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Asymmetric Catalysis

Palladium-Catalyzed Enantioselective Heteroarenyne Cycloisomerization Reaction

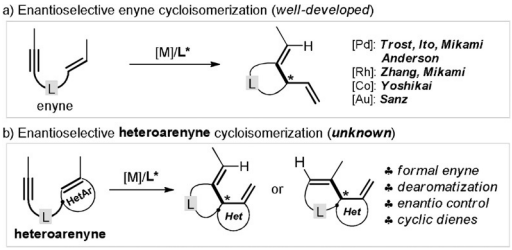
*Ren-Xiao Liang, Ling-Jie Song, Jin-Bo Lu, Wei-Yan Xu, Chao Ding, and Yi-Xia Jia**

Dedicated to Professor Peter Kündig on the occasion of his 75th birthday

Abstract: *The extensively developed ene-type enantioselective cycloisomerization of classical 1,n-enynes provides an efficient approach to chiral cyclic 1,4-dienes. In contrast, the catalytic asymmetric heteroarenyne (heteroarene–alkyne) cycloisomerization involving the dearomative transformation of endocyclic aromatic C=C bonds remains unknown. Herein, we communicate a PdH-catalyzed enantioselective heteroarenyne cycloisomerization reaction of alkyne-tethered indole substrates (formal 1,5- and 1,6-enynes). Based on this strategy, a variety of structurally diverse chiral spiro and fused indoline derivatives bearing quaternary stereocenters and exocyclic C=C bonds are afforded in moderate to excellent yields and excellent enantioselectivities (up to 98 % ee). The classical ene-type enantioselective 1,5-enyne cycloisomerization of N-vinyl-propiolamides is also developed to afford chiral 2-pyrrolones in good to excellent ee values.*

Introduction

Ene-type cycloisomerization of 1,*n*-enynes represents a synthetically appealing approach for the synthesis of cyclic 1,4-diene molecules in a high atom-economy fashion.[1] Since Trost's seminal report of 1,6-enyne cycloisomerization,[2] transition-metal-catalyzed enyne cycloisomerization reaction has been extensively developed. Enantioselective versions are also well-established by using the complexes of palladium,[3] rhodium,[4] cobalt,[5] and gold[6] as chiral catalysts, rendering the conversion of 1,*n*-enynes to optically active five- or six-membered carbo- and hetero- cyclic compounds straightforward and efficient (Scheme 1 a).[7] As a sharp comparison, enantioselective heteroarenyne cycloisomerization, the reaction of heteroarene-alkyne substrates, involving dearomative transformation of endocyclic aromatic C=C bond via a migratory insertion/β-H elimination sequence under the PdH catalysis, is very challenging and remains unknown (Scheme 1 b).[8] Exploration of new catalytic asymmetric ene-type cycloisomerization reaction is highly desirable towards the construction of ring molecules with structural complexity.



Scheme 1. Ene-type enantioselective enyne and heteroarenyne cycloisomerization.

Recently, asymmetric dearomatization reaction based on dearomative migratory insertion strategy has received considerable attention.[9,10] By employing endocyclic aromatic C=C bonds as coupling partners, enantioselective or racemic Heck reactions,[11] reductive Heck reactions,[12] and domino Heck/alkyl-metal termination sequences[13] have been extensively studied. Relying on these transformations, a range of structurally unique hetero- or carbocyclic molecules as well as natural products have been efficiently synthesized.[11a,14] We envisioned that a PdH-catalyzed enantioselective heteroarenyne cycloisomerization reaction might be possible through intermolecular alkyne hydropalladation[15] and subsequent intramolecular dearomative Heck vinylation.[11] Herein, we communicate our primary results of catalytic enantioselective cycloisomerization of alkyne-tethered indoles. As shown in Scheme 2 a, PdH-catalyzed cycloisomerization of C2-alkyne-tethered indole, a formal 1,6-enyne substrate, in the presence of chiral phosphoramidite ligand and Ph_3CCO_2H afforded spirocyclic indolines in 80–98 % *ee*. Note that chiral spiroheterocycle could also be afforded by classical 1,7-enyne cycloisomerization.[3e,f] Further, heteroarenyne cycloisomerization of *N*-alkyne-tethered indole, a formal 1,5-enyne substrate, proceeds smoothly through a possible *E*-to-*Z* isomerization of vinyl-Pd species (Scheme 2 b).[16] In this case, polycyclic indolines bearing tetrasubstituted stereocenters are afforded in excellent enantioselectivities (up to 98 % *ee*) with (*S*)-^{t}Bu-PHOX as the chiral ligand and $NEt_3{\cdot}HOTf$ as the hydride donor. The resulting fused indolines constitute the core structures of a number of natural products (Scheme 2 c).[17] Asymmetric ene-type cycloisomerization of classical 1,5-enyne substrates is also developed to deliver chiral 2-pyrrolones in good to excellent enantioselectivities.

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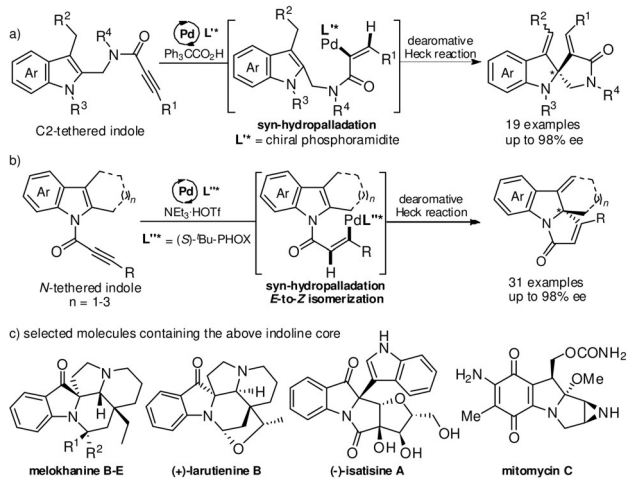


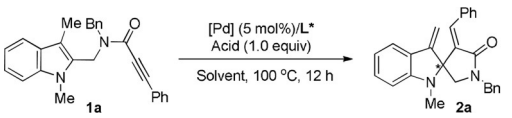
Scheme 2. PdH-catalyzed enantioselective heteroarenyne cycloisomerization and selected natural products containing the indoline core.

Results and Discussion

At the outset, we chose *N*-(indol-2-yl)methyl-propiolamide **1a** as model substrate to study the heteroarenyne cycloisomerization reaction. As shown in Table 1, initial tests using $Pd(OAc)_2$ as the catalyst failed to afford the desired spiro-product **2a** with bidentate ligands **L1**–**L3** and hydride source HCO_2H (entries 1–3). Nevertheless, **2a** was observed in 72% *ee* with a poor yield in the presence of chiral phosphoramidite ligand **L4** (entry 4). Other acids were then examined. CH_3CO_2H, PivOH, and $PhCO_2H$ could improve the yield, while the enantioselectivity was decreased (entries 5 and 7,8). No reaction occurred in the presence of TsOH (entry 6). To our delight, product **2a** was obtained in 46% yield and 73% *ee* when Ph_3CCO_2H was used (entry 9). Changing the catalyst to $Pd(dba)_2$ remarkably improved the yield to 80% and the *ee* to 87% (entry 10). Solvent testing showed 1,4-dioxane was the best choice, although comparable *ee* values were achieved in THF and toluene (entries 11–13). Further optimization focused on chiral phosphoramidite ligands by varying the amino moieties. Slightly lower yield and *ee* were observed for the ^{i}Pr ligand **L7**, while enhanced *ee* was achieved for the morpholino ligand **L8** (entries 14 and 15). Inferior results were obtained for the MonoPhos-PE ligands **L10** and **L11** (entries 16 and 17). Gratifyingly, ligands **L5** and **L9** bearing 3,3′-methyl groups improved the *ee* to 96% along with 85% and 78% yield, respectively (entries 18 and 20). As a comparison, poor yield and moderate *ee* were afforded for the 3,3′-diphenyl ligand **L6** (entry 19).

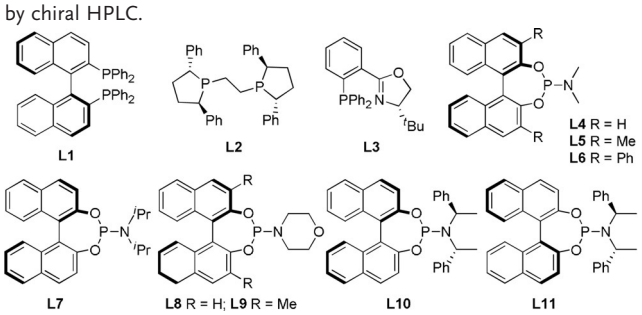
Having the optimal conditions in hand, we next evaluated the scope of this heteroarenyne cycloisomerization reaction. A number of *N*-(indol-2-yl)methylpropiolamides **1** were treated to the reactions and the results were summarized in Scheme 3. Both electron-donating and electron-withdrawing substituents at the para-position of benzene ring attached to alkyne were well-tolerated to afford spiro-indolines **2b**–**2h** in moderate to excellent yields (60–90%) and excellent enantiomeric excesses (90–96%). Product **2i** derived from 3-methyl-substrate **1i** was obtained in 74% yield and 90% *ee*.

Table 1: Optimization of conditions for the reaction of C2-tethered indole **1a**.[a]

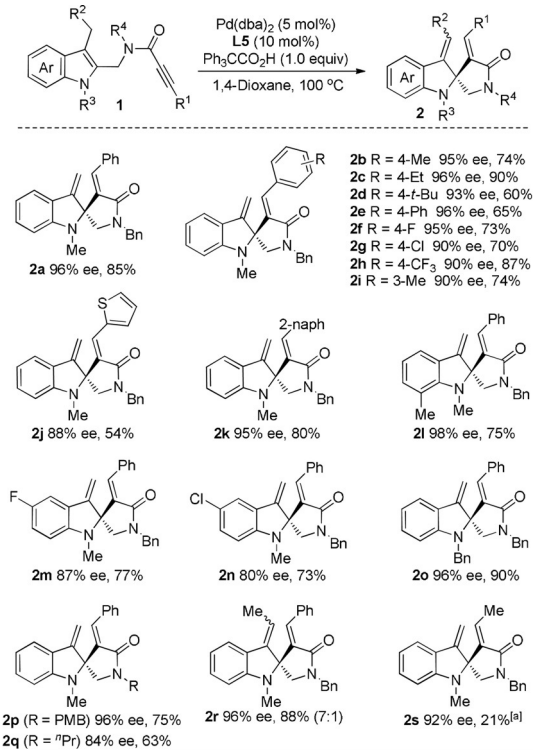


No.	[Pd]	L*	Acid	Solvent	Yield [%][b]	*ee* [%][c]
1	$Pd(OAc)_2$	**L1**	HCO_2H	1,4-dioxane	nd	–
2	$Pd(OAc)_2$	**L2**	HCO_2H	1,4-dioxane	nd	–
3	$Pd(OAc)_2$	**L3**	HCO_2H	1,4-dioxane	nd	–
4	$Pd(OAc)_2$	**L4**	HCO_2H	1,4-dioxane	<10	72
5	$Pd(OAc)_2$	**L4**	CH_3CO_2H	1,4-dioxane	19	63
6	$Pd(OAc)_2$	**L4**	$TsOH·H_2O$	1,4-dioxane	nr	–
7	$Pd(OAc)_2$	**L4**	PivOH	1,4-dioxane	31	60
8	$Pd(OAc)_2$	**L4**	$PhCO_2H$	1,4-dioxane	43	60
9	$Pd(OAc)_2$	**L4**	Ph_3CCO_2H	1,4-dioxane	46	73
10	$Pd(dba)_2$	**L4**	Ph_3CCO_2H	1,4-dioxane	80	87
11	$Pd(dba)_2$	**L4**	Ph_3CCO_2H	THF	65	85
12	$Pd(dba)_2$	**L4**	Ph_3CCO_2H	toluene	70	84
13	$Pd(dba)_2$	**L4**	Ph_3CCO_2H	DCE	41	72
14	$Pd(dba)_2$	**L7**	Ph_3CCO_2H	1,4-dioxane	74	84
15	$Pd(dba)_2$	**L8**	Ph_3CCO_2H	1,4-dioxane	75	90
16	$Pd(dba)_2$	**L10**	Ph_3CCO_2H	1,4-dioxane	21	35
17	$Pd(dba)_2$	**L11**	Ph_3CCO_2H	1,4-dioxane	12	16
18	$Pd(dba)_2$	**L5**	Ph_3CCO_2H	1,4-dioxane	85	96
19	$Pd(dba)_2$	**L6**	Ph_3CCO_2H	1,4-dioxane	19	71
20	$Pd(dba)_2$	**L9**	Ph_3CCO_2H	1,4-dioxane	78	96

[a] Reaction conditions: **1a** (0.2 mmol), [Pd] (5 mol%), **L*** (**L1**–**L3**, 5 mol%; **L4**–**L11**, 10 mol%), and acid (1.0 equiv) in 2.0 mL solvent at 100°C for 12 h. [b] Isolated yields; nd = not determined. [c] Determined by chiral HPLC.



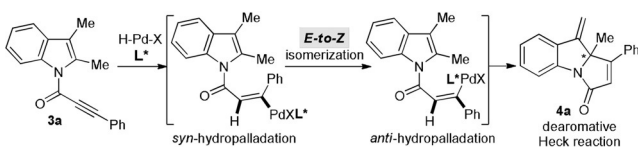
Other aryl groups linked to alkyne were also examined. Product **2k** having a 2-naphthyl group was obtained in 80% yield and 95% *ee*. 2-Thiophenyl group was also compatible in the reaction, furnishing product **2j** in 88% *ee* with a relatively lower yield. The influence of substituent on the indole ring was then investigated. Relatively lower enantioselectivities were achieved for the reactions of 5-F- and 5-Cl-substrates, although the yields of products **2m** and **2n** remained moderate. In addition, the reactions of 7-methyl and *N*-benzyl substrates led to **2l** and **2o** in excellent enantioselectivities and excellent yield for the latter. Other *N*-protecting groups of propiolamides were also examined. Products **2p** and **2q** having PMB and n-propyl groups were obtained in 96% *ee* and 84% *ee*, respectively. Moreover, the reaction of 3-ethyl-indole derived substrate led to the desired product **2r** in 88% yield as 7:1 isomeric mixture with 96% *ee* for the major. The reaction of substrate bearing a methyl on alkyne resulted in product **2s** with a lower yield of 21% and 92% *ee* in the presence of $PhCO_2H$ as additive.



Scheme 3. Substrate scope of **1**. [a] With $PhCO_2H$ instead of Ph_3CCO_2H.

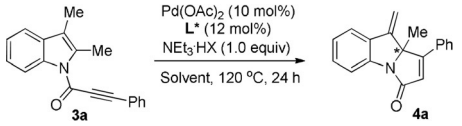
Encouraged by the above success, we further considered to develop heteroarenyne cycloisomerization of *N*-alkyne-tethered indoline **3a**, which could be regarded as formal 1,5-enyne substrate. Probably due to the unfavourable conformation of the vinyl-Pd species arising from alkyne *syn*-hydropalladation, the palladium-catalyzed ene-type 1,5-enyne cycloisomerization remains very rare. Recently, Lautens and co-workers have revealed that isomerization of (*E*)-vinyl-Pd species to its *Z*-conformation constituted a key step for hydrohalogenation of 1,6-enynes or cycloisomerization of 1,6-diynes.[16] Inspired by this result, we decided to investigate the enantioselective heteroarenyne cycloisomerization reaction of indole **3a**. As proposed in Scheme 4, the initial alkyne s*yn*-hydropalladation of **3a** would lead to (*E*)-vinyl-Pd intermediate. Subsequent *E*-to-*Z* isomerization followed by an intramolecular Heck vinylation affords polycyclic diene-product **4a**.

The optimal condition for the reaction of **1a** was found inapplicable to the transformation of **3a**→**4a**. Therefore, systematic condition optimization for the reaction of **3a** was conducted. As shown in Table 2, we first investigated the



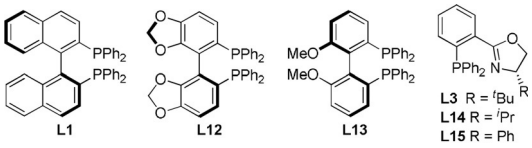
Scheme 4. Proposed pathway for heteroarenyne cycloisomerization of **3a**.

Table 2: Optimization of conditions for the reaction of *N*-tethered indole **3a**.[a]



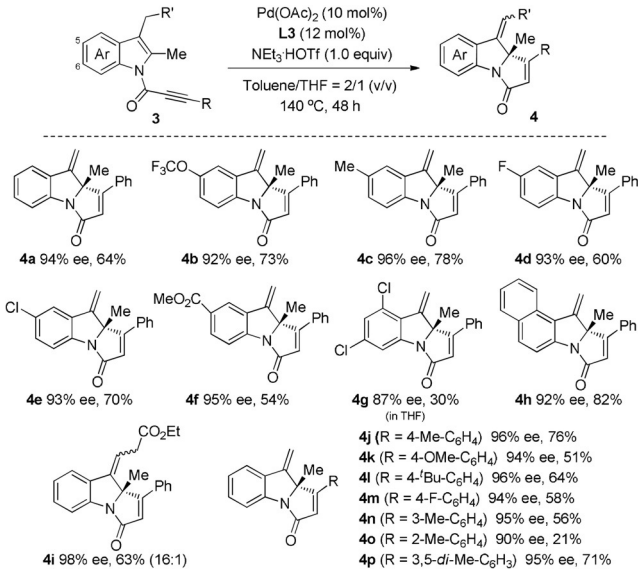
No.	L*	NEt_3·HX	Solvent	Yield [%][b]	*ee* [%][c]
1	**L1**	NEt_3·HCl	toluene	trace	–
2	**L1**	NEt_3·HBr	toluene	17	rac
3	**L1**	NEt_3·HI	toluene	28	rac
4	**L1**	NEt_3·HOTf	toluene	42	45
5	**L12**	NEt_3·HOTf	toluene	34	65
6	**L13**	NEt_3·HOTf	toluene	31	52
7	**L3**	NEt_3·HOTf	toluene	39	98
8	**L14**	NEt_3·HOTf	toluene	18	95
9	**L15**	NEt_3·HOTf	toluene	22	74
10[d]	**L3**	NEt_3·HOTf	toluene	17	95
11	**L3**	NEt_3·HOTf	1,4-dioxane	31	76
12	**L3**	NEt_3·HOTf	DMF	29	94
13	**L3**	NEt_3·HOTf	THF	26	90
14[e]	**L3**	NEt_3·HOTf	toluene/THF	48	96
15[e,f]	**L3**	NEt_3·HOTf	toluene/THF	64	94

[a] Reaction conditions: **3a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), **L*** (12 mol%), and NEt_3·HX (1.0 equiv) in 2.0 mL solvent at 120 °C for 24 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] 5 mol% $Pd_2(dba)_3$·$CHCl_3$ was used. [e] Toluene/THF = 2/1 (v/v), 3 mL. [f] At 140 °C for 48 h.

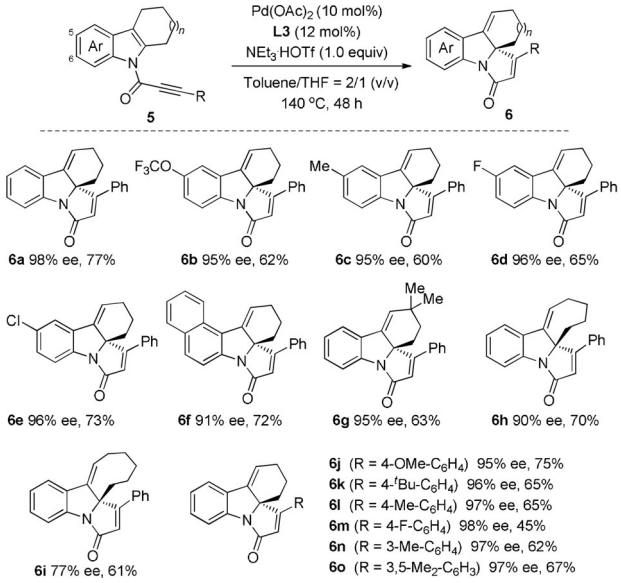


effect of ammonium salt NEt_3·HX,[16] which would react with Pd^0 to generate PdH species (entries 1–4). In the presence of NEt_3·HBr or NEt_3·HI, the reaction in toluene at 120 °C employing $Pd(OAc)_2$/(*S*)-BINAP as a catalyst delivered the desired product **4a** in 17% and 28% yield, respectively, while no any enantioselectivity was observed (entries 2 and 3). In the case of NEt_3·HCl, only trace amount of **4a** was detected (entry 1). To our delight, the use of NEt_3·HOTf afforded **4a** in 42% yield with 45% *ee* (entry 4). In order to improve the yield and *ee*, other chiral bidentate ligands were examined. Diphosphine ligands (*S*)-SEGPHOS **L12** and (*S*)-MeO-BIPHEP **L13** led to higher enantioselectivities (entries 5 and 6). Chiral PHOX ligands **L3**, **L14**, and **L15** resulted in moderate to excellent enantioselectivities, among which (*S*)-^{t}Bu-PHOX **L3** afforded **4a** in 98% *ee* with a moderate yield of 39% (entries 7–9). Catalyst precursor and solvent were further investigated. $Pd_2(dba)_3$ led to a decreased yield (entry 10). Other solvents, such as 1,4-dioxane, DMF, and THF, failed to improve the yield and *ee* (entries 11–13), while the mixed solvent of toluene/THF improved the yield to 48% with a slightly lower *ee* of 96% (entry 14). The yield was further improved to 64% with 94% *ee* by elevating the temperature to 140 °C and prolonging reaction time to 48 h (entry 15).

We subsequently investigated the scope of *N*-propynoyl-2,3-disubstituted indoles **3** (Scheme 5). Substituent effect on the indole ring was first examined. Either electron-donating



Scheme 5. Substrate scope of **3**.



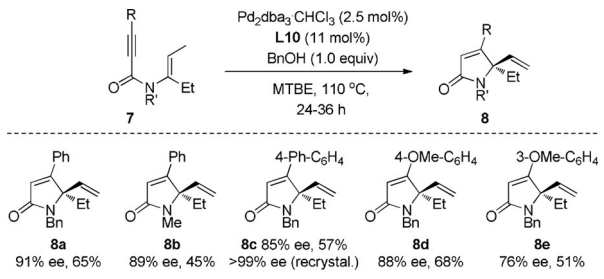
Scheme 6. Substrate scope of **5**.

(-Me) or electron-withdrawing groups (-OCF_3, -F, -Cl, and -CO_2Me) at C5 of indole ring led to the desired products **4b**–**4f** bearing exocyclic C=C double bonds in excellent enantioselectivities (92–96%) and with moderate yields. Due to lower solubility of 4,6-dichloro-substrate **3g** in toluene/THF solvent, only trace amount of product **4g** was obtained under the optimal conditions. Changing the solvent to THF led to **4g** in 30% yield and 87% *ee*. 4,5-Benzoindole was also a suitable substrate and the reaction furnished **4h** in 82% yield and 92% *ee*. Moreover, the reaction of 3-ethoxycarbonylethyl indole achieved product **4i** as a 16:1 isomeric mixture with 63% yield and 98% *ee* for the major isomer. A number of substituents bearing on the benzene ring of propiolamide moiety were then examined. Methyl (**4j**), methoxyl (**4k**), *tert*-butyl (**4l**), and fluoride (**4m**) at the *para*-position as well as methyl (**4n**) and dimethyl (**4p**) at the *meta*-position were well tolerated, affording the corresponding products in 51–76% yields and 94–96% *ee* values. Steric effect was observed in the reaction of *ortho*-methyl substrate **3o**; product **4o** was obtained in 21% yield while with an excellent *ee* of 90%.

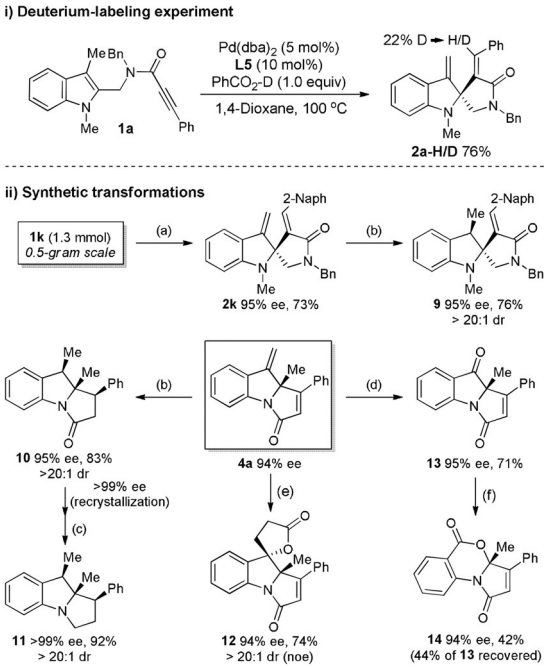
As shown in Scheme 6, the substrate scope was further extended to 2,3-fused indole substrates **5**. The reactions of tetrahydrocarbolines bearing CF_3O-, Me-, and halides at C5 of indole ring afforded tetracyclic indolines **6a**–**6e** in moderate yields (60–77%) and excellent enantioselectivities (95–98%). Product **6f** was achieved in 72% yield and 91% *ee* from the reaction of 4,5-benzoindole substrate **5f**. In addition, a *gem*-dimethyl substituted tetrahydrocarboline afforded **6g** in 63% yield and 95% *ee*. Moreover, products **6j**–**6o** bearing *meta*- or *para*-substituents on the benzene ring linked to propiolamide moiety were obtained in excellent *ee* values (95–98%) with moderate yields. Other than tetrahydrocarboline substrates, indoles bearing 2,3-fused seven- and eight-membered carborings were also investigated. It was found that the product *ee* was decreased with the increase of ring size. Seven- and eight-membered products **6h** and **6i** were afforded in 90% and 77% *ee*, respectively.

Encouraged by the success in the transformation of **3**→**4**, we then tested the asymmetric cycloisomerization of *N*-vinylpropiolamides **7**, the classic 1,5-enyne substrates. Gratifyingly, the reactions proceeded smoothly to afford the desired chiral 2-pyrrolones **8** in good to excellent enantioselectivities and moderate yields in the presence of $Pd_2dba_3{\cdot}CHCl_3$ catalyst and **L10** ligand with BnOH as an additive (Scheme 7). The absolute configuration of product **8c** was determined to be *R* by X-ray analysis of its single crystal (Deposition Number 2039287 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.).

To confirm the hydride source of PdH species, the reaction of **1a** was conducted with 1.0 equiv $PhCO_2D$ as additive. Product **2a** with 22% D incorporation was isolated in 76% yield, which implied that the hydride might be from the acid additive (Scheme 8i). Synthetic transformations of products **2k** and **4a** were then conducted to demonstrate the practical utilities of the enantioselective heteroarenyne cycloisomerization reaction. As presented in Scheme 8, a 0.5-gram scale reaction of **1k** was conducted to furnish product **2k** in



Scheme 7. Enantioselective 1,5-enyne cycloisomerization of *N*-vinylpropiolamide **7**.



Scheme 8. Control experiment and synthetic transformations. a) **1k** (1.3 mmol), $Pd(dba)_2$ (5 mol%), **L5** (10 mol%), and Ph_3CCO_2H (1.0 equiv) in 1,4-dioxane at 100 °C for 12 h. b) **2k** or **4a** (0.15 mmol) and Pd/C (10 mol%) in MeOH under H_2 balloon at room temperature for 12 h. c) **10** (0.15 mmol) and $LiAlH_4$ (3.0 equiv) in THF at reflux for 12 h. d) step 1: **4a** (0.5 mmol) under O_3 atmosphere in DCM/MeOH (1/1 v/v) at −78 °C for 10 min; step 2: PPh_3 (4.0 equiv) for 3 h at room temperature. e) **4a** (0.15 mmol) and $Mn(OAc)_3{\cdot}2H_2O$ (3.0 equiv) in Ac_2O (0.3 mL)/AcOH (1.0 mL) at 120 °C for 40 min. f) **13** (0.15 mmol) and *m*-CPBA (10.0 equiv) in DCM at room temperature for 24 h.

73% yield with 95% *ee*. Pd/C-catalyzed hydrogenation of **2k** under H_2 balloon resulted in compound **9** containing vicinal tertiary and quaternary stereocenters in 76% yield, 95% *ee*, and >20:1 dr value. The electron-deficient exocyclic C=C bond remained inert in this hydrogenation reaction at room temperature. The absolute configuration of compound **9** was determined to be (2*S*,3*R*) based on its X-ray crystallographic analysis (Deposition Number 2025742 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.), which revealed the *S* configuration of product **2k**. In contrast, both of the two C=C bonds in product **4a** were reduced under the same conditions, affording compound **10** in 83% yield, 95% *ee*, and >20:1 dr. Ee value of **10** was further improved to over 99% by simple recrystallization. Further reduction of amide moiety of **10** (>99% *ee*) using $LiAlH_4$ in reflux THF delivered compound **11** in 92% yield and with >99% *ee*. In addition, a $Mn(OAc)_3$-mediated [3+2] cycloaddition of **4a** with acetic acid was developed to furnish spiro-product **12** in 74% yield and 94% *ee*. On the other hand, oxidation of **4a** under O_3 atmosphere afforded ketone **13** in 71% yield and 95% *ee*. Moreover, ketone **13** was converted to lactone **14** in 94% *ee* and 42% yield along with 44% of starting material recovered through a Baeyer–Villiger oxidation reaction. The absolute configuration of compound **10** was determined to be (1*R*,9*R*,9*aR*) by X-ray crystallographic analysis (Deposition Number 1974781 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.), which implied the *R* configuration of product **4a**.

Conclusion

In summary, we have developed a PdH-catalyzed enantioselective heteroarenyne cycloisomerization reaction by employing alkyne-tethered indoles as substrates. A variety of spiro- or fused- indolines bearing quaternary stereocenters were afforded in moderate to excellent yields and excellent enantioselectivities (up to 98% *ee*). Monodentate phosphoramidite **L5** turned out to be an optimal ligand for the reaction of C2-alkyne-tethered indoles, while bidentate (*S*)-^{t}Bu-PHOX was the best ligand in the reaction of *N*-alkyne-tethered indoles. In addition, classical enantioselective cycloisomerization of 1,5-enynes was achieved in the presence of chiral monodentate phosphoramidite **L10**. Synthetic transformations of the products were conducted to deliver structurally diverse heterocycles with no erosion of *ee* values.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · cycloisomerization · dearomatization · heteroarenynes · palladium

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