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Asymmetric construction of pyrido[1,2-*a*]-1*H*-indole derivatives via a gold-catalyzed cycloisomerization†

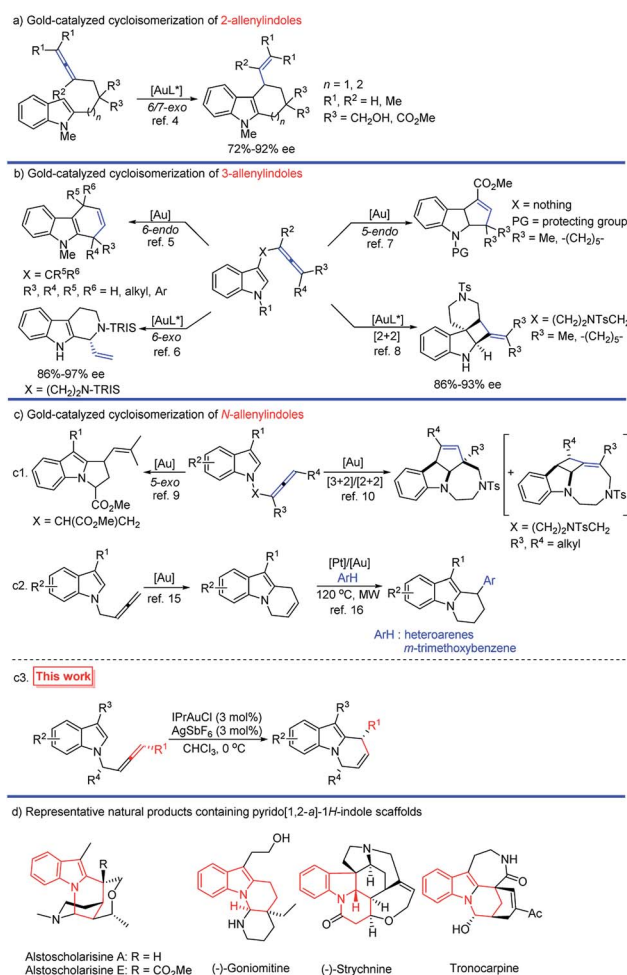
Feng Jiang, Chunling Fu and Shengming Ma*

Pyrido[1,2-*a*]-1*H*-indoles are important scaffolds found in many biologically active compounds. Herein, we first developed an IPrAuCl/AgSbF₆-catalyzed cycloisomerization of *N*-1,3-disubstituted allenyl indoles affording pyrido[1,2-*a*]-1*H*-indoles. Then the axial-to-central chirality transfer starting from enantio-enriched *N*-1,3-disubstituted allenylindoles affording optically active pyrido[1,2-*a*]-1*H*-indoles has been realized in excellent yields and enantioselectivities. A mechanism has been proposed based on mechanistic studies. Synthetic applications have also been demonstrated.

Introduction

Polycycles containing indole units are prevalent ring systems distributed in many bioactive alkaloids and pharmaceuticals.¹ Gold-catalyzed cycloisomerizations of different types of allenyl indoles have contributed greatly to this topic.^{2–10} In 2006, Widenhofer and his group reported the pioneering work on the synthesis of tetrahydrocarbazoles and cyclohepta[*b*]indoles via a 6- and 7-*exo* cycloisomerization of 2-allenyl indoles (Scheme 1a).⁴ As for 3-allenyl indoles, the gold-catalyzed 6-*endo*,⁵ 6-*exo*,⁶ and 5-*endo*⁷ annulations as well as [2 + 2] cycloaddition⁸ successfully furnished the construction of varied indole scaffolds (Scheme 1b); however, annulations of *N*-allenyl indoles have been less explored.^{9,10} Toste's group reported the construction of dihydropyrroloindole skeletons via a 5-*exo* cyclization of *N*-allenyl indoles (Scheme 1(c1)).⁹ Shi and co-workers realized the construction of indole-fused tricyclic systems via a [3 + 2] or [2 + 2] cycloaddition of *N*-allenyl indoles under varied reaction conditions (Scheme 1(c1)).¹⁰

Pyrido[1,2-*a*]-1*H*-indoles are core motifs in ubiquitous biologically active alkaloids (Scheme 1d).¹¹ Extensive efforts have been devoted to the development of new methods for their efficient synthesis. General approaches developed are the RCM reaction of diallyl indoles,¹² Michael addition of α,β -unsaturated ketones¹³ and radical cyclization of *N*-alkylindoles,¹⁴ mostly suffering from the substrate scope, selectivity, and efficiency. Recently, González's¹⁵ and Muñoz's¹⁶ groups reported the elegant Au- or Pt-Au catalyzed cycloisomerization of *N*-2,3-

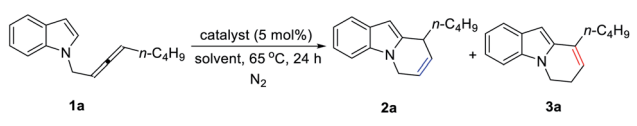


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† Electronic supplementary information (ESI) available. CCDC 1956055 and 1956072. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc05619g

Scheme 1 Gold-catalyzed cycloisomerization of allenylindoles and representative natural products containing pyrido[1,2-*a*]-1*H*-indole scaffolds.



Table 1 Optimization of the reaction conditions for cyclization of the racemic **1a**^a


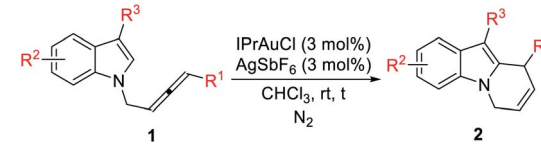
Entry	Catalyst	Solvent	Yield of 2a ^b (%)	Yield of 3a ^b (%)	Recovery ^b (%)
1	IPrAuCl/AgNTf ₂	Toluene	81	1	—
2	AuCl/AgNTf ₂	Toluene	—	—	84
3	AuCl(PPh ₃)/AgNTf ₂	Toluene	14	3	61
4	AuCl(PMe ₃)/AgNTf ₂	Toluene	14	4	62
5 ^c	[Au ₂ Cl ₂ (dppm)]/AgNTf ₂	Toluene	15	4	50
6	AuCl(LB-phos)/AgNTf ₂	Toluene	26	3	50
7	IPrAuCl/AgBF ₄	Toluene	66	16	—
8	IPrAuCl/AgOTs	Toluene	—	—	91
9	IPrAuCl/AgPF ₆	Toluene	—	69	—
10	IPrAuCl/AgSbF ₆	Toluene	70	13	—
11 ^d	IPrAuCl/AgSbF ₆	Toluene	92	—	—
12 ^d	IPrAuCl/AgSbF ₆	CH ₃ CN	9	—	87
13 ^d	IPrAuCl/AgSbF ₆	CH ₂ Cl ₂	91	—	—
14 ^d	IPrAuCl/AgSbF ₆	CHCl ₃	95	—	—

^a Reaction conditions (unless otherwise noted): **1a** (0.2 mmol) and catalyst (5 mol%) in 5.0 mL of solvent at 65 °C. ^b Yields were determined by the ¹H NMR analysis of the crude products with mesitylene as the internal standard. ^c 2.5 mol% [Au₂Cl₂(dppm)] was used. ^d The reaction was carried out at room temperature for 12 h.

butadienylindoles affording 6,9-dihydropyrido[1,2-*a*]-1*H*-indoles, which further reacted with heteroarenes or the electron-rich *m*-trimethoxybenzene to furnish racemic 9-aryl-6,7,8,9-tetrahydropyrido[1,2-*a*]-1*H*-indoles (Scheme 1(c2)). Enantioselective syntheses have not been developed. We envisaged that the cycloisomerization of optically active *N*-(2,3-allenyl)indoles would provide an efficient approach to various 9-substituted pyrido[1,2-*a*]-1*H*-indoles with high ee provided that the efficiency of chirality transfer may be ensured (Scheme 1(c3)).

Results and discussion

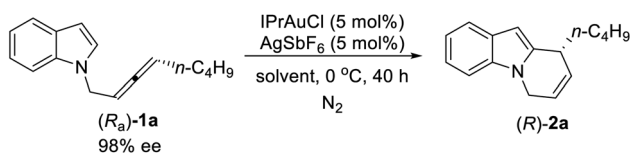
Initially, we conducted the reaction of racemic *N*-(2,3-allenyl) indole **1a** in toluene under the catalysis of [IPrAuCl]/[AgNTf₂], and the expected 6-*endo* cycloisomerization product **2a** was afforded in 81% yield, accompanied by 1% of the C=C bond migration by-product **3a** (entry 1, Table 1). Then we tested different neutral gold catalysts, AuCl, AuCl(PPh₃), AuCl(PMe₃), Au₂Cl₂(dppm), and AuCl(LB-phos); they all led to high recoveries of **1a** (entries 2–6, Table 1). We reasoned that the cationic gold catalyst may have a much higher philicity towards the C=C bond in allenes to increase the overall reactivity. Thus, different silver salts were added:¹⁷ when AgSbF₆ was applied, the expected product **2a** and the C=C bond migration product **3a** were formed in the yields of 70% and 13%, respectively (entry 10, Table 1). Considering that the high reaction temperature may have accelerated the C=C bond migration, the reaction was conducted at room temperature to successfully form **2a** in 92% yield, exclusively (entry 11, Table 1). Further screening of solvents (entries 12–14, Table 1) revealed that CHCl₃, CH₂Cl₂, and toluene were the best. Finally, we defined the standard

Table 2 Gold-catalyzed cyclization reaction of racemic *N*-allenylindoles **1a**^a


Entry	R ¹	R ²	R ³	t/h	Yield of 2 (%)
1	<i>n</i> -C ₄ H ₉	H	H (1a)	12	71 (2a)
2	<i>n</i> -C ₁₀ H ₂₁	H	H (1b)	12	68 (2b)
3	CH ₂ =CH(CH ₂) ₈	H	H (1c)	12	72 (2c)
4	<i>n</i> -C ₄ H ₉	5-OMe	H (1d)	12	78 (2d)
5	<i>n</i> -C ₄ H ₉	4-Me	H (1e)	12	77 (2e)
6	<i>n</i> -C ₄ H ₉	6-Cl	H (1f)	12	84 (2f)
7	<i>n</i> -C ₄ H ₉	H	Me (1g)	17	96 (2g)
8	Cl(CH ₂) ₅	H	Me (1h)	10	92 (2h)
9	BnCH ₂	H	Me (1i)	12	94 (2i)
10	3-Pentyl	H	Me (1j)	12	98 (2j)
11	<i>n</i> -C ₄ H ₉	H	Ethyl (1k)	14	97 (2k)
12	<i>n</i> -C ₄ H ₉	H	TBSO(CH ₂) ₂ (1l)	12	100 (2l)
13	<i>n</i> -C ₄ H ₉	6-Cl	Me (1m)	12	96 (2m)
14	<i>n</i> -C ₄ H ₉	5-OMe	Cl (1n)	13	98 (2n)
15 ^b	Ph	H	Me (1o)	16	96 (2o)
16 ^b	2-BrC ₆ H ₄	H	Me (1p)	12	93 (2p)
17	4-FC ₆ H ₄	H	Me (1q)	12	86 (2q)
18	4-BrC ₆ H ₄	H	Me (1r)	12	80 (2r)
19 ^c	4-BrC ₆ H ₄	H	TBSO(CH ₂) ₂ (1s)	14	83 (2s)

^a Reaction conditions: **1** (1 mmol), IPrAuCl (3 mol%) and AgSbF₆ (3 mol%) in CHCl₃ (5.0 mL) at room temperature unless otherwise noted. ^b The reaction was performed on a 0.2 mmol scale in 5.0 mL of CHCl₃. ^c The reaction was performed on a 2.8 mmol scale with 1.6 mol% catalyst.



Table 3 Optimization of the reaction conditions for the intramolecular cyclization of (*R_a*)-1a^a


Entry	Solvent	Yield/ee of (<i>R</i>)-2a (%) ^b (%) ^c	Recovery/ee of (<i>R_a</i>)-1a (%) ^b (%) ^c
1	CHCl ₃	93/91	—
2	DCE	74/90	13/84
3	CH ₂ Cl ₂	98/90	—
4	Toluene	56/92	47/93
5	CH ₃ CN	—	100/98
6	THF	88/84	—
7	Dioxane	52/60	—
8	DMF	54/66	31/87
9 ^{d,f}	CHCl ₃	—	92/98
10 ^{e,f}	CHCl ₃	—	91/98
11 ^g	CHCl ₃	90/87	—
12 ^{f,g,h}	CHCl ₃	94/90	—

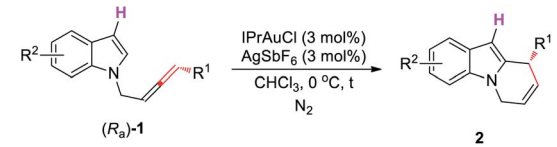
^a Reaction conditions: (*R_a*)-1a (0.2 mmol), catalyst (5 mol%) in solvent (5.0 mL) at 0 °C under a N₂ atmosphere unless otherwise noted. ^b Yields were determined by ¹H NMR using mesitylene as the internal standard. ^c The ee was determined by HPLC analysis using a chiral stationary phase. ^d Without AgSbF₆. ^e Without IPrAuCl. ^f Reaction was carried out at 0 °C for 48 h. ^g The reaction was performed on a 1 mmol scale. ^h 3 mol% catalyst was used.

conditions as follows: IPrAuCl and AgSbF₆ in CHCl₃ at room temperature.

With the optimal conditions in hand, the substrate scope of this gold-catalyzed cycloisomerization of racemic *N*-(2,3-allenyl) indoles has been examined (Table 2). Both alkyl- and aryl-substituted allenylindoles could work smoothly. Functional groups such as the C=C bond, OMe, Cl, OTBS, Br, F, are all compatible (entries 3–4, 6, 12, and 16–17, Table 2). Substitution on the indoles with electron-withdrawing and -donating substituents at positions 3, 4, 5, or 6 has a very little impact on the yield (entries 4–7 and 11–14, Table 2). Furthermore, it was worth noting that when R³ = Me, Et, Cl, TBSO(CH₂)₂, the yields of 2 were much higher, as compared with R³ = H (compare entries 10–14 with entries 1–6, Table 2).

With these encouraging results, we then began the investigation of the cycloisomerization of the optically active substrates with (*R_a*)-1a as the model substrate. Such optically active substrates are readily available *via* the enantioselective allenation of terminal alkynes (EATA) reaction.¹⁸ Initially, the combination of IPrAuCl and AgSbF₆ was tested in CHCl₃ at 0 °C, the product (*R*)-2a was formed in 93% yield and 91% ee (entry 1, Table 3). Additional screening of solvents showed inferior results (entries 2–8, Table 3). Control experiments showed that essentially no reaction occurred when either IPrAuCl or AgSbF₆ was omitted (entries 9 and 10, Table 3). However, when the reaction was conducted on a 1 mmol scale, the ee of (*R*)-2a dropped again (entry 11, Table 3). Reducing the catalyst loading solved this problem, thus, the optimal conditions have been successfully re-defined by running the reaction with 3 mol% each of IPrAuCl and AgSbF₆ in CHCl₃ at 0 °C (entry 12, Table 3).

Having identified the optimal conditions, we aimed to define the scope of both the allene part and the indole part. First, we conducted a brief study of the substrate scope for R³ = H. As shown in Table 4, R¹ could be a butyl, decyl, or decenyl group (entries 1–3, Table 4). For the indole part, substrates with substituents at positions of 4 or 5 also reacted smoothly with high yields and ee values (entries 4 and 5, Table 4). However, when the weak electron-withdrawing group Cl was employed, the ee of the product decreased (entry 6, Table 4).

Table 4 Gold-catalyzed cycloisomerization reaction of 3-unsubstituted (*R_a*)-1^a


Entry	(<i>R_a</i>)-1/(ee%)	<i>t</i> (h)	2	
			Yield (%)	ee (%)
1	<i>n</i> -C ₄ H ₉ /H ((<i>R_a</i>)-1a)/97	48	94 ((<i>R</i>)-2a)	90
2	<i>n</i> -C ₁₀ H ₂₁ /H ((<i>R_a</i>)-1b)/98	48	95 ((<i>R</i>)-2b)	90
3	CH ₂ =CH(CH ₂) ₈ /H ((<i>R_a</i>)-1c)/96	51	96 ((<i>R</i>)-2c)	92
4	<i>n</i> -C ₄ H ₉ /5-OMe ((<i>R_a</i>)-1d)/98	53	95 ((<i>R</i>)-2d)	91
5 ^b	<i>n</i> -C ₄ H ₉ /4-Me ((<i>R_a</i>)-1e)/98	48	88 ((<i>R</i>)-2e)	90
6	<i>n</i> -C ₄ H ₉ /6-Cl ((<i>R_a</i>)-1f)/98	58	93 ((<i>R</i>)-2f)	78

^a Reaction conditions: (*R_a*)-1 (1 mmol), IPrAuCl (3 mol%), and AgSbF₆ (3 mol%) in CHCl₃ (25.0 mL) at 0 °C unless otherwise noted. ^b 5 mol% catalyst was used.



Table 5 Gold-catalyzed cyclization reaction of 3-substituted (R_a)-**1**^a

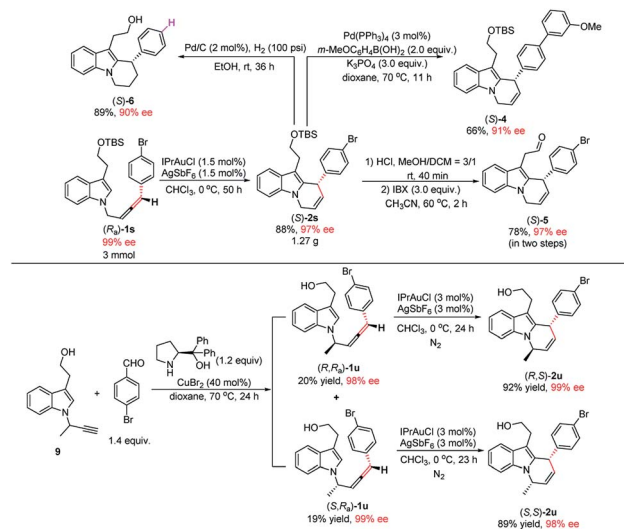
Entry	$R^1/R^2/R^3$	(R_a) - 1 (ee%)		
		<i>t</i> (h)	Yield (%)	ee (%)
1 ^b	<i>n</i> -C ₄ H ₉ /H/Me ((R_a)- 1g)/98	59	90 ((R)- 2g)	96
2	Cl(CH ₂) ₅ /H/Me ((R_a)- 1h)/98	48	99 ((R)- 2h)	99
3	BnCH ₂ /H/Me ((R_a)- 1i)/97	48	98 ((R)- 2i)	98
4	3-Pentyl/H/Me ((R_a)- 1j)/98	48	89 ((R)- 2j)	90
5	<i>n</i> -C ₄ H ₉ /H/ethyl ((R_a)- 1k)/99	48	98 ((R)- 2k)	97
6	<i>n</i> -C ₄ H ₉ /H/TBSO(CH ₂) ₂ ((R_a)- 1l)/98	48	98 ((R)- 2l)	96
7	<i>n</i> -C ₄ H ₉ /6-Cl/Me ((R_a)- 1m)/98	48	97 ((R)- 2m)	95
8	<i>n</i> -C ₄ H ₉ /5-OMe/Cl ((R_a)- 1n)/98	42	98 ((R)- 2n)	98
9	Ph/H/Me ((R_a)- 1o)/99	48	99 ((S)- 2o)	95
10	2-BrC ₆ H ₄ /H/Me ((R_a)- 1p)/96	48	98 ((S)- 2p)	96
11	4-FC ₆ H ₄ /H/Me ((R_a)- 1q)/98	48	89 ((S)- 2q)	95
12	4-BrC ₆ H ₄ /H/Me ((R_a)- 1r)/98	48	91 ((S)- 2r)	96
13	4-BrC ₆ H ₄ /H/TBSO(CH ₂) ₂ ((R_a)- 1s)/99	48	90 ((S)- 2s)	92

^a Reaction conditions: (R_a)-**1** (1 mmol), IPrAuCl (3 mol%) and AgSbF₆ (3 mol%) in CHCl₃ (25.0 mL) at 0 °C unless otherwise noted. ^b 5 mol% catalyst was used.

We further studied the scope of substrates for $R^3 \neq H$ and observed higher yields and ee values. As shown in Table 5, both alkyl- (entries 1–8) and aryl-substituted allenes (entries 9–13) could work smoothly. For aryl-substituted allenes, both F and Br may survive (entries 10–13, Table 5). Furthermore, the Br atom installed at the *ortho*- or *para*-positions of the phenyl ring had little effect on the yield and ee of (S)-**2**. For the indole part, electron-donating as well as electron-withdrawing substituents and functional groups, including OTBS, OMe, and Cl, which could further be elaborated, were well tolerated (entries 6–8 and 13, Table 5).

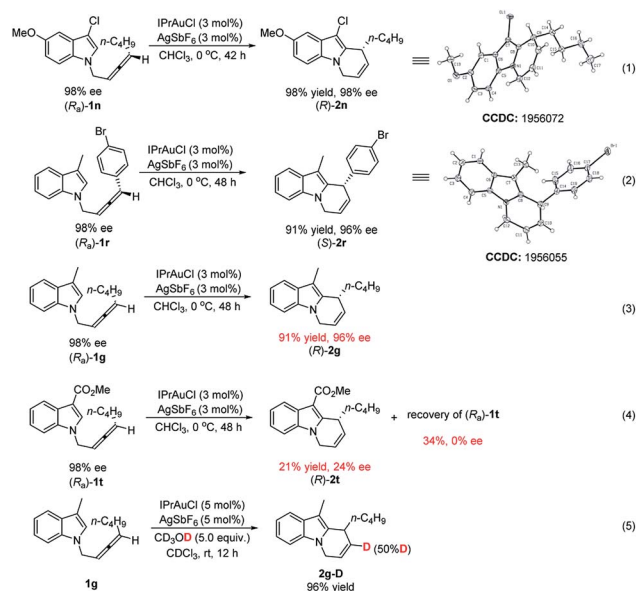
Notably, this reaction could be easily scaled up to 3.0 mmol and the loading of IPrAuCl/AgSbF₆ may further be reduced to 1.5 mol%, providing 1.27 g of (S)-**2s** (88% yield) in 97% ee (Scheme 2). To illustrate the synthetic potential of this protocol, the transformations of cycloisomerization product (S)-**2s** were demonstrated: Suzuki coupling of (S)-**2s** with 3-methoxyphenyl boronic acid gave product (S)-**4** in 66% yield and 91% ee.¹⁹ Treatment of (S)-**2s** with HCl and IBX successively afforded aldehyde (S)-**5** in 78% yield and 97% ee. The hydrogenation of (S)-**2s** gave product (S)-**6** in 89% yield and 90% ee (Scheme 2). Products (S)-**2s** and (S)-**6** contain the core unit in goniomitine.^{11b} Then, an extra chiral centre was further introduced to the 1-position of the allene side chain by including a methyl group. The reaction of (R,R_a)-**1u** and (S,R_a)-**1u** could also work smoothly, providing diastereomers (R,S)-**2u** (92% yield) and (S,S)-**2u** (89% yield) in 99% ee and 98% ee respectively. These results provide a possibility to synthesize a library of (–)-goniomitine derivatives (Scheme 2).

In order to unveil the nature of the stereoselectivity of the reaction, the absolute configurations of the starting materials



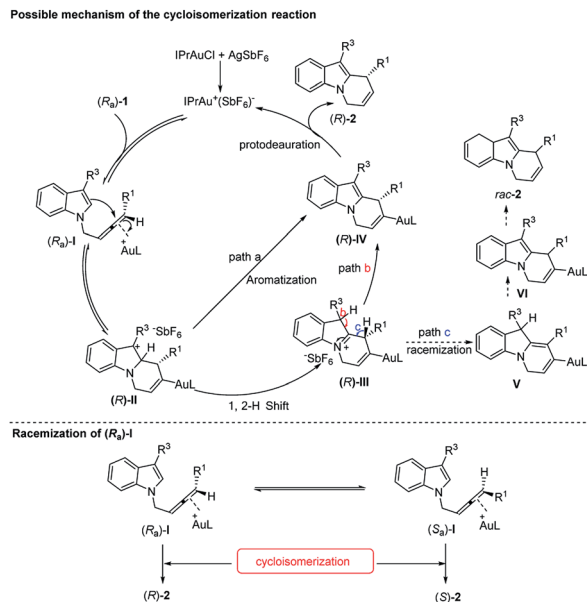
Scheme 2 A gram-scale reaction and the syntheses of simplified analogues of (–)-goniomitine.

(R_a)-**1n** and (R_a)-**1r** have been established based on the literature.^{18c,20} The absolute configurations of their corresponding products were unambiguously established by X-ray single crystal diffraction analysis of (R)-**2n** and (S)-**2r** (eqn (1) and (2), Scheme 3). The electronic effect of the 3-position substituent of indole on chirality transfer has been studied by conducting the parallel reactions of (R_a)-**1g** ($R^3 = Me$) and (R_a)-**1t** ($R^3 = CO_2Me$) under standard conditions (eqn (3) and (4), Scheme 3): the reaction of (R_a)-**1g** proceeded smoothly to afford the product (R)-**2g** in 91% yield and 96% ee while the reaction of (R_a)-**1t** afforded the target product (R)-**2t** in 21% yield with only 24% ee. Interestingly, we found the ee value of the recovered (R_a)-**1t** is 0,



Scheme 3 Determination of absolute configurations and control experiments.





Scheme 4 Proposed mechanism.

indicating the potential competitive racemization and cycloisomerization of *N*-(2,3-allenyl)indoles. This also explains why the loading of the catalyst has an effect on the efficiency of chirality transfer. Furthermore, a control experiment of exposing **1g** and CD_3OD to the gold catalyst in CHCl_3 afforded **2g-D** with 50% deuterium incorporation, confirming the process of proto-deauration (eqn (5), Scheme 3).

Based on these experimental data, we proposed a plausible mechanism^{15,21} of the reaction (Scheme 4): firstly, the catalytically active cationic Au(I) species generated *in situ* coordinated with the “distal” double bond of the allene unit (R_a) -I. Subsequent anti-attack of the C2 atom at the coordinated C=C bond formed (R) -II with a high stereoselectivity. At this stage, when $R^3 = \text{Me, Et, Cl, and TBSO}(\text{CH}_2)_2$, because of the higher stability of carbon cation (R) -II, the direct aromatization (path a) was prone to proceed, affording the alkenyl-gold species (R) -IV. Alternatively, highly active cationic species (R) -II could also undergo the 1,2-H shift to afford intermediate (R) -III (path b), which would undergo subsequent aromatization and proto-deauration to afford the optically active final products (R) -2, and released the catalytically active cationic gold catalyst back into the catalytic cycle. The final step was confirmed by the D-labeling experiment in eqn (5) of Scheme 3. While deprotonation of (R) -III followed by a 1,3-H shift of complex **V** and proto-deauration of complex **VI** would generate *rac*-2 (path c, Scheme 4), explaining the lower ee and yield for R^3 being H and CO_2Me . Also, racemization of the starting allene (R_a) -I and further cycloisomerization may be an alternative pathway for the erosion of the optical purity as confirmed by the parallel reaction in eqn (3) and (4) of Scheme 3.

Conclusions

In summary, we have developed a Au^+ -catalyzed intramolecular cycloisomerization of *N*-1,3-disubstituted allenylindoles.

Various functionalized 6,9-dihydro-pyrido[1,2-*a*]-1*H*-indoles can be accessed directly. Furthermore, the optically active 6,9-dihydro-pyrido[1,2-*a*]-1*H*-indoles can be prepared with high yields and ee values *via* an efficient transfer of the axial chirality to central chirality. The core structure of (–)-goniomitine has been prepared in excellent yields and ee values. This protocol features simple operation, mild conditions, and good functional group compatibility. We anticipated that this protocol may provide a new route for the synthesis of natural product analogues and pharmaceuticals containing the core unit of the pyrido[1,2-*a*]-1*H*-indole unit.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) J. Song, D.-F. Chen and L.-Z. Gong, *Natl. Sci. Rev.*, 2017, **4**, 381; (b) J. Hájíček, *Collect. Czech. Chem. Commun.*, 2011, **76**, 2023; (c) S. E. O'Connor and J. J. Maresh, *Nat. Prod. Rep.*, 2006, **23**, 532; (d) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2004, **21**, 278.
- For recent reviews on gold-catalyzed cyclization reactions, see: (a) J. L. Mascareñas, I. Varela and F. López, *Acc. Chem. Res.*, 2019, **52**, 465; (b) Y. Wei and M. Shi, *ACS Catal.*, 2016, **6**, 2515; (c) W. Yang and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2014, **43**, 2941; (d) B. Alcaide and P. Almendros, *Acc. Chem. Res.*, 2014, **47**, 939; (e) A. Marinetti, H. Jullien and A. Voituriez, *Chem. Soc. Rev.*, 2012, **41**, 4884; (f) N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994; (g) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria and A. Simonneau, *Chem. Rev.*, 2011, **111**, 1954; (h) M. Bandini, *Chem. Soc. Rev.*, 2011, **40**, 1358.
- For selected recent examples of gold-catalyzed cyclization reactions, see: (a) F. M. Miloserdov, M. S. Kirillova, M. E. Muratore and A. M. Echavarren, *J. Am. Chem. Soc.*, 2018, **140**, 5393; (b) Z. L. Niemeyer, S. Pindi, D. A. Khrakovsky, C. N. Kuzniewski, C. M. Hong, L. A. Joyce, M. S. Sigman and F. D. Toste, *J. Am. Chem. Soc.*, 2017, **139**, 12943; (c) W. Zi, H. Wu and F. D. Toste, *J. Am. Chem. Soc.*, 2015, **137**, 3225; (d) L. Huang, H.-B. Yang, D.-H. Zhang, Z. Zhang, X.-Y. Tang, Q. Xu and M. Shi, *Angew. Chem., Int. Ed.*, 2013, **52**, 6767; (e) A. S. K. Hashmi, W. Yang and F. Rominger, *Adv. Synth. Catal.*, 2012, **354**, 1273; (f) C. Ferrer, C. H. M. Amijs and A. M. Echavarren, *Chem.-Eur. J.*, 2007, **13**, 1358; (g) C. Ferrer and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2006, **45**, 1105; (h) P.-L. Zhu, X.-Y. Tang and M. Shi, *Chem. Commun.*, 2016, **52**,



- 7245; (i) B. Alcaide, P. Almendros, I. Fernández, F. Herrera and A. Luna, *Chem.-Eur. J.*, 2018, **24**, 1448; (j) For the seminal report on gold-catalyzed cyclization of allenes, see: A. S. K. Hashmi, L. Schwarz, J.-H. Choi and T. M. Frost, *Angew. Chem. Int. Ed.*, 2000, **39**, 2285.
- 4 (a) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2006, **128**, 9066; (b) C. Liu and R. A. Widenhoefer, *Org. Lett.*, 2007, **9**, 1935.
- 5 E. Álvarez, P. García-García, M. A. Fernández-Rodríguez and R. Sanz, *J. Org. Chem.*, 2013, **78**, 9758.
- 6 Y. Wang, P. Zhang, X. Di, Q. Dai, Z.-M. Zhang and J. Zhang, *Angew. Chem., Int. Ed.*, 2017, **56**, 15905.
- 7 B. Chen, W. Fan, G. Chai and S. Ma, *Org. Lett.*, 2012, **14**, 3616.
- 8 (a) V. Magné, Y. Sanogo, C. S. Demmer, P. Retailleau, A. Marinetti, X. Guinchard and A. Voituriez, *ACS Catal.*, 2020, **10**, 8141; (b) Y.-Y. Zhang, Y. Wei and M. Shi, *Chem. Commun.*, 2019, **55**, 4210.
- 9 R. M. Zeldin and F. D. Toste, *Chem. Sci.*, 2011, **2**, 1706.
- 10 L.-Y. Mei, Y. Wei, X.-Y. Tang and M. Shi, *J. Am. Chem. Soc.*, 2015, **137**, 8131.
- 11 (a) X. Liang, S.-Z. Jiang, K. Wei and Y.-R. Yang, *J. Am. Chem. Soc.*, 2016, **138**, 2560; (b) M. Mizutani, F. Inagaki, T. Nakanishi, C. Yanagihara, I. Tamai and C. Mukai, *Org. Lett.*, 2011, **13**, 1796; (c) M. Mori, *Heterocycles*, 2010, **81**, 259; (d) T.-S. Kam and K.-M. Sim, *Heterocycles*, 1999, **51**, 345.
- 12 For selected examples of RCM reactions of indoles, see: (a) T. Mandal, G. Chakraborti, S. Karmakar and J. Dash, *Org. Lett.*, 2018, **20**, 4759; (b) M. A. Abozeid, S. Sairenji, S. Takizawa, M. Fujita and H. Sasai, *Chem. Commun.*, 2017, **53**, 6887; (c) P. González-Pérez, L. Pérez-Serrano, L. Casarrubios, G. Domínguez and J. Pérez-Castells, *Tetrahedron Lett.*, 2002, **43**, 4765.
- 13 For selected examples of Michael addition reactions of indoles, see: (a) C. Zhao, F. D. Toste and R. G. Bergman, *J. Am. Chem. Soc.*, 2011, **133**, 10787; (b) Q. Cai, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2010, **49**, 8666.
- 14 For selected examples of radical cyclization of *N*-alkylindoles, see: (a) A. R. O. Venning, P. T. Bohan and E. J. Alexanian, *J. Am. Chem. Soc.*, 2015, **137**, 3731; (b) J. W. Tucker, J. M. R. Narayanam, S. W. Krabbe and C. R. J. Stephenson, *Org. Lett.*, 2010, **12**, 368; (c) S.-C. Lu, X.-Y. Duan, Z.-J. Shi, B. Li, Y.-W. Ren, W. Zhang, Y.-H. Zhang and Z.-F. Tu, *Org. Lett.*, 2009, **11**, 3902; (d) J. Magolan and M. A. Kerr, *Org. Lett.*, 2006, **8**, 4561; (e) C. J. Moody and C. L. Norton, *J. Chem. Soc. Perkin Trans. I*, 1997, **1**, 2639; (f) S. Caddick, K. Aboutayab and R. West, *Synlett*, 1993, 231.
- 15 J. Barluenga, M. Piedrafitra, A. Ballesteros, Á. L. Suárez-Sobrinó and J. M. González, *Chem.-Eur. J.*, 2010, **16**, 11827.
- 16 (a) J. M. Alonso and M. P. Muñoz, *Angew. Chem., Int. Ed.*, 2018, **57**, 4742; (b) L. Cooper, J. M. Alonso, L. Eagling, H. Newson, S. Herath, C. Thomson, A. Lister, C. Howsham, B. Cox and M. P. Muñoz, *Chem.-Eur. J.*, 2018, **24**, 6105.
- 17 For the significance of counter anions in the optimization of gold catalysts, see: (a) J. Schießl, J. Schulmeister, A. Doppiu, E. Wörner, M. Rudolph, R. Karch and A. S. K. Hashmi, *Adv. Synth. Catal.*, 2018, **360**, 3949; (b) J. Schießl, J. Schulmeister, A. Doppiu, E. Wörner, M. Rudolph, R. Karch and A. S. K. Hashmi, *Adv. Synth. Catal.*, 2018, **360**, 2493; (c) M. Jia and M. Bandini, *ACS Catal.*, 2015, **5**, 1638; (d) Z. Lu, J. Han, H. B. Hammond and B. Xu, *Org. Lett.*, 2015, **17**, 4534.
- 18 (a) X. Huang and S. Ma, *Acc. Chem. Res.*, 2019, **52**, 1301; (b) D. Ma, X. Duan, C. Fu, X. Huang and S. Ma, *Synthesis*, 2018, **50**, 2533; (c) X. Huang, T. Cao, Y. Han, X. Jiang, W. Lin, J. Zhang and S. Ma, *Chem. Commun.*, 2015, **51**, 6956.
- 19 For other sequences using gold catalysis of halogenated substrates and subsequent palladium-catalyzed steps, see: (a) P. García-Domínguez and C. Nevado, *J. Am. Chem. Soc.*, 2016, **138**, 3266; (b) A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Ackermann, J. D. B. Becker, M. Rudolph, C. Scholz and F. Rominger, *Adv. Synth. Catal.*, 2012, **354**, 133; (c) Y. Shi, K. E. Roth, S. D. Ramgren and S. A. Blum, *J. Am. Chem. Soc.*, 2009, **131**, 18022; (d) A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Rudolph, T. D. Ramamurthi and F. Rominger, *Angew. Chem., Int. Ed.*, 2009, **48**, 8243.
- 20 (a) Y. Qiu, J. Zhou, J. Li, C. Fu, Y. Guo, H. Wang and S. Ma, *Chem.-Eur. J.*, 2015, **21**, 15939; (b) J. Ye, S. Li, B. Chen, W. Fan, J. Kuang, J. Liu, Y. Liu, B. Miao, B. Wan, Y. Wang, X. Xie, Q. Yu, W. Yuan and S. Ma, *Org. Lett.*, 2012, **14**, 1346.
- 21 (a) A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2010, **49**, 5232; (b) H. Li, R. J. Harris, K. Nakafuku and R. A. Widenhoefer, *Organometallics*, 2016, **35**, 2242.

