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Gold-Catalyzed Asymmetric Intramolecular Cyclization of N-Allenamides for the Synthesis of Chiral Tetrahydrocarbolines

Yidong Wang†, Peichao Zhang†, Xiaoyu Di, Qiang Dai, Zhan-Ming Zhang and Junliang Zhang*

Abstract: *The highly enantioselective gold-catalyzed intramolecular cyclization of N-allenamides was implemented utilizing a designed chiral sulfinamide phosphine ligand (**PC-Phos**), which, of note, represents the first example of highly enantioselective intramolecular cyclization of N-allenamides. The practicality of this reaction was validated in the total synthesis of (R)-Desbromoarborescidine A and formal synthesis of (R)-Desbromoarborescidine C and (R)-Deplancheine. Moreover, the catalyst system **PC-Phos**/AuNTf$_2$ proved to be specifically efficient to promote the desymmetrization of N-allenamides in excellent yields with satisfactory ees.*

Gold-catalyzed intramolecular cyclization of functionalized allenes are one of the most powerful and straightforward synthetic tool for the atom-economical construction of cyclic skeletons in modern organic chemistry.[1,2] As opposed to the well-documented cyclization reactions with a highly nucleophilic functionality such as nitrogen, oxygen, or active methylene, cyclization through functionalization of an aromatic C-H bond has scarcely been explored.[3] *N*-allenamides, the unique allenic scaffold readily from available from amide and propargyl bromide,[4] have emerged as versatile building blocks in a variety of transformations, including [m+2] cycloadditions/annulations with suitable synthons.[5] Despite considerable success in gold(I)-catalyzed intermolecular cycloaddtion reaction of *N*-allenamides has been made, intramolecular process is significantly less developed.[6] Notably, no example of asymmetric intramolecular cyclization of *N*-allenamides catalyzed by gold has been reported to date. The lack of method for intramolecular cyclization of *N*-allenamides, especially in asymmetric version, reflects wider difficulties of this proposition: e.g., reaction manifold, substrate scope, as well as regio- and stereocontrol.

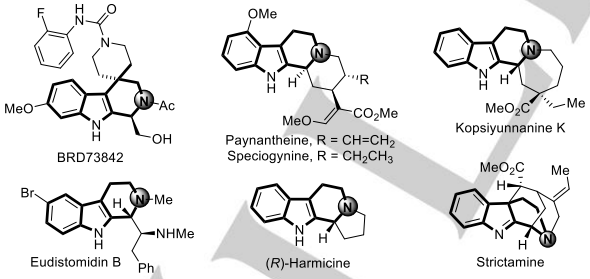

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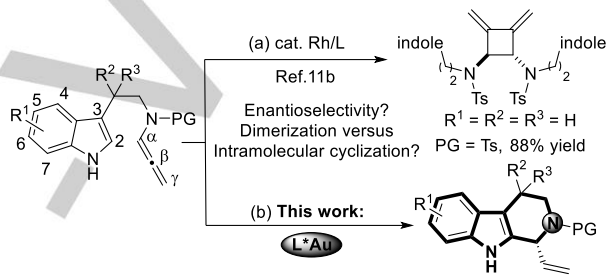
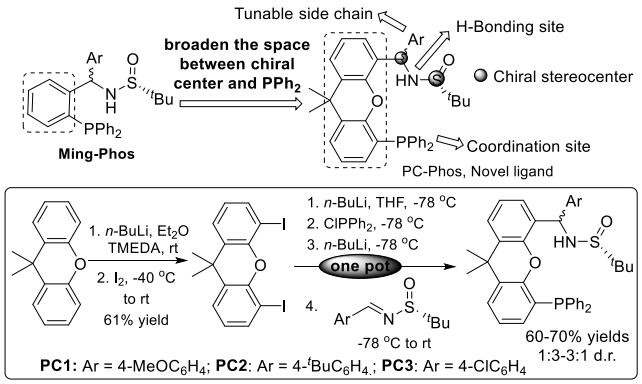
Figure 1. Biologically active alkaloids containing THCs.

Substituted tetrahydro-1H-β-carbolines (THCs) are core motifs in ubiquitous biologically active alkaloids (Figure 1),[7] and building blocks for rapid synthesis of multiple scaffolds.[8] Consequently, the synthesis of enantiomerically pure substituted THCs are in great demand.[9,10] In this context, the enantioselective Pictet-Spengler reaction has been deemed to one of the most efficient approach,[10] apart from the enantioselective hydrogenation of cyclic imines.[9c,9d] What's more, asymmetric intramolecular alkylation of indoles provides another straightforward route to enantioenriched THCs. [9a]



Scheme 1. Previous and this work.

During our continuous efforts in developing asymmetric gold-catalyzed reactions of *N*-allenamides, [5f,5g] we became intrigued by the possibility of asymmetric cyclization of *N*-allenamides attached with indoles (Scheme 1b). If it succeeds, the enantioselective synthesis of THCs will be achieved. However, this designed tactic may pose considerable challenges: (a) chemoselective intramolecular cyclization *vs* intermolecular dimerization.[11] In 2016, Kang and co-workers demonstrated that this type of N-allenamides would undergo an intermolecular head-to-head [2+2] dimerization between two molecular of allenamide in a highly regio- and stereo-selective manner under the Rh-catalysis (Scheme 1a);[11b] (b) regioselective cyclization at C2 vs C3 positions of indole[12] and α vs γ positions of *N*-allenamide[4]; (c) asymmetric gold catalysis is highly challenging due to its linear binding mode render the chiral ligand is far away to the reactive site.[13] Herein, we wish to report an asymmetric gold-catalyzed intramolecular cyclization of *N*-allenamides, which provides a facile access to enantioenriched fused THC derivatives in excellent yields with high *ees*.



Scheme 2. Concise synthetic approach to PC-Phoses.

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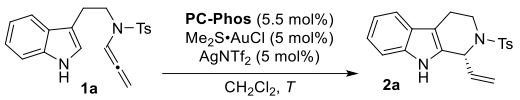
Table 1. Investigation of chiral ligands.[a]



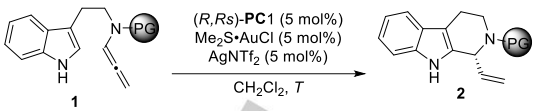
Entry	PC-Phoses	*T* (°C)	*t* (h)	*Ee* (%)[b]
1	(*S,Rs*)-**PC1**	25	1	48
2	(*R,Rs*)-**PC1**	25	1	63 (70)[c]
3	(*S,Rs*)-**PC2**	25	1	55
4	(*R,Rs*)-**PC2**	25	1	59
5	(*S,Rs*)-**PC3**	25	1	34
6	(*R,Rs*)-**PC3**	25	1	52
7	(*R,Rs*)-**PC1**	-20	5	79 [c]
8	(*R,Rs*)-**PC1**	-40	17	82 [c]
9[d]	(*R,Rs*)-**PC1**	-40	17	82 [c]
10[e]	(*R,Rs*)-**PC1**	-40	48	81 [c]
11	(*R,Rs*)-**PC1**	-50	24	84 [c]
12[f]	(*R,Rs*)-**PC1**	-60	48	86 [c]

[a] All reactions were carried out with 0.1 mmol of **1a** and 5 mol% of catalyst in 2.0 mL CH_2Cl_2. [b] Determined by HPLC analysis. [c] AgCl was filtered out. [d] $AgSbF_6$ was used. [e] AgOTf was used. [f] 50% conversion, 48% yield.

To confirm the feasibility of this strategy, *N*-allenamide **1a** was exposed to a cationic Au(I) system ($Ph_3PAuCl/AgSbF_6$), which resulted in conversion to (±)-**2a** in 90% yield rather than the dearomative cyclization or dimerization products. Encouraged by this result, we next focused on the asymmetric version of this cyclization. To our disappointment, evaluation of a range of gold complexes derived from privileged chiral bis(phosphine) ligands, phosphoramidites or other chiral trivalent phosphine ligands all failed to enhance the enantioselectivity (up to 36% *ee*). Gratifyingly, the performance of chiral ligands designed by our group (Ming-Phos, Xiang-Phos, etc).[14] give promising up to 44% *ee* (see the supporting information for details).

Thus, a related but structurally novel sulfonamide monophosphine ligand (named **PC-Phos**) was then designed by merging the moieties of Ming-Phos with commonly used and privileged ligand Xant-Phos, which broadens the space and change the angle between phosphine and sulfinamide (Scheme 2). Notably, **PC-Phos** could be easily prepared in gram-scale from commercially available 9,9-dimethylxanthene in two 'one-pot' synthesis, that is, diiodination, lithium-iodine exchange with *n*-BuLi and subsequent treatment with $ClPPh_2$, then a second lithium-iodine exchange with *n*-BuLi, followed by addition of chiral (*Rs*)-sulfinimines, furnishing two diastereoisomeric **PC1–PC3** in moderate yields. To our delight, these PC-Phoses were more effective for enantioselective induction (34-63% *ee*s), although the enantioselectivity was still far from ideal (Table 1, Entries 1-6). In addition, the performance of (*R, Rs*)-**PC-Phoses** were better than the (*S,Rs*)-PC-Phoses. Notably, the enantioselectivity could be inmproved to 70% *ee*, when AgCl was filtered out (Table 1, Entry 2). A variation of the silver salts from $AgNTf_2$ to AgOTf and $AgSbF_6$ did not bring benefit to the enantioselectivity (Table 1, Entries 9-10). The *ee* was increased to 84% after lowering the temperature to -50 °C (Table 1, Entry

Table 2. Evaluation of different sulfonamide.[a]

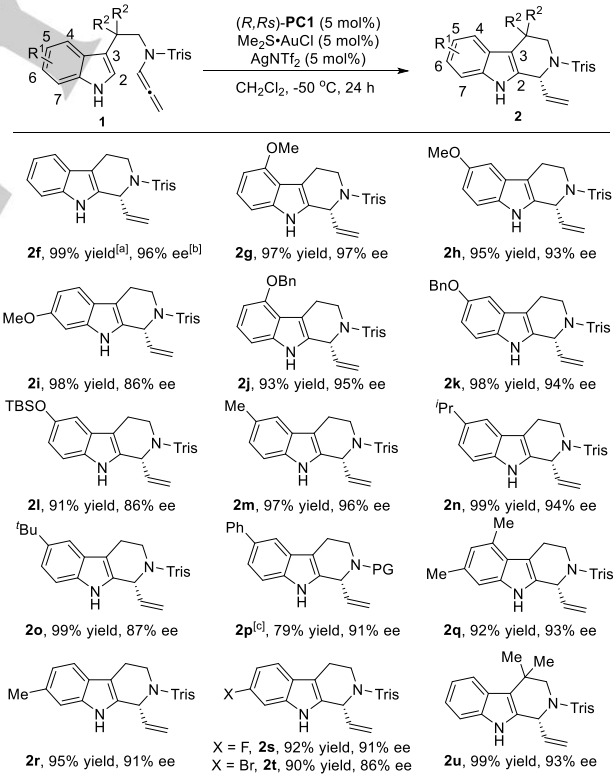


Entry	PG	*T* (°C)	*t* (h)	Yield[b] (%)	*Ee* (%)
1	Ts (**1a**)	-50	24	95	84
2[c]	Ns (**1b**)	-20	12	90	77
3[c]	3,5-$(CF_3)_2C_6H_2SO_2$ (**1c**)	-20	12	88	80
4	Ms (**1d**)	-50	24	92	91
5	2,4,6-$Me_3C_6H_2SO_2$(**1e**)	-50	24	99	92
6[d]	Tris (**1f**)	-50	24	99	96

[a] AgCl was filtered out. [b] Isolated yield. [c] The solubility was not good at < -20 °C. [d] Tris = 2,4,6-^{i}Pr$_3C_6H_2SO_2$.

11). Running the reaction at -60 °C delivered a better *ee* but much lower conversion (Table 1, Entry 12).

Further optimization focused on the adjustment of the protecting group (PG) of nitrogen. Compounds **1b** and **1c** were not dissolved in CH_2Cl_2 at -50 °C and thus runing the reactions at -20 °C delivered the corresponding products in 77% and 80% *ee*s, respectively (Table 2, Entries 2-3). Surprisingly, a slight increase in enantioselectivity occurred when the PG was switched to Ms (Table 2, Entry 4, 91% *ee*). To our delight, a better enantioselectivity (96% *ee*) was achieved with Tris instead of Ts as protecting group (Table 2, Entry 6).



Scheme 3. Exploration of Substrates Scope. Reaction conditions: **1** (0.2 mmol), chiral gold complexes (5 mol%), CH_2Cl_2 (4 mL), -50 °C, AgCl was filtered out; [a] Isolated yield, [b] *Ee* was determined by HPLC. [c] PG = 2,4,6-$Me_3C_6H_2SO_2$.

After the optimal reaction condition was established, the generality of this asymmetric cyclization was investigated by variation of the substitution patterns on indole moiety (Scheme

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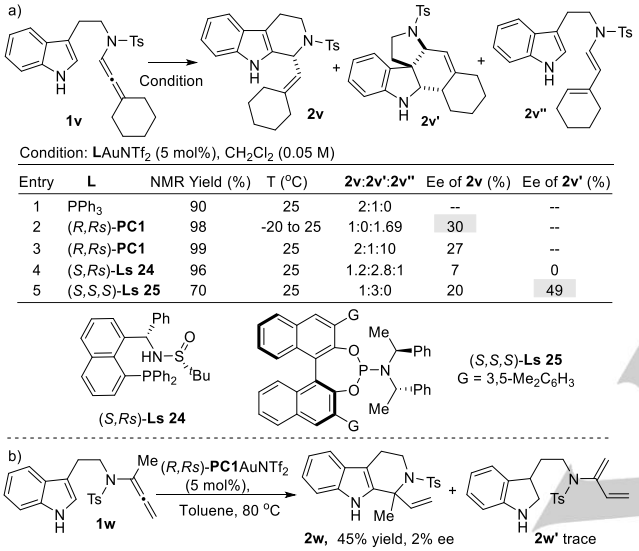
3). In general, the substrate scope is quite general and all the cyclization can be conducted in excellent yields (up to 99% yield) with good to excellent enantioselectivities (up to 97% *ee*). Electron-donating groups (OMe, OBn) at 4-, 5-, 6-positions of the indole ring were well tolerated, delivering the cyclization products in excellent yield with high enantioselectivity (**2g-2k**). A variety of diverse aryl or alkyl substituted indoles were also evaluated and the desired products were isolated in up to 99% yield with up to 96% *ee* (**2l-2r**). Moreover, electron-withdrawing groups such as F and Br at the 6-position still performed well (**2s**, **2t**). Finally, the reaction of *N*-allenamide **1u** with a gem-dimethyl subunit at the α-position could also works well, furnishing the desired product **2u** in 99% yield with 93% *ee*.

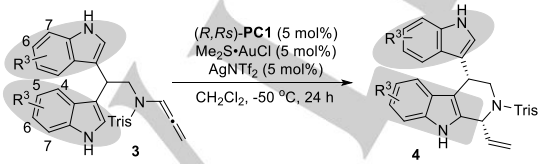


Entry	L	NMR Yield (%)	T (°C)	2v:2v':2v''	Ee of 2v (%)	Ee of 2v' (%)
1	PPh_3	90	25	2:1:0	--	--
2	(*R,Rs*)-**PC1**	98	-20 to 25	1:0:1.69	30	--
3	(*R,Rs*)-**PC1**	99	25	2:1:10	27	--
4	(*S,Rs*)-**Ls 24**	96	25	1.2:2.8:1	7	0
5	(*S,S,S*)-**Ls 25**	70	25	1:3:0	20	49

Scheme 4. Exploration of substituted *N*-allenamides.

Next, we attempted the reactions of α- or γ-substituted *N*-allenamides (Scheme 4). The reaction of γ-disubstituted *N*-allenamide **1v** could give the desired product **2v** but in only 15% yield with 30% *ee* and 1-amido diene **2v''** via isomerization as the major product under the standard conditions.[4e,4f] Notably, the cycloaddition product **2v'** was obtained in 49% ee by using (*S,S,S*)-**Ls 25** ligand.[4e] In contrast, the temperature should be improved to 80 °C for the cyclization of α-substituted N-allenamide **1w**, leading to the desired cyclization product **2w** in 45% yield in only 2% ee and a trace amount of dinene **2w'** (see other conditions in the SI).

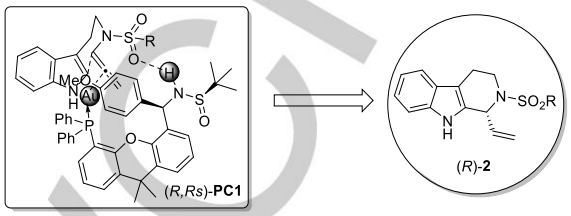
Table 3. Gold-catalyzed desymmetrization reaction.[a]



Entry	R^3 (**3**)	D.r.	Yield (%)[b]	*Ee* (%)[c]
1	H (**3a**)	13:1	99 (**4a**)	95
2	5-OMe (**3b**)	10:1	94 (**4b**)	86
3	5-Me (**3c**)	7:1	97 (**4c**)	92
4	6-Me (**3d**)	22:1	95 (**4d**)	93
5	6-F (**3e**)	9:1	97 (**4e**)	94

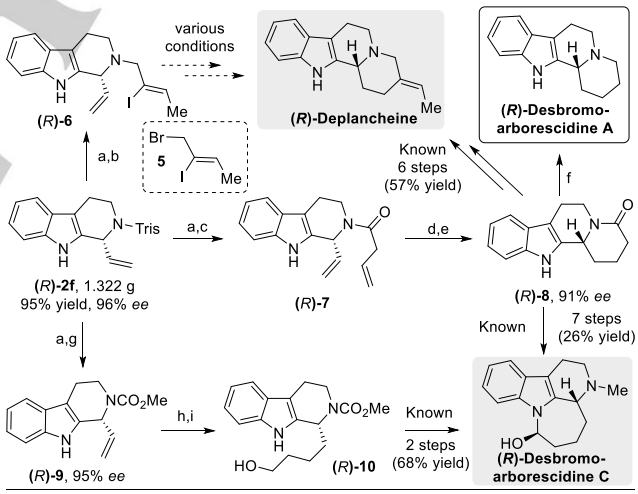
[a] Reaction conditions: **3** (0.2 mmol), chiral gold complexes (5 mol%), CH_2Cl_2 (4 ml), -50 °C, AgCl was filtered out; [b] Isolated yield. [c] Determined by HPLC analysis.

Gold-catalyzed asymmetric desymmetrizative cyclization has drawn extensive interest during the past decade.[15] Thus we wondered whether our catalyst system of (*R,Rs*)-**PC1**/$AuNTf_2$ can be applied to the desymmetrizative cyclization of *N*-allenamides **3**. To our delight, the desired desymmetrization products **4a**-**4e** were obtained in high yields (up to 99%) with up to 95% *ee* and high diastereoselectivity, which further enlarged the reaction scope.



Scheme 5. Proposed Asymmetric Induction Model.

In light of the structures of the chiral ligand (*R,Rs*)-**PC1** and the product **2**, a catalytic model was proposed for the reaction (Scheme 5). The phosphine of the ligand and the *N*-allenamide **1** coordinate to Au^I center. Meanwhile, the sulfonyl group would form a hydrogen bonding with the hydrogen atom of the catalyst. The *Si* face of allenamide is shielded by the 4-$MeOC_6H_4$ group of the ligand and the indole group attack takes place at the *Re* face to form the product (*R*)-**2** with excellent enantioselectivity.



Reagents and conditions: a) Na/Naphthalene, THF, -78 °C; b) **5**, K_2CO_3, THF, 0 °C, 72 % yield for 2 steps; c) $(COCl)_2$, cat. DMF, vinylacetic acid, Et_3N, CH_2Cl_2, rt, 56% yield for 2 steps; d) Grubb's 2 nd, CH_2Cl_2, 0.01 M, reflux; e) Pd/C, H_2, MeOH/EtOAc, rt, 85% yield for 2 steps; f) AlH_3, THF, 0 °C, 94% yield; g) $ClCO_2Me$, Et_3N, CH_2Cl_2, rt, 60% yield for 2 steps; h) Grubb's 2nd, 3-buten-1-ol, CH_2Cl_2, reflux, 39% yield (brsm), *E/Z* = 3:1; i) Pd/C, H_2, MeOH/EtOAc, rt, 95% yield.

Scheme 6. Synthetic applications of the products.

To illustrate the utility of the new methodology, we next turned to apply the products towards the enantioselective synthesis of (*R*)-Desbromoarborescidine A-C and (*R*)-Deplancheine.[16] A gram-scale reaction of **1f** proceeds smoothly, delivering 1.322 g of (*R*)-**2f** in 95% yield with 96% *ee* (Scheme 6). Towards the (*R*)-Deplancheine, (*R*)-**2f** was deprotected and alkylated with allyl bromide **5** to produce (*R*)-**6**, which unfortunately proved inert in the intramolecular reaction (see details in Supporting Information). Therefore, we modified our synthetic strategy. (*R*)-**2f** was deprotected and acylated, affording (*R*)-**7** in 56% overall yield in two steps. Next, RCM of (*R*)-**7** with Grubbs II catalyst and

subsequent hydrogenation delivered (*R*)-**8** in 85% yield with 91% *ee* in two steps. In addition, an alternate path to (*R*)-**8** and its successful elaboration to (*R*)-Deplancheine by such a sequence was reported by Argade.[16d] Moreover, (*R*)-Desbromoarborescidine A was obtained in 94% yield by reduction of δ-lactam carbonyl group of (*R*)-**8**. Finally, (*R*)-**8** could also deliver the (*R*)-Desbromoarborescidine C via a 7-steps synthetic protocol in good overall yield according to the reported procedure.[16d] In order to optimize the synthetic route of (*R*)-Desbromoarborescidine C, the Tris group was replaced with CO_2Me to provide (*R*)-**9** in 60% yield. Then (*R*)-**9** was transformed via CM with 3-buten-1-ol and hydrogenation to (*R*)-**10**, which could generate (*R*)-Desbromoarborescidine C in 68% yield over two steps. [16d]

In summary, we have developed an asymmetric gold(I)-catalyzed intramolecular cyclization of *N*-allenamides for the efficient synthesis of chiral tetrahydrocarbolines with the use of a well-designed, easily available PC-Phos. Notably, enantioselective desymmetrization of *N*-allenamides was also achieved in good yields with high *ee*s and moderate to excellent diastereoselectivities. Furthermore, synthetic applications of the synthetic valuable THCs products to the key building block for asymmetric total synthesis of (*R*)-Desbromoarborescidine A and formal synthesis of (*R*)-Deplancheine or (*R*)-Desbromoarborescidine C were showcased. Further applications of PC-Phos in other transition-metal catalyzed reactions are underway and will be reported in due course.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Gold • Enantioselectivity • Cyclization • Allenamides •Tetrahydrocarboline

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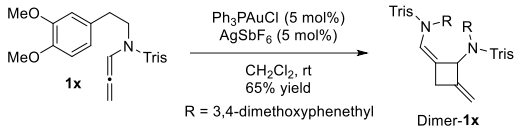

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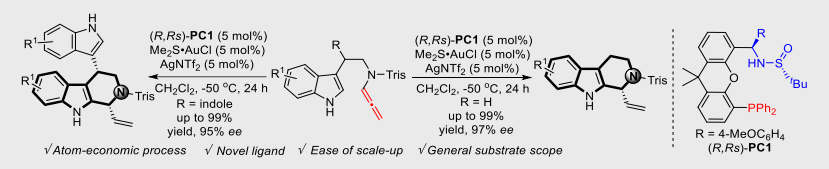

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Gold-Catalyzed Asymmetric Intramolecular Cyclization of N-Allenamides for the Synthesis of Chiral Tetrahydrocarbolines

The first example of highly enantioselective gold-catalyzed intramolecular cyclization of *N*-allenamides was implemented utilizing **PC-Phos**. The practicality of this reaction was validated in the total synthesis of (*R*)-Desbromoarborescidine A.