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Asymmetric Intramolecular Hydroamination to Construct Diverse N−N/C−N Indole Atropisomers via Cooperative Pd(0) and Chiral Phosphoric Acid Catalysis

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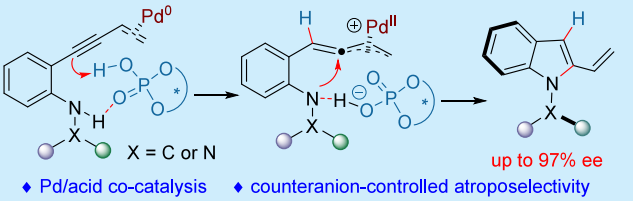
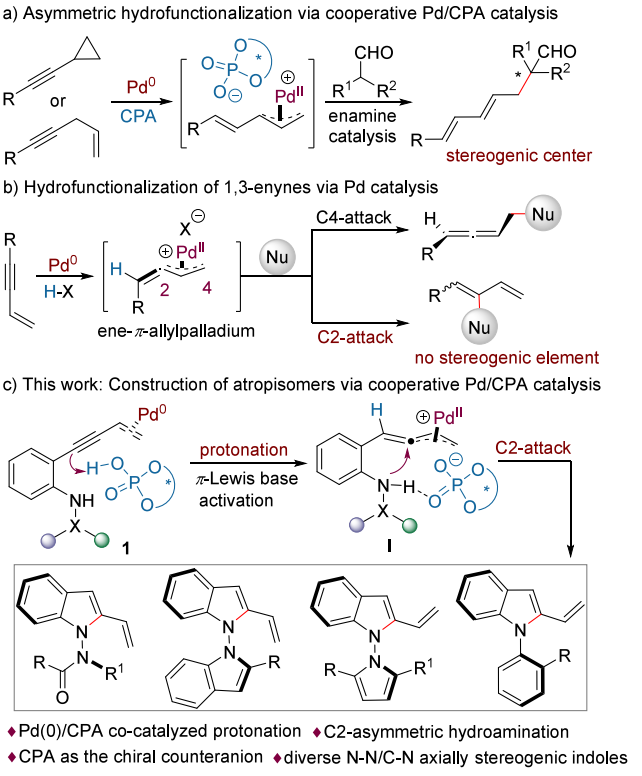
ABSTRACT: Here we present an enantioselective intramolecular hydroamination reaction of *o*-aminophenyl-1,3-enynes via cooperative catalysis of Pd(0) and chiral phosphoric acid. This approach enables the efficient construction of N−N/C−N axially stereogenic indoles with broad skeletal diversity and high levels of enantioselectivity in a completely atom-economic manner. Mechanistic studies indicate that a protonation of the alkyne moiety via Pd(0) π-Lewis base activation is favored, and the chiral phosphate counteranion plays a crucial role in controlling the atroposelectivity in the ring-closure step.



Scheme 1. Hydrofunctionalization Processes of Diverse Unsaturated Systems Involving Cooperative Pd/CPA Catalysis



The cooperative catalysis of transition metals and chiral phosphoric acids (CPAs) has emerged as a powerful strategy in asymmetric synthesis, enabling highly efficient and selective transformations that are difficult or unattainable with a single catalytic system.[1] In particular, a series of challenging asymmetric allylic alkylation reactions have been realized via cooperative Pd/CPA catalysis.[2] Enantioselective hydrofunctionalization of unsaturated hydrocarbons offers a more atom-economical alternative to allylic alkylation,[3] and its success in cooperative Pd/CPA catalysis has also been demonstrated. Gong and co-workers made significant progress in developing asymmetric hydrocarbonation reactions of cyclopropylacetylenes and skipped enynes with enolizable aldehydes, delivering 2,4-dienylation products with a quaternary stereogenic center with excellent enantioselectivity (Scheme 1a).[4] The chiral phosphate played a critical role as an anionic ligand for the π-allylpalladium intermediates, ensuring high enantiocontrol during the allylic alkylation step with in situ-formed enamine species.

On the other hand, the asymmetric hydrofunctionalization of 1,3-enynes represents another protocol to construct multifunctional products, with stereocontrol relying solely on the chiral ligands.[5] The in situ-formed ene-π-allylpalladium species, from either hydropalladation or protonation upon

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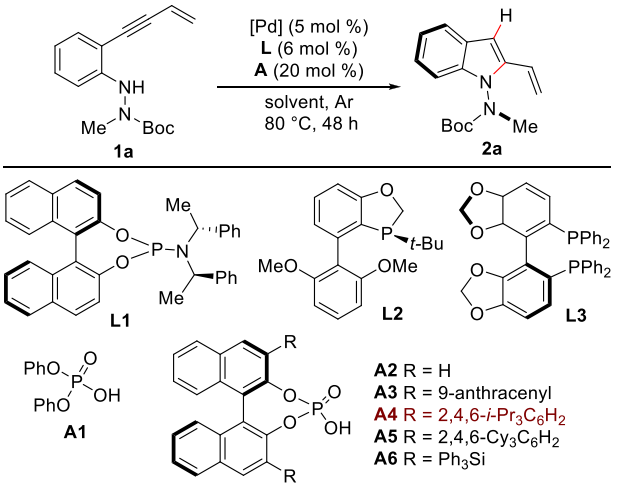
Table 1. Optimization of the Conditions for the Asymmetric Hydroamination of 1a[a]



entry	Pd	L	acid	solvent	yield (%)[b]	ee (%)[c]
1	Pd_2dba_3	PPh_3	**A1**	THF	63	–
2	Pd_2dba_3	**L1**	**A1**	THF	82	<5
3	Pd_2dba_3	**L2**	**A1**	THF	60	<5
4	Pd_2dba_3	**L3**	**A1**	THF	trace	–
5	Pd_2dba_3	PPh_3	**A2**	THF	85	<5
6	Pd_2dba_3	PPh_3	**A3**	THF	44	8
7	Pd_2dba_3	PPh_3	**A4**	THF	92	35
8	Pd_2dba_3	PPh_3	**A5**	THF	93	9
9	Pd_2dba_3	PPh_3	**A6**	THF	48	<5
10[d]	Pd_2dba_3	PPh_3	**A4**	*c*-hexane	95	43
11[e]	Pd_2dba_3	PPh_3	**A4**	*c*-hexane	95	80
12[f]	Pd_2dba_3	PPh_3	**A4**	*c*-hexane	90	80
13[e]	$Pd(PPh_3)_4$	–	**A4**	*c*-hexane	95	84
14[e,g]	$Pd(PPh_3)_4$	–	**A4**	*c*-hexane	95	87
15[e]	$Pd(PPh_3)_4$	–	–	*c*-hexane	nr[h]	–
16[e]	–	–	**A4**	*c*-hexane	nr[h]	–

[a]Unless noted otherwise, reactions were performed with **1a** (0.05 mmol), [Pd] (5 mol %), **L** (6 mol %), and acid **A** (20 mol %) in a solvent (0.5 mL) at 80 °C for 48 h under Ar. [b]Yield of the isolated product. [c]Determined by HPLC analysis on a chiral stationary phase. [d]For 12 h. [e]At 40 °C for 12 h. [f]At 25 °C for 48 h. [g]On a 0.1 mmol scale. [h]No reaction.

Pd(0) activation, can be generally attacked by nucleophiles at the C4 site, affording axially stereogenic allenes.[6] Alternatively, a C2-regioselective attack might occur to produce 1,3-diene products, but without stereogenic information (Scheme 1b).[7] As a result, introducing stereogenic elements via such a reaction pattern would be intriguing. We envisaged that anilines **1** with an *o*-enyne moiety would undergo a protonation process by a CPA via Pd(0) π-Lewis base activation.[8,9] The resultant ene-π-allylpalladium complexes **I** might then participate in an intramolecular C2-regioselective amination to complete the de novo indolization. Importantly, it was found that the counteranion of CPA was crucial for the atroposelectivity,[10] and a broad spectrum of N−N and C−N axially stereogenic indoles with a 2-vinyl functionality were constructed just by tuning the substituents on the aniline motif, representing a promising and straightforward protocol to access such valuable atropisomers.[11,12]

The initial attempt was carried out with *N*-methyl-*N*-Boc-hydrazin-1,3-enyne **1a** under the catalysis of Pd_2dba_3/Ph_3P and diphenyl phosphate **A1** in THF at 80 °C. To our delight, expected 2-vinyl indole **2a** was produced in a moderate yield (Table 1, entry 1). Subsequently, the asymmetric version was explored using different chiral ligands in combination with **A1**, but almost no enantioselectivity was induced with either phosphoramidite **L1** or phosphine **L2** (entry 2 or 3, respectively). In addition, (S_a)-Segphos **L3**, the optimal ligand in Pd(II)-catalyzed hydroamination to construct axially stereogenic indoles,[11a] did not work in the current system (entry 4). As the enantiocontrol was barely affected by chiral ligands,[13] we turned to investigate the effects of CPAs. Though (R_a)-BINOL-derived phosphoric acid **A2** provided racemic **2a** (entry 5), those with bulky substituents (**A3**−**6**) showed apparent enantiocontrol (entries 6−9, respectively), and **A4** was the optimal one (entry 7). Different solvents were tested, as well,[13] and significantly improved reactivity with comparable enantioselectivity was observed in *c*-hexane (entry 10). This likely results from enhanced ion pairing between Pd(II) and the phosphate anion, along with stronger H-bonding interactions between the hydrazine N−H and phosphate in the absence of competitive solvent interactions. Importantly, good enantioselectivity was achieved by conducting the reaction at 40 °C (entry 11). Nevertheless, the data could not be further improved at 25 °C due to poor solubility (entry 12). In addition, slightly improved data and efficacy were obtained with simple $Pd(PPh_3)_4$ (entry 13), and the reaction occurred efficiently on a 0.1 mmol scale (entry 14). In sharp contrast, no reaction occurred in the absence of acid or Pd (entry 15 or 16, respectively), indicating the cooperative Pd/acid catalysis is vital for the hydrofunctionalization.

Consequently, we explored the substrate scope and limitations of the asymmetric hydrofunctionalization of hydrazine-tethered enynes **1** for the construction of N−N indole−amide atropisomers. As summarized in Scheme 2, enynes **1** bearing an *N*-ethyl or allylic group (**2b**−**d**) were quite compatible, and excellent results were attained, even on a 1.0 mmol scale (**2b**).[14] In addition, enynes **1** with variously substituted phenyl groups generally worked well under the standard conditions, affording **2e**−**k** in high yields with excellent enantioselectivity. When the carbamate unit of **1** was changed to an amide, products **2l**−**n** were attained with a slightly lower enantioselectivity. Remarkably, enynes **1** embedded with a biologically important framework, such as indomethacin, isoxepac, naproxen,[15] L-menthol, and dehrocholic acid, were successfully applied to the asymmetric hydroamination reaction, showing good functional group tolerance, and moderate to excellent stereoselectivity was obtained (**2o**−**s**, respectively). Furthermore, products **2r′** and **2s′** were produced with comparable stereoselectivity by employing *ent*-**A4** as the acid.

Apart from indole−amide atropisomers, the *N*-heteroaryl indoles with an N−N axis were furnished via a similar hydroamination strategy (Scheme 3). When *N′*-2-methyl-indole-derived enynes **3** were used under the co-catalysis of Pd and **A4**, bisindoles **4a**−**i** were afforded in excellent yields with good enantioselectivity, even on a larger scale (for **4a**). Interestingly, moderate enantioselectivity was achieved for the indole even without 2-substitution (**4j**). Moreover, indole−pyrrole skeletons **4k**−**o** exhibited comparable data employing *N′*-2-methyl pyrroles **3**.[16]

This success inspired us to expand the current Pd/CPA cooperative catalytic system to enable the atroposelective synthesis of the architectures with a C−N axis. As summarized

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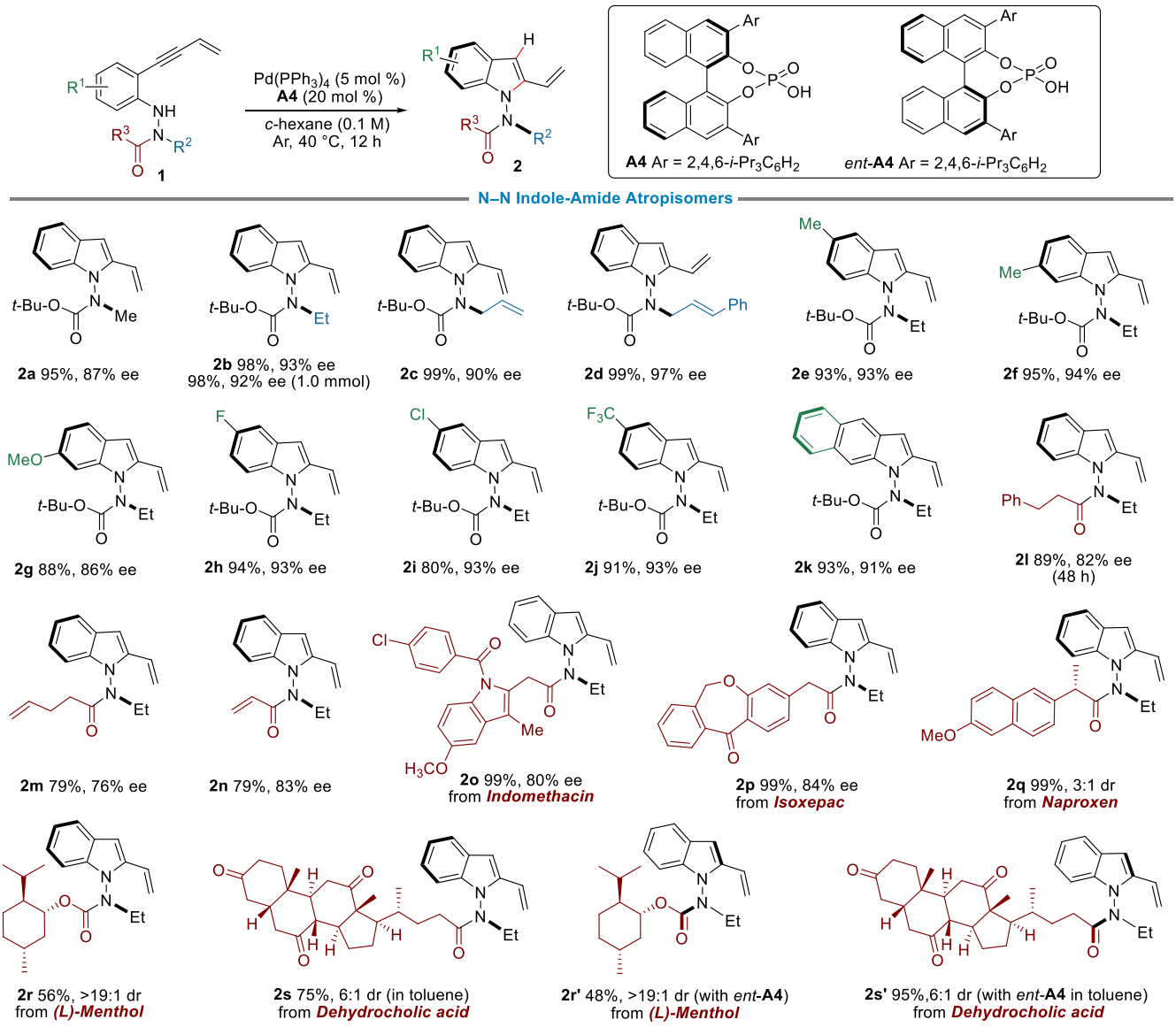
Scheme 2. Substrate Scope and Limitations of N–N Indole–Amide Atropisomers



in Scheme 4, an array of aniline-derived enynes **5**, featuring a 2-*tert*-butylphenyl group, smoothly underwent the hydroamination reaction, delivering products **6a–f** in excellent yields with high enantiocontrol. In addition, moderate enantioselectivity was obtained for the anilines with a less bulky substituent (**6g**).[17]

It is notable that the indole atropisomers exhibit remarkable configurational stability.[13] Importantly, these frameworks possess a vinyl group, enabling diverse synthetic elaborations. As outlined in Scheme 5, the olefin metathesis reaction of **2b** provided the corresponding internal alkenes (**7a** and **7b**) in moderate yields with a little loss of ee.[18] Additionally, **2b** underwent a Diels–Alder reaction with diethyl but-2-ynedioate catalyzed by acid **A1**, giving atroposelective dihydrocarbazole **8** with a slightly reduced enantioselectivity. Interestingly, an intramolecular olefin metathesis reaction of **2o** was successful, and atroposelective product **9** with an eight-membered ring was produced in a fair yield. Furthermore, the vinyl group of **6a** could be chemoselectively converted into an aldehyde group (product **10**), albeit in a fair yield.[11d]

In summary, we uncovered an efficient intramolecular hydroamination reaction of *o*-amino-functionalized phenyl-1,3-enynes under the cooperative catalysis of Pd(0) and chiral phosphoric acid, furnishing a broad spectrum of N–N and C–N axially stereogenic indoles with fair to excellent enantioselectivity. Mechanistic studies revealed that a protonation process at the alkyne group of 1,3-enynes via the vinylogous activation of Pd(0) as the π-Lewis base catalyst was favorable. In addition, the chiral phosphate anion induced high enantioselectivity through multiple noncovalent interactions in the C2-regioselective allylic amination of resultant ene-π-allylpalladium intermediates.[19] This work demonstrates that π-Lewis base catalysis provides a promising platform for expanding hydrofunctionalization reactions from polyunsaturated substrates. In particular, the cooperative catalysis of Pd(0) and chiral Brønsted acids represents an effective approach to such asymmetric transformations, enabling reactions that are inaccessible with conventional chiral ligands.

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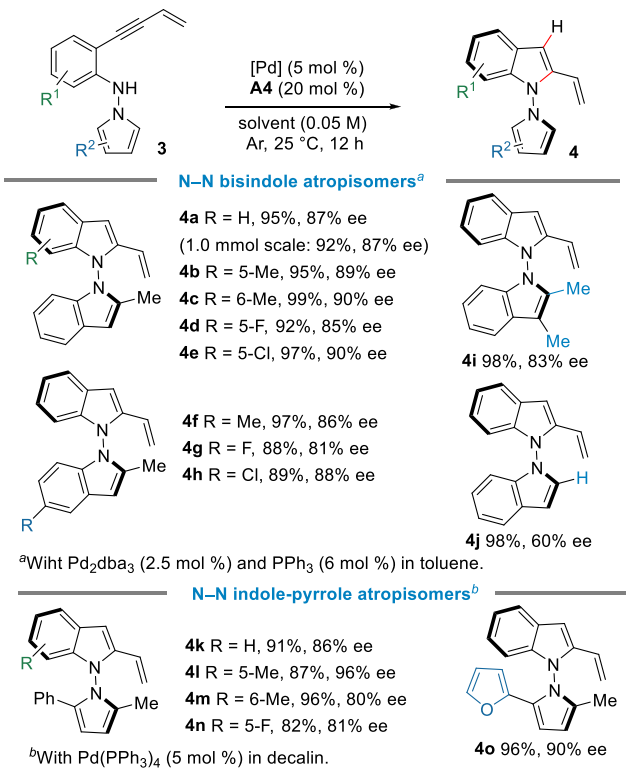
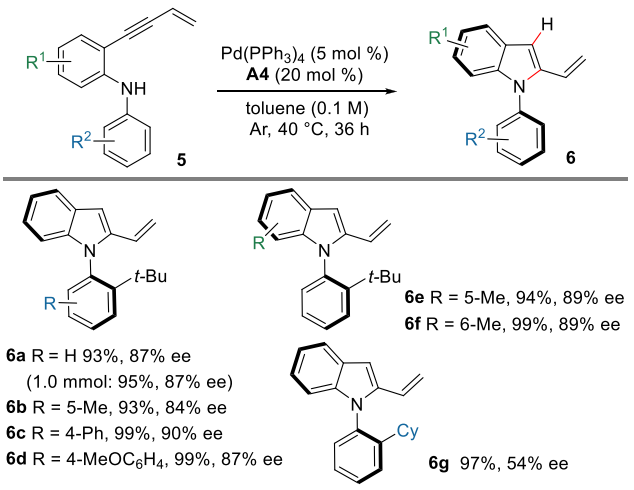
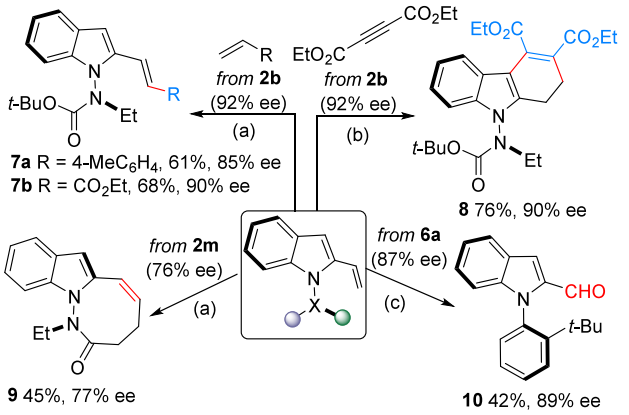
Scheme 3. Construction of N–N Indole–Heteroaryl Atropisomers



Scheme 4. Construction of C–N Indole–Aryl Atropisomers



Scheme 5. Synthetic Transformations of Products



■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c00662.

Complete experimental procedures and characterization of new products, synthetic transformations of products, DFT calculations, NMR and HRMS spectra, and HPLC chromatograms (PDF)

Accession Codes

Deposition Number 2403708 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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(13) For more details, see the Supporting Information.

(14) The absolute configuration of (S_a)-**2d** was assigned based on analysis of experimental and calculated electronic circular dichroism

(ECD) spectra (see the Supporting Information). The other products were assigned by analogy.
(15) Using *ent*-**A4** resulted in significantly reduced reactivity due to the mismatched stereogenic effect.
(16) The absolute configuration of **4j** was determined as S_a by conversion to a known chiral compound (see the Supporting Information). The other products were assigned by analogy.
(17) The absolute configuration of **6a** was determined by X-ray analysis after conversion to product **10**. The other products were assigned by analogy.
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(19) Comprehensive control experiments and density functional calculations to elucidate the reaction mechanism and enantioselectivity were conducted (see the Supporting Information).

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