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Pd-Catalyzed Asymmetric Amination of Enamines: Expedient Synthesis of Structurally Diverse N−C Atropisomers

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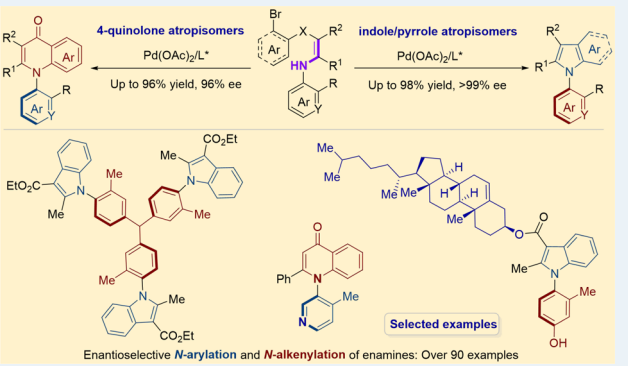
ABSTRACT: The transition-metal-catalyzed cross-coupling of enamines is an attractive method for producing compounds with an N−C chiral axis; however, it faces considerable challenges that remain unresolved. Herein, a palladium-catalyzed amination method was developed to construct structurally diverse five−six biaryl and six−six nonbiaryl N−C atropisomers. The reaction mechanism was explained using density functional theory calculations, which showed that the mechanism involved the Curtin−Hammett control. N−C rotation occurred along the reaction coordinate until an enantio-determining three-centered reductive elimination transition structure established the stereochemistry. The developed method is highly attractive because of its broad substrate scope, high stereoselectivity, simple catalytic system, good functional group tolerance, and dynamic kinetic resolution.



KEYWORDS: *atropisomeric, enamine, palladium, dynamic kinetic transformation, amination*

INTRODUCTION

Atropisomers around an N−C chiral axis, often involving substituted nitrogen and an aromatic ring, are one of the most important classes of axially chiral compounds. They are present in many bioactive compounds,[1] such as murrastifoline-F, marinopyrrole, and tetrabromobiindole. Axially chiral N−C structures display a range of bioactivities,[2] including anti-mitotic, antimicrobial, and anti-human immunodeficiency virus activities. Further, they have applications as chiral ligands in asymmetric catalysis.[3] With the increasing number of N−C atropisomers, organic chemists have been developing efficient methods for their synthesis. Current catalytic approaches for the enantioselective synthesis of axially chiral N−C atropisomers are still limited, and they generally follow one of the following four strategies:[4] *N*-functionalization of anilide derivatives, organocatalyzed enantioselective addition and cyclization, asymmetric functionalization of preformed N−C scaffolds, and metal-catalyzed annulation reactions. However, these strategies usually involve complex catalytic systems and suffer from limited substrate scope. The stereoselective formation of N−C bonds via transition-metal-catalyzed aryl amination, such as Buchwald−Hartwig or Ullmann couplings,[5] is one of the most attractive synthesis approaches for obtaining atropisomers. However, this approach remains less studied,[6] likely due to the sensitivity of aminations to the steric bulk of the reaction partners. Generally, harsh conditions are required to promote bond formation, making it challenging to access this transformation. Therefore, few examples have been studied in this context.[7]

Enamines are one of the most common and widely used structures in organic synthesis,[8] and their asymmetric transformations provide a direct approach for constructing diverse and optically active nitrogenous building blocks (Figure 1a).[9] Despite their high efficiency, the direct enantioselective *N*-functionalization of enamines has remained underdeveloped and challenging.[10] Recently, Li and Belyk reported an enantioselective synthesis of indole point chirality through Pd-catalyzed *N*-arylation of enamine intermediates (Figure 1b).[10a] Meanwhile, Kitagawa reported a method for constructing N−C atropisomers using Pd(II)-catalyzed coupling via enamine intermediates, resulting in low to moderate yields and enantiomeric excess (ee) in the presence of a sterically hindered *tert*-butyl functional group.[10b] Knipe also reported using this method to synthesize axially chiral *N*-arylquinolinium salts in low to moderate enantioselectivities.[10c] Herein, we attempted to address this challenge by developing a general coupling strategy for synthesizing N−C atropisomers. We

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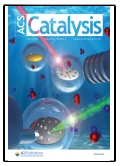

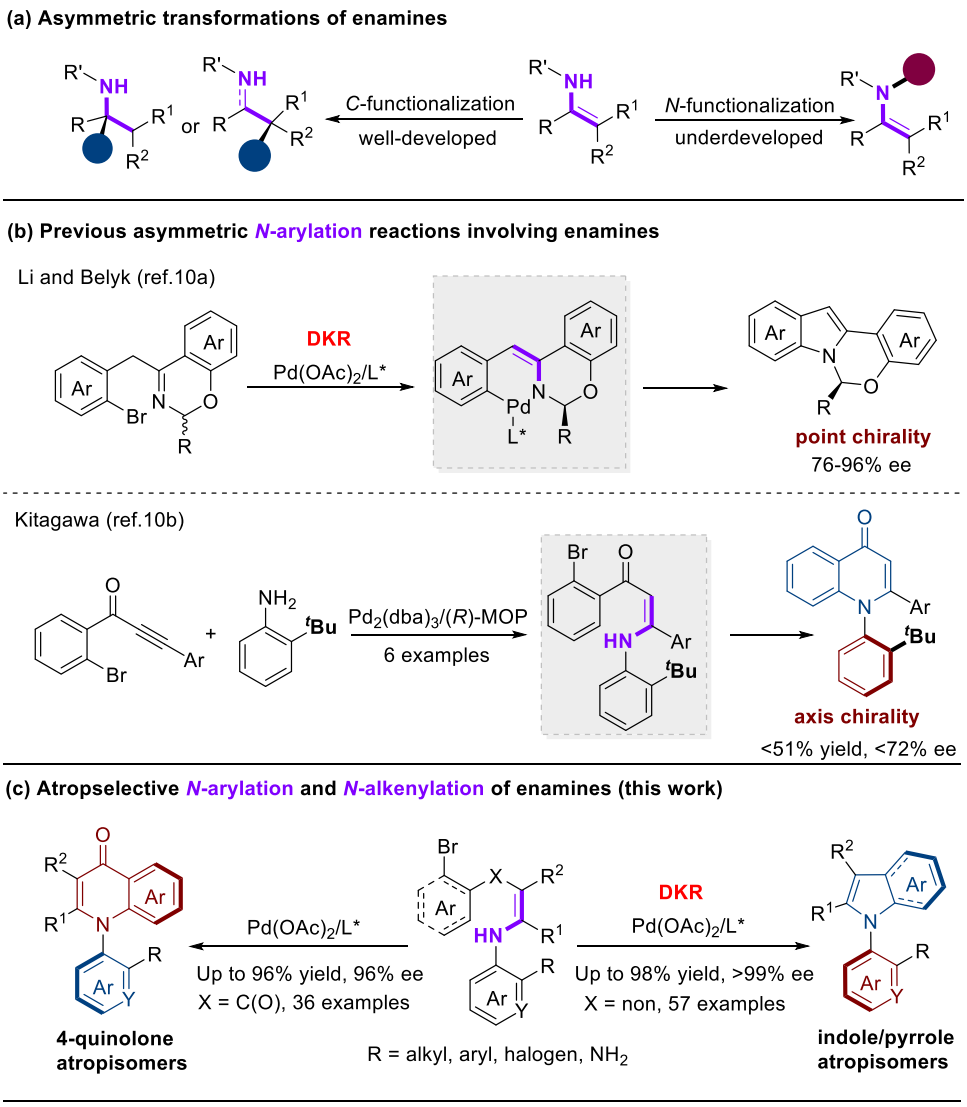

Figure 1. Asymmetric transformations of enamines.

describe the Pd-catalyzed *N*-arylation and *N*-alkenylation of enamines for the expedient enantioselective synthesis of structurally diverse indole and pyrrole biaryl and 4-quinolone nonbiaryl N−C atropisomers (Figure 1c).

RESULTS AND DISCUSSION

The use of optically active indoles as ligands and building blocks has received considerable attention; however, the methods for constructing chiral indoles with N−C axes are still limited.[11] In this study, enamine **3a′** with a C−C chiral axis was selected as the model substrate for constructing chiral indoles through a novel dynamic kinetic resolution (DKR) transformation (Table 1).[12] This step involves intramolecular amination with an axial-to-axial chirality transfer process, where the chirality transfer occurs from the C−C axis to the N−C axis.[13] Enamine **3a′** can be easily accessed by condensing ketoester **1a′** with 4-methoxy-2-methylaniline **2a** as a single *Z*-isomer in high yield (see the Supporting Information for details).[14] The desired product **4a** was obtained in 72% yield from **3a′** using 5 mol % $Pd(OAc)_2$ as the catalyst, dppf as the ligand, and KOH as the base (entry 1). We then focused on discovering an enantioselective variant to access optically active N−C atropisomers. We found that the reaction proceeded smoothly with *S*-BINAP (**L1**), and the desired N−C indole biaryl atropisomeric product **4a** was achieved in 74% yield and 68% ee (entry 2). Switching from iodo-substituted **3a′** to Br-substituted enamine **3a** slightly improved the enantioselectivity of **4a** to 70% (entry 3). However, when NaOH was used, **4a** was obtained in 80% yield and 91% ee (entry 4). The use of Cs_2CO_3 as the base afforded **4a** in 97% yield and 94% ee (entry 8). Other bases, such as NaO^{t}Bu, KO^{t}Bu, and NaH, gave results (entries 5−7, respectively) inferior to that of Cs_2CO_3. Several frequently used chiral biphosphines, such as Tol-BINAP **L2**, Xyl-BINAP **L3**, SEGPHOS **L4**, JOSIPHOS **L5**, BIPHEP **L6**, Trost ligand **L7**, and Ph-BPE **L8**, were examined to further explore amination reactions (entries 9−15, respectively). **L3** and **L6** gave comparable enantioselectivity of **4a** to **L1** but with reduced yields. The yields and enantioselectivities of **4a** afforded by other ligands were not higher than those of **L1**. Notably, reducing the amount of catalyst from 5.0 to 2.5 mol % maintained the ee value of **4a**, albeit the 85% yield (entry 16). Density functional theory (DFT) analysis was conducted regarding the atropisomeric stability of five−six biaryl N−C products. A substantial isomerization barrier was computed for the rotation about the N−C axis, with $\Delta G^{\ddagger}$ = 31.8 kcal/mol. At

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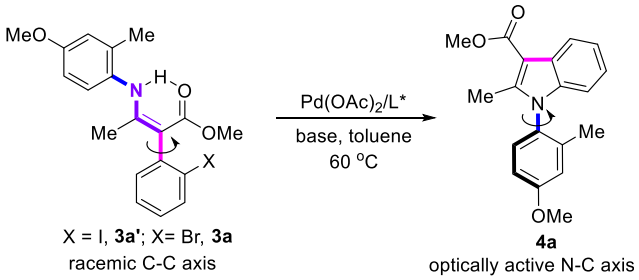
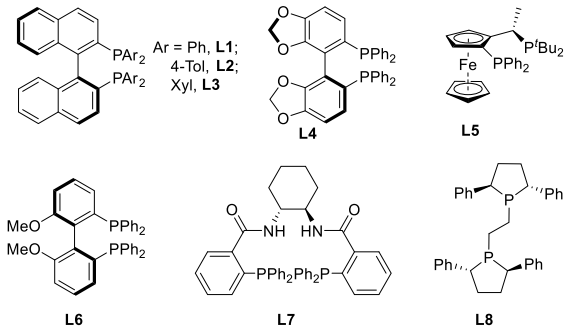
Table 1. Optimization of Conditions for the Synthesis of Indole Atropisomers[b]



X = I, **3a'**; X= Br, **3a**
racemic C-C axis

4a
optically active N-C axis

entry	L*	base	X	yield (%)[b]	ee (%)[c]
1	dppf	KOH	X = I	72	--
2	**L1**	KOH	X = I	74	68
3	**L1**	KOH	X = Br	83	70
4	**L1**	NaOH	X = Br	80	91
5	**L1**	NaO^{t}Bu	X = Br	64	78
6	**L1**	KO^{t}Bu	X = Br	82	92
7	**L1**	NaH	X = Br	90	88
8	**L1**	Cs_2CO_3	X = Br	97	94
9	**L2**	Cs_2CO_3	X = Br	93	90
10	**L3**	Cs_2CO_3	X = Br	87	95
11	**L4**	Cs_2CO_3	X = Br	78	90
12	**L5**	Cs_2CO_3	X = Br	<5	--
13	**L6**	Cs_2CO_3	X = Br	75	94
14	**L7**	Cs_2CO_3	X = Br	<5	--
15	**L8**	Cs_2CO_3	X = Br	85	32
16[d]	**L1**	Cs_2CO_3	X = Br	85	94



[a]Reaction conditions: **3** (0.1 mmol), $Pd(OAc)_2$ (5.0 mol %), **L*** (7.5 mol %), and base (1.2 equiv) in 1.0 mL of toluene at 60 °C for 18 h. [b]Isolated yield. [c]Determined using chiral high-performance liquid chromatography. [d]With 2.5 mol % of $Pd(OAc)_2$ and 3.75 mol % of **L1** for 48 h. dppf: 1,1′-bis(diphenylphosphino)ferrocene.

60 °C, this corresponds to a (transition state theory) kinetic constant of 9.2×10^{-9} s^{-1} and a half-life of >2 years. This suggests that negligible racemization occurs over several days under these conditions, which agrees with the experiment. This computed barrier lies well in excess of Ōki's criterion, which suggests that stable atropisomers should possess a half-life of >1000 s (>22 kcal/mol).[15]

After optimizing the reaction conditions, the scope of enamine **3** was investigated, and it was found that various enamines performed well in the *N*-arylation reaction, affording excellent yields with satisfactory enantioselectivities (Table 2). First, the substrate scope of the aromatic bromide moiety (R) with various substitutions was examined. The reaction of **3** featuring diverse substituents on the aromatic bromide moiety, such as chloro (**4b**), fluoro (**4c** and **4e**), and methoxy (**4d**, **4f**, and **4g**), proceeded smoothly, affording the corresponding atropisomers in 81−94% yields and 94−95% ee. Moreover, *ortho*-F substituent in the aromatic bromide moiety was tolerated, producing **4h** in 88% yield with 65% ee. The versatility proved even higher with R^1 substituents, including multiple phenyl derivatives and a range of heteroaryl groups. The *ortho*-alkyl group in the aniline moiety could be a simple methyl (**4i**). High yields and enantioselectivities were obtained for the dialkyl-substituted arylamines (**4j** and **4o**), and arylamines with halogen (**4k**, **4l**, **4p**, **4q**, and **4u**), trifluoromethyl (**4m** and **4w**), ester (**4n**, **4r**, and **4x**), nitrile (**4v**), and diethylamino (**4t**) groups at different positions afforded the products in 90−95% ee. Substrates with free −OH (**4s**, **4aa**) or $-NH_2$ groups (**4ab**−**4ad**) were tolerated in the reaction, although the enantioselectivity was slightly reduced when the amine group was at the *ortho* position (**4ac**). Moreover, chloride (**4ad**), naphthyl (**4y**), and (tetrahydro)naphthyl scaffolds (**4z**) were tolerated at the *ortho* position of aniline, affording the products in good enantioselectivities. The absolute stereochemistry of **4y** was determined using single-crystal X-ray diffraction analysis. Heterocyclic substrates were also tolerated in the reaction, resulting in indole−quinoline (**4ae**) and indole−pyridine (**4af**) biaryl atropisomers. Using the substrate with the ethyl group at the ortho position, **4ag** was obtained in 92% yield and 91% ee. Furthermore, the C3-nitrile substrate worked efficiently under the reaction conditions, providing **4ah** in 90% yield and 94% ee. A set of different benzoates were also examined,[16] and high ee values were achieved in reactions with Et-(**4ai**), ^{i}Pr-(**4aj**), Bn-(**4ak**), and Cy-esters (**4al**). However, the yield and enantioselectivity of the reaction were considerably reduced (**4am**) when the starting material without a substituent at the R^3-position was used. In this case, the reaction was performed using a one-pot method without the separation of the enamine. This reaction can be partially improved through the asymmetric coupling of allyl ester substrates and the decarboxylation cascade reaction. To further prove the usefulness of the method, the reaction was subjected to various post-functionalizations. Several enamines with the core structures of bioactive molecules (quetiapine, **4ap**; paroxetine, **4aq**), materials (CD4, **4ao**; CD3, **4ar**), and natural products (L-menthol, **4as**; cholesterol, **4at**; D-fructose, **4au**; and D-glucose, **4av**) were examined. All of the indole atropisomers were achieved in good yields with satisfactory diastereoselectivities and enantioselectivities.

Molecules with multiple stereogenic structures provide interesting and complex topologies and unique applications in catalysis and materials.[17] However, the enantioselective synthesis of fused indoles with two or more axes has rarely been studied, presumably owing to the difficulty in controlling both the enantioselectivity and diastereoselectivity. The synthesis of fused indole atropisomers with two or three axes was explored using the Pd-catalyzed amination reaction (Table 3). A series of structurally different diaxial and triaxial indoles was achieved with good enantioselectivities and diastereoselectivities (**6a**−**6h**, 76−97%, 93−>99% ee, and 8:1 to >20:1

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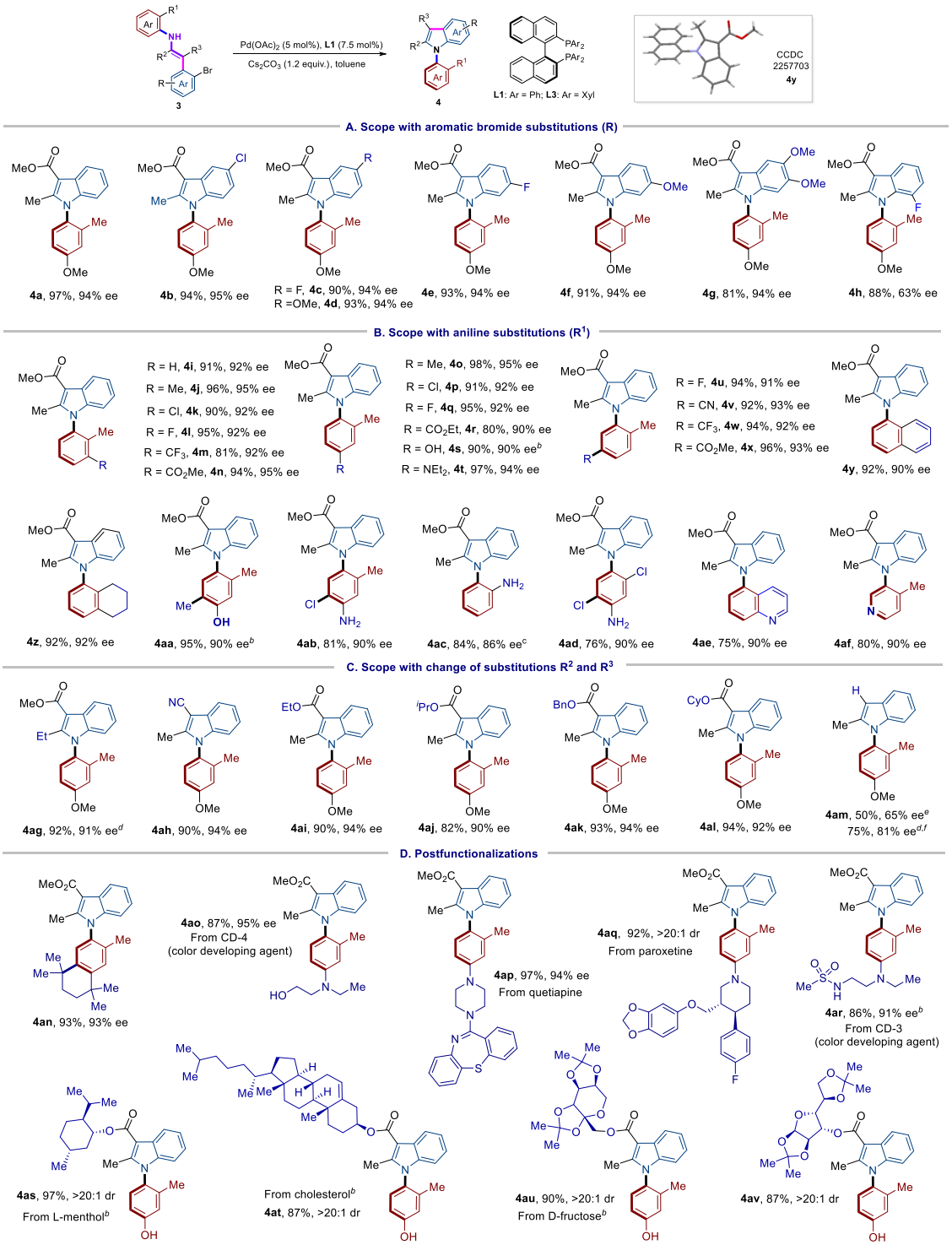
Table 2. Scope of Indole Atropisomers[a]



[a]Reaction conditions: **3** (0.2 mmol), $Pd(OAc)_2$ (5.0 mol %), **L1** (7.5 mol %), and Cs_2CO_3 (1.2 equiv) in 2.0 mL of toluene at 60 °C for 18 h. [b]Cs_2CO_3 (2.4 equiv) was used. [c]At 25 °C with **L3** as the ligand. [d]**L3** was used as the ligand. [e]The reaction was conducted via the one-pot method without separating the enamine intermediate. [f]**4al** was obtained through asymmetric coupling of the allyl ester substrate and decarboxylation cascade reaction.

diastereomeric ratio (dr)) via two or three asymmetric *N*-arylations.

After conducting the asymmetric amination of enamines to construct indole biaryl atropisomers, we focused on the *N*-alkenylation of enamines to achieve the enantioselective synthesis of pyrrole biaryl N−C atropisomers (Table 4).[18] Thus, the reaction of ethyl 4-bromo-2-(1-((4-methoxy-2-methylphenyl)amino)ethylidene)pent-4-enoate (**7**) was tested. Under optimal reaction conditions, pyrrole biaryl N−C atropisomer (**8**) was obtained in poor yield with moderate enantioselectivity through the asymmetric amination reaction and subsequent aromatic isomerization through intermediate

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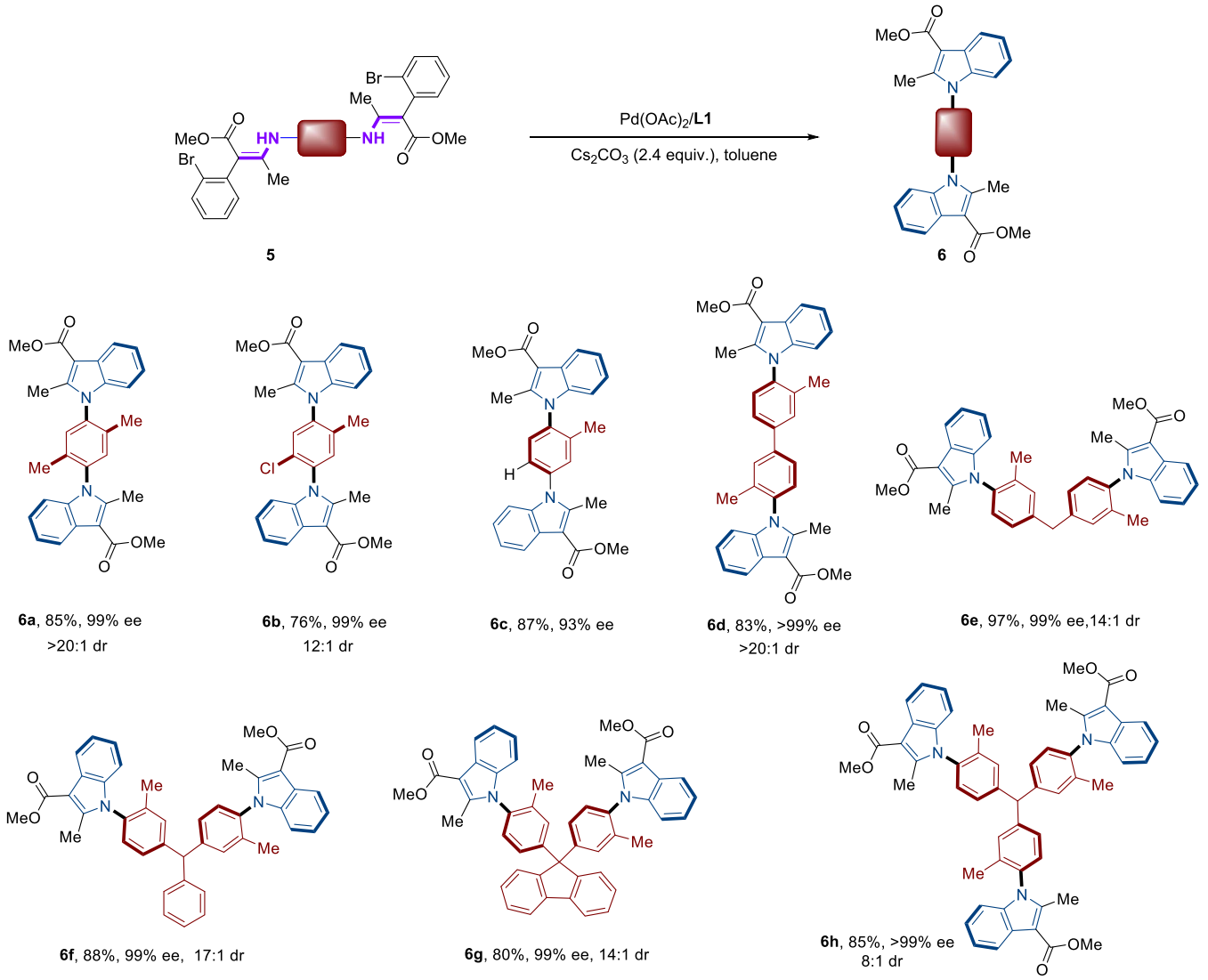
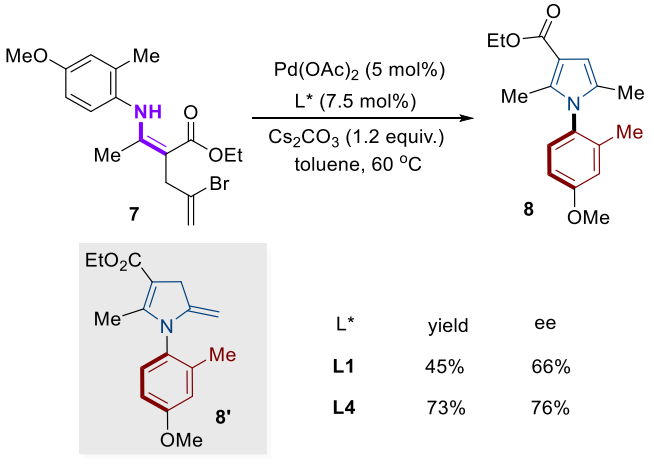
Table 3. Scope of Di- or Tri-Enamines 5 for the Construction of Chiral Indoles[a]



[a]Reaction conditions: **5** (0.2 mmol), $Pd(OAc)_2$ (5.0 mol %), **L1** (7.5 mol %), and Cs_2CO_3 (2.4 equiv) in toluene (2.0 mL) at 60 °C for 36 h.

Table 4. Enantioselective Synthesis of Pyrrole Atropisomers



L*	yield	ee
L1	45%	66%
L4	73%	76%

8′. Further optimization showed that using **L4** as the chiral ligand, **8** could be obtained in 73% yield and 76% ee.

Encouraged by the results for the synthesis of indole and pyrrole biaryl N−C atropisomers, we tested the amination of enaminones to access nonbiaryl atropisomeric 4-quinolones, which are present in many drug-active molecules.[19] Enamine **10** was readily prepared through the conjugate addition of aniline to *α,β*-ynone **9**, and the scope and generality of the process were explored (see the Supporting Information for details optimization of conditions). Table 5 summarizes the results. Generally, enamines (**10**) could be obtained in good yields through filtration. For the aryl bromides, the *N*-arylation reaction proceeded smoothly with either electron-poor (−F and −Cl) or electron-rich (−Me and −OMe) groups at the *meta* or *para* position to afford the corresponding 4-quinolone atropisomers in moderate to good yields with high enantioselectivities (**11a−11f**; 65−88% yield, 92−94% ee). The rotation barrier ($\Delta G^{\ddagger}$) was measured as 31.0 kcal/mol for **11a**, providing sufficient stability for drug-discovery studies. The protocol was also compatible with different substituted aryl and aliphatic groups at the *α*-position of the enamine (R). A set of *meta* or *para* substituents such as fluoride, chloride, methoxy, and alkyl groups could be tolerated (**11g−11n**).

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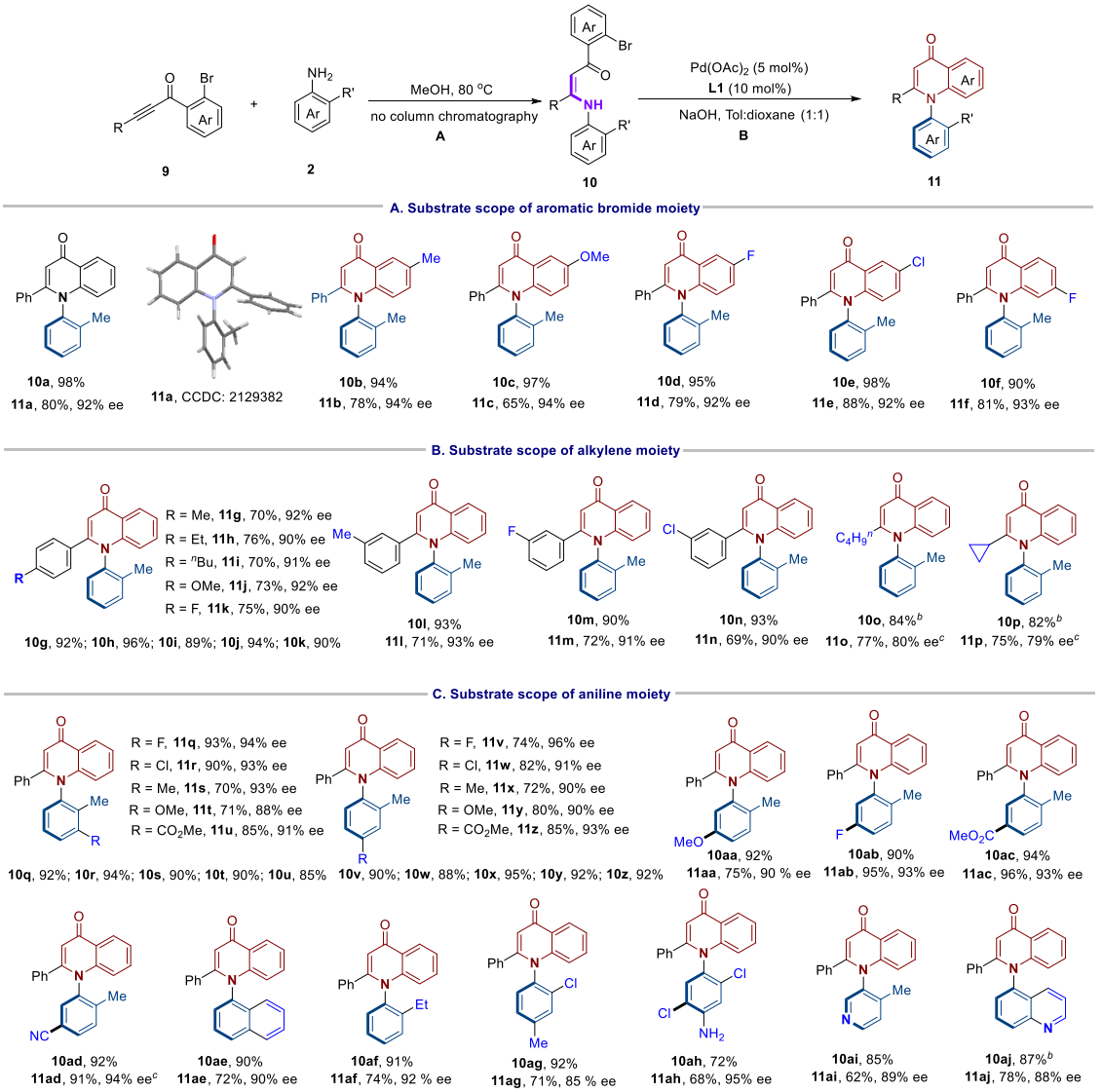
Table 5. Scope of Quinolone Atropisomers[c]



[a]Reaction condition **A**: **9** (0.1 mmol) and **2** (0.11 mmol) in MeOH (1.0 mL) at 80 °C for 0.5−10 h; reaction condition **B**: **10** (0.1 mmol), $Pd(OAc)_2$ (5.0 mol %), **L1** (10 mol %), and NaOH (1.5 equiv) in 1,4-dioxane and toluene (v/v = 1:1) (1.0 mL) at 40 °C for 18 h. [b]Purified using flash column chromatography. [c]Reaction was conducted at 60 °C for 18 h. The structure of racemic **11a** was confirmed using single-crystal X-ray analysis, and the absolute configuration of **11ae** was determined based on the results of a previous study.[10c]

Particularly, the alkyl-containing motifs (**11o** and **11p**) performed well in the arylation reaction, although the enantioselectivity was slightly reduced during cyclization. Subsequently, the arylamine moiety was surveyed. An array of functional groups were tolerated as *meta* or *para* substitutions on the aryl ring, including methyl (**11s** and **11x**), methoxy (**11t**, **11y**, and **11aa**), halogen (**11q**, **11r**, **11v**, **11w**, and **11ab**), ester (**11u**, **11z**, and **11ac**), and nitrile (**11ad**) groups. Notably, all products were obtained with good enantioselectivities. Generally, electron-withdrawing groups afforded products with better results than those of electron-donating groups (**11q** vs **11t** and **11aa** vs **11ab**). The yields were considerably higher for the substrates containing electron-withdrawing groups. Moreover, naphthyl (**11ae**), ethyl (**11af**), and Cl (**11ag**) substituents at the *ortho* position of aniline were well tolerated. However, the enantioselectivity of the chlorinated product **11ag** was not as high as that of the other products. In particular, a free amine group afforded **11ah** in 68% yield with 95% ee. Notably, some heteroaryls were tolerated in the reaction. For example, the pyridine-substituted enamine underwent a smooth reaction to afford **11ai** in 62% yield and 89% ee. The biquinolinone product **11aj** was produced in 78% yield and 88% ee.

Computational studies for determining the reaction mechanism involved in *N*-aryl indole formation were conducted via DFT using the M06/def2-TZVP//B3LYP/6-31G(d)+SDD level of theory with SMD solvation (Figure 2). Overall, we found that a computed sequence of ArBr oxidative addition, deprotonation, followed by cyclization to give the palladacycle after reductive elimination resulted in feasible energetics of transition structures (TSs) and intermediates.[20] Under Curtin−Hammett control, the final irreversible ring C−N bond−forming step controls the enantioselectivity, with the predicted sense and magnitude consistent with those obtained via the experiment.

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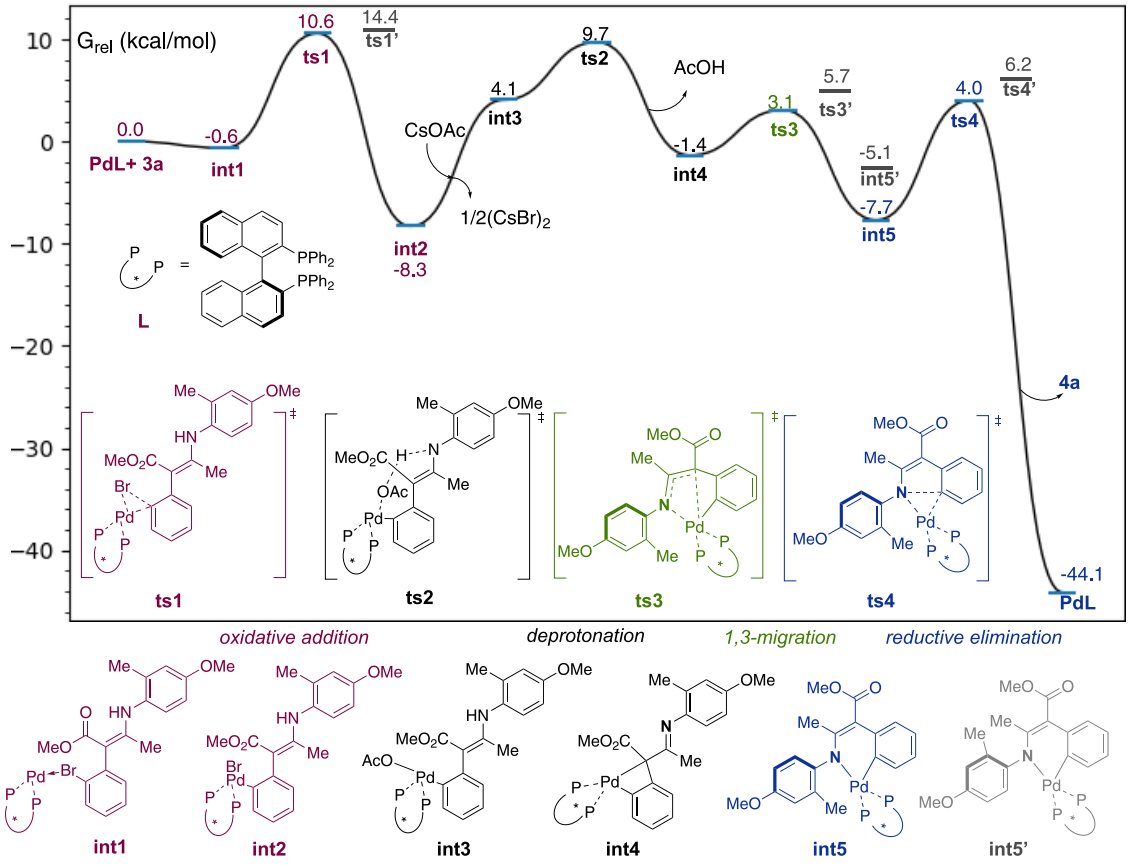

Figure 2. Computed Gibbs energy profile for the proposed mechanism of indole atropisomer synthesis.

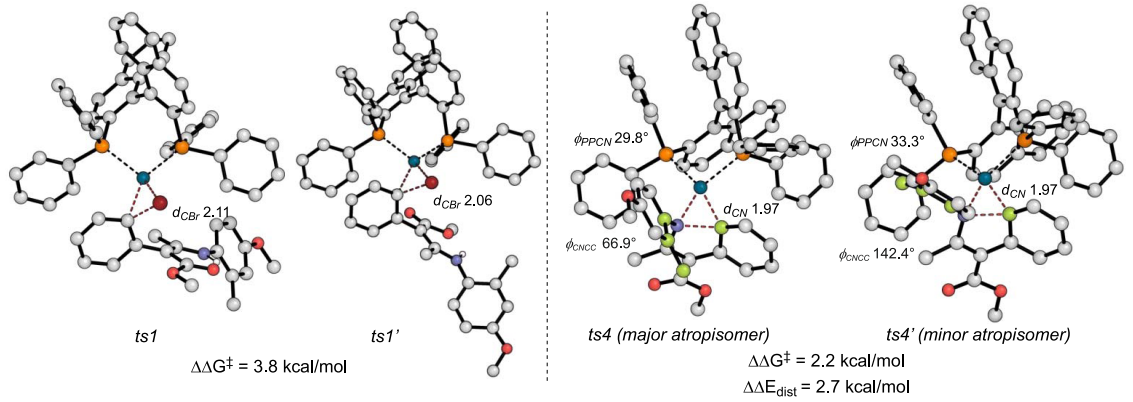

Figure 3. Optimized geometries and the corresponding relative Gibbs free energy (kcal/mol) differences between oxidative addition and reductive elimination TSs.

The oxidative addition of aryl bromide **3a** was computed to occur with an accessible barrier of 11.2 kcal/mol via a three-center TS (**ts1**). Interestingly, **ts1** favored the formation of the major atropisomer, whereas **ts1′** facilitated the formation of the minor atropisomer (Figure 3). The Gibbs free energy of the favored **ts1** was 3.8 kcal/mol lower than that of **ts1′**, affording the experimentally observed major product. Subsequently, we found that the N−H deprotonation achieved using acetate (**ts2**) converted **int3** into the ring-closed adduct **int4**, in which palladation of the developing enamine anion occurred at the α-position. Rearrangement (via a 1,3-shift of Pd in **ts3**) with a small activation free energy of 4.5 kcal/mol led to a six-membered palladacycle **int5**. Reductive elimination to form the five-membered ring occurred via **ts4** with an activation free energy of 11.7 kcal/mol in a highly exergonic and irreversible step.

Notably, the ease of *N*-aryl group rotation was considered at each step along the proposed reaction coordinate. Owing to the presence of the chiral BINAP ligand, rotation about the N−C axis resulted in diastereomeric species. Additionally, the N−C rotation occurred for all intermediates prior to the formation of **ts3**, and **int5** underwent such rotation via **ts5** with an activation free energy of 23.8 kcal/mol. However, in the final ring-closed product, the rotational barrier was high enough to prevent atropisomer interconversion at 60 °C. This established a Curtin−Hammett scenario in which axial chirality rapidly interconverted before an enantio-determining reductive elimination transition state. The Gibbs free energy of the

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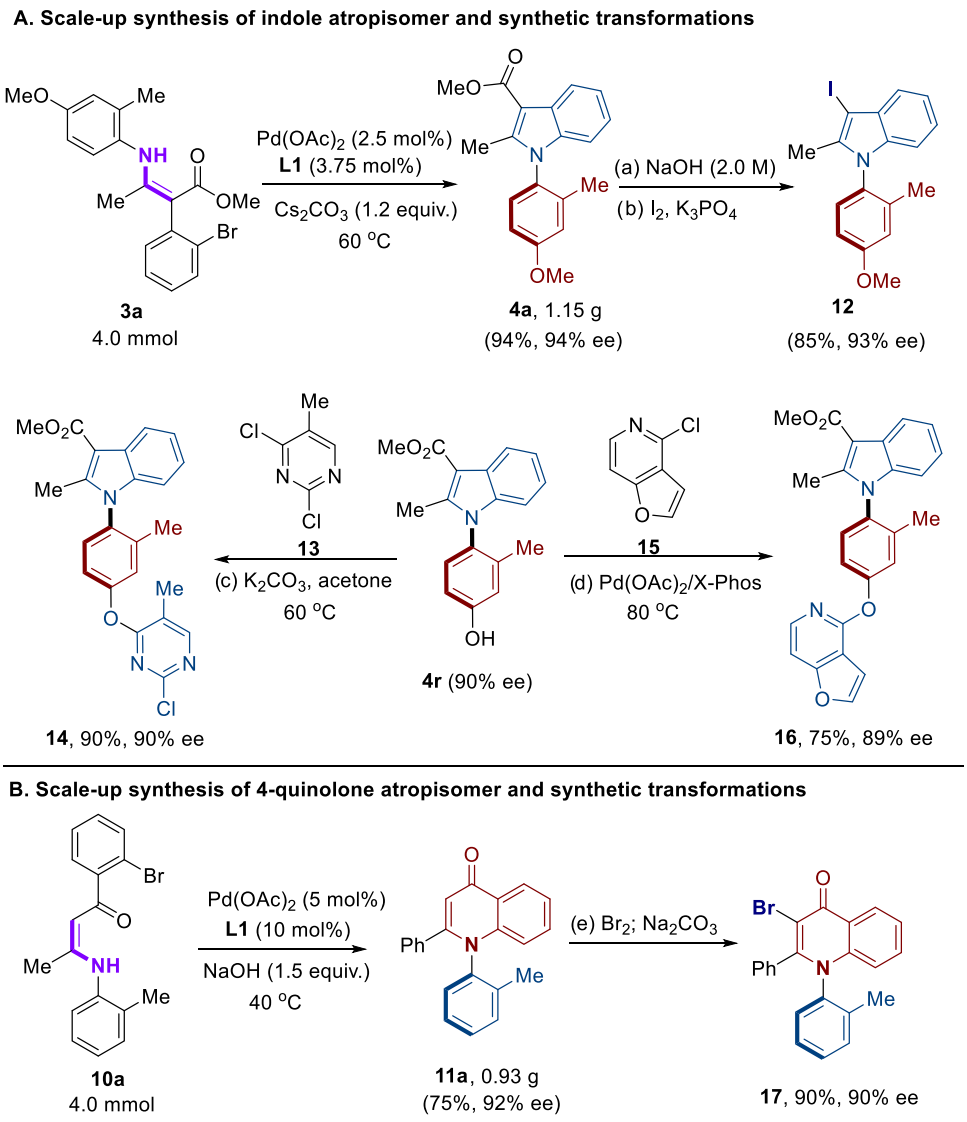

Figure 4. Scale-up synthesis and synthetic transformations.

favored **ts4** was 2.2 kcal/mol lower than that of **ts4′**, leading to the experimentally observed major atropisomer (for which the 94% ee corresponds to a $\Delta\Delta G^{\ddagger}$ of 2.3 kcal/mol at 60 °C). This selectivity resulted from the orientation of the (*N*-aryl) *ortho*-methyl group (Figure 3). In the favored TS, the methyl group was oriented away from the BINAP ligand, while in the disfavored TS, it pointed toward the ligand. To relieve steric strain, two unfavorable structural distortions occurred: the coordinated substrate twisted from the planar Pd(II) geometry and most significantly the N−C dihedral of the substrate twisted (from 67° in **ts4** to 142° in **ts4′**). Single-point energy calculations of the substrates in each conformation suggest that this builds up 2.7 kcal/mol of torsional strain relative to the major pathway.

A gram-scale synthesis of indole biaryl atropisomers was conducted (Figure 4). The treatment of enamine **3a** (4.0 mmol) with 2.5 mol% of Pd catalyst and 3.75 mol % of **L1** provided **4a** in 94% yield and 94% ee. The synthetic utility of this atropisomer was then demonstrated. The hydrolysis/decarboxylative iodination sequences applied to ester **3a** provided transition-metal-free routes for iodo-indole **12**. This is crucial for obtaining diverse biologically active molecules through further cross-coupling reactions. Phenol **4r** successfully underwent C−O cross-coupling reactions with 2,4-dichloro-5-methylpyrimidine **13** or 4-chlorofuro[3,2-*c*]pyridine **15** via a transition-metal-free or a Pd catalysis route to afford products **14** or **16** in good yields, respectively. The six−six 4-quinolone nonbiaryl N−C atropisomer **11a** was synthesized in a gram scale using the developed method. Moreover, polysubstituted 4-quinolones **17** with a high synthetic value could be easily synthesized from **11a** using Br_2 as the bromination reagent. Notably, the enantioselectivity of the product was almost unaffected by the bromination and debromination transformations.

CONCLUSIONS

We have developed a Pd-catalyzed asymmetric *N*-arylation reaction for the expedient enantioselective synthesis of structurally diverse five−six biaryl and six−six nonbiaryl N−C atropisomers. A wide variety of indoles, pyrroles, and 4-quinolone derivatives have been readily prepared in high yields with excellent enantioselectivities, making them suitable for library preparation. Structurally diverse, highly enantioenriched indoles have the potential to be used as hole-transport

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materials with two or three axes. In addition, quinolone N−C atropisomers can be prepared from intermolecular ynones and primary anilines through simple filtration and subsequent cross-coupling reactions. The gram-scale experiment and transformation into useful five−six and six−six atropisomers make this strategy attractive. DFT studies reveal that the enantioselectivity is determined using reductive elimination based on the Curtin−Hammett principle.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c00732.

Experimental procedures; compound characterization data; NMR spectra; chiral high-performance liquid chromatography (HPLC) chromatograms; computed activation energy profile for isomerization between the enantiomers; and computed activation energy profile for **int4** N−C rotation (PDF)

4y_cif (PDF)

11a_cif (PDF)

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Notes

The authors declare no competing financial interest.

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