challenging phenyl-substituted allenylic substrate **1a** with a crowded aldimine *tert*-butyl ester, but also promote the DyKAT process of the

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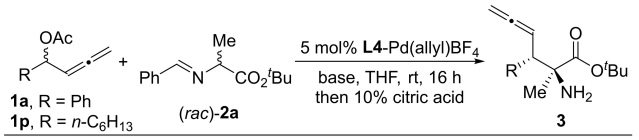
Table 3: The role of chiral copper catalyst in Pd-catalyzed asymmetric allenylic alkylation process.[a]

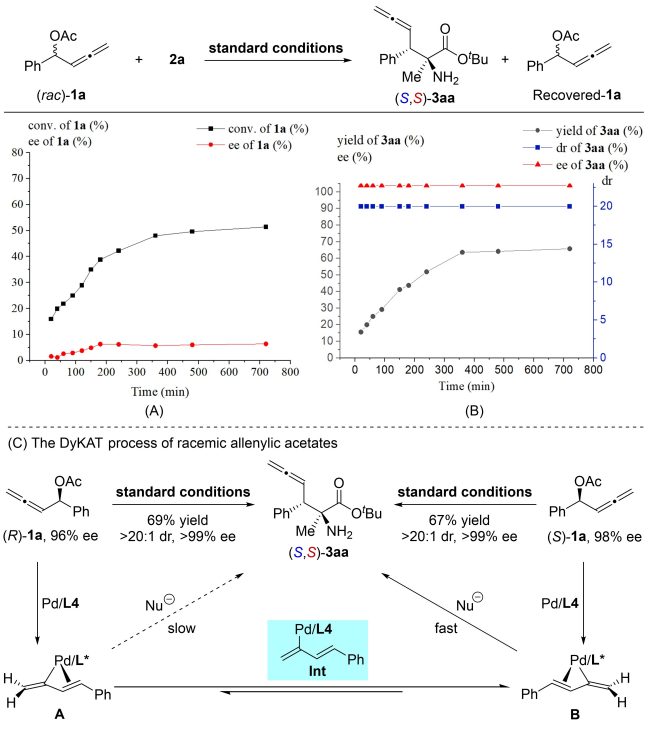


entry	1	base	Cat. Cu	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	Cs_2CO_3	Cu/**L1**	72	>20:1	>99
2	**1a**	Cs_2CO_3	no Cu	nr	--	--
3	**1p**	Cs_2CO_3	no Cu	nr	--	--
4	**1a**	NaH	no Cu	26	1:1	82/81
5	**1a**	Cs_2CO_3	Cu/dppf	37	2.5:1	66/14

[a] Reaction conditions: **1** (0.30 mmol, 1.5 equiv), **2a** (0.20 mmol, 1.0 equiv), (*R*)-**L4**-Pd(allyl)BF_4 (5 mol%), $[Cu(MeCN)_4]PF_6$ (5 mol%), (S,S_p)-**L1** (5.5 mol%), base (1.2 equiv), THF (2 mL), 16 h. [b] Isolated yield of two diastereomers based on the starting material **2a**. nr = no reaction. [c] Determined by ^{1}H NMR integration of the crude reaction mixtures. [d] Determined by HPLC analysis.

racemic allenylic substrate with excellent diastereo- and enantioselectivity.[14]

Subsequently, a kinetic study of the reaction was conducted to further investigate the DyKAT process (Scheme 3). Firstly, the conversions and ee values of *rac*-**1a** at different times were monitored. As seen from Scheme 3A, the recovered **1a** was almost racemic over the reaction time



Scheme 3. Study of the DyKAT process: (A) Yields and ee values of recovered **1a** at different times. (B) The yields, ee and dr values of the crude product **3aa** at different times. (C) The proposed DyKAT process.

period, indicating that (*R*)-**1a** and (*S*)-**1a** are consumed together at nearly the same speed. Additionally, the yield, diastereoselectivity, and enantioselectivity of the corresponding product (*S,S*)-**3aa** were also determined. No change in dr and ee values of **3aa** were found as the yield increased during the course of the reaction (Scheme 3B). Next, reactions with enantiopure allenylic acetates (*R*)-**1a** and (*S*)-**1a** were conducted with aldimine ester **2a** under the standard reaction conditions. The same products (*S,S*)-**3aa** were obtained in almost similar yields (69%/67%), dr and ee (both >20:1 dr, >99% ee, Scheme 3C). These results suggested that the highly efficient interconversion of the electrophilic intermediate **A** derived from (*R*)-**1a** into the intermediate **B** occurred before **A** was attacked by the nucleophile. The two diastereoisomeric intermediates **A** and **B** might transform into each other through the palladium intermediate with a stable Csp^2–Pd bond,[15] which is different from the classic nucleophilic displacement via the palladium(0) species in the Pd-catalyzed DyKAT process of racemic allylic substitution.[16]

Differing from the classic allylic substrates,[2] allenylic acetate is a specific allylic subtrate substituted with the $=CH_2$ group. Accordingly, we investigated the specific structural characteristics of the electrophilic palladium intermediate in this asymmetric allenylic substitution. Two diastereoisomeric intermediates **A** and **B** generated in situ by the oxidative addition of racemic allenylic acetate **1a** with Pd/(*R*)-**L4** were investigated by DFT calculations (Figure 1A).[17] The results suggested that the characteristics of the η^3-butadienyl palladium intermediates were obviously different from that of traditional π-allyl intermediates. The C^2–Pd and C^3–Pd bonds in η^3-butadienyl palladium intermediates **A** and **B** are significantly longer and weaker compared with theC^1–Pd bond [C^1–Pd, C^2–Pd, C^3–Pd: 2.04, 2.20, 2.30 Å for **A**; 2.07, 2.19, 2.24 Å for **B**, respectively].[18,19] Additionally, since C^1 is sp^2 hybridized in **A** and **B**, the typical bond angle of C^0–C^1–C^2 should be 120°. Hence, the distortion of the related angles in **A** and **B** (140.6° and 148.7°) indicated their potential instability. Furthermore, both outward methylene group with steric hindrance and weak C^3–Pd bond favored the substitution at the C^3 position, which is consistent with the excellent regioselectivity observed in our experimental results.

Next, we studied the bonding form of the coordination bond of the η^3-butadienyl palladium intermediate by orbital localization analysis (Figure 1B).[20] In these coordination bonds, palladium contributes one *d* orbital while each of the three carbons C^1–C^3 contributes one orbital, making up two bonding orbitals and two antibonding orbitals. The four electrons from the carbon atoms enter into the two bonding orbitals. The biggest difference between the η^3-butadienyl palladium intermediate and the classic π-allylpalladium intermediate is that a sp^2 orbital of C^1 contributes to the C^1–Pd bond in **A** and **B**, while a *p* orbital of the corresponding C^1 contributes to the C^1–Pd bond in the classic π-allylpalladium intermeidate. In **A** and **B**, the *p* orbital of C^1 participates in the formation of the π bond with C^0, forcing C^1 to use its sp^2 orbital to form a bond with Pd. Furthermore, orbital localization analysis vividly shows

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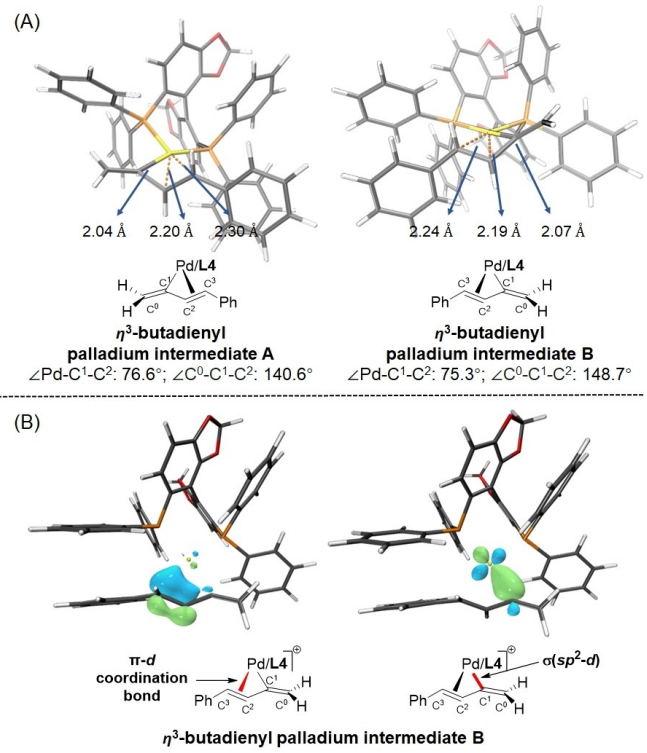
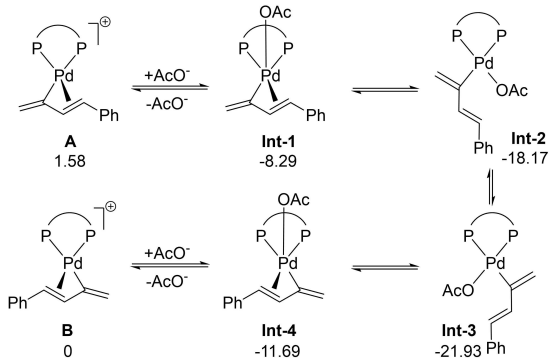


Figure 1. (A) The calculated structures and important structural parameters of electrophilic η^3-butadienyl palladium intermediates **A** and **B**; (B) the bonding orbitals based on orbital localization analysis of the intermediate **B**.

these special bonding forms (Figure 1B). In intermediate **B**, the shapes of the bonding orbitals indicate that the η^3-butadienyl palladium intermediate contains a weak C=C/Pd coordination bond and a strong σ(Csp^2–Pd) bond.[21]

Subsequently, we studied the interconversion between the η^3-butadienyl palladium intermediates **A** and **B** via an η^3-η^1-η^3 process with the help of AcO^-, using DFT calculations (Scheme 4). The result shows that the interconversion between the η^3-butadienyl palladium intermediate **A** and its diastereomer **B** is easy. This can be attributed to the stability of the Csp^2–Pd bond[22] during the interconversion



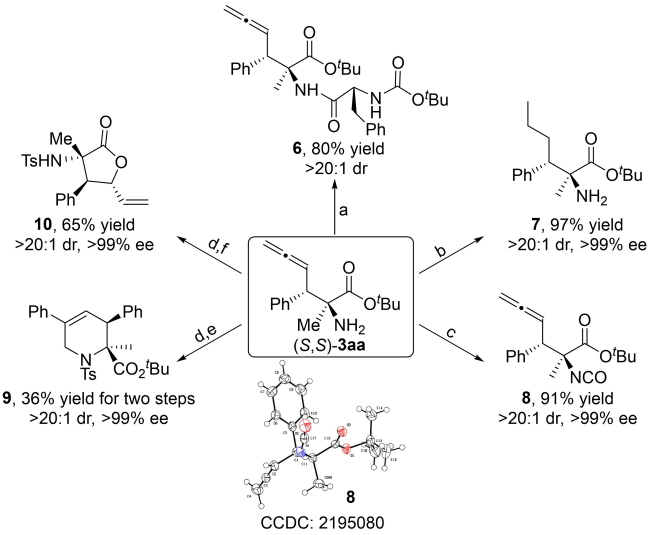
Scheme 4. Gibbs energy profile of the interconversion of the η^3-butadienyl palladium intermediates **A** and **B** (The data were acquired at the PBE0(D3BJ)/cc-pvTz/SMD_{THF} level of theory, unit: kcal mol^{-1}).

between **A** and **B** via **Int 1–4**. This facile interconversion between the two diastereomers **A** and **B** is beneficial for the DyKAT process of racemic allenylic substrates, giving the desired products with excellent enantio- and diastereoselectivities (>99 % ee and >20:1 dr).

In order to verify the synthetic value of the products, several transformations with regards to the amino ester and the allene group were conducted (Scheme 5). The quaternary amino acid (*S*,*S*)-**3aa** could be transformed to dipeptide **6**, benzyl substituted α-amino acid **7**, and isocyanate **8**, smoothly.[23] The product (*S*,*S*)-**3aa** could also be applied to the synthesis of chiral piperidine skeleton **9** by the sequential installation of the Ts protecting step and Pd-catalyzed ring closure.[24] Importantly, piperidine is the core scaffold of around 320 registered drugs.[25] Furthermore, butyrolactone **10** bearing three stereocenters could be obtained in 65 % yield, >20:1 dr, and >99 % ee via the hydrolysis and hydrofunctionalization of the terminal allene.[26]

Conclusion

In conclusion, we have successfully developed a stereodivergent Pd/Cu catalytic system for the enantio- and diastereoselective allenylation of aldimine esters with racemic 2,3-allenylic acetates. Both aryl- and alkyl-substituted allenylic substrates were compatible with the reaction conditions, affording a wide range of chiral non-natural amino acids bearing a terminal allenyl group and with vicinal central chiralities in high yields and with excellent diastereo- and enantioslectivities (up to >20:1 dr and



Scheme 5. Representative transformations of the chiral allenylic products. [a] Reaction conditions: (a) HOBt, EDCI·HCl, DCM, rt. (b) Pd/C, H_2, MeOH, rt. (c) Boc_2O, DMAP, DCM, rt. (d) TsCl, pyridine, DCM, rt. (e) $Pd(PPh_3)_4$, PhI, K_2CO_3, DMF, 80 °C. (f) TFA, DCM, rt; $[Rh(COD)Cl]_2$, DPEphos, 1,2-DCE, 70 °C. HOBt = 1-hydroxybenzotriazole; EDCI·HCl = 1-(3-dimethylaminopropyl)-3-ethylcarbo diimide hydrochloride; Ts = tosyl; TFA = trifluoroacetic acid.

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>99% ee). Control experiments, kinetic studies, and theoretical calculations suggested that: 1) The introduction of the chiral copper catalyst could efficently improve the reactivity, enabling the Pd-catalyzed asymmetric allenylic substitution to be suitable for challenging aryl-substituted allenylic esters and crowded nucleophiles; 2) the easy interconversion between the η^3-butadienyl palladium intermediate possessing a weak C=C/Pd coordination bond and a stable Csp^2–Pd bond is beneficial for the DyKAT process of racemic allenylic substrates.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Allene Compounds · Amino Acids · Asymmetric Catalysis · Bimetallic Catalysis · Stereodivergent Synthesis

[1] a) *Comprehensive Asymmetric Catalysis* (Eds. E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; b) *Classics in Stereoselective Synthesis* (Eds. E. M. Carreira, L. Kvaerno), Wiley, Weinheim, **2009**; c) *Science of Synthesis: Asymmetric Organocatalysis* (Eds. B. List, K. Maruoka), Thieme, Stuttgart, **2012**.

[2] For selected reviews about Pd-catalyzed asymmetric allylic substitution, see: a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422; b) Z. Lu, S. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297; *Angew. Chem.* **2008**, *120*, 264–303; c) N. A. Butt, W. Zhang, *Chem. Soc. Rev.* **2015**, *44*, 7929–7967; d) L. Süsse, B. M. Stoltz, *Chem. Rev.* **2021**, *121*, 4084–4099; e) O. Pàmies, J. Margalef, S. Cañellas, J. James, E. Judge, P. J. Guiry, C. Moberg, J. Bäckvall, A. Pfaltz, M. A. Pericàs, M. Diéguez, *Chem. Rev.* **2021**, *121*, 4373–4505. For selected reviews about Ir-catalyzed asymmetric allylic substitution, see: f) J. F. Hartwig, L. M. Stanley, *Acc. Chem. Res.* **2010**, *43*, 1461–1475; g) J. Qu, G. Helmchen, *Acc. Chem. Res.* **2017**, *50*, 2539–2555; h) S. L. Rössler, D. A. Petrone, E. M. Carreira, *Acc. Chem. Res.* **2019**, *52*, 2657–2672; i) Q. Cheng, H.-F. Tu, C. Zheng, J.-P. Qu, G. Helmchen, S.-L. You, *Chem. Rev.* **2019**, *119*, 1855–1969; j) C. E. Stivala, J. R. Zbieg, P. Liu, M. J. Krische, *Acc. Chem. Res.* **2022**, *55*, 2138–2147. For a classic book, see: k) *Transition-Metal-Catalyzed Enantioselective Allylic Substitution in Organic Synthesis* (Ed.: U. Kazmaier), Springer, Berlin, **2012**.

[3] For selected reviews about transition-metal-catalyzed asymmetric propargylic substitution, see: a) Y. Miyake, S. Uemura, Y. Nishibayashi, *ChemCatChem* **2009**, *1*, 342–356; b) N. Ljungdahl, N. Kann, *Angew. Chem. Int. Ed.* **2009**, *48*, 642–644; *Angew. Chem.* **2009**, *121*, 652–654; c) C.-H. Ding, X.-L. Hou, *Chem. Rev.* **2011**, *111*, 1914–1937; d) X.-H. Hu, Z.-T. Liu, L. Shao, X.-P. Hu, *Synthesis* **2015**, *47*, 913–923; e) H. Tsuji, M. Kawatsura, *Asian J. Org. Chem.* **2020**, *9*, 1924–1941; f) Y. Nishibayashi, *Chem. Lett.* **2021**, *50*, 1282–1288.

[4] For selected reviews on the transformation of allenes, see: a) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067–3126; b) R. W. Bates, V. Satcharoen, *Chem. Soc. Rev.* **2002**, *31*, 12–21; c) L. K. Sydnes, *Chem. Rev.* **2003**, *103*, 1133–1150; d) L.-l. Wei, H. Xiong, R. P. Hsung, *Acc. Chem. Res.* **2003**, *36*, 773–782; e) S. Ma, in *Palladium in Organic Synthesis* (Ed.: Tsuji, J.), Springer, Berlin, **2005**, pp. 183–210; f) S. Ma, *Chem. Rev.* **2005**, *105*, 2829–2872; g) S. Ma, *Acc. Chem. Res.* **2009**, *42*, 1679–1688; h) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Soc. Rev.* **2010**, *39*, 783–816; i) T. Lu, Z. Lu, Z.-X. Ma, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2013**, *113*, 4862–4904; j) B. Alcaide, P. Almendros, *Acc. Chem. Res.* **2014**, *47*, 939–952; k) J. Ye, S. Ma, *Acc. Chem. Res.* **2014**, *47*, 989–1000; l) L. Liu, R. M. Ward, J. M. Schomaker, *Chem. Rev.* **2019**, *119*, 12422–12490; m) Y. Liu, M. Bandini, *Chin. J. Chem.* **2019**, *37*, 431–441. For a selected book on the allene chemistry, see: n) *Modern Allene Chemistry* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**.

[5] For selected reviews on the application of allenes in asymmetric synthesis, see: a) R. K. Neff, D. E. Frantz, *Tetrahedron* **2015**, *71*, 7–18; b) J. M. Alonso, M. T. Quirós, M. P. Muñoz, *Org. Chem. Front.* **2016**, *3*, 1186–1204; c) S. Yu, S. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 3074–3112; *Angew. Chem.* **2012**, *124*, 3128–3167; d) B. Yang, Y. Qiu, J.-E. Bäckvall, *Acc. Chem. Res.* **2018**, *51*, 1520–1531.

[6] For selected reviews on the allenic natural products and pharmaceuticals, see: a) A. Hoffmann-Röder, N. Krause, *Angew. Chem. Int. Ed.* **2004**, *43*, 1196–1216; *Angew. Chem.* **2004**, *116*, 1216–1236; b) P. Rivera-Fuentes, F. Diederich, *Angew. Chem. Int. Ed.* **2012**, *51*, 2818–2828; *Angew. Chem.* **2012**, *124*, 2872–2882.

[7] Only one example was reported concerning the synthesis of the chiral allenes with adjacent stereocenters in 72% yield and with 2.4:1 dr and 85% ee, see: M. Isomura, D. A. Petrone, E. M. Carreira, *J. Am. Chem. Soc.* **2021**, *143*, 3323–3329.

[8] For reports on the asymmetric construction of the single central chirality via Pd-catalyzed allenylic substitution, see: a) Q. Li, C. Fu, S. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 11783–11786; *Angew. Chem.* **2012**, *124*, 11953–11956; b) Q. Li, C. Fu, S. Ma, *Angew. Chem. Int. Ed.* **2014**, *53*, 6511–6514; *Angew. Chem.* **2014**, *126*, 6629–6632.

[9] For reports on the asymmetric construction of the single central chirality via Ir-catalyzed allenylic substitution, see: a) D. A. Petrone, M. Isomura, I. Franzoni, S. L. Rössler, E. M. Carreira, *J. Am. Chem. Soc.* **2018**, *140*, 4697–4704; b) M. Isomura, D. A. Petrone, E. M. Carreira, *J. Am. Chem. Soc.* **2019**, *141*, 4738–4748; c) F. Glatz, D. A. Petrone, E. M. Carreira, *Angew. Chem. Int. Ed.* **2020**, *59*, 16404–16408; *Angew. Chem.* **2020**, *132*, 16546–16550; d) A. Chakrabarty, S. Mukherjee, *Angew. Chem. Int. Ed.* **2022**, *61*, e202115821; *Angew. Chem.* **2022**, *134*, e202115821; The racemic example for the construction of the single central chirality via Ir-catalyzed allenylic substitution, see: e) A. S. Kezuka, K. Kanemoto, R. Takeuchi, *Tetrahedron Lett.* **2004**, *45*, 6403–6406.

[10] For selected reports on the asymmetric construction of the allenyl axial chirality via Pd-catalyzed allenylic substitution, see: a) Y. Imada, K. Ueno, K. Kutsuwa, S.-I. Murahashi, *Chem. Lett.* **2002**, *31*, 140–141; b) B. M. Trost, D. R. Fandrick, D. C. Dinh, *J. Am. Chem. Soc.* **2005**, *127*, 14186–14187; c) T. Nemoto, M. Kanematsu, S. Tamura, Y. Hamada, *Adv. Synth.*

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15213773, 2023, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/anie.202218146 by Epfl Bibliotheque Collections, Wiley Online Library on [07/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Catal. **2009**, *351*, 1773–1778; d) B. Wan, S. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 441–445; *Angew. Chem.* **2013**, *125*, 459–463; e) J. Dai, X. Duan, J. Zhou, C. Fu, S. Ma, *Chin. J. Chem.* **2018**, *36*, 387–391; f) S. Song, J. Zhou, C. Fu, S. Ma, *Nat. Commun.* **2019**, *10*, 507; g) H.-C. Liu, Y.-Z. Hu, Z.-F. Wang, H.-Y. Tao, C.-J. Wang, *Chem. Eur. J.* **2019**, *25*, 8681–8685; h) S. Song, S. Ma, *Chin. J. Chem.* **2020**, *38*, 1233–1238; For selected reports on the asymmetric construction of the single allenyl axial chirality via 1,3-dieny-2-yl halides, see: i) M. Ogasawara, H. Ikeda, T. Nagano, T. Hayashi, *J. Am. Chem. Soc.* **2001**, *123*, 2089–2090; j) M. Ogasawara, K. Ueyama, T. Nagano, Y. Mizuhata, T. Hayashi, *Org. Lett.* **2003**, *5*, 217–219.

[11] For the pioneering work on stereodivergent dual catalysis, see: a) S. Krautwald, D. Sarlah, M. A. Schafroth, E. M. Carreira, *Science* **2013**, *340*, 1065; For a selected perspective on stereodivergent dual catalysis, see: b) S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2017**, *139*, 5627–5639.

[12] For stereodivergent bimetallic catalysis, see: a) X. Huo, R. He, X. Zhang, W. Zhang, *J. Am. Chem. Soc.* **2016**, *138*, 11093–11096; b) X. Jiang, P. Boehm, J. F. Hartwig, *J. Am. Chem. Soc.* **2018**, *140*, 1239–1242; c) L. Wei, Q. Zhu, S.-M. Xu, X. Chang, C.-J. Wang, *J. Am. Chem. Soc.* **2018**, *140*, 1508–1513; d) X. Huo, J. Zhang, J. Fu, R. He, W. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 2080–2084; e) Z.-T. He, X. Jiang, J. F. Hartwig, *J. Am. Chem. Soc.* **2019**, *141*, 13066–13073; f) Q. Zhang, H. Yu, L. Shen, T. Tang, D. Dong, W. Chai, W. Zi, *J. Am. Chem. Soc.* **2019**, *141*, 14554–14559; g) S.-M. Xu, L. Wei, C. Shen, L. Xiao, H.-Y. Tao, C.-J. Wang, *Nat. Commun.* **2019**, *10*, 5553; h) R. He, X. Huo, L. Zhao, F. Wang, L. Jiang, J. Liao, W. Zhang, *J. Am. Chem. Soc.* **2020**, *142*, 8097–8103; i) M. Zhu, Q. Zhang, W. Zi, *Angew. Chem. Int. Ed.* **2021**, *60*, 6545–6552; *Angew. Chem.* **2021**, *133*, 6619–6626; j) S.-Q. Yang, Y.-F. Wang, W.-C. Zhao, G.-Q. Lin, Z.-T. He, *J. Am. Chem. Soc.* **2021**, *143*, 7285–7291; k) J. Zhang, X. Huo, J. Xiao, L. Zhao, S. Ma, W. Zhang, *J. Am. Chem. Soc.* **2021**, *143*, 12622–12632; l) Y. Peng, X. Huo, Y. Luo, L. Wu, W. Zhang, *Angew. Chem. Int. Ed.* **2021**, *60*, 24941–24949; *Angew. Chem.* **2021**, *133*, 25145–25153; m) X. Chang, X. Cheng, X.-T. Liu, C. Fu, W.-Y. Wang, C.-J. Wang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202206517; *Angew. Chem.* **2022**, *134*, e202206517; n) X. Huo, L. Zhao, Y. Luo, Y. Wu, Y. Sun, G. Li, T. Gridneva, J. Zhang, Y. Ye, W. Zhang, *CCS Chem.* **2022**, *4*, 1720–1731; o) Y. Xu, H. Wang, Z. Yang, Y. Zhou, Y. Liu, X. Feng, *Chem* **2022**, *8*, 2011–2022; p) Z. He, L. Peng, C. Guo, *Nat. Synth.* **2022**, *1*, 393–400; For our selected reports on asymmetric synthesis but not stereodivergent by bimetallic catalysis, see: q) X. Huo, R. He, J. Fu, J. Zhang, G. Yang, W. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 9819–9822; r) J. Xiao, H. Xu, X. Huo, W. Zhang, S. Ma, *Chin. J. Chem.* **2021**, *39*, 1958–1964; s) J. Xia, T. Hirai, S. Katayama, H. Nagae, W. Zhang, K. Mashima, *ACS Catal.* **2021**, *11*, 6643–6655; t) Y. Peng, C. Han, Y. Luo, G. Li, X. Huo, W. Zhang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202203448; *Angew. Chem.* **2022**, *134*, e202203448.

[13] For selected reviews on bimetallic catalysis, see: a) E. K. van den Beuken, B. L. Feringa, *Tetrahedron* **1998**, *54*, 12985–13011; b) J. Park, S. Hong, *Chem. Soc. Rev.* **2012**, *41*, 6931–6943; c) D. R. Pye, N. P. Mankad, *Chem. Sci.* **2017**, *8*, 1705–1718; d) J. Fu, X. Huo, B. Li, W. Zhang, *Org. Biomol. Chem.* **2017**, *15*, 9747–9759; e) Y. Nakao, *Science of Synthesis: Dual Catalysis in Organic Synthesis* (Ed. G. A. Molander), Thieme: Stuttgart, **2019**, pp. 3–8; f) U. B. Kim, D. J. Jung, H. J. Jeon, K. Rathwell, S.-G. Lee, *Chem. Rev.* **2020**, *120*, 13382–13433; g) Y. Wu, X. Huo, W. Zhang, *Chem. Eur. J.* **2020**, *26*, 4895–4916; h) S. Martínez, L. Veth, B. Lainer, P. Dydio, *ACS Catal.* **2021**, *11*, 3891–3915; i) X. Huo, G. Li, X. Wang, W. Zhang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202210086; *Angew. Chem.* **2022**, *134*, e202210086; j) C. C. Malakar, L. Dell'Amico, W. Zhang, *Eur. J. Org. Chem.* **2022**, e202201114.

[14] For a comprehensive review, see: V. Bhat, E. R. Welin, X. Guo, B. M. Stoltz, *Chem. Rev.* **2017**, *117*, 4528–4561.

[15] a) D. Djahanbini, B. Cazes, J. Goré, *Tetrahedron Lett.* **1984**, *25*, 203–206; b) D. Djahanbini, B. Cazes, J. Goré, *Tetrahedron* **1984**, *40*, 3645–3655; c) D. Djahanbini, B. Cazes, J. Goré, *Tetrahedron* **1987**, *43*, 3441–3452; d) D. Djahanbini, B. Cazes, J. Goré, F. Gobert, *Tetrahedron* **1985**, *41*, 867–873; e) Z. Ni, A. Padwa, *Synlett* **1992**, *1992*, 869–870; f) T. Moriya, T. Furuuchi, N. Miyaura, *Tetrahedron* **1994**, *50*, 7961–7968; g) M. Mao, L. Zhang, Y.-Z. Chen, J. Zhu, L. Wu, *ACS Catal.* **2017**, *7*, 181–185.

[16] a) T. Takahashi, Y. Jinbo, K. Kitamura, J. Tsuji, *Tetrahedron Lett.* **1984**, *25*, 5921–5924; b) P. B. Mackenzie, J. Whelan, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2046–2054; c) K. L. Granberg, J. E. Backvall, *J. Am. Chem. Soc.* **1992**, *114*, 6858–6863; d) L. Du, P. Cao, J. Xing, Y. Lou, L. Jiang, L. Li, J. Liao, *Angew. Chem. Int. Ed.* **2013**, *52*, 4207–4211; *Angew. Chem.* **2013**, *125*, 4301–4305.

[17] The allenylic carbocation intermediate having an η^2-coordination of Pd^0/(*R*)-**L4** was also investigated by the DFT calculation. But the optimal structure of the allenylic carbocation intermediate was not located.

[18] M. Ogasawara, A. Okada, S. Watanabe, L. Fan, K. Uetake, K. Nakajima, T. Takahashi, *Organometallics* **2007**, *26*, 5025–5029.

[19] Two diastereoisomeric intermediates generated in situ by the oxidative addition of racemic alkyl-substituted allenylic acetate **1n** with Pd/(*R*)-**L4** were carefully investigated by the DFT calculations. The similar results in distances of C–Pd bonds were found. For detailed data, see the Supporting Information.

[20] a) S. Lehtola, H. Jónsson, *J. Chem. Theory Comput.* **2014**, *10*, 642–649; b) I.-M. Høyvik, B. Jansik, P. Jørgensen, *J. Comput. Chem.* **2013**, *34*, 1456–1462.

[21] A enyl [$\sigma(Csp^3–Rh)+\pi$] organorhodium intermediate was proposed, see: P. A. Evans, J. D. Nelson, *J. Am. Chem. Soc.* **1998**, *120*, 5581–5582.

[22] C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; *Angew. Chem.* **2012**, *124*, 5150–5174.

[23] Deposition numbers 2195055 (for (*R*,*S*)-**3aa**) and 2195080 (for (*S*,*S*)-**8**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[24] I. Shimizu, J. Tsuji, *Chem. Lett.* **1984**, *13*, 233–236.

[25] a) Njardarson group website: http:/cbc.arizona.edu/njardarson/group; b) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756; c) http://thomsonreuters.com/en/products-services/pharma-life-sciences/pharmaceutical-research/integrity.html.

[26] A. Lumbroso, N. Abermil, B. Breit, *Chem. Sci.* **2012**, *3*, 789–793.

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