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Asymmetric Synthesis of [3.2.1]Tropane scaffolds via Enantioselective β-H elimination reaction

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ABSTRACT: Tropanes and their related bridged bicyclic systems constitute highly sought-after scaffolds in drug discovery and development. Notably, the enantioselective synthesis of chiral 3-aryltropanes which are compounds widely distributed across bioactive pharmaceutical agents remains underdeveloped. Tropinone is a readily available and cost-effective starting material. By initiating the synthesis from tropinone, it is possible to substantially lower the synthesis costs. Here we describe an enantioselective Pd/**Ming-Phos**-catalyzed β-H elimination reaction of Tropinone-derived *N*-arylsulfonylhydrazones and aryl bromides to give chiral tropanes and oxatropanes. Strikingly, this study achieves enantioselective β-H elimination which needs to simultaneously control over both diastereoselectivity during the migratory insertion and enantioselectivity during the β-H elimination. This approach shows broad functional group tolerance, good enantiocontrol as well as easy scale-up. Moreover, the synthetic value is further demonstrated by the enantioselective catalytic total synthesis of drugs for treating Alzheimer's disease and monoamine transporter ligands. Additionally, both the facile elaborations and the preliminary biological activities of the products demonstrate the application potential.

Introduction

N-bridged [3.2.1]octane (tropane) scaffolds, as a distinguished subclass of the bicyclo[3.2.1] framework, have maintained enduring interest in synthetic and medicinal chemistry, primarily owing to their prevalent occurrence in diverse families of biologically active natural products[1-4]. Notably, 3-aryltropane derivatives exhibit considerable therapeutic potential for the treatment of neurological and psychiatric disorders, and also function as potent ligands for monoamine transporters—key molecular targets in neuropharmacology[5-9](Figure 1a). However, only limited protocols toward asymmetric construction of chiral 3-aryltropanes have been disclosed so far[10]. In 2013，a three-step protocol was reported for the asymmetric synthesis of 3-aryltropanes, encompassing deprotonation of tropanone with stoichiometric amount of chiral lithium amide base[11], treatment with $pyNTf_2$ to form the corresponding enol triflate, and subsequent Fe-catalyzed Kumada coupling with benzylmagnesium bromide (Figure 1b). Following deprotection, reaction with (*S*)-binoPCl in the presence of NEt_3 afforded a phosphoramidite as an inseparable mixture of two diastereomers in a 79:21 ratio[10]. This result confirms that chirality is not preserved during the Fe-catalyzed Kumada coupling, precluding the attainment of chiral 3-aryltropanes with high enantioselectivity. To date, no straightforward methodology exists for the synthesis of chiral 3-aryltropanes through asymmetric catalysis, despite their significance in expanding the structural diversity of tropane derivatives and facilitating the discovery of small-molecule therapeutic agents.

The β-H elimination is a fundamental chemical process that appears in many transition-metal catalyzed transformation[12-21]. However, there have been very limited efforts to investigate the stereoselectivity, as this elimination step converts two sp^3 carbons into an alkene without forming a common stereocenter. The development of methods to achieve enantioselective β-H elimination represents a highly appealing research topic in asymmetric transition-metal catalysis. Meanwhile, as an important class of carbene precursors, sulfonylhydrazones are being increasingly applied in the field of metal-catalyzed carbene transformation reactions[22-34]. Nevertheless, reports on enantioselective β-H elimination reactions involving sulfonylhydrazones are still relatively scarce[30-34]. As shown in Figure 1c, there have been only a few examples of constructing axially chiral[30,33,34] and inherently chiral compounds[31,32], while the construction of bridged ring skeletons remains unexplored. Moreover, previous strategies relied on substrate control to ensure that only one β-H elimination site was available for Pd elimination, thereby simplifying enantioselective control. In recent years, desymmetrization strategies have become one of the important approaches for constructing chiral compounds[35-39]. Recently, the Zi's group reported an elegant desymmetrization β-H elimination strategy that enabled the control of remote stereogenicity in six-membered rings[39]. However, the reaction requires the starting material to be in the trans configuration. Consequently, the trans relationship between the leaving group and the 4-substituent also restricts the elimination to only two of the four theoretically possible β-H atoms, thereby confining chiral induction to merely two β-H elimination pathways and simplifying enantiocontrol.

However, in our reaction, the presence of two distinct β-H

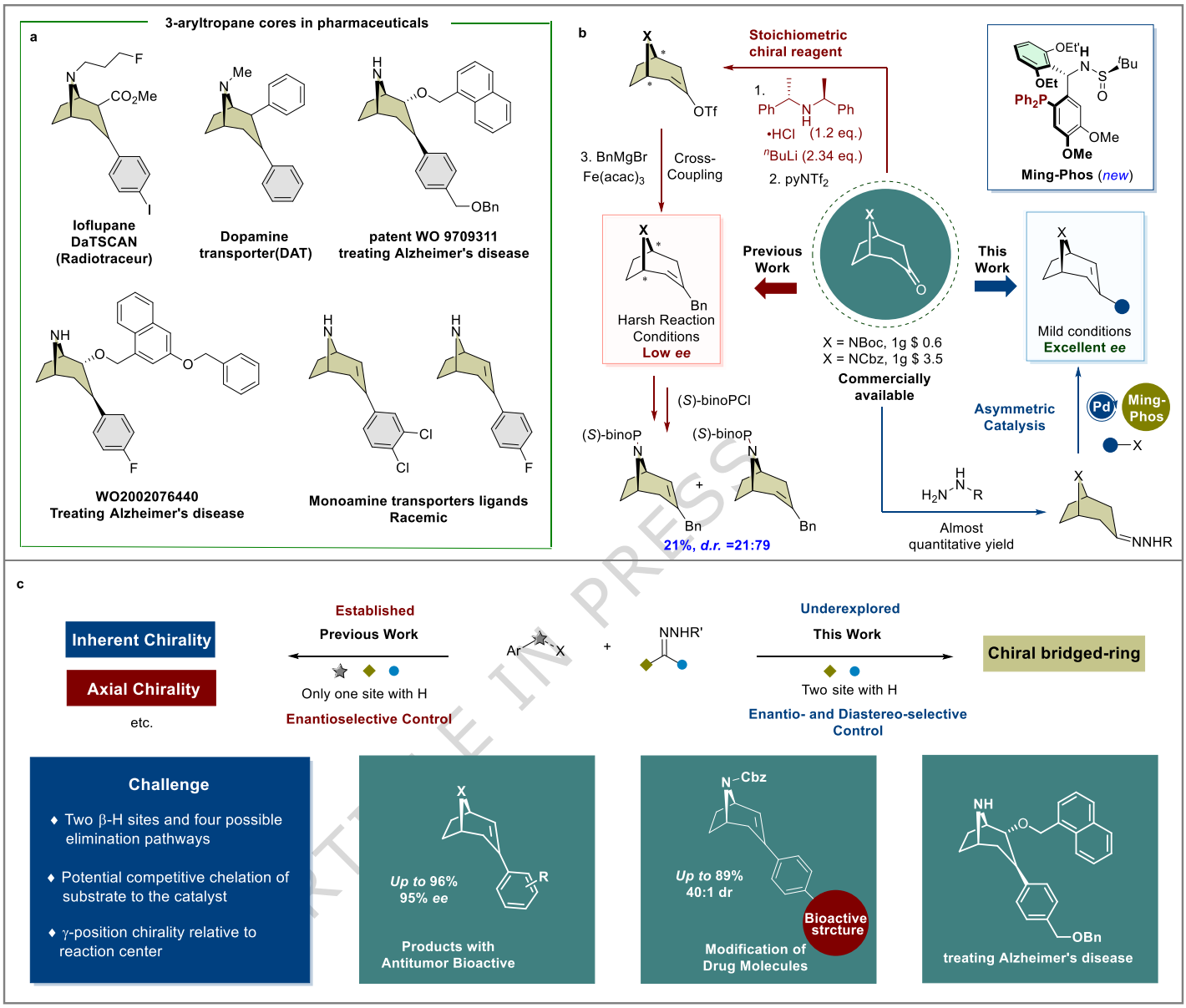
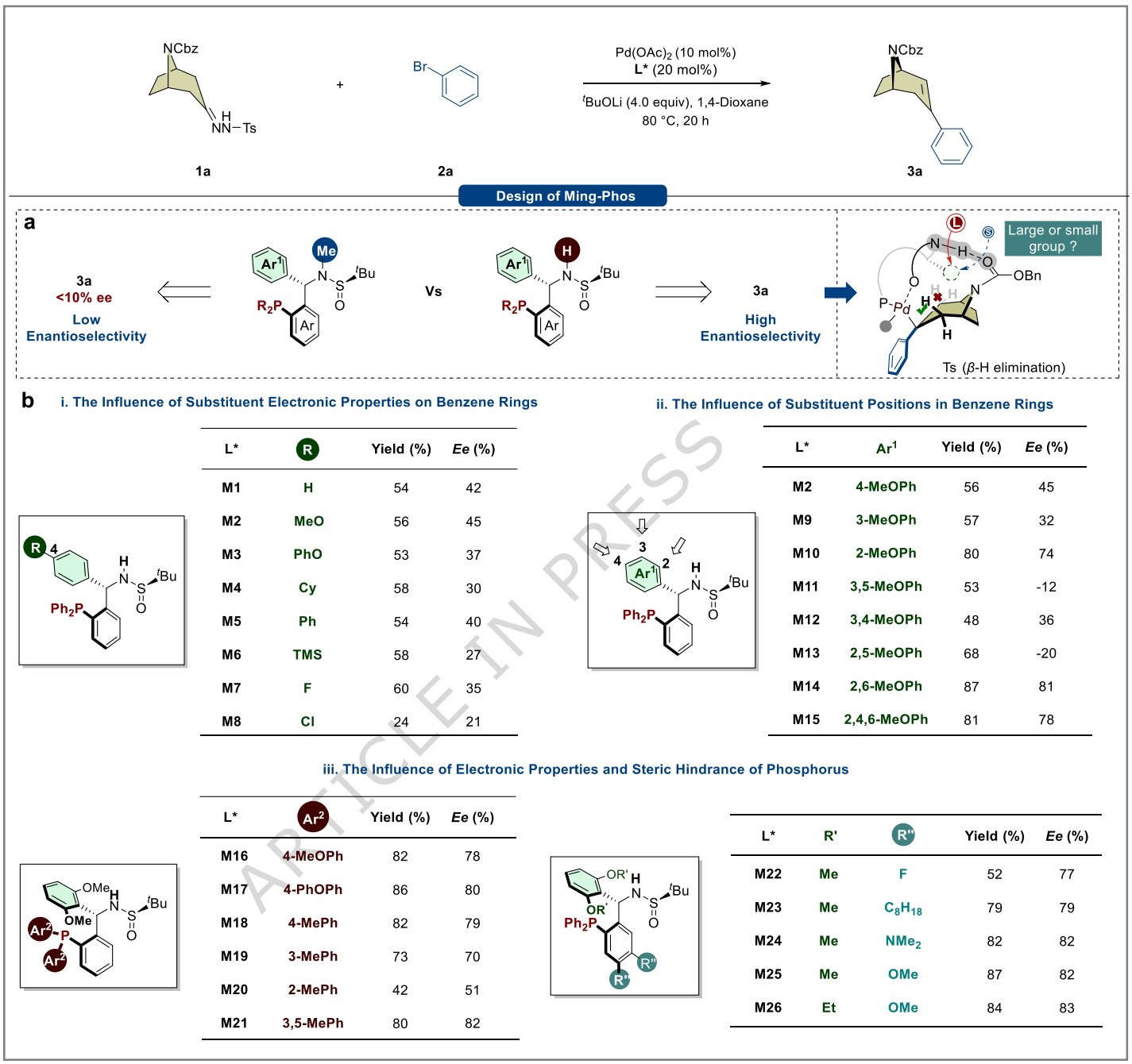


Fig. 1 | Background and discovery. **a,** Selected bioactive molecules possessing tropane cores. **b,** Methods for synthesizing chiral tropanes. **c,** The reaction modes for asymmetric β-H elimination reaction from carbene coupling. This work: Pd/**Ming-Phos**-catalyzed asymmetric synthesis of tropanes.



L*	R	Yield (%)	*Ee* (%)
M1	H	54	42
M2	MeO	56	45
M3	PhO	53	37
M4	Cy	58	30
M5	Ph	54	40
M6	TMS	58	27
M7	F	60	35
M8	Cl	24	21

L*	Ar^1	Yield (%)	*Ee* (%)
M2	4-MeOPh	56	45
M9	3-MeOPh	57	32
M10	2-MeOPh	80	74
M11	3,5-MeOPh	53	-12
M12	3,4-MeOPh	48	36
M13	2,5-MeOPh	68	-20
M14	2,6-MeOPh	87	81
M15	2,4,6-MeOPh	81	78

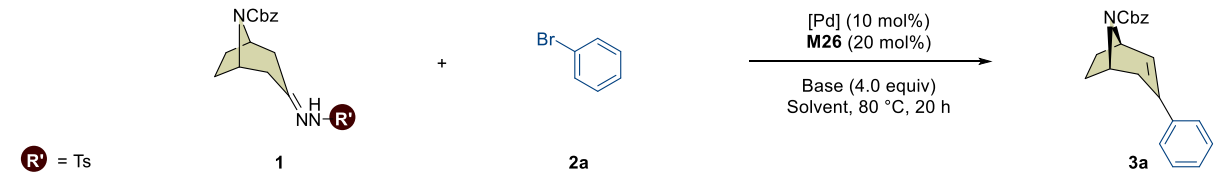
L*	Ar^2	Yield (%)	*Ee* (%)
M16	4-MeOPh	82	78
M17	4-PhOPh	86	80
M18	4-MePh	82	79
M19	3-MePh	73	70
M20	2-MePh	42	51
M21	3,5-MePh	80	82

L*	R'	R''	Yield (%)	*Ee* (%)
M22	Me	F	52	77
M23	Me	C_8H_{18}	79	79
M24	Me	NMe_2	82	82
M25	Me	OMe	87	82
M26	Et	OMe	84	83

Fig. 2 | Optimization of reaction conditions for the design of Ming-Phos ligands a, Proposed interaction model for β-H elimination. Preliminary screening results indicated that the formation of hydrogen bonds between the substrate and the ligand is crucial for enantioselectivity. **b,** Detailed modification and rational design of ligands. Unless otherwise noted, all reactions were GC yield determined with 1,3-Dimethoxybenzene as an internal standard.

elimination sites can lead to four possible elimination pathways during the migratoryinsertion and β-H elimination. This necessitates simultaneous control over both diastereoselectivity during the migratory insertion and enantioselectivity during the β-H elimination. To the best of our knowledge, no literature has been reported the successful achievement of enantioselective β-H elimination in the presence of two distinct β-H sites.

In this work, we report the meticulous design of a Pd/**Ming-Phos** catalyst that enables enantioselective β-H elimination (Figure 1b, c). This catalytic strategy, which initiates from cost-effective tropinone, achieves the synthesis of chiral tropanes and oxatropane scaffolds with good enantiocontrol. Preliminary biological activity evaluations reveal that compound **3l** exhibits promising potential for further development as an anticancer drug. Notably, we introduce a method for the preparation of pharmaceuticals used in the treatment of Alzheimer's disease. Unlike previous synthetic routes that relied on chiral resolution and harsh reaction conditions, our approach offers a more efficient pathway.

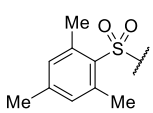


R' = Ts **1** **2a** **3a**

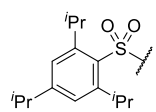
Entry[a]	[Pd]	Solvent	Base	3a Yield[b] [%]	3a *Ee*[c] [%]
1	$Pd(OAc)_2$	1,4-Dioxane	^tBuOLi	84	83
2	$Pd(OAc)_2$	MTBE	^tBuOLi	72	82
3	$Pd(OAc)_2$	*n*-hexane	^tBuOLi	80	79
4	$Pd(OAc)_2$	PhMe	^tBuOLi	72	83
5	$Pd(OAc)_2$	CH_3CN	^tBuOLi	94	82
6	$Pd(OAc)_2$	DMSO	^tBuOLi	13	79
7	$Pd(OAc)_2$	DMA	^tBuOLi	82	86
8	$Pd_2(dba)_3$•$CHCl_3$	DMA	^tBuOLi	81	88
9	Pd(η-allyl)Cl_2	DMA	^tBuOLi	71	84
10	$[Pd(dmba)Cl]_2$	DMA	^tBuOLi	61	79
11	$Pd(TFA)_2$	DMA	^tBuOLi	73	86
12	$Pd(acac)_2$	DMA	^tBuOLi	80	83
13	$Pd_2(dba)_3$•$CHCl_3$	DMA	^tBuONa	55	68
14	$Pd_2(dba)_3$•$CHCl_3$	DMA	Na_2CO_3	trace	43
15	$Pd_2(dba)_3$•$CHCl_3$	DMA	^tBuOK	trace	11
16	$Pd_2(dba)_3$•$CHCl_3$	DMA	K_2CO_3	24	80
17	$Pd_2(dba)_3$•$CHCl_3$	DMA	Cs_2CO_3	84	89
18[d]	$Pd_2(dba)_3$•$CHCl_3$	DMA	Cs_2CO_3	23	91

The effect of substituents on phenylsulfonylhydrazones

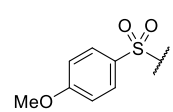
R' =



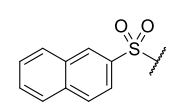
1b
71%, 91% *ee*[e]



1c
88%, 91% *ee*[e]



1d
trace, 83% *ee*



1e
trace, 89% *ee*

Fig. 3 | Optimization of the reaction conditions from solvents, palladium, base and *N*-arylsulfonylhydrazones. Reaction conditions: [a] Unless otherwise noted, all reactions were carried out with 0.1 mmol of **1a** with **M26** as the chiral ligand in 1.0 mL solvent at 80 °C for 20 h. [b] GC yield determined with 1,3-Dimethoxybenzene as an internal standard. [c] Enantioselectivity was determined by HPLC. [d] 50 °C. [e] The reaction was performed at 50 °C for 36 h.

Results and discussion

To test our working hypothesis, we initially reacted *N*-arylsulfonylhydrazone **1a** with phenyl bromide **2a** in the presence of 10% mol $Pd(OAc)_2$, 20 mol% of ligand and ^tBuOLi in 1,4-Dioxane at 80 °C for 20 h. Initially, an exhaustive screening of various types of commercially available ligands failed to yield satisfactory results (See Supplementary information Table S1).

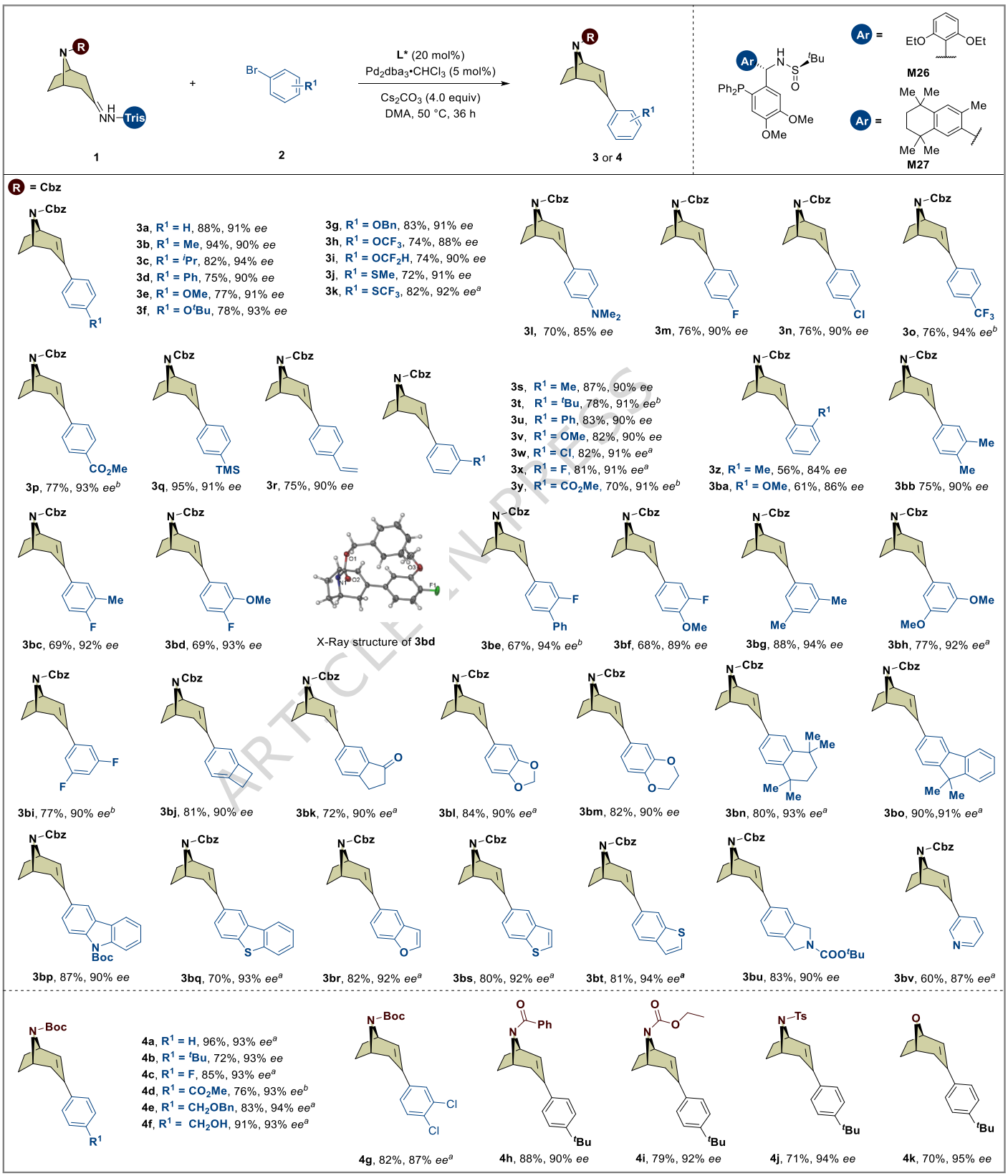


Fig. 4 | Substrate scope for various functionalized aryl bromides and N-arylsulfonylhydrazones. Reaction conditions: Unless otherwise noted, all reactions were performed with **1** (0.3 mmol), **2** (0.36 mmol), Cs_2CO_3 (1.2 mmol), 5 mol% Pd_2dba_3•$CHCl_3$ and 20 mol%

M26 in 3.0 mL DMA at 50 °C for 36 h. Isolated yields were given. The *ee* values were determined by chiral HPLC analysis). [a]Reactions were performed with 20 mol% **M27**. [b]Reactions were performed with 20 mol% **M27** and in 3.0 mL PhMe.

Then, we turned attention to our developed ligands (Sadphos), which have emerged as powerful ligands in various asymmetric catalysis[40-43]. The examination of the Sadphos ligand kit indicated that only N-H ligands could deliver good *ee*, in which **M1** was the optimal choice, affording the tropane product **3a** in 54% yield with 42% *ee*. Additionally, the use of N-Me ligands obviously shut down the enantioselectivity (See SI Table S1).

We next proposed a model for the interaction between **Ming- Phos** and **1a** (Figure 2a). Inspired by the easy synthesis and modification of **Ming-Phos**, we proceeded to screen a series of **Ming-Phos** (Figure 2b). Subsequently, the tuning of the C4-substituted group (R) of **Ming-Phos** (**M2**-**M8**) was first carried out. The OMe-substitution (**M2**) conferred a slightly improvement in *ee* values without yield erosion. By contrast, ligands **M3**-**M8** failed to work satisfactorily. We then systematically evaluated OMe group at different positions of benzene ring, aiming to elucidate aromatic substitution effects. Satisfyingly, when the OMe group was positioned at the ortho-site (**M10**), a significant enhancement in yield (80%) and *ee* (74%) was observed. However, when the OMe group was positioned at the meta- or para-position, irrespective of using mono- or disubstituted ligands, the *ee* and yield of product remained low. These results indicated that the ortho position is closer to the reactive site to control the chiral pocket. Therefore, a series of ortho-OMe-modified ligands were evaluated. Fortunately, **M14** afforded an improved 81% *ee* of **3a**. Next, in view of the matching of the rate between oxidative addition and metal carbene generation, the variation of the aryl group (Ar^2) on P atom was investigated (**M16**-**M21**). Unfortunately, those ligands did not give better results. Finally, on the basis of the ligand model presented in Figure 2a, we hypothesized that the electronic properties of R'' might influence the interaction between the ligand and the β-H atoms. This prompted us to modify the R'' and with electron-donating OMe group, **M26** gave the best *ee* (83%).

With best ligand **M26**, further studies of the influence of the solvent, palladium and temperature were conducted (Figure 3). We systematically evaluated different polar and nonpolar solvents (Figure 3, entries 1-7), and found that the polar solvent DMA performed better (82% yield, 86% *ee*). Subsequently, we focused on the optimization of metal salt and base (entries 8-17). When the metal salt and base were changed to $Pd_2dba_3{\cdot}CHCl_3$ and Cs_2CO_3, respectively, the desired product **3a** was obtained in 84% yield with 89% *ee* (entry 17). At the same time, we found that lowering temperature could improve the *ee* to 91% but resulted in sharply lower yield (entry 18). The unsatisfactory yield of **3a** may be ascribed to the mismatched rates for carbene generation and benzylpalladium intermediate formation. To this end, carbene precursors with distinctive substituents on the sulfonylphenyls were investigated. It is satisfactory to discover that easy-decomposed (2,4,6-triisopropylphenyl) sulfonylhydrazone **1c** outperformed the other carbene precursors screened, affording **3a** in 88% yield with 91% *ee*.

Having established the optimized conditions, the scope of this reaction was examined by using various aryl bromides (Figure 4). The results showed that aryl bromides bearing para-electron-donating groups or electron-withdrawing groups proceeded well to deliver **3a**-**3p**. In regard to the substrates with para-strong electron-withdrawing substituents, the products **3o**-**3p** were exclusively obtained in 76-77% yields with 93-94% *ees* when changing **M26** to **M27**. Some functional groups, such as ester (**3p**), trimethylsilyl (**3q**) and vinyl (**3r**) were incorporated, allowing the products to be amenable to further transformations. Generally, good functional group tolerance was also achieved for meta-substituents of aryl bromides (**3s-3y**). Furthermore, ortho-substituted substrates (**3z-3ba**) achieved good *ees*, although the yields were moderate. This outcome may be attributed to the steric hindrance posed by the bulky substituents. Notably, this strategy could also be extended to disubstituted aryl bromides, generating the products **3bb-3bi** in satisfactory yields and *ees*. We also found that our method was applicable to benzannulated ring systems, regardless of bearing electron-withdrawing or electron-donating substituents (**3bj-3bo**). To explore the scope of our reaction further, we incorporated heterocyclic rings into the aryl bromides, successfully synthesizing products **3bp-3bv** with 60-87% yields and 87-94% *ees*. Notably, the transformation was effective even with the more challenging pyridine substrate (**3bv**). Furthermore, the absolute configuration of the product was unambiguously

confirmed by X-ray diffraction analysis of compound **3bd**.

Next, the effect of substituents on the tropane scaffolds was investigated under the standard reaction conditions (Figure 4). Satisfactorily, this asymmetric β-H elimination was also applicable to the tropanes bearing different *N*-protecting group, delivering the products **4a-4k** with high yields (71-96%) and *ees* (87-95%). Furthermore, changing *N*-substituents to *O*-substituent on the tropanes proceeded smoothly, affording the corresponding products **4k** with satisfactory results.

To ascertain the scope of this method, several aryl bromides derived from the core structures of natural products were further investigated (Figure 5a). All these structurally complex substrates

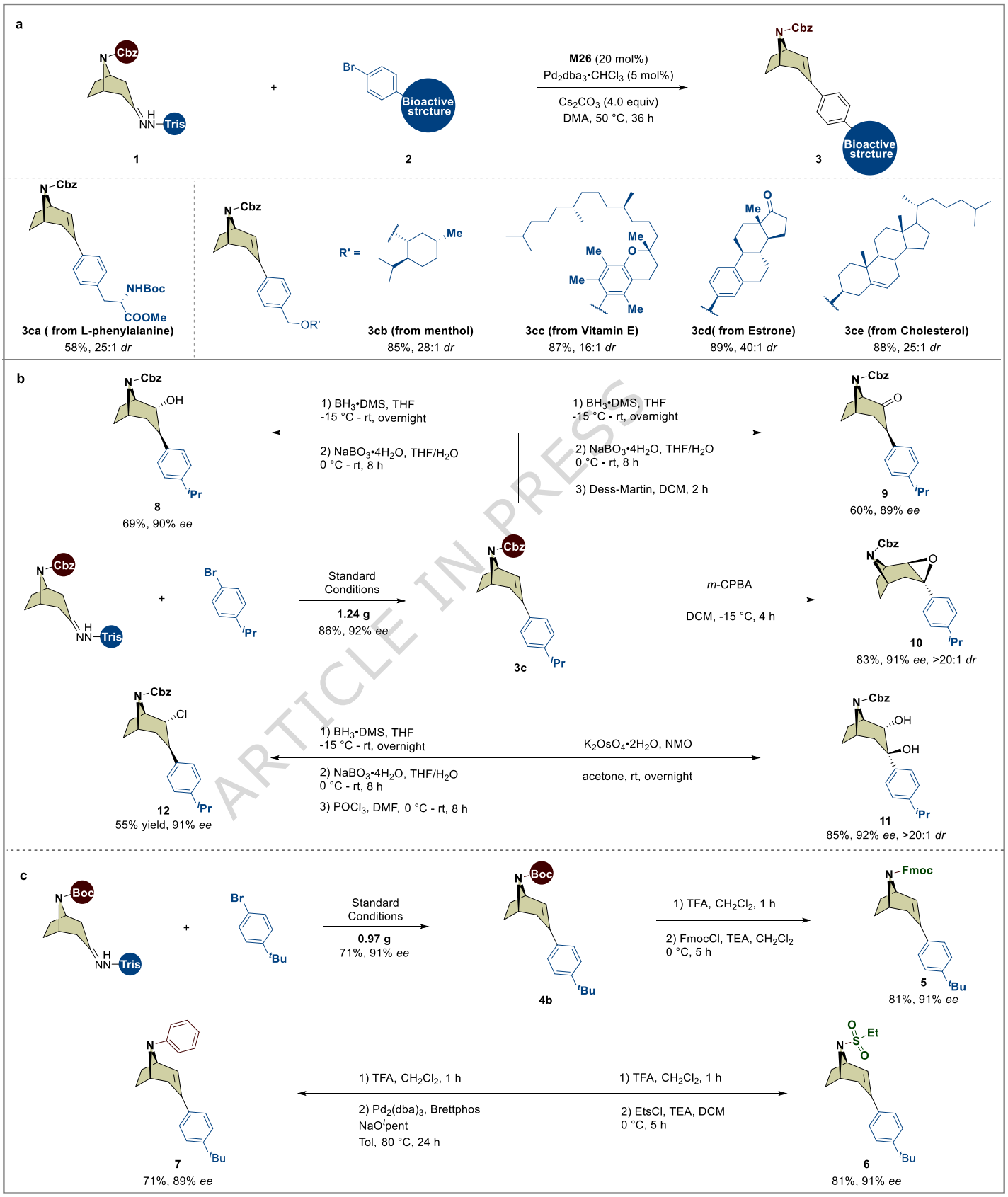


Fig. 5 | The synthetic transformation (All yields in **Fig. 5** refers the isolated yields after flash column chromatography.) **a,** Late-stage

modification of drug molecules. **b,** The functionalization of the product **3c**. **c,** The functionalization of the product **4b**.

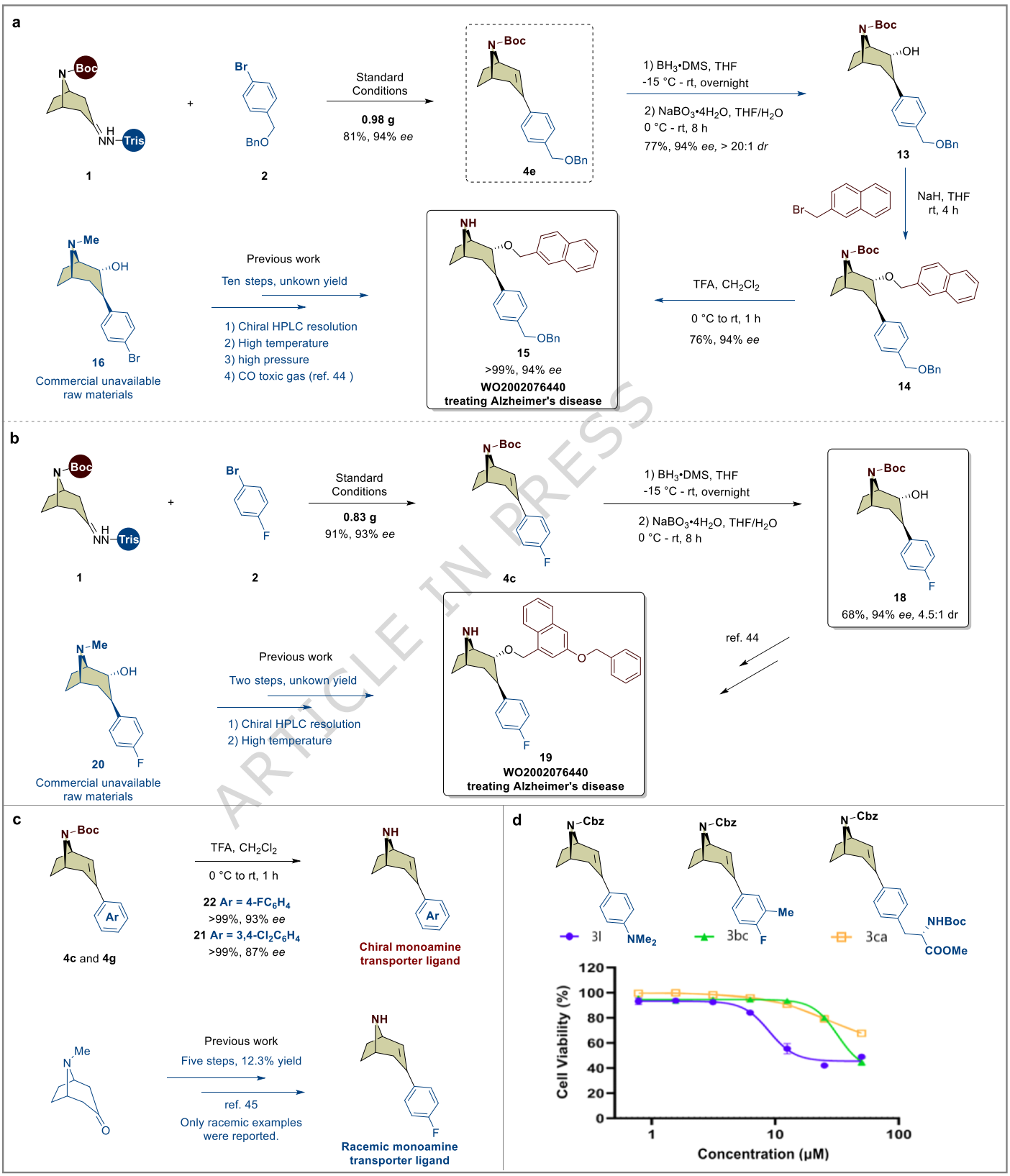


Fig. 6 | Synthetic applications. (All yields in **Fig. 6** refers the isolated yields after flash column chromatography.) **a,** Enantioselective synthesis of **15** which can treat with Alzheimer's disease. **b,** Enantioselective synthesis of **19** which can treat with Alzheimer's disease. **c**, Enantioselective synthesis of monoamine transporter ligands **21** and **22**. **d**, The preliminary biological investigations. Concentration-

dependent inhibitory curves of compounds **3l**, **3bc**, **3ca** in A549 cells. The data are presented as the means ± SEM (n=3).

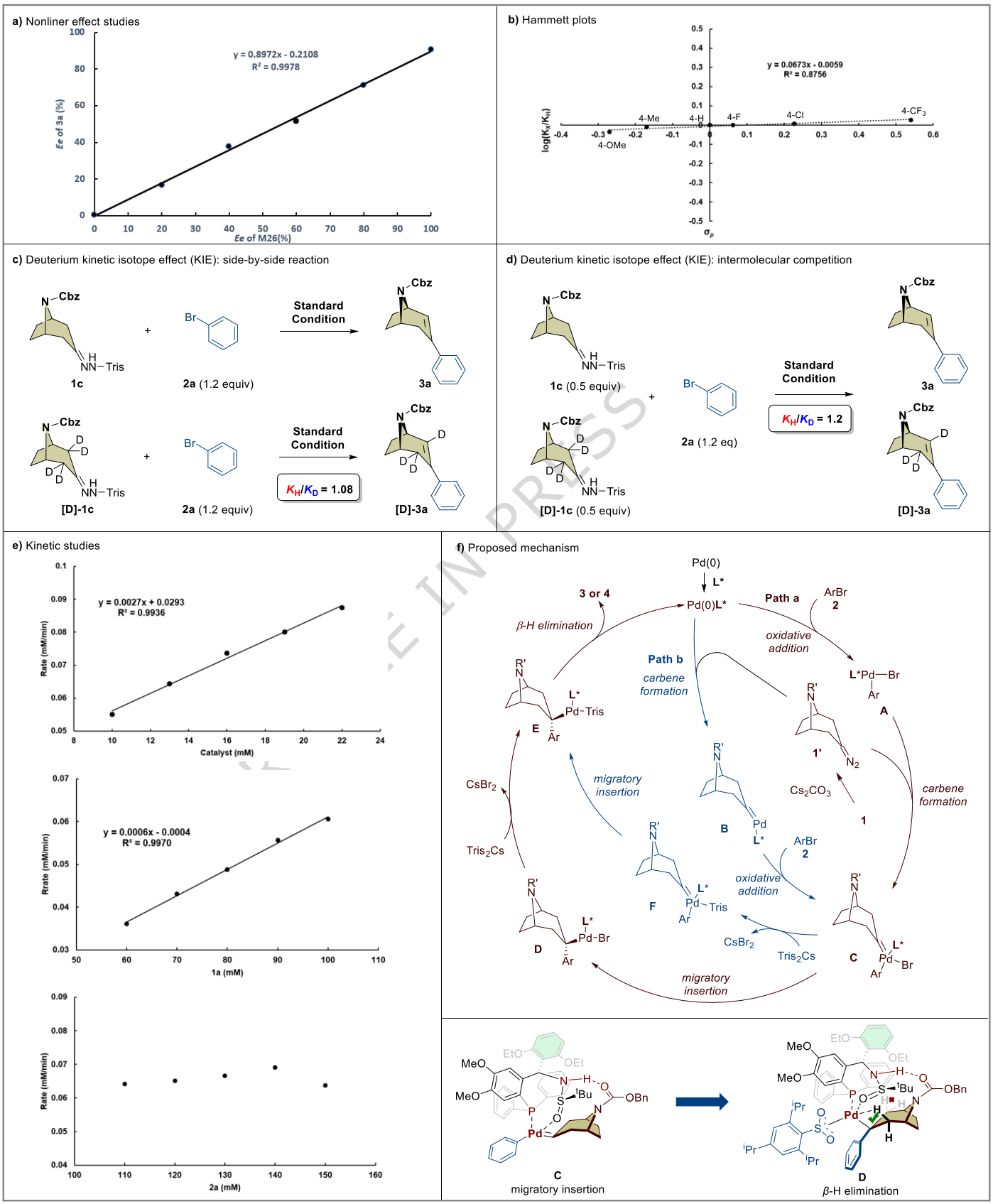


Fig. 7 | Mechanistic investigations. a, Nonlinear experiment. b, Hammett study for the formation of 3 versus the corresponding σ

value (k = reaction rate). **c,** Deuterium kinetic isotope effect (KIE): side-by-side reaction. **d,** Deuterium kinetic isotope effect (KIE): inter-molecular competition. **e,** Kinetic studies of catalyst, substrate **1** and aryl bromides. **f,** Proposed mechanism.

(**3ca**-**3ce**) underwent the β-H elimination to afford the corresponding products in high yields and diastereoselectivities. To illustrate the practicality of this β-H elimination reaction, a larger scale synthesis of **3c** and **4b** were carried out (Figure 5b, 5c). Under the standard conditions, the products **3c** and **4b** were isolated in 86% yield with 92% *ee* and 71% yield with 91% *ee*, respectively. Subsequently, the Boc group could be substituted by different other groups, thus leading to **5-7** in 71-81% yields and 89-91% *ee*. Moreover, upon oxidation by $NaBO_3 \cdot 4H_2O$, the **3c** could undergo hydroboration-oxidation reaction to furnish **8** and further proceeded Dess-Martin oxidation reaction to give unsaturated **9** in overall 60% yield with 89% *ee*. Meanwhile, with the existence of *m*-CPBA, the epoxidation of **3c** could deliver **10** in 83% yield and 91% *ee*. In addition, **3c** was able to afford dihydroxylation product **11** in good yield and *ee*. Finally, enantioenriched compound **12** that bears intrinsically synthetic challenge could be easily accessed via three step transformations of **3c**.

It was found that the chiral *N*-bridged [3.2.1]-Tropane **15** and

19 were present in pharmaceuticals treating Alzheimer' disease (Figure 6a)[44]. Our method provided a straightforward approach to **15** in 58% overall yield and 94% *ee*. In contrast to previous routes, which required chiral resolution and harsh reaction conditions involving high-pressure, high-temperature and toxic CO gas, this reaction produced **15** in high *ee* under mild conditions, significantly reducing the synthesis cost. Furthermore, **4c** could also undergo hydroboration-oxidation and transformed into **18**, which was a key intermediate in the total synthesis of **19** (Figure 6b). To our delight, removal of the Boc group of **4g** and **4c** afforded **21** and **22**, which were recently shown to have affinity and high selectivity for monoamine transporters (Figure 6c)[45]. Therefore, our reaction provided an efficient strategy to prepare analogues by starting with different aryl bromides. It was suited for finding new compounds that display a broad spectrum of monoamine transporter selectivity. In view of the broad bioactive properties of tropanes family, we were intrigued by the potential biological activities of these chiral *N*-bridged [3.2.1]Tropane scaffolds. Accordingly, the cytotoxic effects of these compounds against cancer cells were evaluated by Cell Counting Kit-8 (CCK-8) assay. Our preliminary studies demonstrated that many of them exhibited significant cytotoxic effects on cancer cells at the concentration of 20 μM (see Table S2 in Supplementary information for details). Next, we further determined the cytotoxic IC_{50} Values of some selected active compounds (Figure 6d). Notably, the IC_{50} value of **3l** was in the range of 10-20 μM, which indicated that **3l** showed potential for further development into anticancer drug.

In order to gain insights into this asymmetric β-H elimination reaction, mechanistic investigations were carried out (Figure 7). First, nonlinear effect studies indicated that there was a significant first order dependence on catalyst (Figure 7a). To identify the rate-determining step of the reaction, we next investigated the Hammett plots of various para-substituted aryl bromides (Figure 7b). These results indicated that electronic variation of the aryl bromides had no impact on the rate. Therefore, oxidative addition of aryl bromides might not be the rate-determining step. Additionally, if $0<\rho<1$ (ρ is the slope of Hammett plot), it indicated that rate-determining step involved only minor charge separation and the mechanism or rate-determining step might be concerted[46]. Moreover, we performed experiments with *N*-sulfonylhydrazones **1** and **[D]-1** to measure the initial reaction rate, respectively. The side-by-side experiments provided a K_H/K_D value of 1.08 (Figure 7c). The intermolecular competition reaction of **1** and **[D]-1c** in one pot showed a K_H/K_D value of 1.2 calculated from the generation of **3a** and **[D]-3a** (Figure 7d). These results suggested that the β-H elimination process might not be the rate-determining step. Next, the kinetic analysis experiments were conducted employing **1c** and **2a** (Figure 7e). Based on the kinetic experiment's data, we plotted the logarithm of the reaction rate (-Ln(K)) against the logarithm of the concentration of Pd, sulfonylhydrazones **1c**, PhBr **2a**, respectively. Thus, we obtained the initial reaction rate: $Rate_{initial} = K_{obs}[1c]^{1.01}[2a]^{0.07}[PdL*]^{0.58}$ (Supplementary information Figure S1). Therefore, we determined that the reaction exhibits approximately first-order kinetics with substrate **1c** and fractional order for the catalyst, and approximately zero-order kinetics with PhBr **2a**. Firstly, the kinetic results indicated that the reaction was zero-order in aryl bromide **2a**, which sug-

gested that changes of aryl bromide (bond cleavage or 1,2-migratory insertion) were not involved in the rate-determining intermediate. Secondly, the first-order dependence for **1c** and fractional order for palladium catalyst disclosed that the rate-determining step involved interactions (bond formation or cleavage) between the **Pd** and **1c**. In our reaction, carbene formation involved bond formation between **Pd** and **1c**, and β-H elimination involved bond cleavage between **Pd** and **1c**. Since KIE experiments excluded β-H elimination as the rate-determining step, we inferred that carbene generation might be the rate-determining step and proceeded via a concerted process, which was consistent with the result of the Hammett plot. According to the previous reports[34,35], the decomposition rates of Ts-, Mes- and Tris-groups increased with the steric bulk of the substituent. Finally, we determined the initial reaction rates for **1a** (Ts), **1b** (Mes), **1c** (Tris) at 50 °C, the experimental results showed that the initial reaction rates follow the order **1c** (Tris) > **1b (**Mes) >**1a** (Ts)[47-48], which further supports that carbene formation might be the rate-determining step in this reaction (See SI Figure S9). Additionally, some control experiments were then conducted. We conducted radical inhibition experiments under standard conditions (Supplementary information Figure S10). The reaction was not inhibited regardless of whether TEMPO or BHT was added. Therefore, a single-electron transfer mechanism had been ruled out. Then, after the reaction proceeded under standard conditions for 36 h, the product **3a** was obtained with an 88% yield and 91% *ee*. Then we added additional starting material **1c**, bromobenzene **2a**, and Cs_2CO_3 to the mixture, the product **3a** was still obtained with an 85% yield and 90% *ee* (See SI Figure S11). Therefore, we inferred that no significant catalyst deactivation occurred in this reaction.

Based on the experimental results and previous reports[29,49] , we propose a mechanism as illustrated in Fig 7f. The reaction is initiated with the oxidative addition of phenyl bromide **2** to Pd(0) catalyst. The Pd(II) intermediate **A** is generated, followed by the reaction with diazo compound **1'**, delivering the Pd carbene intermediates **C**. As an alternative, the Pd carbene intermediate **B** is generated by the coordination of Pd(0) with **1'**. Then intermediate **B** undergoes oxidation addition with **2** to furnish the Pd carbene intermediate **C**. Path a is favored over Path b in this reaction[49]. Subsequently, the carbene migratory insertion and ligand exchange occurs to form benzylpalladium species **D** and **E**. Finally, **E** undergoes β-H elimination to afford the final product **3 or 4** as well as regenerate the palladium catalyst with the aid of the base. Alternatively, the ligand can also be exchanged first to generate intermediate **F**, and then carbene migratory insertion to form **E**. The irreversible of β-H elimination process is critical for maintaining the *ee* value of product **3 or 4**. Moreover, based on experiment results and our proposed model, the hydrogen bond between ligand and the substrate is crucial for the reaction to proceed, which enables the substrate to bind with Pd and promote carbene formation (Figure 7f and SI Figure S13).

In summary, we have developed a newly identified **Ming-Phos** ligand, allowing highly enantioselective β-H elimination for the synthesis of multifunctional azabidged [3.2.1]Tropane scaffolds, which requires modulating the reactivity of the strained carbene in an enantioselective and stereospecific manner. The value of these azabidged [3.2.1]tropane scaffolds are demonstrated by the synthesis of drugs for treating Alzheimer's disease and monoamine transporter ligands. Moreover, these tropane compounds exhibit diversified biological activities. Additionally, mechanistic studies indicate that β-H elimination might not be the rate-determining step in this process. We anticipate that this methodology will be of broad interest to researchers in asymmetric β-H elimination reaction and medicinal sciences.

Methods

Representative procedure A for asymmetric arylation of aza-bridged [3.2.1]Tropane derivatives (3 or 4). To a 10 mL oven-dried sealed tube was added substrate **1** (0.30 mmol, 1.0 equiv.), $Pd_2(dba)_3$•$CHCl_3$ (15.5 mg, 0.015 mmol, 5 mol%), **M26** (38.3 mg, 0.06 mmol, 20 mol%), Cs_2CO_3 (391.2 mg, 1.2 mmol, 4.0 equiv.). The flask was evacuated and refilled with argon. Then, substrate **2** (0.36 mmol, 1.2 equiv.), DMA (3 mL) was added to the tube, and stirred at room temperature for 1 h. Then the mixture was stirred at 50 °C for 36-60 h. After the reaction was complete (monitored by TLC), solvent was removed under reduced pressure. The crude product was then purified by flash column chromatography on silica gel to afford the desired product **3**.

Representative procedure B for asymmetric arylation of aza-bridged [3.2.1]Tropane derivatives (3 or **4).** To a 10 mL oven-dried sealed tube was added substrate **1** (0.30 mmol, 1.0 equiv.), $Pd_2(dba)_3$•$CHCl_3$ (15.5 mg,

0.015 mmol, 5 mol%), **M27** (39.3 mg, 0.06 mmol, 20 mol%), Cs_2CO_3 (391.2 mg, 1.2 mmol, 4.0 equiv.). The flask was evacuated and refilled with argon. Then, substrate **2** (0.36 mmol, 1.2 equiv.), DMA (3 mL) was added to the tube, and stirred at room temperature for 1 h. Then the mixture was stirred at 50 °C for 36-60 h. After the reaction was complete (monitored by TLC), solvent was removed under reduced pressure. The crude product was then purified by flash column chromatography on silica gel to afford the desired product **3** or **4**.

Representative procedure C for asymmetric arylation of aza-bridged [3.2.1]Tropane derivatives (3 or **4).** To a 10 mL oven-dried sealed tube was added substrate **1** (0.30 mmol, 1.0 equiv.), $Pd_2(dba)_3$•$CHCl_3$ (15.5 mg, 0.015 mmol, 5 mol%), **M27** (39.3 mg, 0.06 mmol, 20 mol%), Cs_2CO_3 (391.2 mg, 1.2 mmol, 4.0 equiv.). The flask was evacuated and refilled with argon. Then, substrate **2** (0.36 mmol, 1.2 equiv.), PhMe (3 mL) was added to the tube, and stirred at room temperature for 1 h. Then the mixture was stirred at 50 °C for 36-60 h. After the reaction was complete (monitored by TLC), solvent was removed under reduced pressure. The crude product was then purified by flash column chromatography on silica gel to afford the desired product **3** or **4**.

Online content

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Data availability

The data supporting the findings of this study are available within the article and its Supplementary Information. And all data are available from the corresponding author upon request. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2451377 (**3bd**). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions

C. F. carried out the experimental and data-analysis work. J. A. and Q. W. carried out the experimental work. B. X. carried out data-analysis work and wrote the paper. Z.-M. Z. and J. Z. designed the reaction and directed the project and wrote the paper.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at https://.

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Editor's Summary

Tropanes and their related bridged bicyclic systems constitute highly sought-after scaffolds in drug discovery and development. Here, the authors report an enantioselective Pd/Ming-Phos-catalyzed β-H elimination reaction of Tropinone derived N-arylsulfonylhydrazones and aryl bromides to give chiral tropanes and oxatropanes.

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