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Kinetic resolution of 1-(1-alkynyl)cyclopropyl ketones *via* gold-catalyzed divergent (4 + 4) cycloadditions: stereoselective access to furan fused eight-membered heterocycles†

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Chiral eight-membered heterocycles comprise a diverse array of natural products and bioactive compounds, yet accessing them poses significant challenges. Here we report a gold-catalyzed stereoselective (4 + 4) cycloaddition as a reliable and divergent strategy, enabling readily accessible precursors (anthranils and *ortho*-quinone methides) to be intercepted by *in situ* generated gold-furyl 1,4-dipoles, delivering previously inaccessible chiral furan/pyrrole-containing eight-membered heterocycles with good results (56 examples, all >20:1 dr, up to 99% ee). Moreover, we achieve a remarkably efficient kinetic resolution (KR) process (s factor up to 747). The scale-up synthesis and diversified transformations of cycloadducts highlight the synthetic potential of this protocol. Computational calculations provide an in-depth understanding of the stereoselective cycloaddition process.

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Introduction

Eight-membered rings, fused polycyclic ones in particular, represent a structurally diverse group of heterocycles distributed in a wide range of natural products and pharmaceuticals, such as hippobrine, FR-900482, heliannuol A, protosapannin, and PDK inhibitors (Scheme 1a).¹ They possess various interesting biological activities such as anticancer, antiviral, and anti-inflammatory effects. Despite the steady progress in synthetic methods achieved over past decades, the construction of these complex structures is still quite challenging due to the unfavorable enthalpy and entropy factors, as well as the transannular interactions.² Thus, it is highly desirable to develop concise and robust strategies to access these prestigious motifs with a high level of stereo-control.

Among recent methods developed for the construction of eight-membered rings, the intermolecular (4 + 4) cycloaddition has evolved as a prevailing strategy.³ In this scenario, transition-metal (TM) mediated zwitterionic 1,4-dipolar

species have been recognized as privileged building blocks for divergent preparation of chiral eight-membered scaffolds, especially with regard to high diastereo- and enantio-control (Scheme 1b).⁴ However, these dipolar species often lack structural diversity and heterocyclic 1,4-dipoles are seldom studied, hampering the exploration of the (4 + 4) strategy in a broader manner.⁵ To address this long-standing challenge, we wondered whether TM-based furyl species could serve as heterocyclic 1,4-dipoles, which would furnish challenging eight-membered cycloadducts with tetrasubstituted furan scaffolds (Scheme 1c). In 2008, Zhang and co-workers presented one remarkable study of Au-catalyzed racemic (4 + 2) cycloaddition of 1-(1-alkynyl)-cyclopropyl ketones with indoles, where the alkynyl cyclopropyl ketones serve as the Au-furyl 1,4-dipole precursors.⁶ Later, several related gold-catalyzed (4 + 2) and (4 + 3) cycloadditions involving 1-(1-alkynyl)-cyclopropyl ketones have been disclosed, yet mainly in the racemic version.⁷ Despite the considerable successes, catalytic asymmetric (4 + 4) cycloaddition of Au-furyl 1,4-dipoles to afford chiral eight-membered heterocycles remains elusive in the literature.

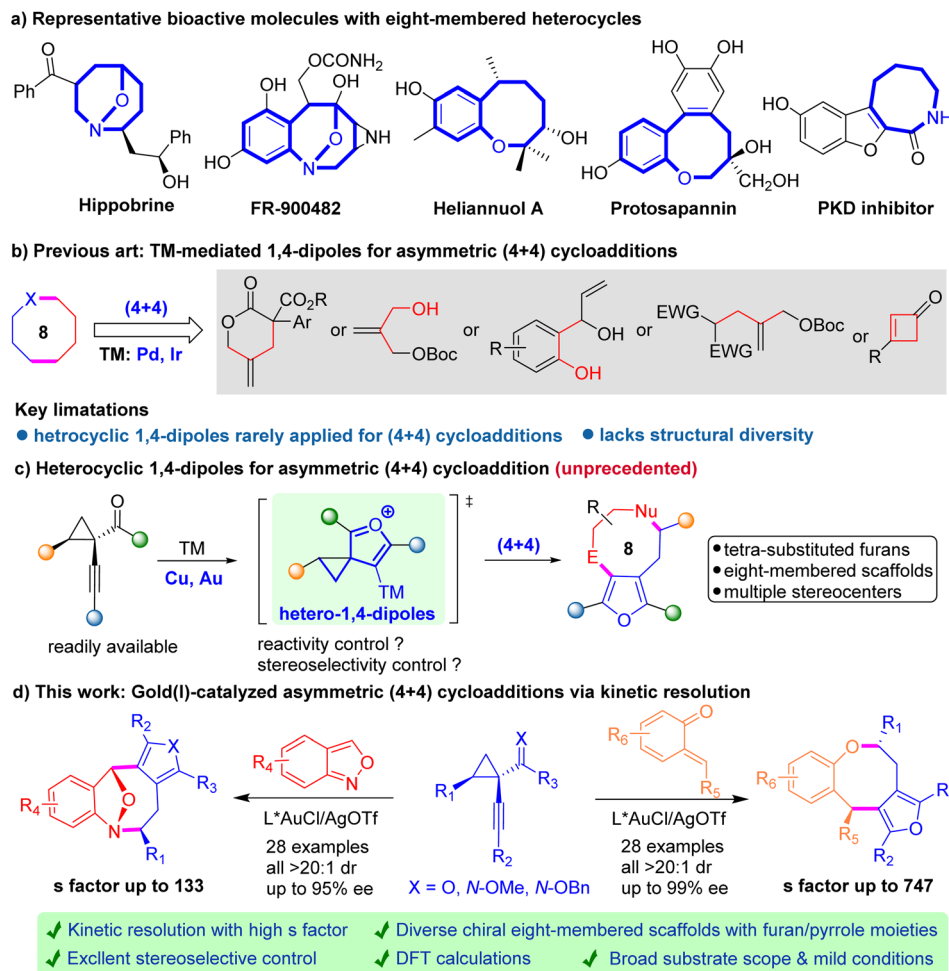
With the growing demand for eight-membered motifs and the desirable bioactivities associated with furan-containing molecules in the pharmaceutical area, we envisioned that integrating Au-furyl 1,4-dipoles with various four-atom synthons could chart a novel path for the rapid assembly of furan-fused eight-membered skeletons, further expanding their chemical space for drug discovery. Even strategically ideal, this proposal still faces several challenges, including

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Scheme 1 Asymmetric (4 + 4) cycloadditions for constructing eight-membered scaffolds.

the particular issue of controlling diastereo- and enantioselectivity during the cycloaddition process due to the unfavorable entropic factors and transannular interactions. Another issue is that it is uncertain whether the Au-furyl 1,4-dipoles are compatible with readily available four-atom acceptors to generate unprecedented eight-membered heterocycles instead of the competitive six-membered rings. In an outgrowth of our ongoing interest,^{4b} herein we report a highly enantio- and diastereoselective gold-catalyzed (4 + 4) cycloaddition for the facile access to valuable chiral eight-membered rings bearing tetrasubstituted furan moieties with diverse structural features (Scheme 1d). This asymmetric approach enables the construction of two types of optically active furan/pyrrole-fused ring systems through the efficient kinetic resolution of 1-(1-alkynyl)-cyclopropyl ketones.⁸ Of note, density functional theory (DFT) investigations shed light on the mechanism of the chiral gold-catalyzed stereoselective cycloaddition. Furthermore, the versatility of this strategy is demonstrated through a series of synthetic

transformations of the resulting enantioenriched eight-membered products.

Results and discussion

To validate our working hypothesis, we began the investigation by evaluating the (4 + 4) cycloaddition reaction involving racemic cyclopropyl ketone **1a** and anthranil **2a** as the model substrates (Table 1). Various metal catalysts were initially screened, and the superior result was obtained with the Au(I) catalyst and AgOTf.⁹ We next optimized the asymmetric cycloaddition by using various chiral gold complexes. To our delight, the desired eight-membered cycloadduct **3a** was formed in reasonable enantiomeric excess (ee) with commercially available bidentate phosphine ligands *via* the KR process (see the ESI† for details). The reaction proceeded smoothly with (*S*)-SEGPHOS, affording the desired **3a** in 55% ee. Encouraged by this result, a variety of sterically more demanding SEGPHOS derivatives were investigated (entries 1–



Table 1 Reaction optimization^a

Entry	Ligand	Solvent	3a yield ^b	ee ^c	s ^d
1	L1	DCM	21%	61%	6
2	L2	DCM	43%	65%	14
3	L3	DCM	35%	55%	7
4	L2	Toluene	15%	60%	10
5	L2	DCE	36%	60%	12
6	L2	CHCl ₃	30%	61%	12
7 ^e	L2	DCM	44%	70%	19
8 ^f	L2	DCM	46%	77%	25
9 ^g	L2	DCM	45%	87%	45

^a All reactions were performed with **1a** (0.1 mmol) and **2a** (0.07 mmol) in the presence of Me₂SAuCl (4.0 mol%), ligand (2.0 mol%), and AgOTf (6.0 mol%) in solvent (1.0 mL) at room temperature or indicated temperature under a nitrogen atmosphere. ^b Isolated yields. ^c Determined by HPLC analysis. ^d Selectivity (*s*) values were calculated through the equation $s = \ln[(1 - C)(1 - ee_{1a})] / \ln[(1 - C)(1 + ee_{1a})]$, where *C* is the conversion; $C = ee_{1a} / (ee_{1a} + ee_{3a})$. ^e The reaction temperature was 0 °C. ^f The reaction temperature was -10 °C. ^g The reaction temperature was -20 °C.

3), and it was found that the enantioselectivity was improved to 61% ee with (*S*)-DM-SEGPHOS L1 (entry 1) and 65% ee with (*S*)-DTBM-SEGPHOS L2 (entry 2), respectively. Surprisingly, the enantioselectivity was not further improved by subsequent modification of the ligand (entry 3). Then, different solvents were examined with (*S*)-DTBM-SEGPHOS as the chiral ligand, showing that the cycloaddition was more efficient in halogenated solvents (entries 4–6). Finally, the reaction temperature was optimized to furnish the product **3a**, the best result, in 45% yield with 87% ee at -20 °C (*s* = 45, entry 9). Notably, excellent diastereoselectivity (all >20 : 1 dr) was obtained for this transformation.

Under the optimal reaction conditions, we investigated the scope of anthranils and cyclopropyl ketones/oximes in this asymmetric (4 + 4) cycloaddition. As demonstrated in Table 2, this method tolerates a broad range of electronically distinct groups at different positions on aryl moieties, delivering the desired furan-fused eight-membered heterocycles **3a–3a'** in good yields with generally high levels of stereoselectivities (*s* factor up to 133, up to 45% yield, up to 95% ee, all >20 : 1 dr). Various functional groups, including fluoro,

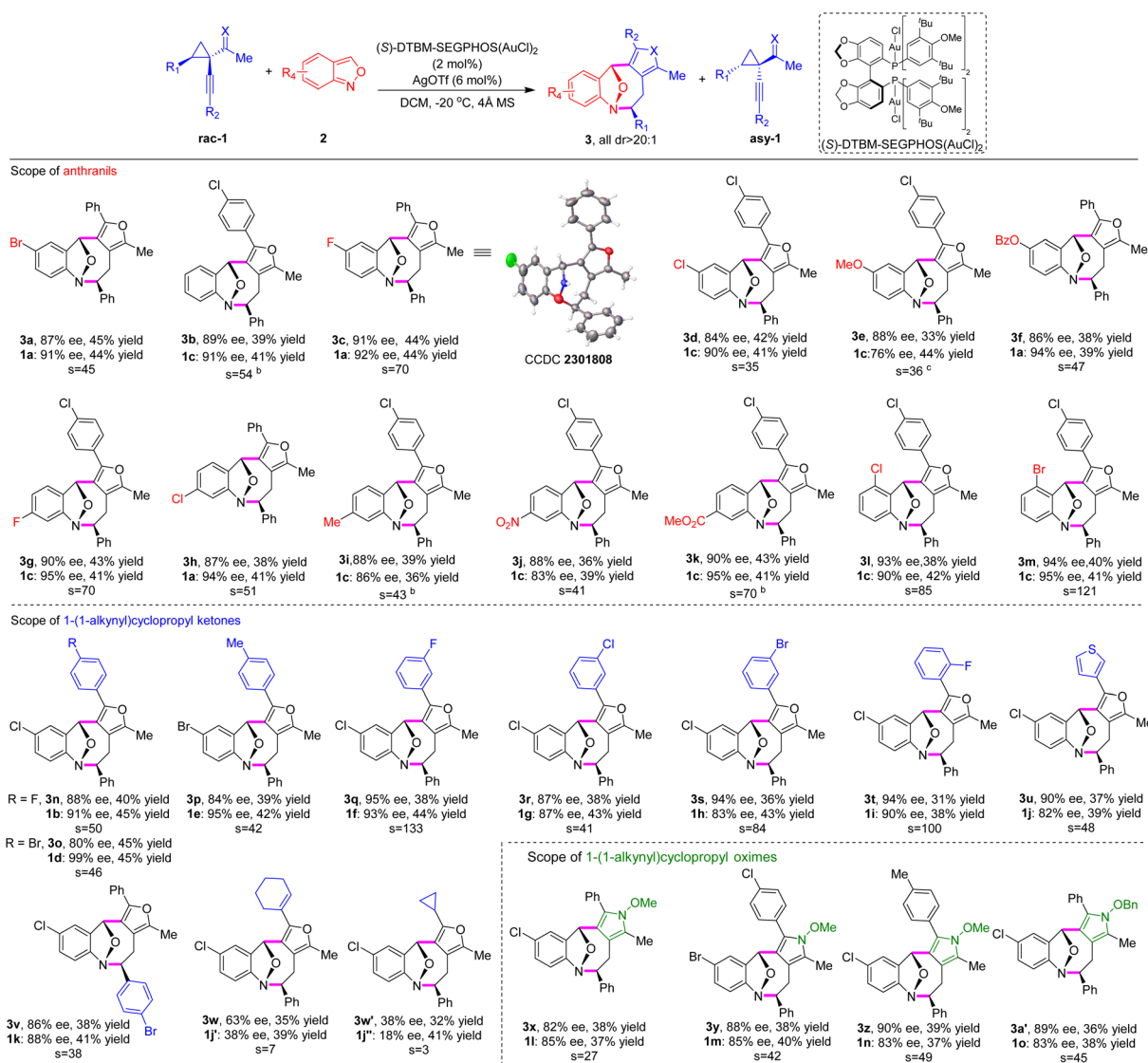
chloro, bromo, alkoxy, methyl ester, benzoate and nitro, were all compatible (**3a–3m**). Note that the substrate bearing a strong electron-donating group (methoxy) afforded the eight-membered adduct **3e** in lower yield (33%) and chiral cyclopropyl ketone **1c** in moderate enantioselectivity (76% ee). Subsequently, we explored the versatility of cyclopropyl ketones **1** with anthranil **2d** as the model component (Table 2). Racemic cyclopropyl ketones bearing methyl or various halogens, regardless of the position on the aromatic ring, were well tolerated, generating the desired products **3n–3w'** in 31–45% yields with 80–95% ee and the corresponding chiral cyclopropyl ketones **1b–1j''** in 38–45% yields with 82–99% ee. 3-Thiophenyl substrate **1j** led to the cycloadduct **3u** in 37% yield with 90% ee.

Furthermore, a similar level of efficiency was observed for cyclopropyl ketone **1k** with 4-bromo phenyl substitution as R₁ (**3v**, 38% yield, and 86% ee). Remarkably, substrate **1j'** bearing a cyclohexenyl group and **1j''** featuring a cyclopropyl moiety performed well under optimized reaction conditions, affording the corresponding products **3w** and **3w'** in 35% yield, >20 : 1 dr, 63% ee, and 32% yield, >20 : 1 dr, 38% ee, respectively. In addition, the absolute configuration of product **3c** was confirmed as (5*S*, 6*R*, 11*R*) by single-crystal X-ray structure analysis.¹⁰

Pyrroles are ubiquitous in natural products and exhibit diverse biological activities.¹¹ It is intriguing to construct complex pyrrole-containing molecules that are needed for biological investigation.¹² We anticipated that the development of new asymmetric methods to build pyrrole-containing scaffolds bearing multistereogenic centers could be valuable yet underdeveloped. When alkynylcyclopropyl oximes were employed, this (4 + 4) cycloaddition strategy proceeded smoothly under the aforementioned reaction conditions, affording the densely substituted pyrrole-fused benzo[*b*]azocines **3x–3a'** with up to 39% yield and 90% ee (Table 2).

To demonstrate the synthetic diversity of this strategy, we continued to extend this method to the stereoselective (4 + 4) cycloaddition with another versatile reactive intermediate *ortho*-quinone methides (*o*-QMs),¹³ providing straightforward access to synthetically challenging furan-fused benzo[*b*]oxocines, which are important structural motifs found in biologically active compounds.¹⁴ Pleasingly, *o*-QMs were suitable cycloaddition partners for this asymmetric (4 + 4) reaction under similar catalytic conditions to those for the anthranil substrates, representing the first gold-catalyzed asymmetric higher-order cycloaddition to construct furan-containing eight-membered cyclic ethers. Initially, the substrate scope of the R₃ substituent of cyclopropyl ketones was examined. As shown in Table 3, for R₃, both alkyl and aryl groups participated well to deliver the cycloadducts **5a–5i** in good yields and excellent enantioselectivities (26–38% yields, 86–99% ee), albeit substrates with aryl groups showed better resolution efficiency than ones with alkyl groups under the optimized conditions. Meanwhile, cycloadduct **5h**



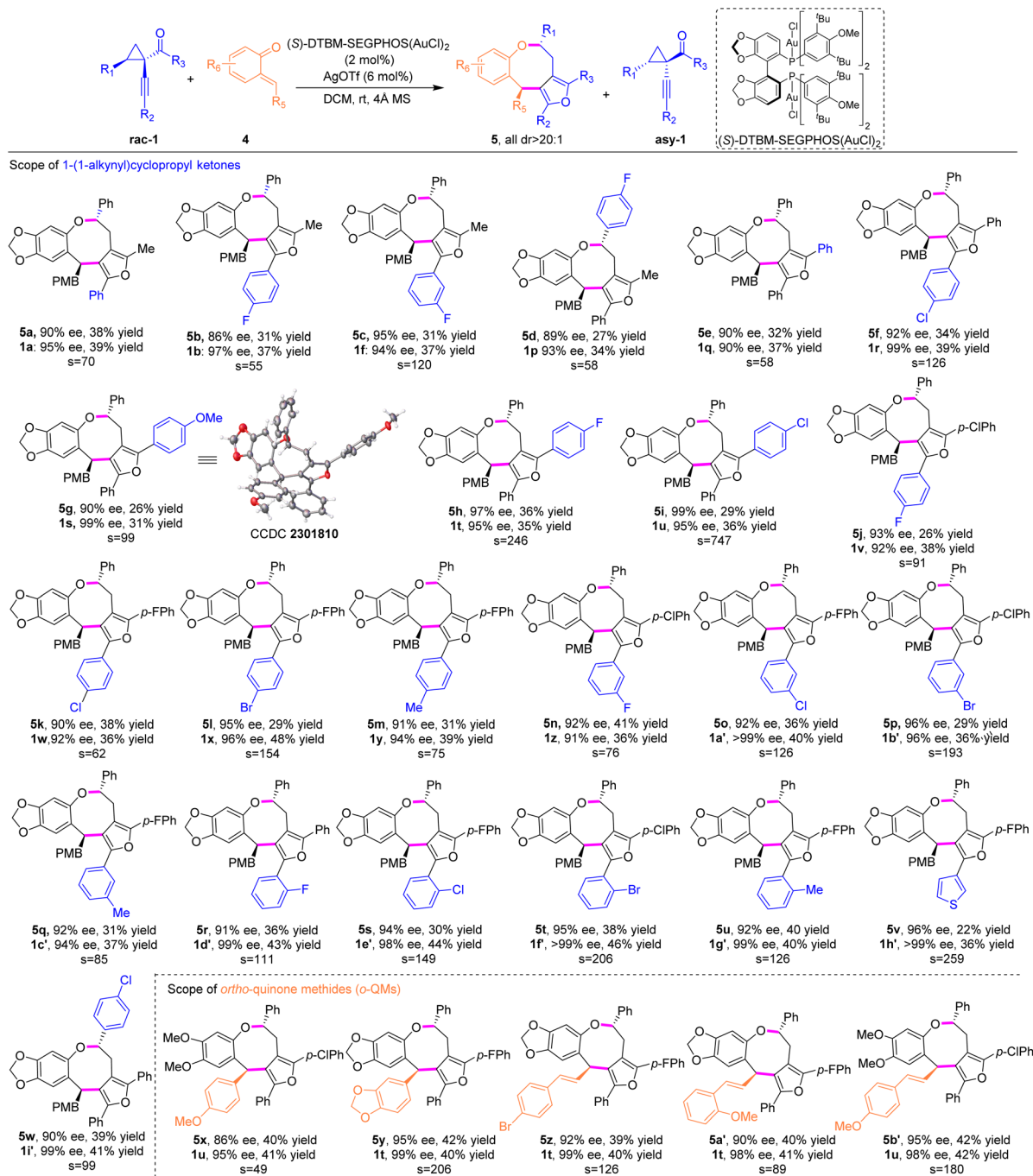
Table 2 Reaction scope of anthranils^a

^a All reactions were performed with **1** (0.2 mmol) and **2** (0.14 mmol) in the presence of (*S*)-DTBM-SEGPHOS(AuCl)₂ (2.0 mol%), and AgOTf (6.0 mol%) in DCM at −20 °C. ^b The reaction temperature was 0 °C. ^c The reaction temperature was 10 °C.

with an electron-withdrawing group was obtained in 36% yield with 97% ee, while product **5g** with an electron-donating group was isolated in lower yield with 90% ee. The *s* factor could be further improved to 747 when the *p*-chlorophenyl substituent was introduced (**5i**). With this information in hand, cyclopropyl ketones bearing R₃ with an electron-deficient aryl substituent were selected to explore the scope of R₂ substituents. Regardless of electronic and steric properties of the R₂ substituents on the phenyl group, for example, F, Cl, Br, and Me, at *ortho*-, *meta*- and *para*-

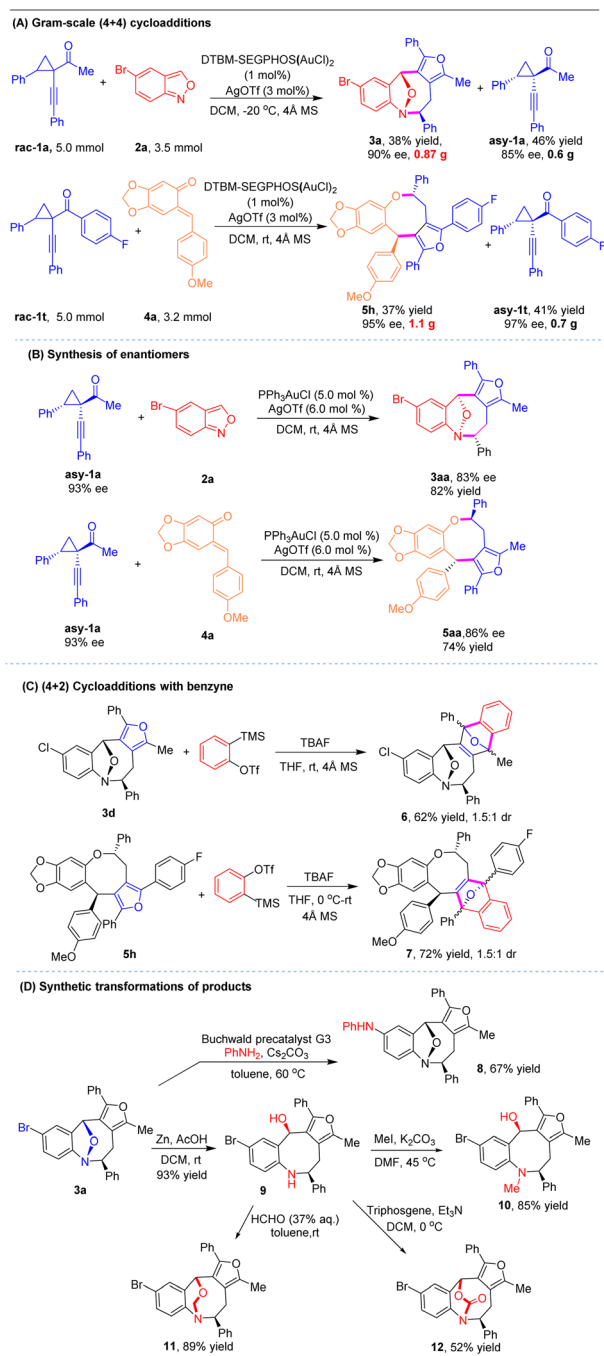
positions, cyclopropyl ketones **1** participated in the corresponding (4 + 4) cycloadditions smoothly, producing a series of furan-fused eight-membered heterocycles **5j**–**5v** with satisfactory results (up to 41% yield, all >20 : 1 dr and 90–96% ee). The chiral cyclopropyl ketones **1v**–**1h'** were prepared in 91–99% ee. In addition, 3-thiophene-cycloadduct **5v** was synthesized in 36% yield and >99% ee. Substitution at the R₁ fragment was also compatible (**5w**). Unfortunately, substrates with R₂ as aliphatic substituents, such as *n*-butyl and cyclopropyl groups, were sluggish in the current reaction



Table 3 Reaction scope of *ortho*-quinone methides^a

^a All reactions were performed with **1** (0.2 mmol) and **4** (0.13 mmol) in the presence of (*S*)-DTBM-SEGPHOS(AuCl)₂ (2.0 mol%), and AgOTf (6.0 mol%) in DCM at room temperature. PMB: *p*-methoxybenzyl; *p*-FPh: *p*-fluorobenzyl; *p*-ClPh: *p*-chlorobenzyl.





Scheme 2 Synthetic transformations.

system. Next, we turned our attention to explore the feasibility of *o*-QMs.

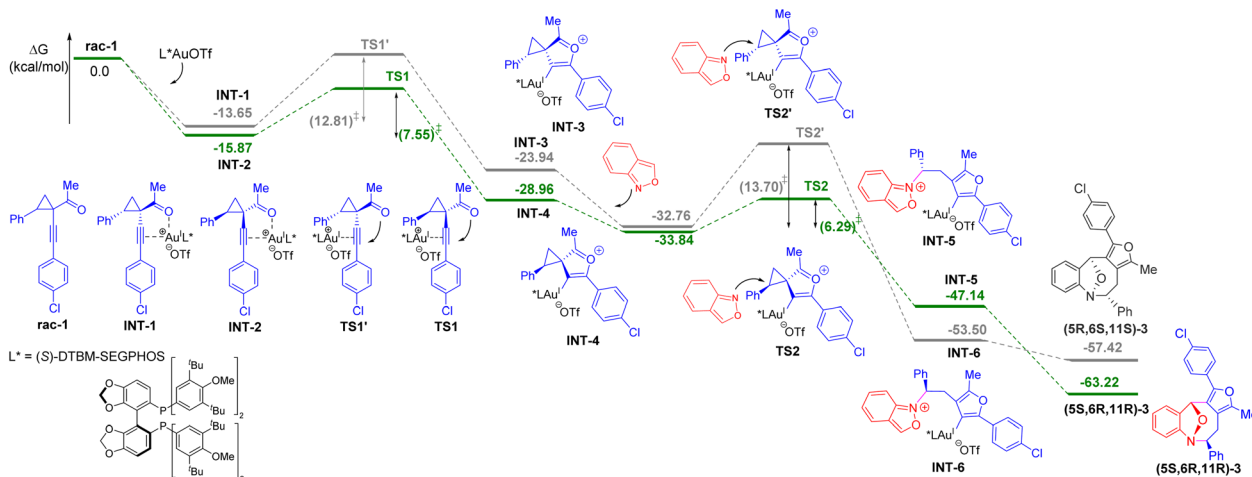
Notably, *o*-QMs bearing electron-rich phenyl substituents and various styryl-substituted groups were transformed into the densely substituted products (**5x–5b'**) in excellent yields and stereoselectivities. The absolute configuration of eight-

membered cyclic ether **5g** was determined by single-crystal X-ray analysis.¹⁰

To evaluate the synthetic utility of this strategy, gram-scale reactions and derivatization of the obtained eight-membered rings were conducted (Scheme 2). The catalytic asymmetric (4 + 4) cycloadditions proceeded well with 1 mol% chiral gold complex, while maintaining the high efficiency and excellent stereochemical outcome as the corresponding small-scale reactions. Subjecting cyclopropyl ketone **1a** (5.0 mmol) and anthranil **2a** (3.5 mmol) under the standard conditions led to chiral cycloadduct **3a** in 38% yield with 90% ee. Another product **5h** was prepared in 1.1 gram by a similar process on a 5.0 mmol scale (37% yield, 95% ee, >20 : 1 dr, Scheme 2A). Upon subjecting the optically active 1-(1-alkynyl)cyclopropyl ketones **asy-1a** to the (4 + 4) cycloaddition with racemic gold catalysis, the resulting chiral eight-membered heterocycles **3aa** and **5aa** were obtained in favorable yields with 83% ee and 86% ee, respectively. This outcome indicates that the cycloaddition predominantly proceeds *via* an S_N2 process (Scheme 2B). Next, synthetic transformations of the product were explored. The furan moiety in products **3d** and **5h** underwent (4 + 2) cycloadditions with *in situ* generated benzyne to provide polycyclic scaffolds **6** and **7** in 62% yield and 72% yield, respectively (Scheme 2C). Cycloadduct **3a** was functionalized *via* Buchwald–Hartwig amination with aniline to generate **8** in 67% yield (Scheme 2D). Moreover, compound **3a** can be further elaborated with Zn powder under acidic conditions to deliver the tetrahydrobenzo[*b*]azocine derivative **9** in 93% yield *via* cleavage of the N–O bond. Methylation of **9** with MeI/K₂CO₃ gave *N*-methylated compound **10** in 85% yield. The complex bridged scaffold **11** could be accessed in 89% yield by treating **9** with formaldehyde. Treatment of **9** with triphosgene afforded another bridged carbamate **12**.

We next carried out density functional theory (DFT) calculations to rationalize the mechanism of the asymmetric (4 + 4) cycloaddition method (see the ESI† for details). The energy profile is outlined in Scheme 3. The kinetic resolution process was realized by the activation of racemic 1-(1-alkynyl)cyclopropyl ketone **1** with the (*S*)-DTBM-SEGPHOS gold complex, generating two gold- π -alkyne intermediates **INT1** and **INT2** with the energy barrier of 2.22 kcal mol⁻¹. The formation of **INT2** with cyclopropyl ketone **1** as (1*R*, 2*S*) configuration has lower energy compared to **INT1**. The following intramolecular ring closure to generate gold-mediated 1,4-dipole intermediate **INT4** is more favored than the formation of **INT3** by 5.26 kcal mol⁻¹. For **INT4**, the subsequent stereoselective (4 + 4) cycloaddition is highly exothermic and energetically feasible with the energy barrier of 6.29 kcal mol⁻¹. Comparing the energies of **TS2** and **TS2'** reveals that the observed cycloadduct (5*S*, 6*R*, 11*R*)-**3** is 7.41 kcal mol⁻¹ more favorable than the formation of cycloadduct (5*R*, 6*S*, 11*S*)-**3**. These results are consistent with the synthetic observations.





Scheme 3 DFT calculations.

Conclusions

We herein present two distinct chiral gold-catalyzed stereoselective (4 + 4) cycloadditions of cyclopropyl ketones with anthranils/*o*-QMs under mild reaction conditions, which offers a straightforward and promising approach for preparing densely substituted furan/pyrrole-fused eight-membered scaffolds featuring multiple stereocenters. High reaction efficiency (s factor up to 747) and excellent stereoselectivities were obtained, which are challenging within the asymmetric intermolecular higher-order cycloaddition arsenal. The broad substrate scope as well as good functional group tolerance makes this strategy appealing to the synthetic community. DFT calculations illustrated the kinetic resolution and (4 + 4) cycloaddition model. This strategy would not only expand the current library of furan/pyrrole-containing molecules with pharmaceutical importance, but also offer insights to explore unconventional chiral medium-sized structures.

Data availability

The data (experimental procedures, characterization data and DFT calculations) that support this article is available within the article and its ESI.†

Author contributions

X. Li conceived and supervised the project. X. Wang and R. Lv conducted the experiments and organized all data. X. Li wrote the manuscript with the consultation of all authors.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) T.-Y. Ke, S.-W. Wang, S.-R. Chen, D.-M. Huang, Y.-S. Lin, T.-L. Hwang, W.-C. Sun and Y.-B. Cheng, *J. Nat. Prod.*, 2023, **86**, 719; (b) T. Fukuyama, L. Xu and S. Goto, *J. Am. Chem. Soc.*, 1992, **114**, 383; (c) B. Harrison and P. Crews, *J. Org. Chem.*, 1997, **62**, 2646; (d) F. A. Macias, R. M. Varela, A. Torres, J. M. G. Molinillo and F. R. Fronczek, *Tetrahedron Lett.*, 1993, **34**, 1999; (e) F. A. Macias, J. M. G. Molinillo, R. M. Varela, A. Torres and F. R. Fronczek, *J. Org. Chem.*, 1994, **59**, 8261; (f) L.-C. Fu, X.-A. Huang, Z.-Y. Lai, Y.-J. Hu, H.-J. Liu and X.-L. Cai, *Molecules*, 2008, **13**, 1923; (g) K. M. George, M.-C. Frantz, K. Bravo-Altamirano, C. R. LaValle, M. Tandon, S. Leimgruber, E. R. Sharlow, J. S. Laz, Q. J. Wang and P. Wipf, *Pharmaceutics*, 2011, **3**, 186.
- (a) L. Yet, *Chem. Rev.*, 2000, **100**, 2963; (b) I. Shiina, *Chem. Rev.*, 2007, **107**, 239; (c) A. Hussain, S. K. Yousuf and D. Mukherjee, *RSC Adv.*, 2014, **4**, 43241; (d) J. R. Donald and W. P. Unsworth, *Chem.-Eur. J.*, 2017, **23**, 8780; (e) D. McLeod, M. K. Thøgersen, N. I. Jessen, K. A. Jørgensen, C. S. Jamieson, X.-S. Xue, K. N. Houk, F. Liu and R. Hoffmann, *Acc. Chem. Res.*, 2019, **52**, 3488; (f) Y.-J. Hu, L.-X. Li, J.-C. Han, L. Min and C.-C. Li, *Chem. Rev.*, 2020, **120**, 5910; (g) R. L. Reyes, T. Iwai and M. Sawamura, *Chem. Rev.*, 2021, **121**, 8926.
- (a) S. M. N. Sieburth and N. T. Canard, *Tetrahedron*, 1996, **52**, 6251; (b) Z.-X. Yu, Y. Wang and Y. Wang, *Chem.-Asian J.*, 2010, **5**, 1072; (c) T. A. Palazzo, R. Mose and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2017, **56**, 10033; (d) N. De and E. J. Yoo, *ACS Catal.*, 2018, **8**, 48; (e) B. Niu, Y. Wei and M. Shi, *Org. Chem. Front.*, 2021, **8**, 3475; (f) M.-M. Zhang, B.-L. Qu, B. Shi, W.-J. Xiao and L.-Q. Lu, *Chem. Soc. Rev.*, 2022, **51**, 4146; (g) J. Otevel, M. Eugui, S. Ričko and K. A. Jørgensen, *Nat. Synth.*, 2023, **2**, 1142; (h)



- B. Xu, Q. Wang, C. Fang, Z.-M. Zhang and J. Zhang, *Chem. Soc. Rev.*, 2024, **53**, 883; (i) M. Tori and R. Mizutani, *Molecules*, 2010, **15**, 4242; (j) K. Clarke and W. P. Unsworth, *Chem. Sci.*, 2020, **11**, 2876; (k) S.-S. Qi, H. Yin, Y.-F. Wang, C.-J. Wang, H.-T. Han, T.-T. Man and D.-Q. Xu, *Org. Lett.*, 2021, **23**, 2471; (l) T. Yao, J. Li, C. Jiang and C. Zhao, *Chem Catal.*, 2022, **2**, 2929; (m) V. Corti, C. L. Barløse, N. L. Østergaard, A. Kristensen, N. I. Jessen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2023, **145**, 1448.
- 4 (a) M. Mathiew, J. K. Tan and P. W. H. Chan, *Angew. Chem., Int. Ed.*, 2018, **57**, 14235; (b) C. Gao, X. Wang, J. Liu and X. Li, *ACS Catal.*, 2021, **11**, 2684; (c) Q. Li, R. Pan, M. Wang, H. Yao and A. Lin, *Org. Lett.*, 2021, **23**, 2292; (d) M.-M. Zhang, P. Chen, W. Xiong, X.-S. Hui, L.-Q. Lu and W.-J. Xiao, *CCS Chem.*, 2021, **3**, 3383; (e) W.-L. Yang, Y.-L. Wang, W. Li, B.-M. Gu, S.-W. Wang, X.-Y. Luo, B.-X. Tian and W.-P. Deng, *ACS Catal.*, 2021, **11**, 12557; (f) G.-H. Chen, Y. Ye, D.-X. Zhang, H.-J. Li, N. Zhang, G.-J. Liang, D. Zhang, J. Zhou and H. Zhou, *Org. Chem. Front.*, 2023, **10**, 4698; (g) J. Pan, T. O. Ho, Y.-C. Chen, B.-M. Yang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2023, **62**, e202317703.
- 5 (a) B. M. Trost, Z. Jiao, Y. Liu, C. Min and C.-I. J. Hung, *J. Am. Chem. Soc.*, 2020, **142**, 18628; (b) B. M. Trost and Z. Jiao, *J. Am. Chem. Soc.*, 2020, **142**, 21645; (c) J. Du, Y.-D. Hua, Y.-J. Jiang, S. Huang, D. Chen, C.-H. Ding and X.-L. Hou, *Org. Lett.*, 2020, **22**, 5375; (d) Y. Chen, M. Zang, W. Wang, Y.-Z. Liu, X. Luo and W.-P. Deng, *Chin. J. Chem.*, 2023, **41**, 2825.
- 6 (a) G. Zhang, X. Huang, G. Li and L. Zhang, *J. Am. Chem. Soc.*, 2008, **130**, 1814. For selected reviews, see: (b) R. Antonio and M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028; (c) T. Wang and A. S. K. Hashmi, *Chem. Rev.*, 2021, **121**, 8948; (d) L. De, W. Zang, M. J. Bird, C. J. T. Hyland and M. Shi, *Chem. Rev.*, 2021, **121**, 8685; (e) M. Mato, A. Franchino, C. García-Morales and A. M. Echavarren, *Chem. Rev.*, 2021, **121**, 8613; (f) C. C. Chintawar, A. K. Yadav, A. Kumar, S. P. Sancheti and N. T. Patil, *Chem. Rev.*, 2021, **121**, 8478; (g) D. Campeau, D. F. L. Rayo, A. Mansour, K. Muratov and F. Gagosz, *Chem. Rev.*, 2021, **121**, 8756; (h) L.-W. Ye, X.-Q. Zhu, R. L. Sahani, Y. Xu, P.-C. Qian and R.-S. Liu, *Chem. Rev.*, 2021, **121**, 9039; (i) L. Rocchigiani and M. Bochmann, *Chem. Rev.*, 2021, **121**, 8364; (j) S. Witzel, A. S. K. Hashmi and J. Xie, *Chem. Rev.*, 2021, **121**, 8868; (k) A. F. L. Rojas, S. H. Kyne and P. W. H. Chan, *Acc. Chem. Res.*, 2023, **56**, 1406.
- 7 (a) J. F. Bai, J. Ren and Z. Wang, *Chem.–Eur. J.*, 2009, **15**, 8975; (b) Y. Bai, W. Tao, J. Ren and Z. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 4112; (c) Y. Zhang and J. Zhang, *Adv. Synth. Catal.*, 2012, **354**, 2556; (d) Y. Zhang and J. Zhang, *Chem. Commun.*, 2012, **48**, 4710; (e) Z.-M. Zhang, P. Chen, W. Li, Y. Niu, X.-L. Zhao and J. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4350; (f) Y. Zhang and Y. X. J. Zhang, *Synthesis*, 2016, **48**, 512.
- 8 T. Peng, S. Li, D. Yang and L. Wang, *Org. Chem. Front.*, 2023, **10**, 3401.
- 9 See ESI† for details.
- 10 Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as **1c** (CCDC 2301807), **3c** (CCDC 2301808) and **5g** (CCDC 2301810).
- 11 (a) V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman and P. Sharma, *RSC Adv.*, 2015, **5**, 15233; (b) G. Li Petri, V. Spanò, R. Spatola, R. Holl, M. V. Raimondi, P. Barraja and A. Montalbano, *Eur. J. Med. Chem.*, 2020, **208**, 112783.
- 12 (a) V. Estévez, M. Villacampa and J. C. Menéndez, *Chem. Soc. Rev.*, 2014, **43**, 4633; (b) N. Singh, S. Singh, S. Kohli, A. Singh, H. Asiki, G. Rathee, R. Chandra and E. A. Anderson, *Org. Chem. Front.*, 2021, **8**, 5550; (c) T. Shi, G. Yin, X. Wang, Y. Xiong, Y. Peng, S. Li, Y. Zeng and Z. Wang, *Green Synth. Catal.*, 2023, **4**, 20.
- 13 (a) W.-J. Bai, J. G. David, Z.-G. Feng, M. G. Weaver, K.-L. Wu and T. R. R. Pettus, *Acc. Chem. Res.*, 2014, **47**, 3655; (b) B. Yang and S. Gao, *Chem. Soc. Rev.*, 2018, **47**, 7926; (c) C. Dorsch and C. Schneider, *Synthesis*, 2022, **54**, 3125; (d) X. Li, Z. Li and J. Sun, *Nat. Synth.*, 2022, **1**, 426.
- 14 (a) F. A. Macías, J. M. G. Molinillo, R. M. Varela and A. Torres, *J. Org. Chem.*, 1994, **59**, 8261; (b) C.-J. Wu, C.-W. Li and C.-B. Cui, *Mar. Drugs*, 2014, **12**, 1815; (c) M. Mueller, D. Weinmann, S. Toegel, W. Holzer, F. M. Unger and H. Viernstein, *Food Funct.*, 2016, **7**, 1671.

