Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c02150 • Publication Date (Web): 19 Apr 2020

Stereodivergent Pd/Cu Catalysis for the Dynamic Kinetic Asymmetric Transformation of Racemic Unsymmetrical 1,3-Disubstituted Allyl Acetates

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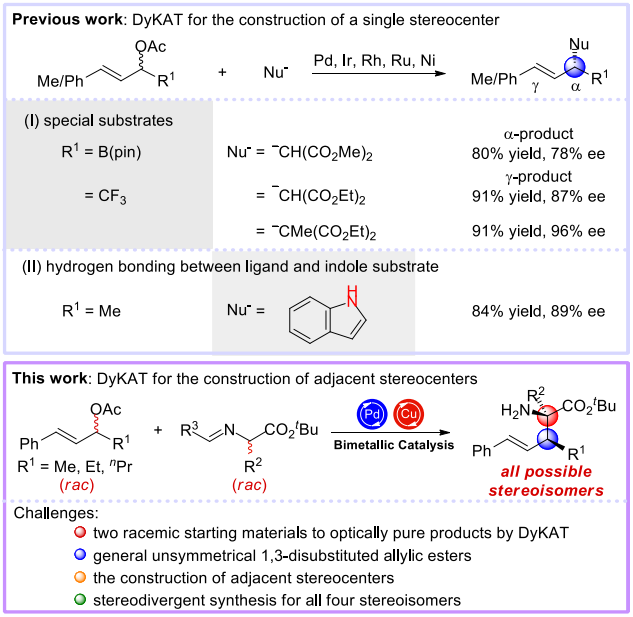
Supporting Information Placeholder

ABSTRACT: A stereodivergent Pd/Cu catalyst system has been developed for the unprecedented dynamic kinetic asymmetric transformation (DyKAT) of racemic unsymmetrical 1,3-disubstituted allylic acetates with prochiral aldimine esters. A series of α,α-disubstituted α-amino acids bearing vicinal stereocenters were easily prepared with excellent enantioselectivities (up to >99% ee) and diastereoselectivities (up to >20:1 dr). By simply changing the configurations of the two chiral metal catalysts, all four stereoisomers of the product can be readily obtained. Furthermore, our work highlights the power of synergistic Pd/Cu catalysis consisting of two common bidentate chiral ligands for stereodivergent synthesis.

Transition-metal-catalyzed asymmetric allylic alkylation (AAA) has proved to be a powerful method for the construction of carbon–carbon bonds. A large number of investigations concerning the AAA of monosubstituted allylic esters and symmetrical 1,3-disubstituted allylic esters have been reported.[1-2] However, there are only limited examples of asymmetric reactions with unsymmetrical 1,3-disubstituted allylic esters. In general, this transformation proceeds via a net retention mechanism (double inversion)[3-5] or kinetic resolution process[6], giving racemic products or up to 50% of the theoretical maximum yield. Accordingly, full conversion of racemic and unsymmetrical 1,3-disubstituted allylic esters to a single, enantioenriched product, known generally as dynamic kinetic asymmetric transformation (DyKAT),[7] is highly desired but still remains a challenge.[8-10] Although significant progress in the area of AAA has been reported recently through the elegant contribution from the research groups of Pucheault, Liao, Kawatsura, and Zhang, special substrates with γ-borylate, CF_3, and ethylene carbonate groups[9] and weak interactions[10] (hydrogen bonding between the nucleophile and ligand) are required for the DyKAT to proceed smoothly (Scheme 1). Furthermore, these stereoconvergent transformations with prochiral nucleophiles would provide an effective and convenient method for the construction of adjacent stereocenters. However, the development of such a process would become much more challenging not only due to the difficult handling of the DyKAT process but also because of problems associated with the remote stereocontrol of the prochiral nucleophiles.[1-2] Therefore, the development of new catalytic systems for the DyKAT of common unsymmetrical 1,3-disubstituted allylic esters with prochiral nucleophiles (even common nucleophiles) is greatly required (Scheme 1).

Scheme 1. Bimetallic Catalyzed DyKAT of AAA for the Stereodivergent Construction of Adjacent Stereocenters



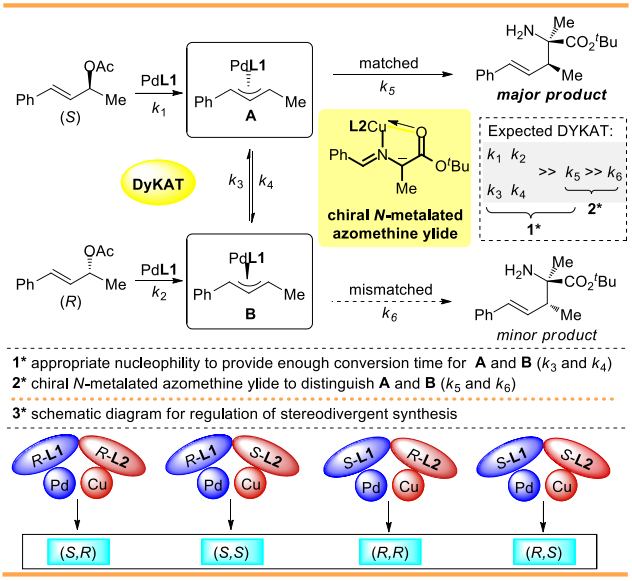
In recent years, cooperative bimetallic catalysis has received increasing attention due to its potential advantages over classic single catalytic methodologies in terms of reactivity and selectivity;[11-13] this has been demonstrated by the development of novel nucleophiles, the stereocontrol of prochiral nucleophiles and even stereodivergent synthesis.[14-16] In continuation of our research on bimetallic catalysis,[12a-c,g; 13h,j,k] we envisioned using this strategy to realize the first DyKAT of racemic and unsymmetrical 1,3-disubstituted allylic substrates for the stereodivergent construction of adjacent stereocenters (Scheme 1).

In the DyKAT process, the ionization of racemic and unsymmetrical allyl acetates initially generates the two π-allylpalladium intermediates **A** and **B**, which can convert between each other (Scheme 2). If

interconversion of **A** and **B** is favorable and the nucleophiles attack **A** and **B** at different speeds, an effective DyKAT would occur. The specific performance of this bimetallic catalysis strategy in the DyKAT most likely exists: 1) By introducing the other copper catalyst, the *N*-metalated azomethine ylides that are generated *in situ* as a "softer" and more crowded three-dimensional nucleophile compared to before, leads to a reduction in nucleophilicity. Accordingly, this strategy could favor greater interconversion between **A** and **B** (for 1*); 2) The enantiopure and rigid structure of the five-membered azomethine ylide could be beneficial to distinguishing between the diastereomeric **A** and **B** in the presence of chiral ligands. Both factors mentioned above could together promote the DyKAT to give a major enantiomer of a product with satisfactory stereoselectivity (for 2*); 3) All four stereoisomers of a desired product are expected to be obtained if each catalyst allows for full control over the configuration of each respective stereocenter (for 3*).

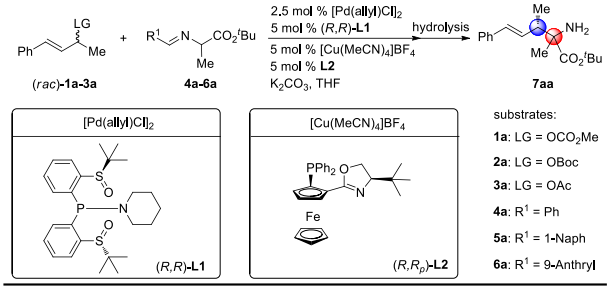
Herein, we successfully implement this bimetallic catalysis strategy for the AAA of racemic and acyclic unsymmetrical 1,3-disubstituted allylic substrates with prochiral aldimine esters. A series of optically active α-allyl-α-alkyl α-AAs containing vicinal stereocenters could be easily synthesized in high yields and with excellent stereoselectivities;[17] these important structural motifs are present in a number of biologically active natural products and pharmaceuticals (e.g., lactacystin, sulfonamide altemicidin, and neooxazolomycin).[18] This methodology would not only provide a versatile library of enantioenriched building blocks with divergent activities for drug screening but also facilitate the exploration of structure-activity relationships.

Scheme 2. Exploring the Specific Performance of Bimetallic Catalysis Strategy in DyKAT



Initially, racemic unsymmetrical 1,3-disubstituted allylic esters **1a-3a** were selected as the model substrates for the AAA of aldimine Schiff bases **4a-6a** (Table 1). To test the effect of the leaving group on the allyl moiety, several allylic esters were subjected to the reaction conditions (entries 1-3). Conducting the reaction with allylic acetate **3a** and aldimine Schiff base **4a** (R^1 = Ph) gave (*S*,*R*)-**7aa** with the best stereoselectivity of 6:1 dr and 99% ee (entry 3).[19] In order to gain insight into the nature of the cooperative effect, control experiments were conducted. No reaction occurred using only the Cu/**L2** catalyst (entry 4). The reaction proceeded with substantially lower reactivity when only Pd/**L1** catalyst was used (entry 5). The Pd and Cu complexes are indispensable for the transformation. When K_3PO_4 was used instead of K_2CO_3, the yield improved to 88% with 7:1 dr (entry 6). Guided by the reaction mechanism (Scheme 2), the inefficient interconversion of the two π-allylpalladium intermediates may be the main reason for the moderate stereoselectivity. To achieve higher diastereoselectivity, the volume of reaction solvent was increased to reduce the reaction rate, which may allow for more obvious distinction between the two π-allylpalladium diastereomers (entries 7 and 8). As expected, the desired product (*S*,*R*)-**7aa** was obtained in 89% yield with excellent diastereoselectivity (14:1 dr) and enantioselectivity (>99% ee) when using 4 mL of THF (entry 8). To our delight, no regioisomeric product of the allylic substrate **3a** was detected in our Pd/Cu catalyst system.[10]

Table 1. Optimization of the Reaction Conditions[a]



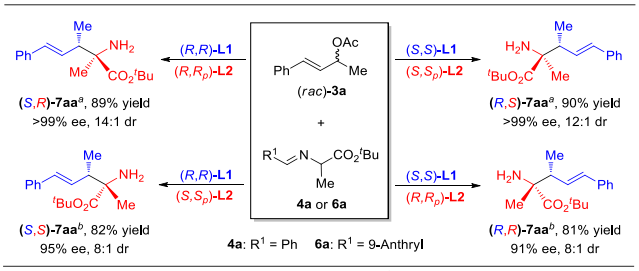
entry	sub.		L for Pd	L for Cu	yield (%)[b]	dr[c]	ee (%)[d] (config.)
1	**1a**	**4a**	(*R*,*R*)-**L1**	(*R*,*R*$_p$)-**L2**	74	2:1	98 (*S*,*R*)
2	**2a**	**4a**	(*R*,*R*)-**L1**	(*R*,*R*$_p$)-**L2**	85	2:1	99 (*S*,*R*)
3	**3a**	**4a**	(*R*,*R*)-**L1**	(*R*,*R*$_p$)-**L2**	81	6:1	99 (*S*,*R*)
4	**3a**	**4a**	no Pd	(*R*,*R*$_p$)-**L2**	nr	--	--
5	**3a**	**4a**	(*R*,*R*)-**L1**	no Cu	trace	--	--
6[e]	**3a**	**4a**	(*R*,*R*)-**L1**	(*R*,*R*$_p$)-**L2**	88	7:1	99 (*S*,*R*)
7[e,f]	**3a**	**4a**	(*R*,*R*)-**L1**	(*R*,*R*$_p$)-**L2**	83	11:1	>99 (*S*,*R*)
8[e,g]	**3a**	**4a**	(*R*,*R*)-**L1**	(*R*,*R*$_p$)-**L2**	89	14:1	>99 (*S*,*R*)
9[e,f]	**3a**	**4a**	(*R*,*R*)-**L1**	(*S*,*S*$_p$)-**L2**	35	1:2	97 (*S*,*S*)
10[e,h]	**3a**	**4a**	(*R*,*R*)-**L1**	(*S*,*S*$_p$)-**L2**	61	1:3	99 (*S*,*S*)
11[e,h]	**3a**	**5a**	(*R*,*R*)-**L1**	(*S*,*S*$_p$)-**L2**	77	1:3	94 (*S*,*S*)
12[e,h]	**3a**	**6a**	(*R*,*R*)-**L1**	(*S*,*S*$_p$)-**L2**	29	1:5	55 (*S*,*S*)
13[e,h,i]	**3a**	**6a**	(*R*,*R*)-**L1**	(*S*,*S*$_p$)-**L2**	74	1:8	95 (*S*,*S*)
14[e,h,j]	**3a**	**6a**	(*R*,*R*)-**L1**	(*S*,*S*$_p$)-**L2**	82	1:8	95 (*S*,*S*)

[a]Reaction conditions: **1a-3a** (0.125 mmol, 1.0 equiv.), **4a-6a** (0.150 mmol, 1.2 equiv.), $[Pd(allyl)Cl]_2$ (2.5 mol %), (*R*,*R*)-**L1** (5 mol %), $[Cu(MeCN)_4]BF_4$ (5 mol %), (*R*,*R*$_p$) or (*S*,*S*$_p$)-**L2** (5 mol %), K_2CO_3 (1.2 equiv.), rt, THF (1 mL), 12 h. [b]Isolated yield of all diastereoisomers. nr = no reaction. [c]Ratio of dr determined by ^1H NMR integration. [d]Determined by HPLC analysis using an OD-H column. [e]K_3PO_4 (1.2 equiv.) was used instead of K_2CO_3. [f]THF (2 mL). [g]THF (4 mL), 24 h. [h]THF (0.5 mL). [i]0 °C, 24 h. [j]**6a** (1.5 equiv.), K_3PO_4 (1.5 equiv), 0 °C, 72 h.

Subsequently, we set out to establish the availability of the enantio- and diastereodivergent access to **7aa**. Predictably, by changing (*R*,*R*$_p$)-**L2**, the ligand for Cu, to (*S*,*S*$_p$)-**L2**, (*S*,*S*)-**7aa** was generated successfully but in low yield with unsatisfactory diastereoselectivity (entry 9). When the volume of THF was reduced to 0.5 mL, the reaction yield was increased to 61% (entry 10). In order to obtain higher diastereoselectivity, it is necessary to increase the steric hindrance of the aldimine Schiff base, which makes it easier for the chiral aldimine-Cu complex to distinguish between the two π-allylpalladium diastereomers (entries 11 and 12). Encouragingly, excellent enantioselectivity and moderate diastereoselectivity were observed when **6a** (R^1 = Anthryl) was used, although with the product being obtained in only 29% yield. Interestingly, the reaction liquid became black after 12 h and a certain amount of (*E*)-buta-1,3-dien-1-ylbenzene was detected. Consequently,

β-H elimination of the π-allylpalladium intermediates as the competing reaction led to the low product yield (entry 12). Accordingly, the reaction temperature was reduced to 0 °C to inhibit the β-H elimination process, and the desired product was obtained in 74% yield with good stereoselectivity after 24 h (entry 13). Furthermore, by adding more nucleophile and base in order to increase the reactivity and by extending the reaction time, (*S*,*S*)-**7aa** was obtained in 82% yield with 8:1 dr and 95% ee (entry 14). Finally, all four stereoisomers could be prepared in high yields and with excellent stereoselectivity by changing the configuration of **L1** and **L2** (Scheme 3).

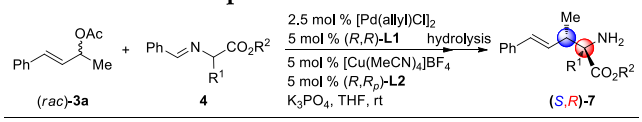
Scheme 3. Synthesis of All Four Stereoisomers of 7aa

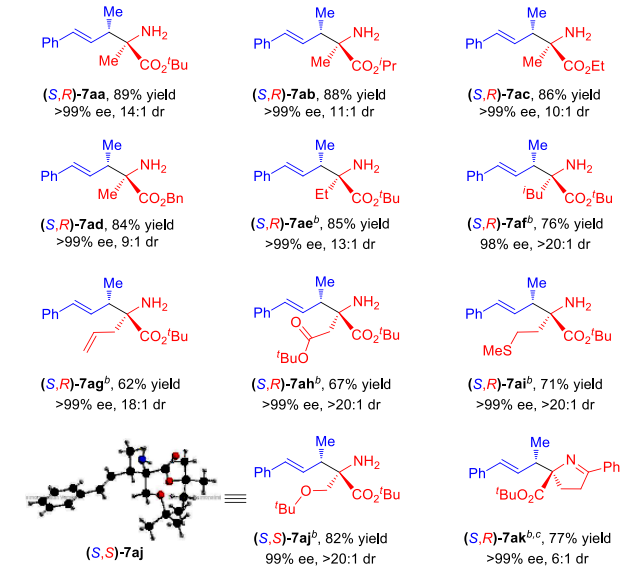


Reaction conditions: [a]See Table 1, entry 8. [b]See Table 1, entry 14.

Next, an array of aldimine Schiff bases derived from α-substituted α-AAs were treated with **3a** under the optimized conditions (Table 2). Substrates with different ester groups performed well under the standard conditions (**7aa**-**7ad**). However, α-AAs substituted with a bulky group (**4e**-**4j**) only afforded the corresponding products in low yields (**7ae**-**7aj**) with a large amount of β-H elimination product being observed. When the temperatue was reduced to 10 °C, the competing reaction was successfully inhibited and the target reactions gave the corresponding α,α-dialkyl α-AAs in good to high yields and with excellent stereoselectivities (up to >99% ee and up to >20:1 dr). The ketimine ester is also suitable for this reaction (**7ak**). The absolute configurations of (*S*,*S*)-**7aj** was determined by X-ray crystallography.

Table 2. Substrate Scope of Aldimine Esters[a]

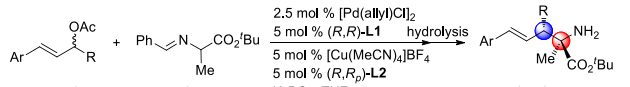


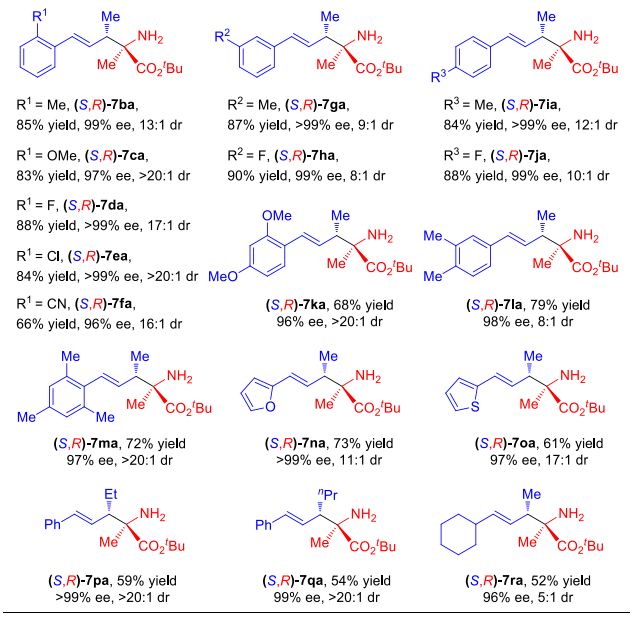


[a]Reaction conditions: See Table 1, entry 8. [b]10 °C, 48 h. [c]Without hydrolysis.

A range of allylic acetates substituted with arenes bearing electron-donating and electron-withdrawing substituents all furnished the corresponding products with high reactivities and excellent selectivities (Table 3, **7ba**–**7ma**), especially for those bearing substituents at the *ortho*-position of the arene functionality. Furyl- and thienyl-substituted allyl acetates were successfully employed to furnish their desired products (**7na** and **7oa**). Furthermore, reactions involving 1-ethyl, 1-propyl and 3-cyclohexyl-substituted allyl acetates also proceeded well to deliver their desired products in good yields and with excellent stereoselectivities (**7pa**-**7ra**).

Table 3. Substrate Scope of 1,3-Disubstituted Allylic Esters[a]



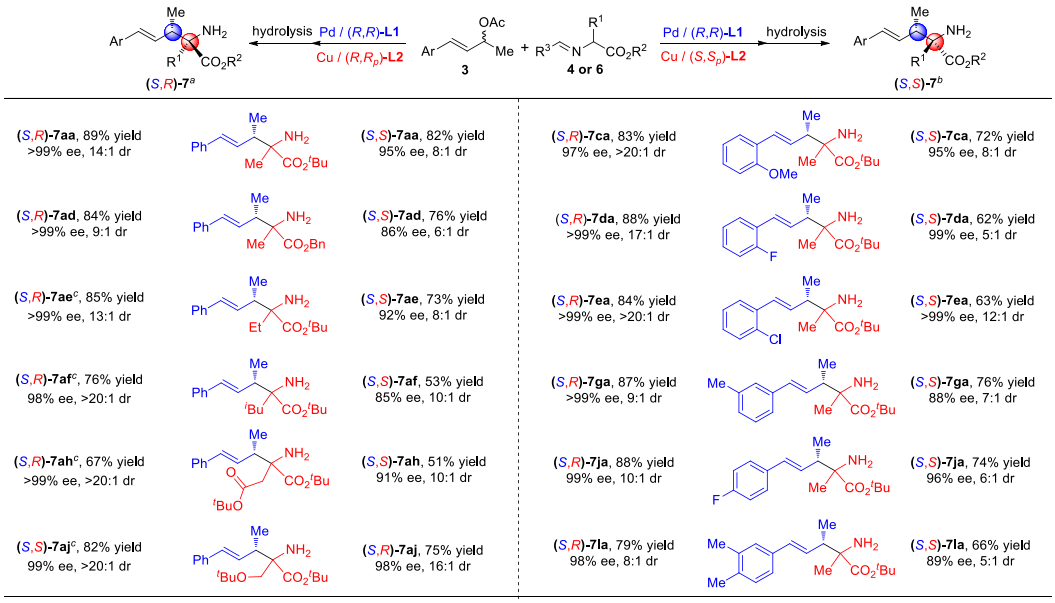


[a]Reaction conditions: See Table 1, entry 8.

Notably, the aldimine esters and allyl acetate scopes were investigated in a stereodivergent manner under the optimal reaction conditions (Table 4). A series of α-substituted aldimine esters derived from DL-alanine and other non-natural α-AAs reacted with **3a** smoothly, providing the non-coded α-AAs (**7aa**, **7ad**-**7af**, **7ah** and **7aj**) in good yields and with high enantio- and diastereoselectivities. It is noteworthy that all these reactions furnished products in a stereodivergent manner, allowing access to both diastereoisomers. Reactions with a range of allylic acetates **3** also gave products (**7ca**-**7ea**, **7ga**, **7ja** and **7la**) with access to two diastereoisomers. It was found that allylic acetates bearing substituents at the *ortho*-, *meta*-, or *para*-position of the phenyl ring were all tolerated in this transformation.

In general, a net retention mechanism or kinetic resolution process is observed for Pd-catalyzed allylic substitutions with unsymmetrical 1,3-disubstituted allylic esters.[3,6] Therefore, we were interested in the specific pathway of this DyKAT process in our Pd/Cu dual catalytic system. At first, the reaction with (*rac*)-**3a** was monitored over different reaction times and the substrate **3a** was recovered and analyzed by HPLC with a chiral AD column (Figure 1, for detailed reaction conditions, see the Supporting Information). The results showed that (*R*)-**3a** and (*S*)-**3a** were consumed together, and that the amount of (*S*)-**3a** decreased more rapidly. After 5 hours, the starting material **3a** was recovered in 13% yield with 30% ee. In order to further increase our

Table 4. Stereodivergent Synthesis



Reaction conditions: [a]See Table 1, entry 8. [b]See Table 1, entry 14. [c]10 °C, 48 h.

understanding of the mechanism, reactions with pure, optically active (*R*)-**3a** and (*S*)-**3a** were conducted, giving the same products (*S*,*R*)-**7aa** with different diastereoselectivity [6:1 dr versus 19:1 dr, respectively] (Scheme 4). Given that no racemization occurred using the pure, optically active (*S*)- and (*R*)-4-phenylbut-3-en-2-yl acetates [(*R*)-**3a** and (*S*)-**3a**],[10] the results mentioned-above both suggested that the combination of (*R*,*R*)-**L1** and (*R*,*R*$_p$)-**L2** matched with (*S*)-**3a** and mismatched with (*R*)-**3a**. The efficient interconversion of the π-allylpalladium species **B** derived from (*R*)-**3a** into the π-allylpalladium species **A**, occured before attacked by the nucleophile.

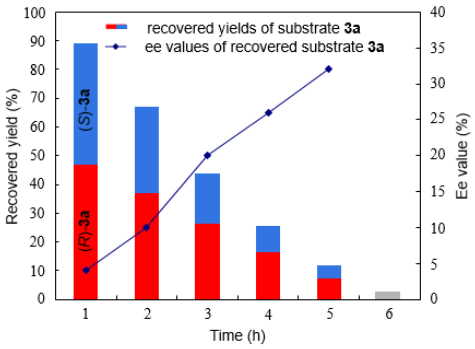
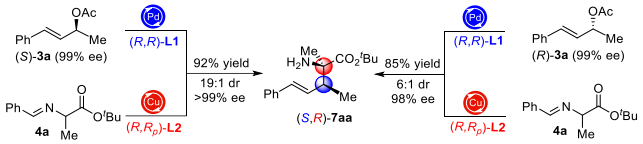


Figure 1. Ee Values and Recovered Yields of Substrate 3a at Different Reaction Times

Accordingly, a DyKAT mechanism in our stereodivergent Pd/Cu catalysis proposed above was further approved (Scheme 2). The oxidative addition of racemic **3a** with Pd/(*R*,*R*)-**L1** initially via a net inversion mechanism, generates the two π-allylpalladium intermediates **A** and **B**. **A** and **B** can transform into each other through nucleophilic displacement via the palladium(0) species.[10,20] The two diastereoisomer products (*S*,*R*)-**7** and (*S*,*S*)-**7** can be obtained via nucleophilic attack on the π-allylpalladium species **A** by the *N*-metalated azomethine ylides with (*R*,*R*$_p$)-**L2** and (*S*,*S*$_p$)-**L2**, respectively.

In summary, we have developed a stereodivergent Pd/Cu catalyst system, which was successfully applied to a DyKAT of racemic unsymmetrical 1,3-disubstituted allyl acetates with prochiral aldimine esters, providing efficient access to enantiopure α,α-disubstituted α-AAs

Scheme 4. The Study on the DyKAT Process



Reaction conditions: See Table 1, entry 8.

bearing vicinal stereocenters in a fully stereodivergent manner. Differing from the previous work based on the hydrogen bonding between the nucleophile and BiSO-P ligand, an enantio- and diastereoselective alkylation of unsymmetrical 1,3-disubstituted allylic esters with commom prochiral nucleophiles has been achieved via Pd/Cu dual catalysis. To the best of our knowledge, this reaction represents an unprecedented example of the enantioselective and diastereodivergent construction of adjacent stereocenters that proceed via a DyKAT process. Compared with the stereodivergent Ir/Cu catalysis containing a metallacyclic iridium complex, this Pd/Cu catalyst system consisting of two common bidentate ligands, could also be utilized for stereodivergent synthesis. Accordingly, the use of classic and commercially available chiral bidentate ligands should allow for the assembly of bimetallic catalyst libraries for stereodivergent synthesis.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all reactions and products, including ^{1}H and ^{13}C NMR spectra, HPLC spectra, and crystallographic data for (*S*,*S*)-**7aj** (CIF) and (*S*,*R*)-**7aj** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported by the Shanghai Sailing Program (19YF1421900), Shanghai Municipal Education Commission (No. 201701070002E00030), China Postdoctoral Science Foundation (No. 2019M663155), and National Natural Science Foundation of China (No. 21831005, 21871251, 21901158, and 21991112). Prof. Ilya D. Gridnev and Ms. Tatiana Gridneva are acknowledged for their assistance with the computation study. Ms. Juan Gui is acknowledged for her assistance with HRMS analysis.

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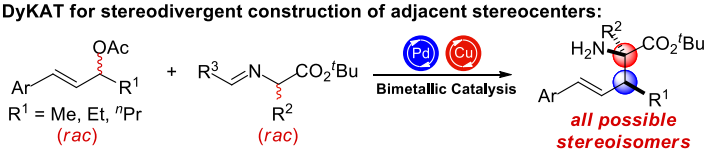
DyKAT for stereodivergent construction of adjacent stereocenters:



Challenges:

- two racemic starting materials to optically pure products by DyKAT
- general unsymmetrical 1,3-disubstituted allylic esters
- the construction of adjacent stereocenters
- stereodivergent synthesis for all four stereoisomers