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Enantioselective gold-catalyzed intermolecular [2+2] versus [4+2]-cycloadditions of 3-styrylindoles with N-allenamides: observation of interesting substituent effects[†]

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A highly enantioselective [2+2] *versus* a [4+2]-cycloaddition of 3-styrylindoles to *N*-allenamides catalyzed by identical gold(i)/chiral phosphoramidite complexes is presented, which provides facile access to synthetically valuable, optically active substituted cyclobutanes and tetrahydrocarbazoles. The cycloaddition mode unexpectedly depends on the electronic nature of the *N*-substituent 3-styrylindoles, the origin of which could be well rationalized using DFT calculations and experimental results. To the best of our knowledge, the present work represents the first example of such an impressive substituent effect in tuning the reaction mode with high chemo-, regio- and enantioselectivity in asymmetric gold catalysis.

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Introduction

Over the past decade, gold-catalyzed intermolecular cycloadditions of two unsaturated components have shown their power for rapid access to various cyclic and polycyclic ring systems in an extremely efficient and stereoselective manner.¹ In this context, due to their unique reactivity and ease of accessibility, N-allenamides² have emerged as unique partners for goldcatalyzed [2+2],³ [3+2],⁴ [4+2],⁵ and cascade cycloadditions,⁶ leading to synthetically useful four to seven membered carbocyclic or heterocyclic scaffolds. However, gold-catalyzed cycloadditions still pose challenges with respect to the cycloaddition mode as well as the enantioselectivity,7 only a few elegant examples of enantioselective cycloadditions involving N-allenamides have been reported to date. For example, González and co-workers^{3e} achieved the first asymmetric [2+2]-cycloaddition with alkenes, leading to optically active cyclobutanes⁸ in good yields. Recently, Mascareñas and López5c explored the elegant asymmetric [4+2]-cycloaddition with 1,3-dienes, leading to cyclohexenes and a cascade cycloaddition with the alkene tethered ketone.6 An efficient asymmetric [3+2]-cycloaddition

with nitrones was successfully realized by Chen.^{4b} Very recently, Rossi, Vicente and their co-workers developed a seminal gold(1)catalyzed intermolecular [4+2]-cycloaddition of 2-vinylindoles with *N*-allenamides, furnishing good yields of racemic tetrahydrocarbazoles (Scheme 1a).^{5b} However, to the best of our knowledge, a cycloaddition mode which depends on the electronic nature of the substituent is unprecedented in asymmetric gold catalysis. As a part of our continual program in developing asymmetric gold-catalyzed cycloadditions,⁹ we report the gold catalyzed enantioselective [2+2] and [4+2] cycloadditions of 3styrylindoles with *N*-allenamides (Scheme 1b), furnishing synthetically valuable tetrahydrocarbazole^{10,11} and 3-cyclobutylindole^{12,13} scaffolds, respectively, which frequently appear in natural products and bioactive compounds (Fig. 1).

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Scheme 1 Previous work and this work

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Fig. 1 Natural products and bioactive compounds containing the tetrahydrocarbazole and 3-cyclobutylindole scaffolds.

Results and discussion

3-Styrylindole 1a and N-allenamide 2a were initially chosen as the model substrates to examine a series of chiral ligands (Scheme 2). It was surprising to find that the unexpected [2+2]cycloadduct 3a, rather than the [4+2]-cycloadduct, was always furnished in excellent yields (>95%) under all of the screened reaction conditions. Using BINOL-derived phosphoramidite ligand (S,S,S)-L1 and its diastereomer (S,R,R)-L1, the reactions could give (+)-3a or its enantiomer (-)-3a with the same enantioselectivity (68% ee). Gratifyingly, the enantioselectivity could be significantly improved by the use of the H₈-BINOL-derived phosphoramidite (S,R,R)-L2, furnishing (-)-3a in 90% ee. Notably, (+)-3a was obtained in 76% ee with the application of (R,R,R)-L2 as the chiral ligand. Accordingly, the introduction of a methyl group to the 3- and 3'-positions of the BINOL moiety of L2, denoted as L3, could not increase the enantioselectivity. The changes of the N-substituents in L4 or L5 could not induce a high enantioselectivity either. The BINOL-derived ligand (R,R,R)-L6 with 9-anthracenyl at the 3,3'-positions still could not improve the enantioselectivity. The further variation of other reaction parameters including the solvents, silver salts and concentration did not improve the result, but running the reaction at -60 °C led to the ee increasing to 96%.14 It should be noted that the reaction is easy to handle, and it works well in wet solvents under air without any detriment to the enantioselectivity or yield.

With the optimal reaction conditions in hand, a variety of 3styrylindoles, **1**, with different *N*-protecting groups were prepared and investigated (Table 1). To our delight, those 3styrylindoles with Bn (**1b**), allyl (**1c**) and free H (**1d**) groups could smoothly undergo the [2+2]-cycloaddition, furnishing the corresponding cycloadducts **3b–3d** in 72–92% ee as the single (*Z*)stereoisomer (Table 1, entries 2–4). To our surprise, the [4+2]cycloadducts **4a–4c** rather than the [2+2]-cycloadducts were obtained in 67–95% yields with up to 95% ee and 7.3 : 1 *Z*/*E*selectivity with the use of an identical chiral gold catalyst under condition B (DCE, –30 °C, <1 min) when employing 3-styrylindoles **1e–1g** with electron-withdrawing *N*-protecting groups such as CO₂Et, Ts and acyl (Table 1, entries 5–7). It should be



Scheme 2 Investigation of the chiral ligands

noted that the [4+2]-cycloaddition takes place with a slightly lower Z/E selectivity but with almost the same enantioselectivity under condition A.

The scope of the 3-styrylindole for the asymmetric [2+2]cycloaddition reaction was found to be general (Table 2). For example, the styryl moieties with both electron-rich and electron-deficient aryl groups are compatible, furnishing the desired [2+2]-cycloadducts in 96–99% yield with excellent ee (95–96% ee) (Table 2, entries 1–5). Moreover, different substituents, such as MeO, Me and Br, could be introduced to different positions of the indole moiety and the corresponding [2+2]cycloadducts could be obtained in 76–99% yield with excellent enantioselectivities (Table 2, entries 6–9); however, the reaction required either a higher catalyst loading (5 mol%) or a much longer reaction time (12 h) for those 3-styrylindoles with electron-donating groups such as MeO and Me (Table 2, entries 6

Table 1 The N-substituent effect of 3-styrylindoles^a



^a Condition A: DCM, −60 °C, 20 min; condition B: DCE, −30 °C, <1 min.

and 7). In particular, besides styryl, the R¹ could be a heteroaryl, such as thienyl (**1q**), and the reaction also worked very well to give the desired product **3n** in 90% yield with 93% ee (Table 2, entry 10). Gratifyingly, the reaction of **1r** with an aliphatic R¹ group could produce the desired [2+2] cycloadduct **3o** in 58% yield with an acceptable 82% ee with the use of (*R*,*R*,*P*)-**L6** as the chiral ligand, but the reaction of **1s** with a terminal olefin was very messy (Table 2, entries 11–12). Finally, the reaction scope of this asymmetric [2+2]-cycloaddition was evaluated by variation of R² on the allenamides, **2**. The desired products **3q–3r** could be produced in close to quantitative yield with 96% ee (Table 2, entries 13–14).

In addition to the asymmetric [2+2]-cycloadditions, various substituted *N*-CO₂Et 3-styrylindoles are applicable to [4+2]-cycloadditions, leading to the optically active tetrahy-drocarbazoles in good to excellent yields with a *Z* : *E* selectivity of up to 14 : 1. Gratifyingly, both the *Z*- and *E*-isomers could be obtained in high levels of enantioselectivity (88–97% ee). However, substrates $\mathbf{1r}'$ with aliphatic \mathbb{R}^1 and $\mathbf{1s}'$ with a terminal olefin could not give the corresponding [4+2]-cycloadducts, which is attributed to the lower reactivity of the aliphatic alkenylindole (Table 3, entries 11–12).

To test the practicality of the new methodology, a gram-scale reaction was carried out. To our delight, the catalyst loading could be reduced to only 0.25 mol% on a 4 mmol scale to furnish 1.83 g of **4a** in 88% yield with a 5.5 : 1 Z/E ratio and excellent enantioselectivity (*Z*-**4a**, 96% ee, and *E*-**4a**, 92% ee), indicating that this transformation is easy to scale-up to gram scale without a loss in the efficiency or enantioselectivity (Scheme 3). To showcase the synthetic applications, three

Table 2	Asymmetric [2+2]-	-cycloaddition							
$R^{1} + T_{S} N R^{2} + \frac{Me_{2}SAuCl (1.0 mol\%)}{AgNTf_{2} (1.0 mol\%)} + T_{S} N R^{2} + \frac{(S,R,R)-L2 (1.1 mol\%)}{DCM, -60 °C, 20 min.} + T_{N} R^{2} + T_{N} R^{2} + C_{N} R^{2} + C$									
Entry	1 , R ¹ , R	2 , R ²	3	Yield ^a	ee				
1	1h , 4-BrC ₆ H ₄ /H	2a , Ph	3e	98%	96%				
2	1i , 4-ClC ₆ H ₄ /H	2a	3f	98%	96%				
3	1j , 4-CH ₃ C ₆ H ₄ /H	2a	3g	97%	95%				
4	1k, 4-CF ₃ C ₆ H ₄ /H	2a	3h	99%	96%				
5^b	1l , 4-CH ₃ OC ₆ H ₄ /H	2a	3i	96%	95%				
6 ^{<i>c</i>}	1m , Ph/5-CH ₃ O	2a	3j	76%	96%				
7 ^{<i>c</i>}	1n , Ph/5-CH ₃	2a	3k	91%	95%				
8	10, Ph/5-Br	2a	31	99%	95%				
9	1p , Ph/4-Br	2a	3m	93%	95%				
$10^{c,d}$	1q, 2-thienyl/H	2a	3n	90%	93%				
11^e	1r, <i>n</i> -Pr/H	2a	30	58%	82%				
12^{f}	1s, H/H	2a	3p	—	—				
13	1a	2b , 4-CH ₃ OC ₆ H ₄	3q	98%	96%				
14	1a	2c, 4 -BrC ₆ H ₄	3r	99%	96%				

^{*a*} Isolated yield. ^{*b*} Reacting for 30 min. ^{*c*} 5 mol% of catalyst. ^{*d*} -50 °C for 10 min, then -20 °C for another 5 min. ^{*e*} (*R*,*R*,*R*)-**L6** was used. ^{*f*} The reaction was messy.

Table 3 Asymmetric [4+2]-cycloaddition

R	$1 \qquad \qquad$, <i>R,R</i>)-L AgNT DCE,	2 AuCl] (f ₂ (2.5 m -30 °C, ∙	2.5 mol%) nol%) <1 min.		Ts N. ≕Ś R ²
Entry	$1'^{a}, R^{1}, R$	2, R ²	4	Z: E	Total yield	ee (%) of <i>Z</i> , <i>E</i>
1	1h ′, 4-BrC ₆ H ₄ /H	2a	4d	3.5:1	98%	97, 90
2	1i', 4-ClC ₆ H ₄ /H	2a	4e	3.4:1	95%	95, 90
3	1j ['] , 4-CH ₃ C ₆ H ₄ /H	2a	4f	5.6:1	95%	96, 90
4	1k', 4-CF ₃ C ₆ H ₄ /H	2a	4g	3.8:1	82%	97, — ^b
5	1l ', 4-CH ₃ OC ₆ H ₄ /H	2a	4h	3.0:1	88%	$95, -^{b}$
6	1m ′, Ph/5-CH ₃ O	2a	4i	4.7:1	88%	97, 92
7	1n ′, Ph/5-CH ₃	2a	4j	5.0:1	92%	96, 88
8	10 ′, Ph/5-Br	2a	4k	5.2:1	97%	97, 92
9	1p ′, Ph/4-Br	2a	4l	6.1:1	99%	97, 92
10	1q', 2-thienyl/H	2a	4m	1:1	90%	93, 91
11	1r ′, <i>n</i> -Pr/H	2a	4n	—	0% ^c	—, —
12	1s', H/H	2a	40	—	0% ^c	—, —
13	1e	2b	4p	10:1	89% ^d	90, —
14	1e	2 c	4q	14:1	92% ^d	89, —

^{*a*} **1h**' means the substrate is bearing the same substituents at R and R¹ as **1h** in Table 2 but has a different *N*-substituent. ^{*b*} The ee could not be determined by chiral HPLC. ^{*c*} Only the dimer of **2a** was isolated. ^{*d*} Yield of the isolated (*Z*)-isomer.

transformations of product 4a were carried out. The first transformation was the process involving the selective hydrolysis of the exo enamide moiety and the endocyclic double bond migration of 4a under the catalysis of TsOH at 50 °C, leading to the formation of aldehyde 5a in 66% yield with 96% ee. The second transformation was the selective hydrogenation of the endocyclic double bond of Z-4a at room temperature under the catalysis of 10 mol% Pd/C; the optically active hexahydrocarbazole 6a with three chiral stereocenters could be isolated in 80% yield with 98% ee. The last transformation was the selective endocyclic double bond migration under acidic conditions, producing a new type of tetrahydrocarbazole 7a in 79% yield without the loss of the chiral information. Meanwhile, the exo enamide of 3a could also be hydrogenated at high pressure, and the highly strained cyclobutane 8a with 96% ee could be produced in 95% yield.

To rationalize the origin of this dramatic substituent effect on the cycloaddition mode under the catalysis of gold,¹⁵ we performed Density Functional Theory (DFT) calculations using the M06 method to calculate the reaction pathway. We presumed that both cycloadditions were stepwise reactions.³⁻⁶ The calculated free energy profiles of the cycloaddition reactions of the 3-styrylindole **1a** with **Int-A** at the temperature 298 K are shown in Fig. 2(a). This figure shows the cycloaddition reaction of *N*-methyl 3-styrylindole **1a** and **Int A**. Fig. 3(a) clearly indicates that the electrostatic potential in the vicinity of the *N*-CH₃ is positive due to the effect of the electron-donating methyl. In contrast, the moiety of the double bond in styryl exhibits a



Fig. 2 The free energy profiles ΔG_{sol} for the reaction of 3-styrylindoles 1a and 1e with the Au-allyl cation species Int-A.

negative electrostatic potential, which tends to interact with positively charged species ($E_{\text{TS-1}^{Me}} = 1.7 \text{ kcal mol}^{-1} \text{ vs. } E_{\text{TS}^* \cdot 1^{Me}} = 6.1 \text{ kcal mol}^{-1}$), leading to a quite stable iminium **Int-B** with a releasing energy of 10.7 kcal mol⁻¹. For the second reaction step of the ring closure, the barrier of **TS-2^Me** is still lower than the corresponding **TS*-2^Me** by 1.2 kcal mol⁻¹ ($E_{\text{TS-2}^{Me}} = 9.7 \text{ kcal mol}^{-1} \text{ vs. } E_{\text{TS}^* \cdot 2^{Me}} = 10.9 \text{ kcal mol}^{-1}$). In addition, the formation of the [2+2] cycloaddition may be favoured by the stereo-electronic effect in energetics ($\Delta E_{\text{TS-2}^{Me}-\text{TS}^{**} \cdot 2^{Me}} = 4.8 \text{ kcal mol}^{-1}$). Furthermore, **Int-C** that leads to the [2+2] cycloadduct is more stable than **Int*-C** by 6.1 kcal mol⁻¹. Moreover, the complete (*Z*)-selectivity of the [2+2] cycloaddition product can also be easily explained using the computational calculations (please see the details in the ESI†). Thus, the DFT calculations indicate that the (*Z*)-isomer of the [2+2]-cycloadduct is highly

controlled with the *N*-methyl 3-styrylindole 1a as the substrate and the [2+2] cycloaddition is more favorable than the [4+2] cycloaddition with the *N*-methyl 3-styrylindole 1a as the substrate.

This is in contrast to when the *N*-CO₂Et 3-styrylindole **1e** was used as a substrate (Fig. 2(b)). Fig. 3(b) shows that the calculated electrostatic potential of the *N*-CO₂Et in **1e** is completely contrary to that of **1a**. Due to the electron-withdrawing effect of *N*-CO₂Et, the vicinity of the oxygen atom of the carbonyl group exhibits a large negative electrostatic potential, which strongly induces an electrostatic interaction with the Au-allyl cation species **Int-A**. Thus, the first addition of **Int-A** occurs at the carbonic position of the indole ring in **1e**, rather than at the double bond of the styryl, which leads to the intermediate **Int***-**D** ($\Delta E_{TS^*-ICO_2Et-TS-ICO_2Et} = -4.5$ kcal mol⁻¹). The barriers of



Fig. 3 The calculated contour maps of the electrostatic potentials corresponding to (a) **1a** and (b) **1e** in Fig. 2, respectively.



Scheme 3 Gram-scale synthesis and synthetic applications.

TS*-2^{CO₂Et} leading to the [4+2]-cycloadduct and TS-2^{CO₂Et} leading to the [2+2]-cycloadduct are very close, with energies of 8.1 and 7.9 kcal mol⁻¹, respectively. By avoiding the drastic steric effects in TS*-2^{CO₂Et}, the Int*-D proceeds through the transition state TS*-2^{CO₂Et} ($\Delta E_{TS^*-2CO_2Et} = -19.2$ kcal mol⁻¹). In addition, the Int*-E is thermodynamically more favorable than Int-E. Moreover, the results in which (*Z*) and (*E*)-[4+2] cycloaddition isomers are both obtained, are due to the small steric factor (the *exo*-double bond of the six-membered

ring) and influenced by the substrates,¹⁶ catalysts and ligands. In short, the current DFT calculations could well elucidate the chemoselectivity of the 3-styrylindole with different electrondonating and electron-withdrawing groups.

Conclusions

In summary, we have developed a gold(1)-catalyzed highly enantioselective intermolecular [2+2] or [4+2]-cycloaddition of various substituted 3-styrylindoles with N-allenamides. The discrimination between the anticipated [4+2]-product and the unexpected [2+2]-cycloaddition adduct is dependent on the electronic nature of the N-substituent of the 3-styrylindoles, which is well rationalized by DFT calculations. With electronwithdrawing groups, such as CO_2Et , Ts and Ac, the [4+2] cycloaddition occurs; in contrast, the [2+2]-cycloadditions take place with electron-donating groups such as methyl, benzyl, allyl and even H groups. The salient features of the present method, including using readily available starting materials and catalysts, high enantioselectivity, good yields, the ease of scale-up to gram scale, and atom-economy, make it give extremely facile access to optically active substituted cyclobutanes and tetrahydrocarbazoles, which are highly valuable building blocks in organic synthesis. Further studies, including the design of a new chiral ligand to address the unsatisfactory enantioselectivity issue of the oxazolidinone-based allenamide,16 are under way in this laboratory and will be reported in due course.

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Notes and references

1 For selected accounts and general reviews, see: (a) A. S. K. Hashmi, Chem. Rev., 2007, 107, 3180; (b) E. Jiménez-Núñez and A. M. Echavarren, Chem. Rev., 2008, 108, 3326; (c) D. J. Gorin, B. D. Sherry and F. D. Toste, Chem. Rev., 2008, 108, 3351; (d) S. M. A. Sohel and R. S. Liu, Chem. Soc. Rev., 2009, 38, 2269; (e) A. Fürstner, Chem. Soc. Rev., 2009, 38, 3208; (f) A. Corma, A. Leyva-Perez and M. J. Sabater, Chem. Rev., 2011, 111, 1657; (g) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria and A. Simonneau, Chem. Rev., 2011, 111, 1954; (h) N. Krause and C. Winter, Chem. Rev., 2011, 111, 1994; (i) M. Bandini, Chem. Soc. Rev., 2011, 40, 1358; (j) B.-L. Lu, L. Dai and M. Shi, Chem. Soc. Rev., 2012, 41, 3318; (k) D. Garayalde and C. Nevado, ACS Catal., 2012, 2, 1462; (l) Y.-W. Sun, Q. Xu and M. Shi, Beilstein J. Org. Chem., 2013, 9, 2224; (m) F. López and J. L. Mascareñas, Beilstein J. Org. Chem., 2013, 9, 2250; (n) G. Cera and M. Bandini, Isr. J. Chem., 2013, 53, 848; (o) W. Yang and A. S. K. Hashmi, Chem. Soc. Rev., 2014, 43, 2941; (p) F. López and J. L. Mascareñas, J. Chem.

Soc. Rev., 2014, 43, 2904; (q) C. Obradors and
A. M. Echavarren, Acc. Chem. Res., 2014, 47, 902; (r)
A. S. K. Hashmi, Acc. Chem. Res., 2014, 47, 864; (s)
L. Zhang, Acc. Chem. Res., 2014, 47, 877; (t) F. López and
J. L. Mascareñas, Beilstein J. Org. Chem., 2011, 7, 1075; (u)
D. Qian and J. Zhang, Chem. Rec., 2014, 14, 280; (v) D. Qian and
J. Zhang, Chem. Soc. Rev., 2015, 44, 677.

- 2 For general reviews on allenamides, see: (a) L.-L. Wei, H. Xiong and R. P. Hsuang, Acc. Chem. Res., 2003, 36, 773;
 (b) T. Lu, Z. Lu, Z.-X Ma, Y. Zhang and R. P. Hsung, Chem. Rev., 2013, 113, 4862.
- 3 For examples of [2+2]-cycloadditions, see: (a) S. Suárez-Pantiga, C. Hernández-Díaz, M. Piedrafita, E. Rubio and J. M. González, Adv. Synth. Catal., 2012, 354, 1651; (b) X.-X. Li, L.-L. Zhu, W. Zhou and Z. Chen, Org. Lett., 2012, 14, 436; (c) H. Faustino, P. Bernal, L. Castedo, F. López and J. L. Mascareñas, Adv. Synth. Catal., 2012, 354, 1658; (d) P. Bernal-Albert, H. Faustino, A. Gimeno, G. Asensio, J. L. Mascareñas and F. López, Org. Lett., 2014, 16, 6196. For elegant asymmetric examples, see: (e) S. Suárez-Pantiga, C. Hernández-Díaz, E. Rubio and J. M. González, Angew. Chem., Int. Ed., 2012, 51, 11552; (f) M. Jia, M. Monari, Q. Q. Yang and M. Bandini, Chem. Commun., 2015, 51, 2320.
- 4 For examples of [3+2]-cycloadditions, see: (a) W. Zhou,
 X. X. Li, G. H. Li, Y. Wu and Z. Chen, *Chem. Commun.*,
 2013, 49, 3552. For an example of a highly enantioselective version, see: (b) G.-H. Li, W. Zhou, X.-X. Li, Q.-W. Bi,
 Z. Wang, Z.-G. Zhao, W.-X. Hu and Z. Chen, *Chem. Commun.*, 2013, 49, 4770.
- 5 For examples of [4+2]-cycloadditions, see: (a) H. Faustino,
 F. López, L. Castedo and J. L. Mascareñas, *Chem. Sci.*, 2011,
 2, 633; (b) V. Pirovano, L. Decataldo, E. Rossi and
 R. Vicente, *Chem. Commun.*, 2013, 49, 3594. For an impressive asymmetric example, see: (c) J. Francos,
 F. Grande-Carmona, H. Faustino, J. Iglesias-Sigüenza,
 E. Díez, I. Alonso, R. Fernández, J. M. Lassaletta, F. López and J. L. Mascareñas, *J. Am. Chem. Soc.*, 2012, 134, 14322.
- 6 (a) H. Faustino, I. Alonso, J. Mascareñas and F. López, Angew. Chem., Int. Ed., 2013, 52, 6526; (b) H. Faustino, I. Varela, J. Mascareñas and F. López, Chem. Sci., DOI: 10.1039/ c5sc00295h.
- 7 For recent reviews or accounts on enantioselective gold-catalysis, see: (a) R. A. Widenhoefer, Chem.-Eur. J., 2008, 14, 5382; (b) N. Bongers and N. Krause, Angew. Chem., Int. Ed., 2008, 47, 2178; (c) A. S. K. Hashmi and C. Hubbert, Angew. Chem., Int. Ed., 2010, 49, 1010; (d) S. Sengupta and X. Shi, ChemCatChem, 2010, 2, 609; (e) M. Rudolph and A. S. K. Hashmi, Chem. Soc. Rev., 2012, 41, 2448; (f) Y.-M. Wang, A. D. Lackner and F. D. Toste, Acc. Chem. Res., 2014, 47, 889. For selected recent examples of enantioselective gold-catalysis: (g) 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; (h) B. Liu, K.-N. Li, S.-W. Luo, J.-Z. Huang, H. Peng and L.-Z. Gong, J. Am. Chem. Soc., 2013, 135, 3323; (i) R. Guo, K.-N. Li, B. Liu, H. -J. Zhu, Y.-M. Fan and L.-Z. Gong, Chem. Commun.,

2014, **50**, 5451; (*j*) S. D. Lee, J. C. Timmerman and R. A. Widenhoefer, *Adv. Synth. Catal.*, 2014, **356**, 3187; (*k*) K. Ji, Z. Zheng, Z. Wang and L. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 1245.

- 8 For selected recent asymmetric syntheses of cyclobutanes, see: (a) M. R. Luzung, P. Mauleón and F. D. Toste, J. Am. Chem. Soc., 2007, 129, 12402; (b) H. Teller, S. Flügge, R. Goddard and A. Fürstner, Angew. Chem., Int. Ed., 2010, 49, 1949; (c) A. Z. González, D. Benitez, E. Tkatchouk, W. A. Goddard, III and F. D. Toste, J. Am. Chem. Soc., 2011, 133, 5500. For recent reviews on racemic [2+2] cycloadditions, see: (d) B. Alcaide, P. Almendros and C. Aragoncillo, Chem. Soc. Rev., 2010, 39, 783; (e) A. Brandi, S. Cicchi, F. Cordero and A. Goti, Chem. Rev., 2014, 114, 7317. For a nice example of the synthesis of racemic cyclobutanes, see (f) L. Zhang, J. Am. Chem. Soc., 2005, 127, 16804.
- 9 (a) F. Liu, D. Qian, L. Li, X. Zhao and J. Zhang, Angew. Chem., Int. Ed., 2010, 49, 6669; (b) G. Zhou, F. Liu and J. Zhang, Chem.-Eur. J., 2011, 17, 3101; (c) Z.-M. Zhang, P. Chen, W. Li, Y. Niu, X. Zhao and J. Zhang, Angew. Chem., Int. Ed., 2014, 53, 4350; (d) D. Qian and J. Zhang, Chem.-Eur. J., 2013, 19, 6984; (e) D. Qian, H. Hu, F. Liu, B. Tang, W. Ye, Y. Wang and J. Zhang, Angew. Chem., Int. Ed., 2014, 53, 13751; (f) F. Liu, Y. Wang, W. Ye and J. Zhang, Org. Chem. Front., 2015, 2, 221.
- 10 For examples of natural compounds with tetrahydrocarbazole scaffolds, see: (a) M. G. Levkovich, P. K. Yuldashev, M. M. Mirzaeva and B. Tashkhodzhaev, Chem. Nat. Compd., 2012, 48, 440; (b) J. Bonjoch and D. Solé, Chem. Rev., 2000, 100, 3455; (c) A. B. Dounay, L. E. Overman and A. D. Wrobleskiand, J. Am. Chem. Soc., 2005, 127, 10186; (d) H. Ishikawa, G. I. Elliott, J. Velcicky, Y. Choi and D. L. Boger, J. Am. Chem. Soc., 2006, 128, 10596; (e) A. Nikitenko, D. Evrard, A. L. Sabb, R. L. Vogel, G. Stack, M. Young, M. Lin, B. L. Harrison and J. R. Potoski, Org. Process Res. Dev., 2008, 12, 76; (f) J. Dai, J. I. Jimenez, M. Kelly and P. G. Williams, J. Org. Chem., 2010, 75, 2399; (g) D. Kato, Y. Sasaki and D. L. Boger, J. Am. Chem. Soc., 2010, 132, 3685; (h) P. Liu, J. Wang, J. Zhang and F. G. Qiu, Org. Lett., 2011, 13, 6426; (i) B. Jones, B. Simmons, A. Mastracchio and S. D. W. C. MacMillan, Nature, 2011, 475, 183. and references cited therein.
- 11 For selected recent asymmetric syntheses of tetrahydrocarbazoles, Х. see: (a)Han and R. A. Widenhoefer, Org. Lett., 2006, 8, 3801; (b) C. Liu and R. A. Widenhoefer, Org. Lett., 2007, 9, 1935; (c) C. Gioia, A. Hauville, L. Bernardi, F. Fini and A. Ricci, Angew. Chem., Int. Ed., 2008, 47, 9236; (d) H. Huang and R. Peters, Angew. Chem., Int. Ed., 2009, 48, 604; (e) M. Bandini and A. Eichholzer, Angew. Chem., Int. Ed., 2009, 48, 9533; (f) X. F. Wang, J. R. Chen, Y. J. Cao, H. G. Cheng and W.-J. Xiao, Org. Lett., 2010, 12, 1140; (g) B. Tan, G. Hernández-Torres and C. F. Barbas, III, J. Am. Chem. Soc., 2011, 133, 12354; (h) S. Müller, M. J. Webber and B. List, J. Am. Chem. Soc., 2011, 133, 18534; (i) C. C. J. Loh,

G. Raabe and D. Enders, *Chem.-Eur. J.*, 2012, 18, 13250; (j)
Q. Cai and S. L. You, *Org. Lett.*, 2012, 14, 3040; (k)
Q.-F. Wu, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2012, 51, 1680; (l) M. Kawano, T. Kiuchi, S. Negishi,
H. Tanaka, T. Hoshikawa, J.-i. Matsuo and H. Ishibashi, *Angew. Chem., Int. Ed.*, 2013, 52, 906.

- 12 W. R. Gutekunst and P. S. Baran, J. Org. Chem., 2014, 79, 2430.
- 13 K. S. Jandu, V. Barrett, M. Brockwell, D. Cambridge, D. R. Farrant, C. Foster, H. Giles, R. C. Glen, A. P. Hill, H. Hobbs, A. Honey, G. R. Martin, J. Salmon, D. Smith, P. Woollard and D. L. Selwood, *J. Med. Chem.*, 2001, 44, 681.
 14 Please find more screening conditions in the ESI[†]
- 15 For selected recent references, which rationalize the mechanism of gold-catalyzed reactions using DFT calculations, see: (a) W. Yang and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2014, 43, 2941; (b) M. H. Vilhelmsen and A. S. K. Hashmi, *Chem.-Eur. J.*, 2014, 20, 1901; (c) S. Montserrat, H. Faustino, A. Lledós, J. L. Mascareñas, F. López and G. Ujaque, *Chem.-Eur. J.*, 2013, 19, 15248; (d) T. D. Haro, E. Gómez-Bengoa, R. Cribiú, X. Huang and C. Nevado, *Chem.-Eur. J.*, 2012, 18, 6811; (e)

A. S. K. Hashmi, A. M. Schuster, S. Litters, F. Rominger and M. Pernpointner, *Chem.-Eur. J.*, 2011, **17**, 5661; (*f*) I. Alonso, B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledós and J. L. Mascareñas, *J. Am. Chem. Soc.*, 2009, **131**, 13020.

16 When using the oxazolidinone-based allenamides as the reacting partner, both cycloadditions could proceed smoothly to afford the corresponding products in excellent yields as a single (*Z*)-stereoisomer, with low to moderate ee:

