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Communication

Pd-Catalyzed Enantioselective Three-Component Carboamination of 1,3-Cyclohexadiene

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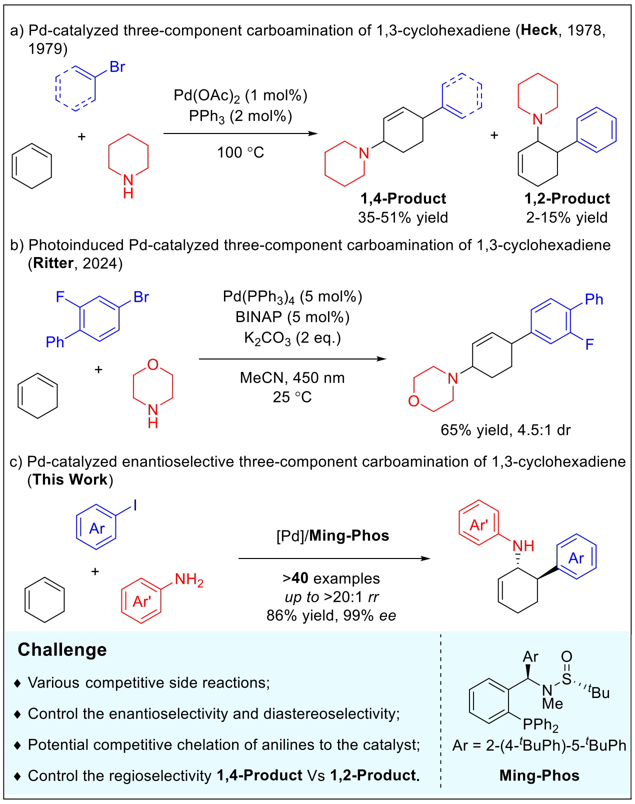
ABSTRACT: Asymmetric Pd-catalyzed three-component carboamination reactions of dienes to construct chiral cyclohexenylamines, which are of great importance in many fields of chemistry, have remained largely unexplored. Here, we demonstrate a highly enantio- and regioselective Pd/**Ming-Phos**-catalyzed carboamination reactions of 1,3-cyclohexadiene with readily available aryl iodides and anilines for facile access to diverse valuable chiral cyclohexenylamines. The process shows excellent functional group tolerance, easy scalability, and mild conditions. Moreover, mechanistic studies suggest that this reaction has a first-order dependence on the concentration of the palladium catalyst and aniline.

Chiral cyclohexenylamines, a particularly important class of chiral cycloalkyl amine, are widely applied in pharmaceutical and perfume industries and serve as momentous building blocks for various alkaloids,[1] such as aphanorphine, sarain A, hetisine, etc. Moreover, the retaining carbon−carbon double bond in chiral cyclohexenylamines renders them more amenable to versatile transformations. For instance, chiral cyclohexylamines, which are ubiquitous core structures in cariprazine, glimepiride, and so on,[2] can be easily obtained from cyclohexenylamines. As such, the development of expedient and efficient synthetic protocols enroute to these compounds is of great importance.

Transition-metal-catalyzed carboamination reactions of dienes have provided a valuable strategy for simultaneous construction of C−C and C−N bonds in one-pot operations.[3] Compared with two-component carboamination,[4,5] a three-component system[6,7] features many advantages; without the need for prefunctionalized olefins and with short synthetic steps, the use of feedstock chemicals has emerged as a versatile route for rapid buildup of molecular complexity. In 1978, Heck's group[6a,b] reported the first example of Pd(0)-catalyzed three-component difunctionalization of 1,3-dienes, in which 1,3-cyclohexadiene reacted with piperidine and bromobenzene or 2-bromopropene to provide both 1,2- and 1,4-products (Scheme 1a). Since the pioneering research by Heck et al., three-component carboamination of 1,3-cyclohexadiene with halides and amines has been recognized as a powerful protocol to prepare cyclohexenylamine derivatives. Very recently, another example of three-component carboamination of 1,3-cyclohexadiene with the use of photoinduced palladium catalyst and morpholine as the aminating reagent was developed by Ritter and co-workers,[6m] delivering 1,4-addition product with a 4.5:1 dr value (Scheme 1, b). However, to the best of my knowledge, these are the only two existing literature reports of three-component carboamination to access cyclohexenylamines to date, indicating that achieving three-component carboamination of 1,3-cyclohexadiene with high

Scheme 1. Palladium-Catalyzed Three-Component Carboamination of 1,3-Cyclohexadiene



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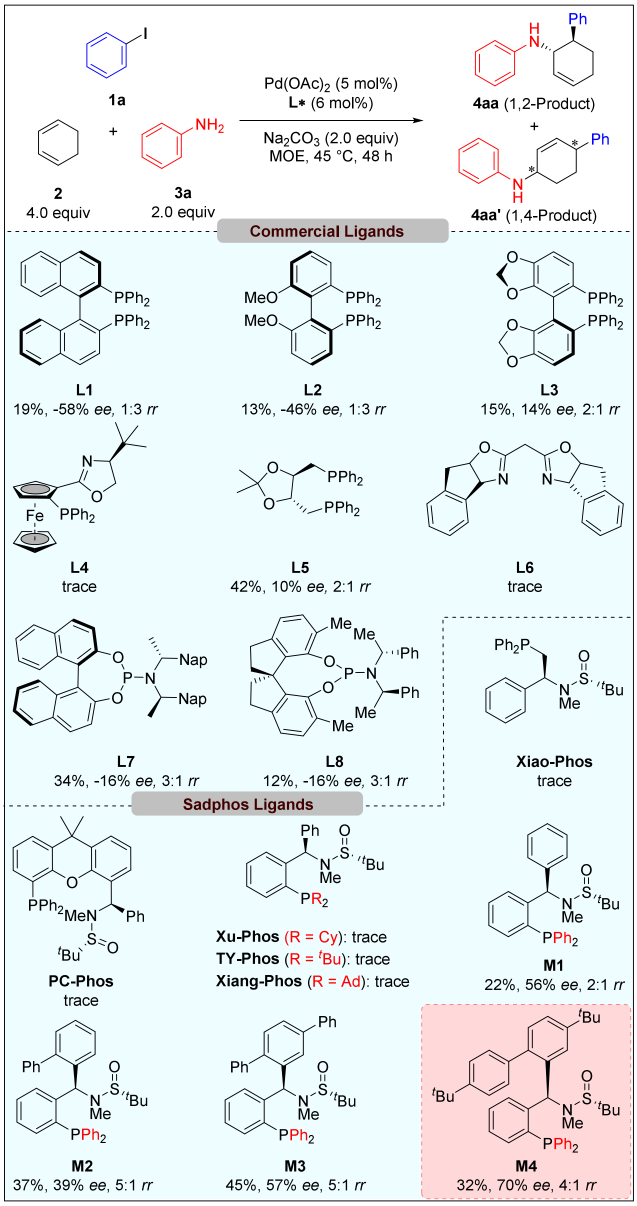
selectivity, especially in enantioselectivity, is a considerable challenge.

Considering the significance of chiral cyclohexenylamines and in connection of our ongoing interest in carboamination reactions,[5j,m,o,8] we were intrigued to develop an efficient catalyst system to realize Pd-catalyzed enantioselective three-component carboamination of 1,3-cyclohexadiene with aryl iodides and anilines.

The following issues should be considered: (1) the existence of various competitive side reactions, such as Buchwald–Hartwig aminations, hydroamination reactions, Heck reactions, etc. (2) how to control the regioselectivity to avoid the formation of regioisomers; (3) the potential competitive chelation of anilines to the catalyst may lead to the erosion of enantioselectivity. Herein, with the use of aryl iodides as carbon electrophiles and anilines as nitrogen nucleophiles, we disclose a Pd/Ming-Phos-catalyzed enantioselective three-component carboamination of 1,3-cyclohexadiene in a highly controlled fashion, offering an unprecedented efficient route in the modular assembly of diverse chiral cyclohexenylamines (Scheme 1, c).

To begin with our investigation, we employed iodobenzene **1a**, 1,3-cyclohexadiene **2**, and aniline **3a** as model substrates. Various chiral ligands were examined with Pd(OAc)$_2$ in an MOE at 45 °C for 48 h (Scheme 2). At the outset, we screened commercially available ligands **L1**–**L8**, finding that **L4** and **L6** failed to afford the desired product. Employing **L1** or **L2** as a chiral ligand could prefer to deliver the 1,4-addition product **4aa′** in low yield with moderate enantioselectivity. The remaining ligands all performed with low yield, enantio- and regioselectivity. Inspired by the excellent performance of **SadPhos** ligands lately,[9] we then screened our own developed **SadPhos** ligand kit to inspect the catalytic reactivity in this three-component reaction. Although almost all of the **SadPhos** ligands, such as **Xiao-Phos**, **PC-Phos**, **Xu-Phos**, **TY-Phos**, and **Xiang-Phos** could not deliver the desired product, **Ming-Phos** could show promising result. Fortunately, through further modification, ligand **M4** was found to be a competent ligand, leading to the formation of 1,2-addition product **4aa** in 32% yield with 70% *ee* and 4:1 *rr*.

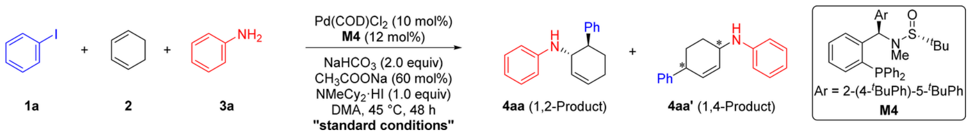
Scheme 2. Screening of Commercial Ligands and Optimization of the Ming-Phos Ligands



Afterward, with **M4** as the optimal ligand, the survey of various reaction conditions were conducted, identifying Pd(COD)Cl$_2$, **M4**, NaHCO$_3$, CH$_3$COONa, NMeCy$_2$·HI, and DMA as the optimized conditions to furnish **4aa** in 68% yield with 93% *ee* and 19:1 *rr* (Table 1, entry 1). Other parameters varying from the standard conditions were also evaluated. For example, we attempted to replace the palladium salts, bases, and solvents, yet leading to either lower yield, inferior enantioselectivity, or regioselectivity (entries 2–13). Then we investigated the importance of additives. Lower yield of the product was obtained in the absence of the NaHCO$_3$ (entry 14). When we removed CH$_3$COONa from our reaction system, the enantioselectivity and regioselectivity were infected (entry 15). Removing NMeCy$_2$·HI would result in an extremely lower yield of 49% (entry 16). NMeCy$_2$·HCl and NMeCy$_2$·HBr were also evaluated here, yet they gaining no better result (entries 17–18). Based on the performance of Ag$_3$PO$_4$ (for more detail see the Supporting Information section 3.2), we attempted to add Ag$_3$PO$_4$ into the standard conditions, finding that it neither increased yield, *ee* nor *rr* (entry 19). At the same time, the change from iodobenzene to bromobenzene and the lower loading of catalyst all gave unsatisfactory results (entries 20–21). Then, we tried to expand 1,3-cyclohexadiene to higher dienes but failed to obtain the target product (entries 22–23).

With the optimal reaction conditions in hand, we next explored the substrate universality of this strategy. First and foremost, a series of substituted iodobenzene were tested (Scheme 3). Generally, a good functional group tolerance was achieved for *para-* and *meta-*substituents of iodobenzene (**4aa-4ma**). Electronic-rich substituents, such as methyl, tertiary butyl, methoxy, and thiomethyl, could obtain the corresponding products **4ba-4ea**, **4la** in 72–85% yield with 89–92% *ee*. In regard to the substrates with electronic-poor substituents, the 1,2-addition products **4fa-4ka** were exclusively obtained with moderate yield and excellent enantioselectivity. This strategy could also be extended to disubstituted indobenzene, giving products **4na-4ra** in satisfactory yields and enantio- and regioselectivity. However, we found that the *ortho*-substituted substrates obtained poor regioselectivity, which might be due to the relatively crowded steric resistance of the substituents.

Table 1. Optimization of Reaction Conditions[a]



Entry	[Pd]	Yield (%)[b]	*ee* (%)[c]	*rr* (4aa/4aa′)[d]
1	None	68	93	19:1
2	$Pd(OAc)_2$ instead of $Pd(COD)Cl_2$	55	90	16:1
3	$Pd(TFA)_2$ instead of $Pd(COD)Cl_2$	55	91	16:1
4	$Pd(acac)_2$ instead of $Pd(COD)Cl_2$	56	91	16:1
5	$Pd_2(dba)_3$ instead of $Pd(COD)Cl_2$	45	89	13:1
6	Na_2CO_3 instead of $NaHCO_3$	52	86	12:1
7	Cs_2CO_3 instead of $NaHCO_3$	19	96	>20:1
8	K_3PO_4 instead of $NaHCO_3$	42	94	13:1
9	Et_3N instead of $NaHCO_3$	54	90	13:1
10	Toluene instead of DMA	21	84	3:1
11	THF instead of DMA	19	85	6:1
12	DCM instead of DMA	22	69	8:1
13	CH_3CN instead of DMA	46	75	5:1
14	No $NaHCO_3$	48	91	19:1
15	No CH_3COONa	42	67	8:1
16	No $NMeCy_2\bullet HI$	49	93	>20:1
17	$NMeCy_2\bullet HCl$ instead of $NMeCy_2\bullet HI$	34	94	16:1
18	$NMeCy_2\bullet HBr$ instead of $NMeCy_2\bullet HI$	58	93	9:1
19	Added Ag_3PO_4	68	93	19:1
20	PhBr instead of PhI (**1a**)	6	94	19:1
21	$Pd(COD)Cl_2$ (5 mol %) and **M4** (6 mol %)	38	88	16:1
22	1,3-Cyclooctadiene instead of cyclohexadiene (**2**)	ND	-	-
23	1,3-Cycloheptadiene instead of cyclohexadiene (**2**)	ND	-	-

[a] Unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), **2** (0.4 mmol), **3a** (0.1 mmol), $Pd(COD)Cl_2$ (10 mol %), **M4** (12 mol %), $NaHCO_3$ (2.0 equiv), CH_3COONa (60 mol %), and $NMeCy_2{\cdot}HI$ (1.0 equiv) in DMA (0.5 mL) at 45 °C for 48 h. [b] GC yield with 1,3-dimethoxybenzene as an internal standard. [c] Enantioselectivities were determined by chiral-phase HPLC. [d] Regioselectivity was measured by GC of the unpurified mixture with respect to an internal standard.

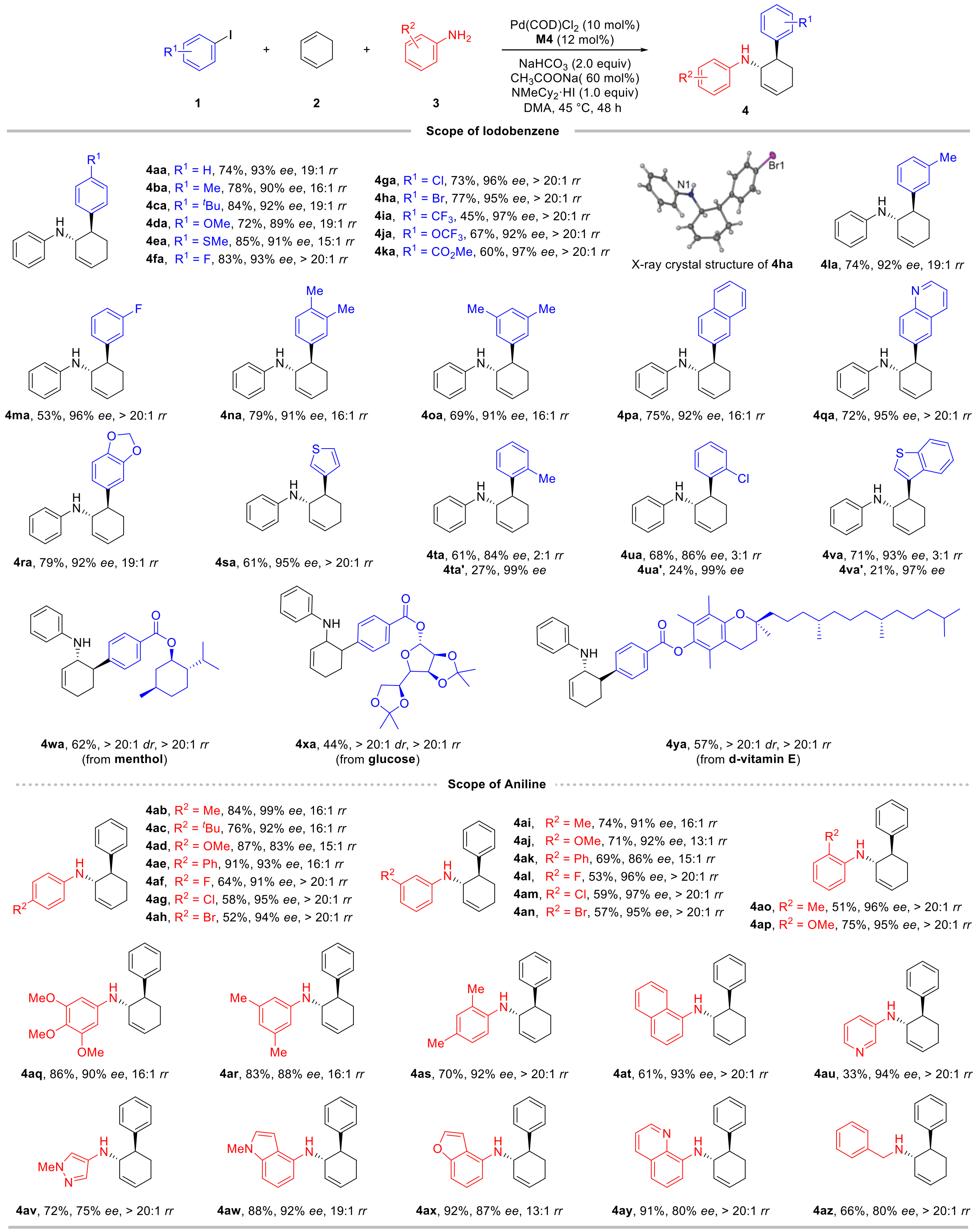
For example, 2-iodotoluene generated the mixture of **4ta** and **4ta′** with 2:1 *rr*, and 1-chloro-2-iodobenzene also obtained a similar result. In this instance, although 1,4-addition products were the inferior isomer, they had excellent enantioselectivity (97−99%). Subsequently, we examined the tolerance of the heterocyclic substrate. 3-Iodothiophene could be compatible with this reaction, delivering **4sa** in 61% yield with 95% *ee*, while 3-iodo-1-benzothiophene delivered **4va** in 71% yield with 93% *ee* and 3:1 *rr*. Afterward, we employed iodobenzene derived from bioactive complexes and pharmaceuticals to the optimal reaction conditions, which could convert to the target products (**4wa-4ya**) in moderate yields with excellent diastereoselectivities. The absolute configuration of **4ha** was confirmed by an X-ray crystallographic analysis and could be extended to the other products.

Next, we turned our attention to investigating the scope of aniline under the optimal reaction conditions (Scheme 3). Through thoroughly examination, we found that the electronic effect played a significant role with respect to the reactivity of this reaction. Aniline bearing electron-rich groups could smoothly transform to the corresponding products (**4ab-4ae**, **4ai-4ak**) in 69−91% yield with 83−99% *ee* and relatively good regioselectivity (13:1−16:1 *rr*). However, the electron-poor groups would deteriorate the reaction efficiency.

For example, the halogen groups (F, Cl, Br) exclusively afforded the target 1,2-addition products (**4af-4ah**, **4al-4an**) in moderate yield (52−64%) with 91−97% *ee*. Meanwhile, the steric effect was also important. The *ortho*-substituted substrates (**4ao-4ap**) got better enantioselectivity compared to the *para*- and *meta*- substituted substrates, where the regioselectivity has been improved greatly at the same time. Furthermore, the disubstituted and trisubstituted substrates were also examined and found to be compatible with this strategy. Among these, 3,4,5-trimethoxyaniline and 3,5-dimethylaniline afforded **4aq-4ar** in 83−86% yield with 88−90% *ee*. The substrates having ortho steric hindrance, such as 2,4-dimethyl aniline and 1-naphthylamine, delivered the desired products (**4as-4at**) with excellent enantio- and regioselectivity. Additionally, we expanded more types of aniline to heterocycles examples. We tried the six-membered heterocycle 3-aminopyridine and five-membered heterocycle 4-amino-1-methylpyrazole in our system. To our delight, we obtained the desired product **4au** in 33% yield with 94% *ee* and 20:1 *rr*, **4av** in 72% yield with 75% *ee* and >20:1 *rr*. Then we investigated benzohetercyclic derivatives, also gaining satisfactory results (**4aw-4ay**). Next, benzyl amine was investigated, which could react smoothly, affording the corresponding product **4az** in 66% yield with 80% *ee* and excellent regioselectivity.

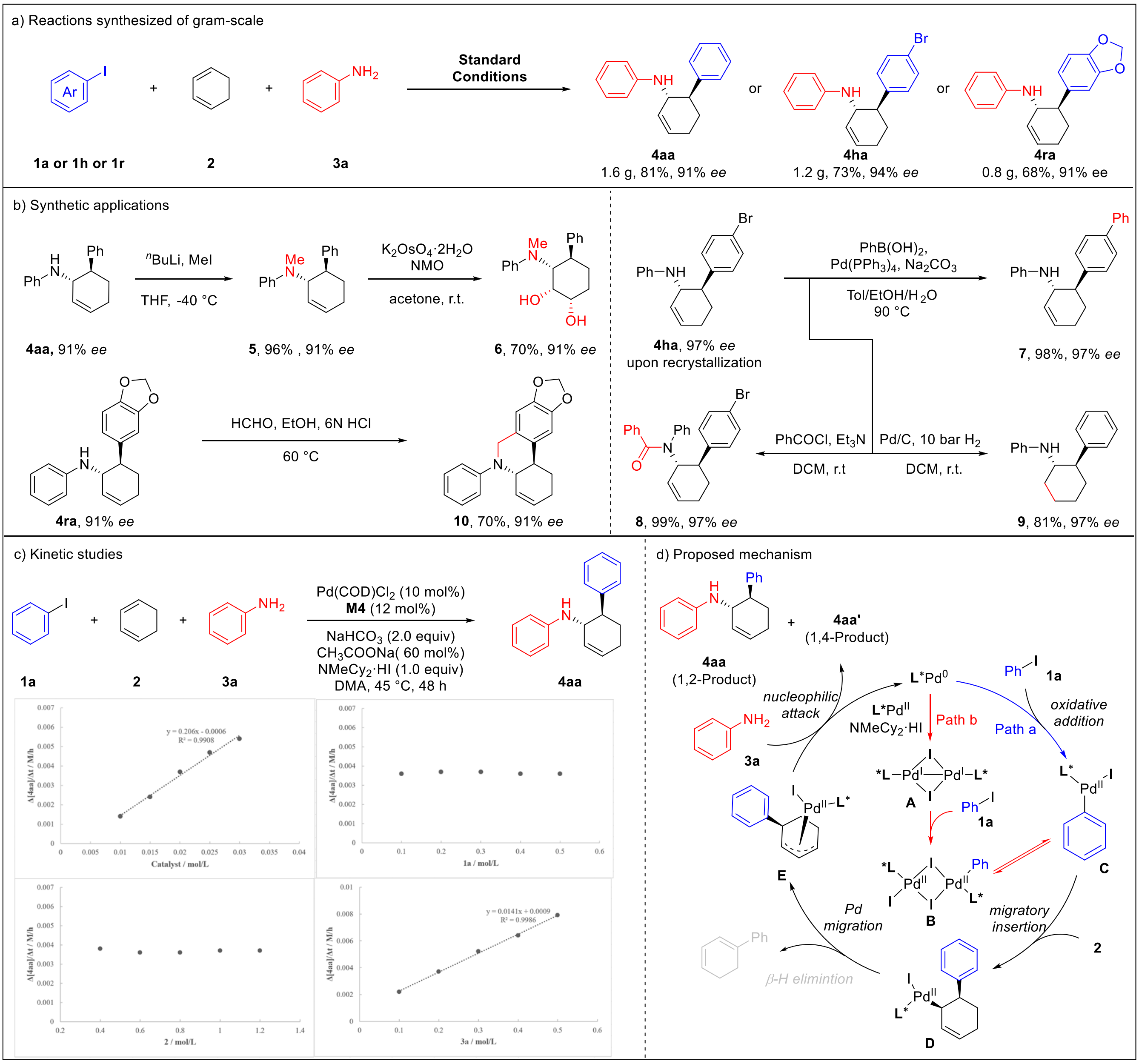
To verify the practicability of this strategy, we conducted the reaction of **1a**, **1h**, **1r** with **2** and **3a** on a gram scale, delivering the desired 1,2-addition products **4aa** in 81% yield with 91% *ee*, **4ha** in 73% yield with 94% *ee*, and **4ra** in 68% yield with 91% *ee*, respectively (Scheme 4a). And then the potential for

Scheme 3. Substrate Scopes[a]



[a] Unless otherwise noted, all reactions were performed with **1** (0.60 mmol), **2** (1.20 mmol), **3** (0.30 mmol), Pd(COD)Cl$_2$ (10 mol %), **M4** (12 mol %), NaHCO$_3$ (2.0 equiv), CH$_3$COONa (60 mol %) ,and NMeCy$_2$•HI (1.0 equiv) in DMA (1.5 mL) at 45 °C for 48 h.

Scheme 4. Gram Scale, Synthetic Applications, Kinetic Studies, and Proposed Mechanism



synthetic applications of the products were examined (Scheme 4b). First, the methylation of the N−H group and subsequent dihydroxylation of the double bond of **5** with $K_2OsO_4 \cdot 2H_2O$ could deliver product **6** in 70% yield with 91% *ee*. With the existence of bromine, an N−H group, and a double bond, **4ha** could be converted through multiple routes. For instance, the reaction with phenylboronic acid could give coupled product **7** in 98% yield with 97% *ee*. The benzoylation of the N−H group could deliver the optically pure product **8** in 99% yield. The hydrogenation of **4ha** in the presence of Pd/C and H_2 would result in product **9** in 81% yield with no loss of enantioselectivity. Furthermore, to our delight, **4ra** was able to afford the cyclized product **10** in 70% yield with 91% *ee* under the Pictet−Spengler cyclization reaction conditions.

In order to gain insight into this three-component reaction, we carried out mechanism studies. Kinetic analysis experiments[10] were conducted employing iodobenzene **1a**, 1,3-cyclohexadiene **2** and aniline **3a** under optimal reaction conditions (Scheme 4c). The result indicated the first-order dependence on the concentration of the palladium catalyst and aniline **3a**. Meanwhile the zero-order dependence on the concentration of iodobenzene **1a** and 1,3-cyclohexadiene **2**. These results disclosed that the nucleophilic attack step was the rate-determining step. Then we proposed two possible mechanisms (Scheme 4d). As shown in path a, first, iodobenzene **1a** underwent the oxidative addition process to form arylpalladium species **C**, followed by migratory insertion to 1,3-cyclohexadiene **2** to generate divalent palladium intermediate **D**. Subsequently, intermediate **D** would undergo palladium migration to form *π*-allyl palladium intermediate **E**. Meanwhile, intermediate **D** might also undergo *β*-H elimination process to deliver the Heck-type byproduct. Finally, nucleophilic attack of aniline **3a** would afford the 1,2-addition product **4aa** and regenerated the Pd catalyst.

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Alternatively, in the presence of NMeCy$_2$·HI, Pd(0) complex reacted with Pd(II) intermediate to furnish iodide-bridged palladium(I) dimer **A**, followed by oxidative addition with iodobenzene **1a** to generate iodide-bridged palladium(II) dimer **B**.[11] Subsequent dissociation of complex **B** afforded the monomeric arylpalladium(II) species **C**, which underwent migratory insertion, palladium migration, and nucleophilic attack to generate the desired product.

In conclusion, we developed a highly regio-, diastereo-, and enantioselective palladium-catalyzed three-component arylation/amination reaction of 1,3-cyclohexadiene. The newly synthesized ligand **M4** played an important role in improving the enantio- and regioselectivity of this reaction. This strategy represented the first enantioselective example of three-component arylation/amination of conjugated cyclic diene, which will open up new vistas for expedient access to chiral cyclohexenylamines and motivate the design of more novel catalyst systems for challenging asymmetric three-component carboamination.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c07382.

> Experimental procedures, compound characterization data, NMR spectra, and chiral HPLC chromatograms (PDF)

Accession Codes

CCDC 2357543 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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