# Chemical Science



### **EDGE ARTICLE**

View Article Online
View Journal | View Issue



Cite this: Chem. Sci., 2021, 12, 696

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 12th October 2020 Accepted 21st October 2020

DOI: 10.1039/d0sc05619g

rsc.li/chemical-science

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

Feng Jiang, (D) Chunling Fu and Shengming Ma (D)\*

Pyrido[1,2-a]-1H-indoles are important scaffolds found in many biologically active compounds. Herein, we first developed an IPrAuCl/AgSbF<sub>6</sub>-catalyzed cycloisomerization of N-1,3-disubstituted allenyl indoles affording pyrido[1,2-a]-1H-indoles. Then the axial-to-central chirality transfer starting from enantio-enriched N-1,3-disubstituted allenylindoles affording optically active pyrido[1,2-a]-1H-indoles has been realized in excellent yields and enantioselectivities. A mechanism has been proposed based on mechanistic studies. Synthetic applications have also been demonstrated.

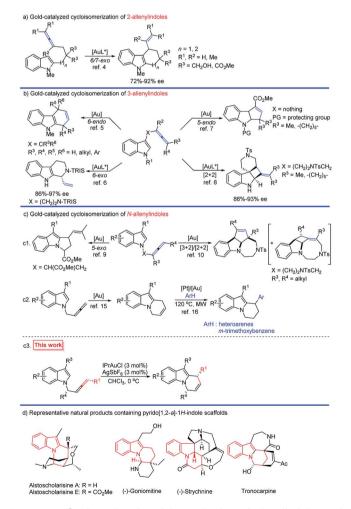
#### Introduction

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, Widenhoefer 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 6endo, 6 6-exo, 6 and 5-endo 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 coworkers 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]-1H-indoles are core motifs in ubiquitous biologically active alkaloids (Scheme 1d). 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, Michael addition of  $\alpha,\beta$ -unsaturated ketones and radical cyclization of N-alkylindoles, mostly suffering from the substrate scope, selectivity, and efficiency. Recently, González's and Muñoz's groups reported the elegant Au- or Pt–Au catalyzed cycloisomerization of N-2,3-

Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, Zhejiang, People's Republic of China. E-mail: masm@sioc.ac.cn

† 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

Entry	Catalyst	Solvent	Yield of $2a^b$ (%)	Yield of $3a^b$ (%)	Recovery $^b$ (%)
1	IPrAuCl/AgNTf <sub>2</sub>	Toluene	81	1	_
2	AuCl/AgNTf <sub>2</sub>	Toluene	<u> </u>	_	84
3	AuCl(PPh <sub>3</sub> )/AgNTf <sub>2</sub>	Toluene	14	3	61
4	AuCl(PMe <sub>3</sub> )/AgNTf <sub>2</sub>	Toluene	14	4	62
5 <sup>c</sup>	[Au <sub>2</sub> Cl <sub>2</sub> (dppm)]/AgNTf <sub>2</sub>	Toluene	15	4	50
6	AuCl(LB-phos)/AgNTf <sub>2</sub>	Toluene	26	3	50
7	IPrAuCl/AgBF <sub>4</sub>	Toluene	66	16	_
8	IPrAuCl/AgOTs	Toluene	_	_	91
9	IPrAuCl/AgPF <sub>6</sub>	Toluene	_	69	_
10	IPrAuCl/AgSbF <sub>6</sub>	Toluene	70	13	_
$11^d$	IPrAuCl/AgSbF <sub>6</sub>	Toluene	92	_	_
$12^d$	IPrAuCl/AgSbF <sub>6</sub>	CH <sub>3</sub> CN	9	_	87
$13^d$	IPrAuCl/AgSbF <sub>6</sub>	$CH_2Cl_2$	91	_	_
$14^d$	IPrAuCl/AgSbF <sub>6</sub>	$\mathrm{CHCl}_3$	95	_	_

<sup>&</sup>lt;sup>a</sup> Reaction conditions (unless otherwise noted): 1a (0.2 mmol) and catalyst (5 mol%) in 5.0 mL of solvent at 65 °C. <sup>b</sup> Yields were determined by the <sup>1</sup>H NMR analysis of the crude products with mesitylene as the internal standard. <sup>c</sup> 2.5 mol% [Au<sub>2</sub>Cl<sub>2</sub>(dppm)] was used. <sup>d</sup> The reaction was carried out at room temperature for 12 h.

butadienylindoles affording 6,9-dihydropyrido[1,2-a]-1Hindoles, 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-(2,3allenyl)indoles would provide an efficient approach to various 9substituted pyrido[1,2-a]-1H-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]/[AgNTf<sub>2</sub>], 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(PPh<sub>3</sub>), AuCl(PMe<sub>3</sub>), Au<sub>2</sub>Cl<sub>2</sub>(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 AgSbF<sub>6</sub> 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 CHCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, and toluene were the best. Finally, we defined the standard

Table 2 Gold-catalyzed cyclization reaction of racemic N-allenylindoles  $\mathbf{1}^a$ 

	1					
Entry	R <sup>1</sup>	$\mathbb{R}^2$	$\mathbb{R}^3$	t/h	Yield of 2 (%)	
1	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	Н	H (1a)	12	71 <b>(2a)</b>	
2	n-C <sub>10</sub> H <sub>21</sub>	Н	H (1b)	12	68 ( <b>2b</b> )	
3	$CH_2 = CH(CH_2)_8$	Н	H (1c)	12	72 <b>(2c)</b>	
4	n-C <sub>4</sub> H <sub>9</sub>	5-OMe	H (1d)	12	78 (2d)	
5	n-C <sub>4</sub> H <sub>9</sub>	4-Me	H (1e)	12	77 ( <b>2e</b> )	
6	n-C <sub>4</sub> H <sub>9</sub>	6-Cl	H (1f)	12	84 (2f)	
7	n-C <sub>4</sub> H <sub>9</sub>	Н	Me (1g)	17	96 ( <b>2g</b> )	
8	$Cl(CH_2)_5$	Н	Me (1h)	10	92 ( <b>2h</b> )	
9	$BnCH_2$	Н	Me (1i)	12	94 (2i)	
10	3-Pentyl	Н	Me ( <b>1j</b> )	12	98 ( <b>2j</b> )	
11	n-C <sub>4</sub> H <sub>9</sub>	Н	Ethyl (1k)	14	97 ( <b>2k</b> )	
12	n-C <sub>4</sub> H <sub>9</sub>	Н	$TBSO(CH_2)_2$ (11)	12	100 (2l)	
13	n-C <sub>4</sub> H <sub>9</sub>	6-Cl	Me (1m)	12	96 (2m)	
14	n-C <sub>4</sub> H <sub>9</sub>	5-OMe	Cl (1n)	13	98 (2n)	
$15^b$	Ph	Н	Me (10)	16	96 ( <b>20</b> )	
$16^b$	$2$ -Br $C_6H_4$	Н	Me (1p)	12	93 ( <b>2p</b> )	
17	4-FC <sub>6</sub> H <sub>4</sub>	Н	Me (1q)	12	86 ( <b>2q</b> )	
18	$4$ -Br $C_6$ H $_4$	Н	Me (1r)	12	80 (2r)	
19 <sup>c</sup>	$4$ -Br $C_6$ H $_4$	H	$TBSO(CH_2)_2 (1s)$	14	83 ( <b>2s</b> )	

<sup>2</sup> Reaction conditions: 1 (1 mmol), IPrAuCl (3 mol%) and AgSbF<sub>6</sub> (3 mol%) in CHCl3 (5.0 mL) at room temperature unless otherwise The reaction was performed on a 0.2 mmol scale in 5.0 mL of CHCl<sub>3</sub>. <sup>c</sup> 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<sup>a</sup>

Entry Solvent		Yield/ee of ( <i>R</i> )-2a $(\%)^b (\%)^c$	Recovery/ee of $(R_a)$ -1a $(\%)^b$ $(\%)^c$	
1	CHCl <sub>3</sub>	93/91	_	
2	DCE	74/90	13/84	
3	$CH_2Cl_2$	98/90	<u> </u>	
4	Toluene	56/92	47/93	
5	CH <sub>3</sub> 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 <sub>3</sub>	_	91/98	
11 <sup>g</sup>	CHCl <sub>3</sub>	90/87	<del>_</del>	
$12^{f,g,h}$	CHCl <sub>3</sub>	94/90	_	

<sup>&</sup>lt;sup>a</sup> Reaction conditions:  $(R_a)$ -1a (0.2 mmol), catalyst (5 mol%) in solvent (5.0 mL) at 0°C under a N<sub>2</sub> atmosphere unless otherwise noted. <sup>b</sup> Yields were determined by <sup>1</sup>H NMR using mesitylene as the internal standard. <sup>c</sup> The ee was determined by HPLC analysis using a chiral stationary phase. <sup>d</sup> Without AgSbF<sub>6</sub>. <sup>e</sup> Without IPrAuCl. <sup>f</sup> Reaction was carried out at 0 °C for 48 h. <sup>g</sup> The reaction was performed on a 1 mmol scale. <sup>h</sup> 3 mol% catalyst was used.

conditions as follows: IPrAuCl and  $AgSbF_6$  in  $CHCl_3$  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  $R^3 = Me$ , Et, Cl, TBSO(CH<sub>2</sub>)<sub>2</sub>, the yields of 2 were much higher, as compared with  $R^3 = H$  (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 AgSbF<sub>6</sub> was tested in CHCl<sub>3</sub> 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 AgSbF<sub>6</sub> 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 AgSbF<sub>6</sub> in CHCl<sub>3</sub> 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  $R^3 = H$ . As shown in Table 4,  $R^1$  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  $(R_a)$ - $1^a$ 

	$(R_a)$ -1/ $(ee\%)$		2		
Entry	$R^1/R^2$	<i>t</i> (h)	Yield (%)	ee (%)	
1	n-C <sub>4</sub> H <sub>9</sub> /H ((R <sub>a</sub> )- <b>1a</b> )/97	48	94 ((R)-2a)	90	
2	$n\text{-}C_{10}H_{21}/H((R_a)\text{-}\mathbf{1b})/98$	48	95 ((R)-2b)	90	
3	$CH_2 = CH(CH_2)_8/H ((R_a)-1c)/96$	51	96 ((R)-2c)	92	
4	$n$ -C <sub>4</sub> H <sub>9</sub> /5-OMe (( $R_a$ )-1d)/98	53	95 ((R)-2d)	91	
$5^b$	$n-C_4H_9/4-Me ((R_a)-1e)/98$	48	88 ((R)-2e)	90	
6	$n-C_4H_9/6-Cl((R_a)-1f)/98$	58	93 ((R)-2f)	78	

 $<sup>^</sup>a$  Reaction conditions: (*R*<sub>a</sub>)-1 (1 mmol), IPrAuCl (3 mol%), and AgSbF<sub>6</sub> (3 mol%) in CHCl<sub>3</sub> (25.0 mL) at 0  $^{\circ}$ C unless otherwise noted.  $^b$  5 mol% catalyst was used.

**Table 5** Gold-catalyzed cyclization reaction of 3-substituted  $(R_a)$ -1<sup>a</sup>

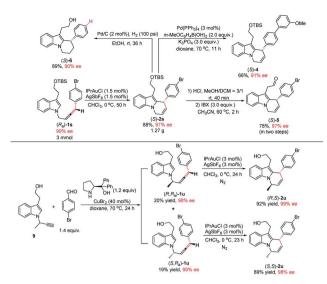
	$(R_a)-1/(ee\%)$		2	
Entry	$R^1/R^2/R^3$	t (h)	Yield (%)	ee (%)
$1^b$	$n-C_4H_9/H/Me((R_a)-1g)/98$	59	90 ((R)-2g)	96
2	$Cl(CH_2)_5/H/Me((R_a)-1h)/98$	48	99 ((R)-2h)	99
3	BnCH <sub>2</sub> /H/Me (( $R_a$ )-1i)/97	48	98 ((R)-2i)	98
4	3-Pentyl/H/Me $((R_a)-1j)/98$	48	89 ((R)-2j)	90
5	$n$ -C <sub>4</sub> H <sub>9</sub> /H/ethyl $((R_a)$ - <b>1k</b> )/99	48	98 ((R)-2k)	97
6	$n-C_4H_9/H/TBSO(CH_2)_2 ((R_a)-11)/98$	48	98 ((R)-21)	96
7	$n-C_4H_9/6-Cl/Me ((R_a)-1m)/98$	48	97 ((R)-2m)	95
8	$n-C_4H_9/5-OMe/Cl((R_a)-1n)/98$	42	98 ((R)-2n)	98
9	$Ph/H/Me ((R_a)-10)/99$	48	99 ((S)- <b>20</b> )	95
10	$2-BrC_6H_4/H/Me((R_a)-1p)/96$	48	98 ((S)-2p)	96
11	$4-FC_6H_4/H/Me ((R_a)-1q)/98$	48	89 ((S)-2 <b>q</b> )	95
12	$4-BrC_6H_4/H/Me((R_a)-1r)/98$	48	91 ((S)-2r)	96
13	$4-BrC_6H_4/H/TBSO(CH_2)_2 ((R_a)-1s)/99$	48	90 ((S)-2s)	92

<sup>&</sup>lt;sup>a</sup> Reaction conditions: (R<sub>a</sub>)-1 (1 mmol), IPrAuCl (3 mol%) and AgSbF<sub>6</sub> (3 mol%) in CHCl<sub>3</sub> (25.0 mL) at 0 °C unless otherwise noted. <sup>b</sup> 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/AgSbF<sub>6</sub> 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.<sup>19</sup> 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 1position 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).

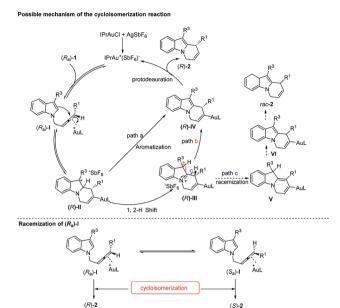
In order to unveil the nature of the stereoselectivity of the reaction, the absolute configurations of the starting materials



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 cyclo-isomerization 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  $\mathbf{1g}$  and  $\mathrm{CD_3OD}$  to the gold catalyst in  $\mathrm{CHCl_3}$  afforded  $\mathbf{2g}$ - $\mathbf{D}$  with 50% deuterium incorporation, confirming the process of proto-deauration (eqn (5), Scheme 3).

Based on these experimental data, we proposed a plausible mechanism<sup>15,21</sup> of the reaction (Scheme 4): firstly, the catalytically active cationic Au(1) species generated in situ coordinated with the "distal" double bond of the allene unit  $(R_a)$ -I. Subsequent antiattack of the C2 atom at the coordinated C=C bond formed (R)-II with a high stereoselectivity. At this stage, when  $R^3 = Me$ , Et, Cl, and TBSO(CH<sub>2</sub>)<sub>2</sub>, 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<sup>3</sup> being H and CO<sub>2</sub>Me. 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<sup>+</sup>-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

Financial support from the National Natural Science Foundation of China (21690063 and 21572202) is greatly appreciated. Shengming Ma is a Qiu Shi Adjunct Professor at Zhejiang University. We thank Mr Weifeng Zheng in our group for reproducing the results: *rac-*2n, (*R*)-2e, and (*S*)-2r.

#### 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.
- 2 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.
- 3 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,

**Edge Article** 

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:

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. Piedrafita, A. Ballesteros, Á. L. Suárez-Sobrino 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.