A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Synergistic Palladium/Copper-Catalyzed 1,4-Difunctionalization of 1,3-Dienes for Stereodivergent Construction of 1,5-Nonadjacent Stereocenters

Authors: Hongfa Wang, Ruiyuan Zhang, and Weiwei Zi

To be cited as: *Angew. Chem. Int. Ed.* **2024**, e202402843

Link to VoR: https://doi.org/10.1002/anie.202402843

WILEY VCH

10.1002/anie.202402843

WILEY VCH

RESEARCH ARTICLE

Synergistic Palladium/Copper-Catalyzed 1,4-Difunctionalization of 1,3-Dienes for Stereodivergent Construction of 1,5-Nonadjacent Stereocenters

Hongfa Wang,[a],‡ Ruiyuan Zhang[a],‡ and Weiwei Zi*[a][b]

Dedication ((optional))

[a] Dr. H.Wang, R. Zhang, Prof. Dr. W. Zi
State Key Laboratory and Institute of Elemento-Organic Chemistry
College of Chemistry,Frontiers Science Center for New Organic Matter, Nankai University
Tianjin 300071,China
[b] Prof. Dr. W. Zi
Haihe Laboratory of Sustainable Chemical Transformations, Tianjin 300071, China
E-mail: zi@nankai.edu.cn
[‡] These authors contributed equally to this work.

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate.))

Abstract: The construction of two distal stereocenters through a single catalytic process is of great interest in organic synthesis. While there are some successful reports regarding stereodivergent preparation of 1,3- or 1,4-stereocenters, the more challenged 1,5-nonadjacent stereocenters have never been achieved in a stereodivergent fashion. Herein we describe a synergistic palladium/copper catalysis for 1,4-difunctionalization reactions of 1,3-dienes, providing access to 1,5-nonadjacent quaternary stereocenters. Because each of the two catalysts separately controlled one of the newly formed stereocenters, stereodivergent synthesis of all four diastereomers of the products could readily be achieved simply by choosing an appropriate combination of chiral catalysts. Experimental and computational studies supported a mechanism involving a Heck/Tsuji–Trost cascade reaction, and the origins of the stereoselectivity were elucidated.

Introduction

Catalytic asymmetric construction of 1,*n*-nonadjacent stereocenters in a single transformation is an important strategy for efficiently and economically building up molecular complexity.[1] The bioactivity of chiral molecules relies on all the stereocenters having the proper absolute stereochemistry, and a major challenge to constructing 1,*n*-nonadjacent stereocenters is concisely accessing all the stereoisomers of the products, which requires a stereodivergent catalytic process.[2] In the past decade, synergistic catalysis has found wide application for developing novel transformations that are unapproachable or difficult to realize with single-catalyst systems.[3] In particular, the use of two distinct chiral catalysts has permitted the stereodivergent construction of molecules with vicinal stereocenters.[4,5] In sharp contrast, there are only few examples of stereodivergent construction of compounds with two nonadjacent stereocenters (Figure 1a), yet these chiral motifs are widespread in bioactive molecules. Since 2021, the groups of He[6] and Zhang[7] reported copper/palladium systems and the Luo[8] group reported amine/palladium system, which enabled the stereodivergent construction of allenes bearing 1,3-axial/central chirality. More recently, You et al. used copper/iridium-catalyzed tandem conjugate addition/allylic substitution reactions for stereodivergent construction of 1,3-nonadjacent stereocenters.[9] On the other hand, in 2021, Lautens et al. disclosed the use of sequential rhodium/palladium catalysis for preparing cyclic 1,4-nonadjacent stereocenters.[10] Since 2022, Wang and colleagues reported copper/ruthenium relay catalysis for stereodivergent construction of linear 1,4-nonadjacent stereocenters.[11] To the best of our knowledge, however, no catalytic method for stereodivergent synthesis of 1,5- or 1,7-nonadjacent stereocenters has been reported.

Palladium(0)-catalyzed enantioselective Heck/Tsuji–Trost reaction provides a convenient way to introduce two functional groups into 1,3-dienes and offers rapid access to densely functionalized chiral allylic compounds.[12] Driven by the development of novel catalyst systems, research on this kind of difunctionalization reaction has progressed rapidly (Figure 1b). For example, Gong et al. reported highly enantioselective inter- and intramolecular 1,2-arylalkylation of 1,3-dienes,[13] and Huang et al. disclosed aminomethylamination and aminomethylative etherification reactions of 1,3-dienes to give diamines and amino alcohols, respectively.[14] Taking advantage of the utility of the chiral sulfonamide phosphine ligand SadPhos, Zhang and co-workers developed elegant carboetherification and carboamination reactions of 1,3-dienes for the preparation of heterocycles.[15] Because of steric effects, the above-mentioned difunctionalization reactions occur specifically at the less-hindered double bond of the diene substrates. However, different regioselectivity is also achievable. For example, Shi et al. reported that palladium-catalyzed 3,4-diamination of 1,3-dienes takes place predominantly at the internal double bond.[16] As a sharp contrast, Pd-catalyzed Heck/Tsuji–Trost reaction for 1,4-difunctionalization of 1,3-dienes has been underdeveloped,[17] enantioselective versions of this transformation have not been achieved. Moreover, control of the stereochemistry of the nucleophiles in the Heck/Tsuji–Trost reaction has never been realized. In this study, we explored the use of a dual catalyst

10.1002/anie.202402843

RESEARCH ARTICLE

system to address these challenges. In the method reported herein, a palladium complex catalyzes an intramolecular Heck insertion reaction of a 1,3-diene to form an electrophilic π-allyl-Pd species and produce the C1 stereocenter. Then a copper catalyst activates a nucleophile, which attacks the π-allyl-Pd species, giving rise predominantly to the desired 1,4-difunctionalized product and generating the C5 stereocenter (Figure 1c). The palladium and copper catalysts independently control the stereochemistry of the newly formed nonadjacent quaternary stereocenters at C1 and C5, respectively; in this way, stereodivergent synthesis of all four stereoisomers of the products is possible.

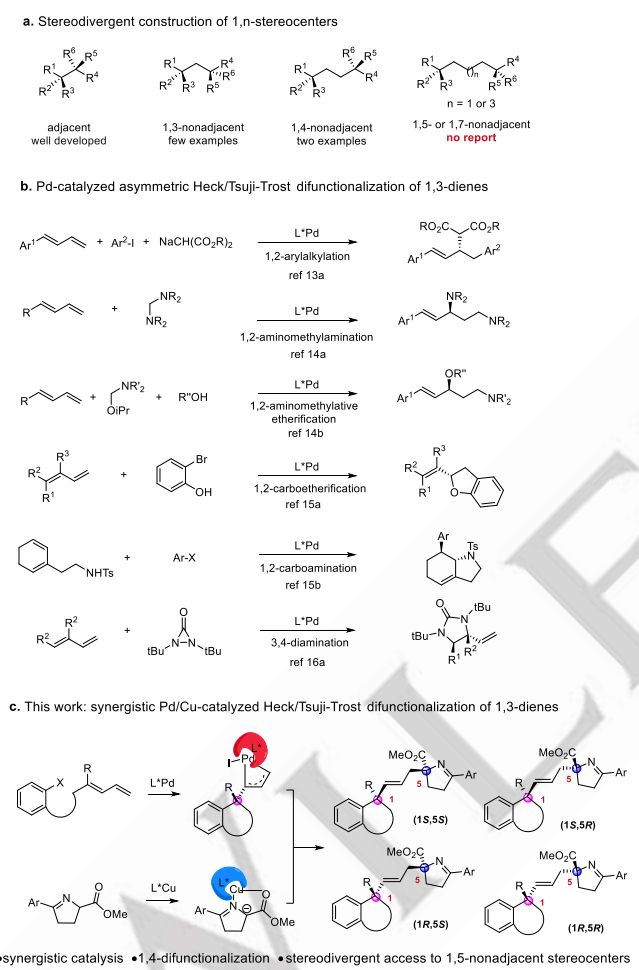


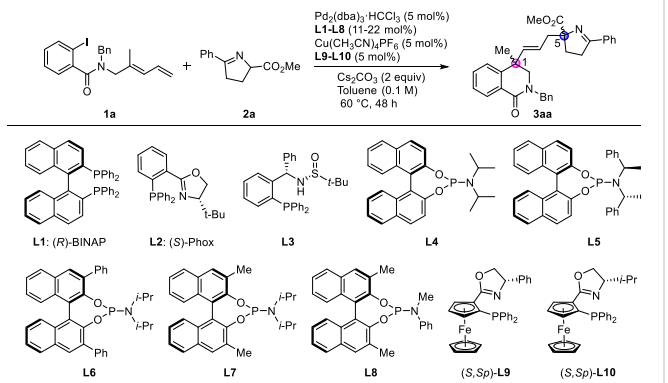
Figure 1. Stereodivergent Construction of 1,5-Nonadjacent Stereocenters.

Results and Discussion

Reaction Development.

To test the feasibility of the Heck/Tsuji–Trost cascade, we began by carrying out reactions of 1,3-diene **1a** and aryl ketimine ester **2a** as model substrates (Table 1). At the outset, we surmised that identifying the proper chiral ligand for the palladium catalyst might be the biggest challenge because this catalyst would participate in all the elemental steps involved in the transformation. First, we examined combinations of $Pd_2(dba)_3{\cdot}HCCl_3$ (dba = dibenzylideneacetone) with chiral ligands **L1**–**L8**, along with $Cu(CH_3CN)_4PF_6$/(S,S_p)-**L9** as the second catalyst and Cs_2CO_3 as the base, for reactions in toluene at 60 °C (Table 1). Unexpectedly, the bidentate ligands (*R*)-BINAP (**L1**) and (*S*)-Phox (**L2**), which are commonly used in asymmetric intramolecular Heck reactions of alkenes,[18] were inactive in our system (entries 1 and 2), a result that indicates a significant difference in reactivity between 1,3-dienes and alkenes in the intramolecular Heck addition step. SadPhos ligand **L3**, which was exploited by the Zhang group and has been successfully used for asymmetric intermolecular Heck/Tsuji–Trost reactions,[15] was also evaluated and found to give unsatisfactory results (entry 3). To our delight, however, electron-deficient phosphoramidite type ligand **L4** afforded desired product **3aa** in excellent yield (99%) with a 7:1 diastereomer ratio (dr) and >99% enantiomeric excess (ee) (entry 4). Encouraged by this result, we synthesized various other phosphoramidite ligands and tested them in our catalytic system (entries 5–8). Phosphoramidite ligands with a bulky amine moiety (**L5**) or a 3,3′-phenyl substituent (**L6**) showed substantially lower yields and stereoselectivities than **L4**, indicating that the reaction was sensitive to steric hindrance. We eventually found that 3,3′-methyl-substituted phosphoramidite ligand **L7** gave **3aa** in 95% yield with 16:1 dr and >99% ee (entry 7). Ligand **L8** performed similarly to **L7**, giving **3aa** in 95% yield with 16:1 dr and >99% ee (entry 8). Notably, decreasing the ligand loading from 22 mol% to 15 mol% did not affect the yield or stereoselectivity (entry 9). We also evaluated Ferrophox ligand (S,S_p)-**L10** for the copper catalyst and observed little difference between this ligand and (S,S_p)-**L9** (entry 10). Using *t*-BuOH as the solvent instead of toluene slightly improved the diastereoselectivity (to 20:1 dr, entry 11). With the optimal catalyst combination, that is, **L8**-Pd/(S,S_p)-**L9**-Cu, we obtained (1*R*,5*S*)-**3aa** as the predominant stereoisomer.

Table 1. Optimization of reaction conditions.[a]



entry	L for Pd	L for Cu	con. (%)[b]	yield (%)[b]	dr[b]	ee (%)[c]
1	**L1**	(S,S_p)-**L9**	<5	<5	—	—
2	**L2**	(S,S_p)-**L9**	15	<5	—	—
3	**L3**	(S,S_p)-**L9**	25	25	1:1	70/18
4	**L4**	(S,S_p)-**L9**	100	99	7:1	>99/−50
5	**L5**	(S,S_p)-**L9**	60	60	3:1	96/−90
6	**L6**	(S,S_p)-**L9**	25	25	2:1	89/−77

10.1002/anie.202402843

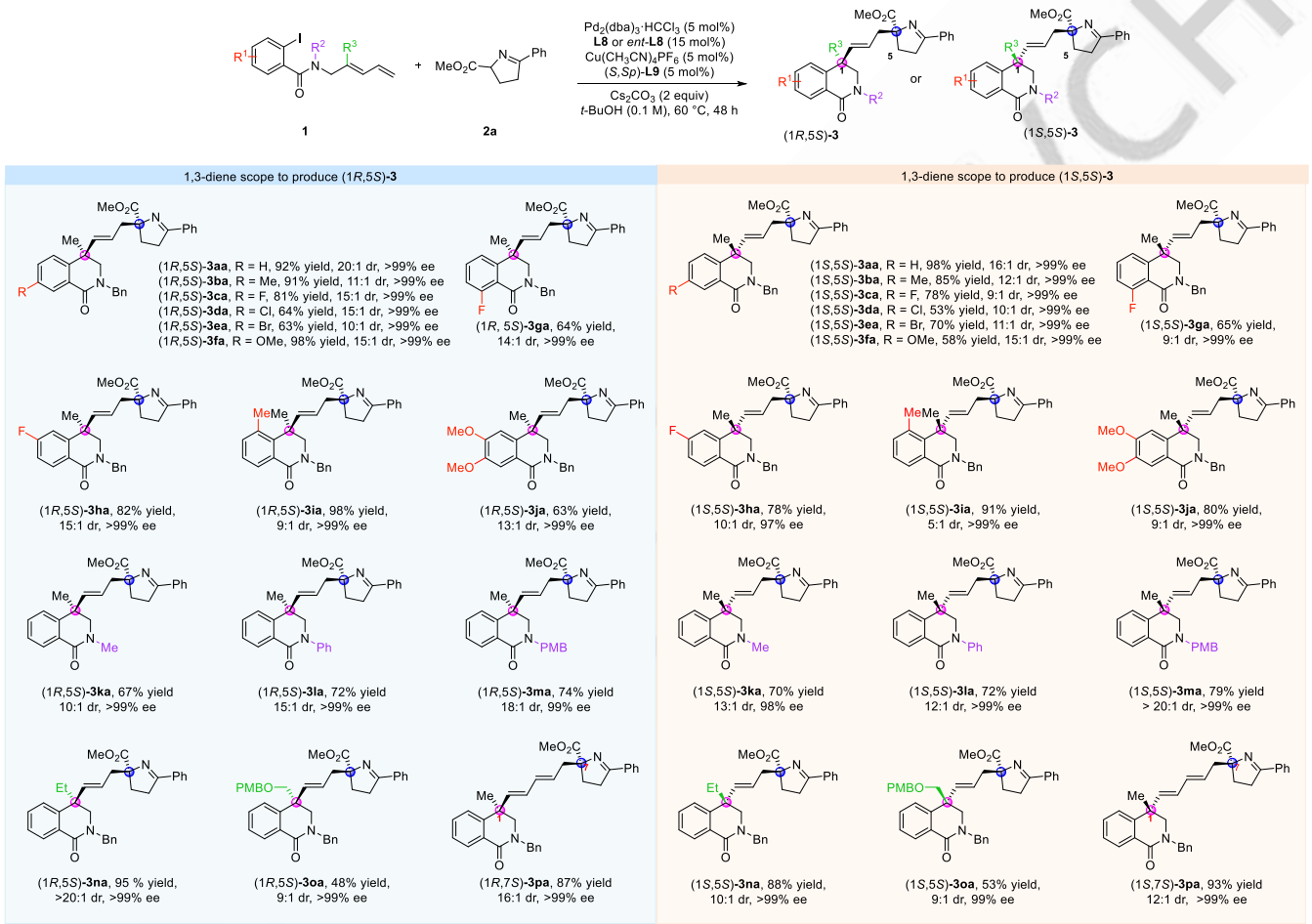
WILEY VCH

RESEARCH ARTICLE

7	**L7**	(*S*,*S*$_p$)-**L9**	100	95	16:1	>99/−26
8	**L8**	(*S*,*S*$_p$)-**L9**	100	95	16:1	>99/7
9[d]	**L8**	(*S*,*S*$_p$)-**L9**	100	95	16:1	>99/5
10[d]	**L8**	(*S*,*S*$_p$)-**L10**	100	95	15:1	>99/25
11[d,e]	**L8**	(*S*,*S*$_p$)-**L9**	100	98 (95)	20:1	>99/9
12[d,e]	**L7**	(*R*,*R*$_p$)-**L9**	100	81	1:2	40/84
13[d,e]	**L8**	(*R*,*R*$_p$)-**L9**	100	95 (94)	1:16	5/>99
14[f]	—	(*S*,*S*$_p$)-**L9**	<5	<5	—	—
15[g]	**L8**	—	<5	<5	—	—

[a] Reaction conditions: **1a** (0.05 mmol, 1 equiv), **2a** (0.1 mmol, 2 equiv), $Pd_2(dba)_3{\cdot}HCCl_3$ (5 mol%), **L1**–**L3** (11 mol%) or **L4**–**L8** (22 mol%), $[Cu(CH_3CN)_4]PF_6$ (5 mol%), **L9** or **L10** (5 mol%), Cs_2CO_3 (2 equiv), toluene, 60 °C, 48 h. [b] Conversions (con.), yields, and dr values were determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as the internal standard. [c] The ee values were determined by chiral HPLC. [d] 15 mol% of ligand was used. [e] *t*-BuOH was used instead of toluene. [f] Without Pd catalyst. [g] Without Cu catalyst.

Table 2. Substrate Scope with Respect to the 1,3-Dienes.[a]



[a] See SI for reaction details. Isolated yields are reported. The dr values were determined by ^{1}H NMR analysis of the crude reaction mixture, and the ee values were determined by chiral HPLC.

To establish the reaction's utility for enantio- and diastereodivergent access to all the stereoisomers of **3aa**, we attempted to reverse the dr value simply by using the enantiomer of (*S*,*S*$_p$)-**L9** as the copper ligand while keeping **L7** or **L8** as the palladium ligand. Although the desired diastereoselectivity switch was indeed observed with the **L7**-Pd/(*R*,*R*$_p$)-**L9**-Cu combination, the ratio of diastereoisomers was very poor (entry 12). Fortunately, combining **L8** with (*R*,*R*$_p$)-**L9** smoothly gave the desired diastereoisomer in 95% yield with 1:16 dr and >99% ee (entry 13). These two reactions demonstrated some potential matched and mismatched interactions between the catalyst pairs. Additionally, control experiments showed that no reaction occurred in the absence of the palladium or copper catalyst (entries 14 and 15), highlighting the importance of synergistic catalysis for the construction of 1,5-nonadjacent stereocenters. In summary, we could obtain (1*R*,5*S*)-**3aa** with **L8**-Pd/(*S*,*S*$_p$)/**L9**-Cu and (1*R*,5*R*)-**3aa** with **L8**-Pd/(*R*,*R*$_p$)-**L9**-Cu in similar yields with similar stereoselectivities.

Substrate Scope.

With the optimal reaction conditions in hand, we examined the generality of our dual catalytic system for enantio- and

10.1002/anie.202402843

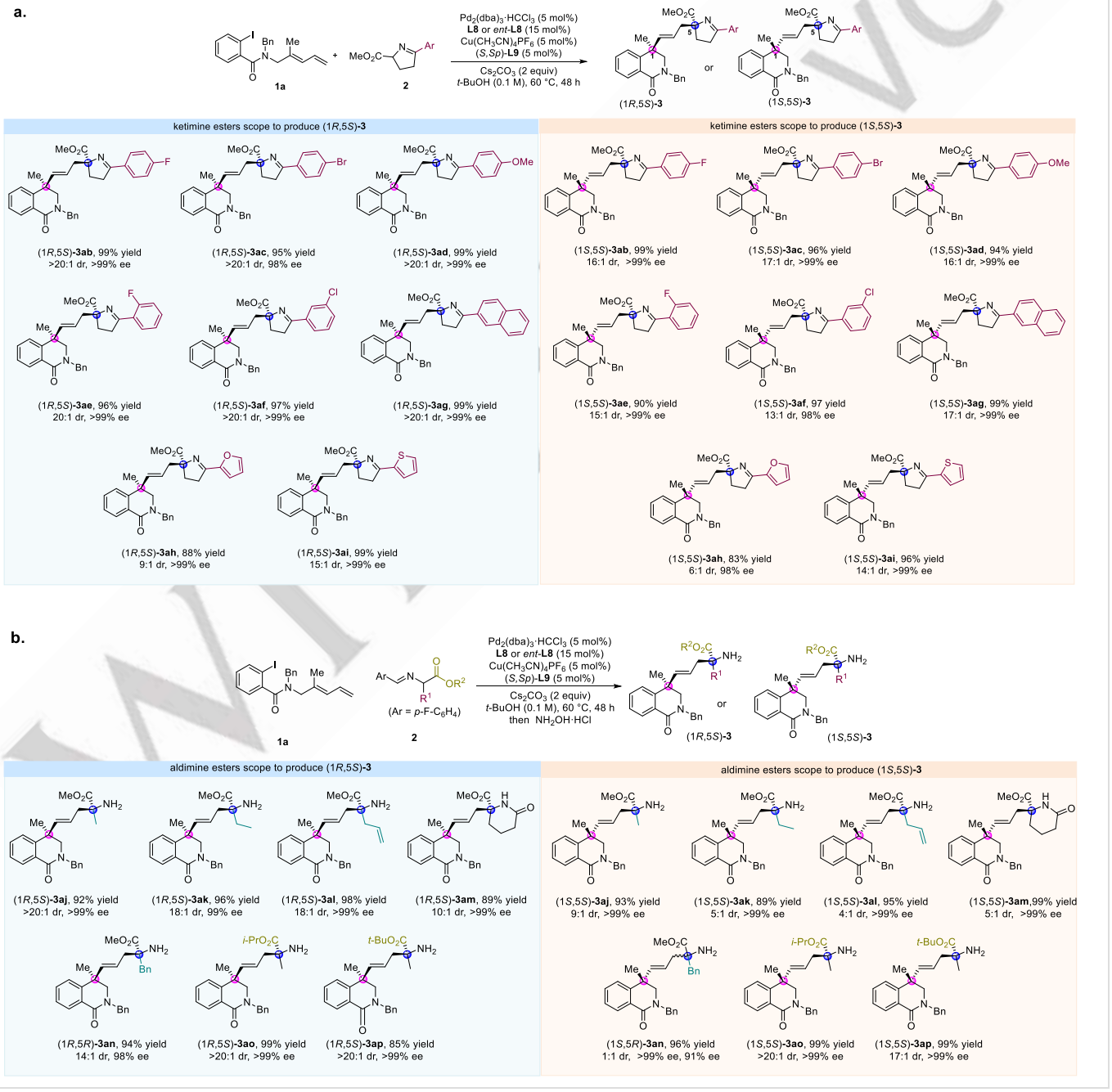
WILEY VCH

RESEARCH ARTICLE

diastereodivergent syntheses (Table 2). Various 1,3-dienes **1** bearing an electron-donating or electron-withdrawing R^1 group at the *para* position of the phenyl ring (R^2 = Bn, R^3 = Me) successfully underwent the desired reaction with activated aryl ketimine ester **2a**, giving chiral dihydroisoquinolinones (1*R*,5*S*)-**3aa–3fa** and their complementary diastereomers, (1*S*,5*S*)-**3aa**–**3fa**, in moderate to excellent yields (up to 98%) with good to excellent diastereoselectivities and enantioselectivities (up to 20:1 dr and >99% ee). Moreover, 1,3-dienes with *meta* or *ortho*-substituted or 3,4-disubstituted phenyl rings readily reacted with **2a** to afford corresponding coupling products (1*R*,5*S*)- and (1*S*,5*S*)-**3ga**–**3ja** with high diastereoselectivities and excellent enantioselectivities.

We also found that the mild reaction conditions were compatible with methyl, phenyl, and *p*-methoxybenzyl protecting groups on the amide moiety (**3ka**–**3ma)**. In addition to a methyl group, R^3 could also be ethyl or $PMBOCH_2$ (**3na** and **3oa**). Perhaps most remarkable was that this dual catalytic system could be used to accomplish a Heck/Tsuji–Trost cascade reaction of a 1,3,5-triene, which exclusively gave 1,6-difunctionalized products with 1,7-nonadjacent stereocenters: specifically, (1*R*,7*S*)-**3pa** was obtained in 87% yield with 16:1 dr, >99% ee, and a >20:1 regioisomer ratio; and (1*S*,7*S*)-**3pa** was obtained in 93% yield with 12:1 dr, >99% ee, and a >20:1 regioisomeric ratio.

Table 3. Substrate Scope with Respect to the Nucleophiles.[a]



10.1002/anie.202402843

[a] See SI for reaction details. Isolated yields are reported. The dr values were determined by ^{1}H NMR analysis of the crude reaction mixture, and the ee values were determined by chiral HPLC. Abbreviations: Bn, benzyl; PMB, *para*-methoxylbenzyl.

We next explored the scope of this diastereodivergent reaction with respect to the nucleophiles (Table 3a). We found that aryl ketimine esters with a *para*-F, *para*-Br, *para*-OMe, *ortho*-F, or *meta*-Cl substituent on the phenyl ring were capable of furnishing the corresponding coupling products, (1*R*,5*S*)- and (1*S*,5*S*)-**3ab**–**3af**, with excellent enantio- and diastereoselectivities (13:1 to >20:1 dr and 98% to >99% ee). The broad scope of the reaction was further demonstrated by the conversion of fused aryl- and heteroaryl ketimine ethers **2g**–**2i**; these three ketimine esters all successfully underwent the desired reaction, giving the corresponding products in 83% to >99% yields, with 6:1 to >20:1 dr and 98% to >99% ee.

Aldimine esters derived from *α*-substituted *α*-amino acids were also feasible nucleophiles, smoothly reacting with **1a** to afford dihydroisoquinolinones bearing an *α*,*α*-dialkyl α-amino acid moiety at the end of the side chain (Table 3b). Notably, we found that these mild conditions were compatible with methyl, ethyl, allyl, benzyl, and ester groups at R^1, giving products (1*R*,5*S*)-**3aj**–**3an** with excellent stereoselectivities when **L8**-Pd was combined with (*S*,*S*$_p$)-**L9**-Cu. In addition, and (1*S*,5*S*)-**3aj–3an** could be obtained by combining *ent*-**L8**-Pd with (*S*,*S*$_p$)-**L9**-Cu. However, the dr values of the latter products were relatively low (between 1:1 and 9:1). We concluded that the steric bulk of the R^1 group strongly affect the stereoselectivity of the reaction that produced (1*S*,5*S*)-**3**: bulkier R^1 groups led to worse diastereoselectivity. For example, when the R^1 group was changed from methyl to ethyl, the dr decreased from 9:1 to 5:1, and when R^1 was an even bulkier benzyl group, the dr value dropped dramatically (to 1:1), although the enantioselectivity remained excellent. This phenomenon may have been due to a mismatched interaction between *ent*-**L8**-Pd and (*S*,*S*$_p$)-**L9**-Cu in the asymmetric allylic substitution step. The combination of poor diastereoselectivity and retained enantioselectivity can be attributed to the fact that the enantioselectivity originated from the C1 stereocenter, the stereochemistry of which was controlled mainly by the asymmetric migratory insertion step, with the palladium catalyst acting as the predominant influence. Previous research has indicated that aldimine esters with bulky ester groups, such as isopropyl and *tert*-butyl, enhance stereocontrol in copper-catalyzed nucleophilic reactions.[19] We were able to take advantage of this fact to improve the diastereoselectivity for the mismatched catalyst system, as exemplified by the formation of (1*S*,5*S*)-**3ao** and **3ap** with excellent dr values.

Synthetic Applications.

To demonstrate the stereodivergent construction of 1,5-nonadjacent stereocenters, we carried out Heck/Tsuji–Trost reactions of substrates **1a** and **2a** with catalysis by **L8**-Pd/(*S*,*Sp*)-**L9**-Cu, *ent*-**L8**-Pd/(*S*,*Sp*)-**L9**-Cu, *ent*-**L8**-Pd/(*R*,*Rp*)-**L9**-Cu, and **L8**-Pd/(*R*,*Rp*)-**L9**-Cu (Fig. 4a). In this way, we were able to concisely prepare (1*R*,5*S*)-**3aa**, (1*S*,5*S*)-**3aa,** (1*S*,5*R*)-**3aa**, and (1*R*,5*R*)-**3aa** in good yields with excellent enantio- and diastereoselectivities (Figure 2a). To demonstrate the practicality of the method, we scaled up the reaction of **1a** and **2o** to a gram scale and obtained the corresponding products, (1*R,*5*S*)-**3ao** and (1*S,*5*S*)-**3ao**, with no decrease in yields or stereoselectivities (Figure 2b).

These products were rich in functionality that could be transformed to useful structural motifs (Figure 2c). Taking (1*R,*5*S*)-**3ao** as an example, hydrogenation of the alkene moiety gave compound **4** in 88% yield. Treatment of **3ao** with lithium aluminum hydride in THF reduced both the amide and the ester groups, furnishing amino alcohol **5** in 86% yield. Interestingly, an *N*-bromosuccinimide-mediated degradation of **3ao** was achieved, giving allylic bromide **6** in 51% yield.[20] Protection of the amine of **3ao** as a sulfonamide afforded **7**, which was treated with K_2OsO_4/*N*-methylmorpholine *N*-oxide for a dihydroxylation/lactonization cascade reaction that afforded compound **8**, which bears four stereocenters, with 4:1 dr.[21]

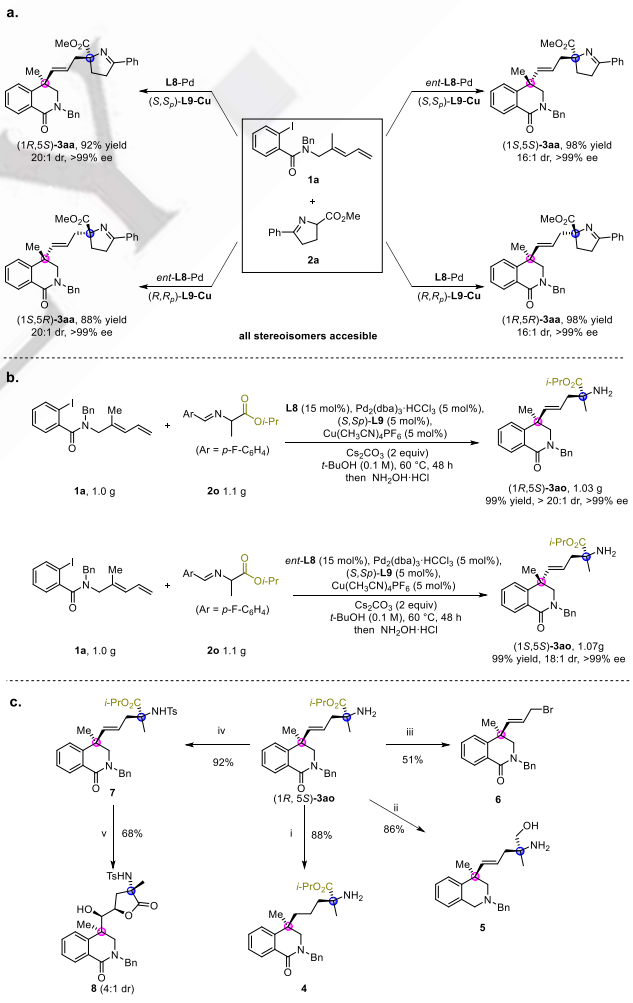


Figure 2. Synthetic application. (a) Stereodivergent construction of all four stereoisomers. (b) Gram-scale preparation. (c) Synthetic transformation of the products. Reaction conditions: (i) Pd(OH)$_2$/C (10 wt %), H_2, MeOH, room temperature (r.t.), 12 h. (ii) $LiAlH_4$, THF, 0 °C to r.t., 6 h. (iii) *N*-Bromosuccinimide, Na_2CO_3, CH_3CN, r.t., 24 h. (iv) TsCl, 4-dimethylaminopyridine, Et_3N,

10.1002/anie.202402843

dichloromethane, 0 °C to r.t., 12 h. (v) $K_2OsO_4{\cdot}2H_2O$, *N*-methylmorpholine *N*-oxide, acetone, H_2O, r.t., 48 h.

Mechanistic Studies.

We next investigated the mechanism of the reaction by performing some control experiments. To understand the origin of the C1 stereochemistry, we used dimethyl malonate (**9**) instead of a ketimine ester as the nucleophile (Figure 3a). We found that in the absence of a copper catalyst, **L8**-$Pd_2(dba)_3{\cdot}HCCl_3$ could catalyze the Heck/Tsuji–Trost reaction to give product **10** in 69% yield together with a 16% yield of doubly substituted product **11**. The ee value for **10** was 93%, indicating that the C1 stereochemistry was controlled solely by the palladium catalyst. We prepared an **L8**-Pd(allyl)Cl complex and obtained its single-crystal X-ray structure, which showed that one **L8** ligand, one chloride ion, and one η^3-allyl group were coordinated to the palladium center in a square-planar geometry. Furthermore, the ee values of optically active ligand **L8** and product **10** were linearly related, suggesting that mono-**L8**-complexed palladium was the active catalyst.

A stoichiometric reaction of **1a** with catalysis by $Pd_2(dba)_3{\cdot}HCCl_3$ and **L8** gave a mixture of Heck reaction intermediates π-allyl-Pd **12a** and **12b** in a 4:1 ratio and a combined yield of 82% (Figure 3b). The structure of **12b** was confirmed by single-crystal X-ray analysis, and the absolute configuration at C1 was determined to be *R*.[22] Moreover, reaction of **12a** with one equiv of **9** in *t*-BuOH containing Cs_2CO_3 afforded **10** and **11** in 38% and 14% yields, respectively (Figure 3c). The above-described results indicate that **12a** was involved in the Heck/Tsuji–Trost reaction.

We used density functional theory to calculate the energy profile of the 1,4-difunctionalization reaction between 1,3-diene **1k** and malonate **9** with catalysis by **L8**-$Pd_2(dba)_3{\cdot}HCCl_3$ (Figure 4). The calculations revealed that the reaction is initiated by oxidative addition of Pd(0) to the Ar–I bond of **1k** to form Pd(II) intermediate **Int 2** via transition state **TS 1**, with an energy barrier of 22.5 kcal/mol. Coordination of the internal double bond to the metal center (replacing the oxygen atom) gives **Int 3A**, and then migratory insertion of Ar–Pd into the internal alkene from the *si* face forms η^1 π-allyl-Pd intermediate **Int 5B** via transition state **TS 4A**, with an energy barrier of 12.5 kcal/mol. Notably, the migratory insertion can also occur from the *re* face of the alkene via **TS 4B**, the energy barrier to which is 1.2 kcal/mol higher than that for insertion from the *si* face. This result is consistent with our experimental observation that catalysis by **L8**-$Pd_2(dba)_3{\cdot}HCCl_3$ afforded the *R* configuration at C1 of **10** (93% ee). **Int 5B** is rapidly converted to η^3 π-allyl-Pd intermediate **Int 6**, a process that is exothermic by 19.6 kcal/mol. For the allylic substitution step, nucleophilic allylic attack of π-allyl-Pd **Int 6** by the cesium enolate occurs via **TS 7**, with an energy barrier of 8.8 kcal/mol, to give **Int 8**. In this process, oxidative addition is the rate-limiting step, and the irreversible migratory insertion step determines the C1 stereochemistry.

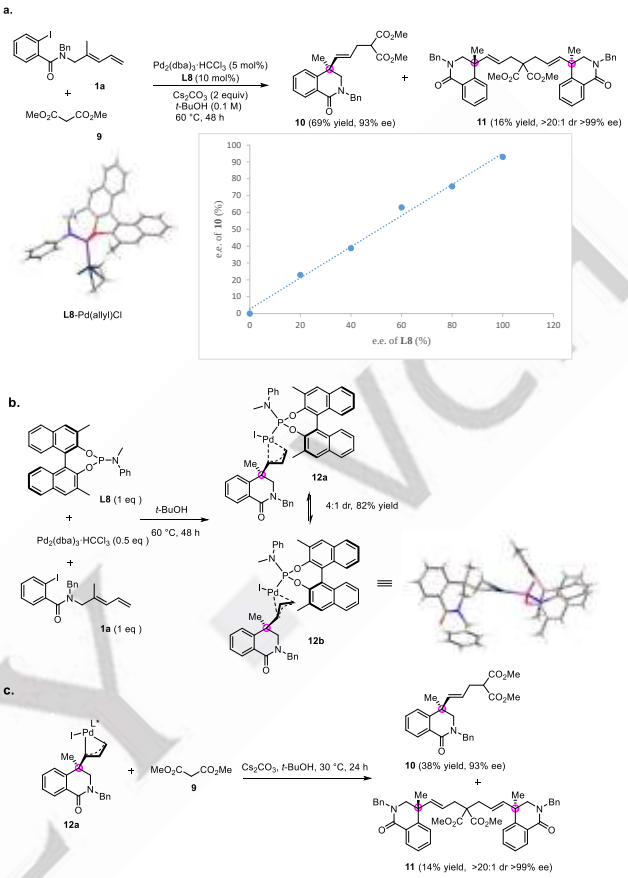


Figure 3. Mechanistic studies.

To understand the origin of the C5 stereochemistry, we investigated the transition states for the allylic substitution step of a reaction involving a ketimine ester as the nucleophile (Figure 5). With (*S*,*Sp*)-**L9**-Cu(I) as the catalyst and Cs_2CO_3 as the base, ketimine ester **2a** was converted to Cu-enolate species Nu-Cu(*R*) and Nu-Cu(*S*), with the former being 2.3 kcal/mol more stable than the latter. Formation of a C–C bond between **Int 6** and Nu-Cu(*R*) or between **Int 6** and Nu-Cu(*S*) was then calculated. The transition states for these two possibilities, **TS 8A** and **TS 8B**, respectively, were located, and the former was found to be favored by 2.5 kcal/mol, indicating that the (*S*)-C5 stereoisomeric product should predominate, which is in agreement with the experimental results.

10.1002/anie.202402843

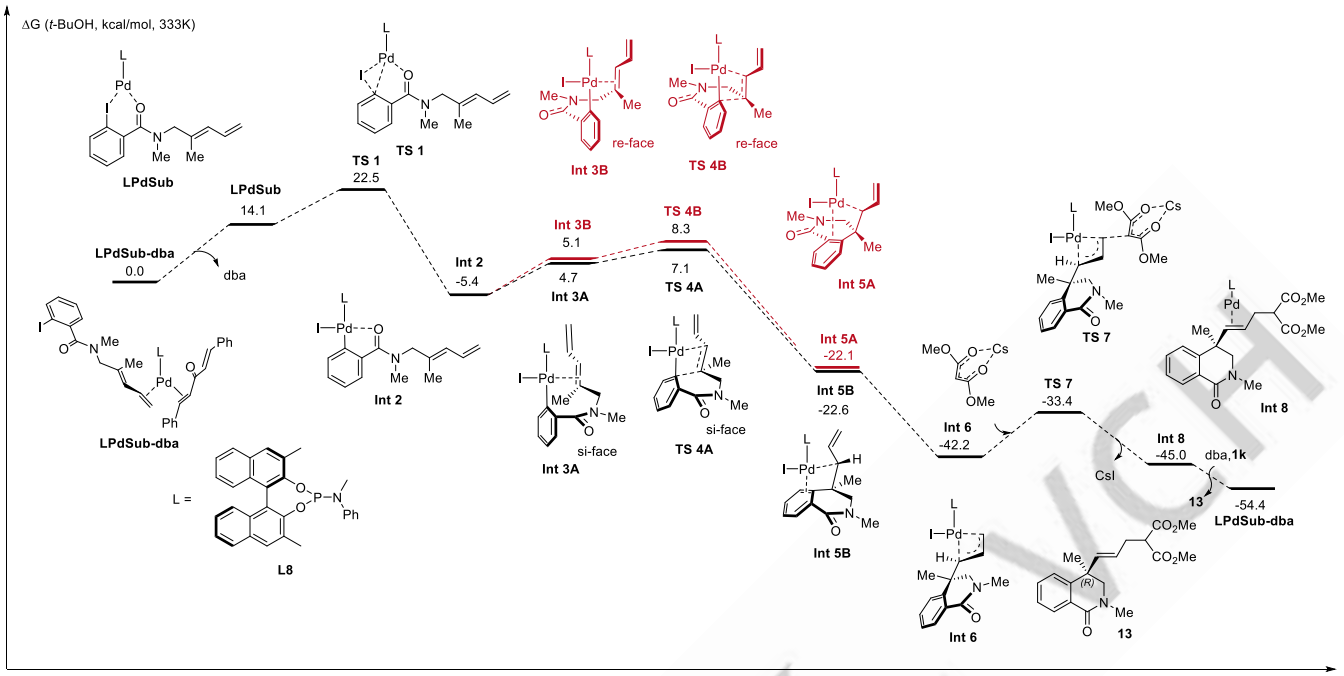


Figure 4. Calculated energy profile for reaction of 1,3-diene **1k** with cesium dimethyl malonate. Density functional theory calculations were carried out at the ωB97XD/def2-TZVP (SMD)//ωB97XD/6-31g(d)/Lanl2dz (SMD) level of theory.

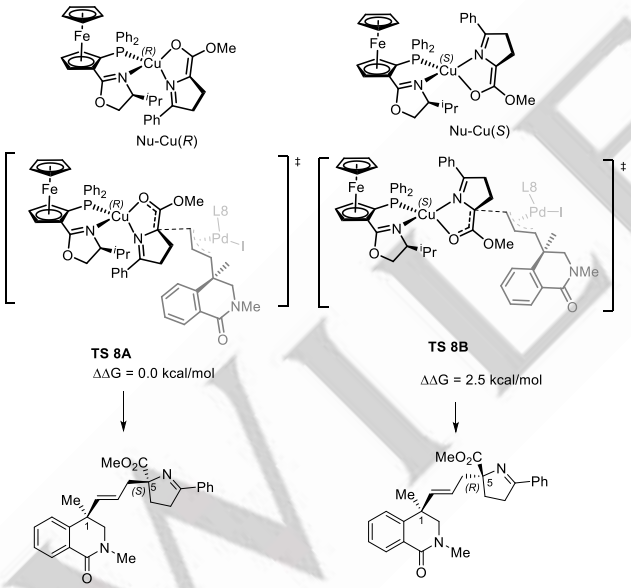


Figure 5. Rationalization of C5-stereochemistry.

Conclusion

In summary, we have realized a synergistic palladium/copper-catalyzed 1,4-difunctionalization reactions of 1,3-dienes for stereodivergent construction of compounds with 1,5-nonadjacent stereocenters. The method has a wide substrate scope and could be extended to the preparation of products with 1,7-nonadjacent stereocenters. Both experimental and computational studies supported a mechanism involving a Heck/Tsuji–Trost cascade and the palladium and copper catalysts separately control the newly formed stereocenters at C1 and C5, respectively. The work described herein not only provides a general method for constructing compounds with 1,5- or 1,7-remote stereocenters but also represents the first successful manipulation of the chirality of a nucleophile in a Heck/Tsuji–Trost cascade reaction. Our results can be expected to inspire other studies on catalytic stereodivergent synthesis.

Acknowledgements ((optional))

We gratefully acknowledge funding support from the National Key R&D Program of China (no. 2022YFA1503700, 2023YFA1506700), the National Natural Science Foundation of China (nos. 22071118, 22271162, and 22188101), and the Natural Science Foundation of Tianjin (no. 21JCZDJC00350). We thank the Haihe Laboratory of Sustainable Chemical Transformations and Frontiers Science Center for New Organic Matter for financial support. W. Zi thanks Prof. Biji Li for helpful disccustions.

Keywords: synergistic catalysis • stereodivergent • 1,3-dienes • palladium/copper • Heck/Tsuji–Trost

[1] For review and selected examples on catalytic asymmetric construction of 1,*n*-nonadjacent stereocenters: a) K. Mikami, M. Shimizu, H.-C. Zhang, B. E. Maryanoff, *Tetrahedron* **2001**, *57*, 2917-2951; b) Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 3928-3930; c) J. A. Enquist Jr, B. M. Stoltz, *Nature* **2008**, *453*, 1228-1231; d) C. R. Davis, I. K. Luvaga, J. M. Ready, *J. Am. Chem. Soc.* **2021**, *143*, 4921-4927; e) M. Kong, Y.

Tan, X. Zhao, B. Qiao, C.-H. Tan, S. Cao, Z. Jiang, *J. Am. Chem. Soc.* **2021**, *143*, 4024-4031.

[2] a) S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2017**, *139*, 5627-5639; b) I. P. Beletskaya, C. Nájera, M. Yus, *Chem. Rev.* **2018**, *118*, 5080−5200.

[3] For reviews on synergistic catalysis: a) A. E. Allen, D. W. C. Macmillan, *Chem. Sci.* **2012**, *3*, 633-658; b) C. S. Schindler, E. N. Jacobsen, *Science* **2013**, *340*, 1052-1053; c) D. -F. Chen, Z. -Y. Han, X. -L. Zhou, L. -Z. Gong, *Acc. Chem. Res.* **2014**, *47*, 2365-2377; d) S. Martínez, L. Veth, B. Lainer, P. Dydio, *ACS Catal.* **2021**, *11*, 3891-3915; e) D.-F. Chen, L.-Z. Gong, *J. Am. Chem. Soc.* **2022**, *144*, 2415–2437; f) C. C. Malakar, L. Dell'Amico, W. Zhang, *Eur. J. Org. Chem.* **2023**, *26*, e202201114. DOI: 10.1002/ejoc.202201114; g) L. Wei, C.-J. Wang, *Chem Catal.* **2023**, *3*, 100455.

[4] For recent reviews on catalytic stereodivergent construction of vicinal stereocenters: a) M. T. Oliveira, M. Luparia, D. Audisio, N. Maulide, *Angew. Chem. Int. Ed.* **2013**, *52*, 13149-13152; *Angew.Chem*. **2013**, *125*, 13387-13390; b) X. Huo, G. Li, X. Wang, W. Zhang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202210086; *Angew.Chem*. **2022**, *134*, e202210086; c) H. Wang, Q. Zhang, W. Zi, *Acc. Chem. Res.* **2024**, 10.1021/acs.accounts.3c00639;

[5] For selected examples on catalytic stereodivergent construction of vicinal stereocenters: a) S. Krautwald, D. Sarlah, M. A. Schafroth, E. M. Carreira, *Science* **2013**, *340*, 1065-1068; b) X. Huo, R. He, X. Zhang, W. Zhang, *J. Am. Chem. Soc.* **2016**, *138*, 11093−11096; c) X. Jiang, J. J. Beiger, J. F. Hartwig, *J. Am. Chem. Soc.* **2017**, *139*, 87−90; d) F. A. Cruz, V. M. Dong, *J. Am. Chem. Soc.* **2017**, *139*, 1029−1032; e) X. Huo, J. Zhang, J. Fu, R. He, W. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 2080−2084; f) L. Wei, Q. Zhu, S.-M. Xu, X. Chang, C.-J. Wang, *J. Am. Chem. Soc.* **2018**, *140*, 1508−1513; g) Q. Zhang, H. Yu, L. Shen, T. Tang, D. Dong, W. Chai, W. Zi, *J. Am. Chem. Soc.* **2019**, *141*, 14554-14559; h) H. Wang, R. Zhang, Q. Zhang, W. Zi, *J. Am. Chem. Soc.* **2021**, *143*, 10948-10962; i) R. He, X. Huo, L. Zhao, F. Wang, L. Jiang, J. Liao, W. Zhang, *J. Am. Chem. Soc.* **2020**, *142*, 8097−8103; j) S. Singha, E. Serrano, S. Mondal, C. G. Daniliuc, F. Glorius, *Nat. Catal.* **2020**, *3*, 48−54; k) D.-X. Zhu, J.-G. Liu, M.-H. Xu, *J. Am. Chem. Soc.* **2021**, *143*, 8583-8589; l) M. Zhu, Q. Zhang, W. Zi, *Angew. Chem. Int. Ed.* **2021**, *60*, 6545-6552; *Angew.Chem*. **2021**, *133*, 6619-6626; m) Y. Peng, X. Huo, Y. Luo, L. Wu, W. Zhang, *Angew. Chem. Int. Ed.* **2021**, *60*, 24941-24949; *Angew. Chem.* **2021**, *133*, 25145-25153; n) L. Xiao, L. Wei, C.-J. Wang, *Angew. Chem. Int. Ed.* **2021**, *60*, 24930-24940; *Angew. Chem.* **2021**, *133*, 25134-25144; o) M. Zhu, P. Wang, Q. Zhang, W. Tang, W. Zi, *Angew. Chem. Int. Ed.* **2022**, *61*, e202207621; *Angew. Chem.* **2022**, *134*, e202207621; p) Y. Xu, H. Wang, Z. Yang, Y. Zhou, Y. Liu, X. Feng, *Chem* **2022**, *8*, 2011-2022; q) Q. Hu, Z. He, L. Peng, C. Guo, *Nat. Synth.* **2022**, *1*, 322-331; r) Q. Zhang, M. Zhu, W. Zi, *Chem* **2022**, *8*, 2784-2796; s) T. P. Le, S. Tanaka, M. Yoshimura, K. Sato, M. Kitamura, *Nat. Commun.* **2022**, *13*, 5876; t) J. Han, R. Liu, Z. Lin, W. Zi, *Angew. Chem. Int. Ed.* **2023**, *62*, e202215714; *Angew. Chem.* **2023**, *135*, e202215714; u) Y. Luo, Y. Ma, G. Li, X. Huo, W. Zhang, *Angew. Chem. Int. Ed.* **2023**, *62*, e202313838; *Angew. Chem.* **2023**, *135*, e202313838; v) Y.-H. Wen, F. Yang, S. Li, X. Yao, J. Song, L.-Z. Gong, *J. Am. Chem. Soc.* **2023**, *145*, 4199-4207; w) L. Zhao, Y. Luo, J. Xiao, X. Huo, S. Ma, W. Zhang, *Angew. Chem. Int. Ed.* **2023**, *62*, e202218146; *Angew. Chem.* **2023**, *135*, e202218146; x) L. Peng, M. Wang, J. Huang, C. Guo, L.-Z. Gong, J. Song, *J. Am. Chem. Soc.* **2024**, *145*, 28085-28095; y) J. Zhang, W. Zhu, Z. Chen, Q. Zhang, C. Guo, *J. Am. Chem. Soc.* **2024**, *146*, 1522-1531.

[6] S.-Q. Yang, Y.-F. Wang, W.-C. Zhao, G.-Q. Lin, Z.-T. He, *J. Am. Chem. Soc.* **2021**, *143*, 7285−7291.

[7] J. Zhang, X. Huo, J. Xiao, L. Zhao, S. Ma, W. Zhang, *J. Am. Chem. Soc.* **2021**, *143*, 12622–12632.

[8] C. You, M. Shi, X. Mi, S. Luo, *Nat. Commun.* **2023**, *14*, 2911.

[9] J.-H. Xie, Y.-M. Hou, Z. Feng, S.-L. You, *Angew. Chem. Int. Ed.* **2023**, *62*, e202216396; *Angew.Chem*. **2023**, *135*, e202216396.

[10] J. Masson-Makdissi, L. Prieto, X. Abel-Snape, M. Lautens, *Angew. Chem. Int. Ed.* **2021**, *60*, 16932-16936; *Angew.Chem*. **2021**, *133*, 17069-17073.

[11] a) 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; b) C. Fu, L. He, X. Chang, X. Cheng, Z.-F. Wang, Z. Zhang, V. A. Larionov, X.-Q. Dong, C.-J. Wang, *Angew. Chem. Int. Ed.* **2024**, *63*, e202315325; *Angew. Chem.* **2024**, *134*, e202315325.

[12] a) X. Wu, L.-Z. Gong, *Synthesis* **2019**, *51*, 122-134; b) G. Li, X. Huo, X. Jiang, W. Zhang, *Chem. Soc. Rev.* **2020**, *49*, 2060−2118.

[13] a) X. Wu, H.-C. Lin, M.-L. Li, L.-L. Li, Z.-Y. Han, L.-Z. Gong, *J. Am. Chem. Soc.* **2015**, *137*, 13476-13479; b) H.-C. Shen, Y.-F. Wu, Y. Zhang, L.-F. Fan, Z.-Y. Han, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2018**, *57*, 2372-2376; *Angew.Chem*. **2018**, *130*, 2396-2400.

[14] a) Y. Liu, Y. Xie, H. Wang, H. Huang, *J. Am. Chem. Soc.* **2016**, *138*, 4314-4317; b) R. Chang, S. Cai, G. Yang, X. Yan, H. Huang, *J. Am. Chem. Soc.* **2021**, *143*, 12467-12472.

[15] a) Y. Tu, B. Xu, Q. Wang, H. Dong, Z.-M. Zhang, J. Zhang, *J. Am. Chem. Soc.* **2023**, *145*, 4378-4383; b) J. Feng, J. Shi, L. Wei, M. Liu, Z. Li, Y. Xiao, J. Zhang, *Angew. Chem. Int. Ed.* **2023**, *62*, e202215407; *Angew.Chem*. **2023**, *135*, e202215407; c) W. Zhang, P.-C. Zhang, Y.-L. Li, H.-H. Wu, J. Zhang, *J. Am. Chem. Soc.* **2022**, *144*, 19627-19634.

[16] a) H. Du, W. Yuan, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 11688-11689; b) B. Zhao, H. Du, S. Cui, Y. Shi, *J. Am. Chem. Soc.* **2010**, *132*, 3523-3532.

[17] a) B. A. Patel, J. E. Dickerson, R. F. Heck, *J. Org. Chem.* **1978**, *43*, 5018-5020; b) R. Grigg, V. Sridharan, S. Sukirthalingam, T. Worakun, *Tetrahedron Lett.* **1989**, *30*, 1139-1142.

[18] a) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945-2964; b) A. N. Reznikov, M. A. Ashatkina, Y. N. Klimochkin, *Org. Biomol. Chem.* **2021**, *19*, 5673-5701.

[19] a) L. Wei, X. Chang, C.-J. Wang, *Acc. Chem. Res.* **2020**, *53*, 1084-1100; b) Y. Wu, X. Huo, W. Zhang, *Chem. Eur. J.* **2020**, *26*, 4895-4916.

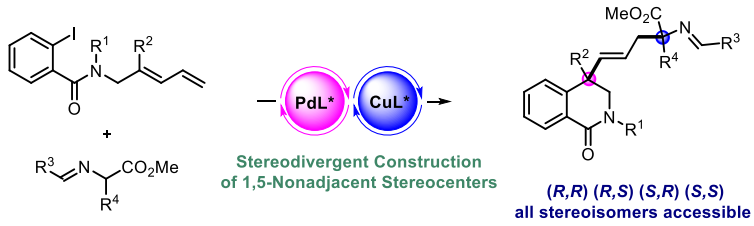
[20] A proposed mechanism for formation of **6** is given in supporting information.

[21] Similar dihydroxylation/lactonization cascade was reported: H. Yu, Q. Zhang, W. Zi, *Nat. Commun.* **2022**, *13*, 2470.

[22] Deposition numbers 2272219 for (1*R*,5*S*)-**3ba**, 2272220 for **12b**, 2272221 for **L8**-Pd(allyl)Cl 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.

10.1002/anie.202402843

Entry for the Table of Contents



A synergistic palladium/copper-catalyzed 1,4-functionalization of 1,3-dienes was reported for stereodivergent construction of 1,5-nonadjacent stereocenters. Mechanistic studies indicated a mechanism involving a Heck/Tsuji–Trost cascade. DFT calculation disclosed that the palladium and copper catalysts separately controlled the newly formed stereocenters at C1 and C5.