Chemical Science



EDGE ARTICLE

View Article Online



Cite this: Chem. Sci., 2018, 9, 4488

Gold-catalyzed (4 + 2)-annulations between α -alkyl alkenylgold carbenes and benzisoxazoles with reactive alkyl groups†

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Received 1st March 2018 Accepted 21st April 2018

DOI: 10.1039/c8sc00986d

rsc.li/chemical-science

This work reports new (4 + 2)-annulations of α -alkyl vinylgold carbenes with benzisoxazoles to afford 3,4dihydroquinoline derivatives with high anti-stereoselectivity. The annulations are operable with carbenes in both acyclic and cyclic forms. This reaction sequence involves an initial formation of imines from αalkylgold carbenes and benzisoxazoles, followed by a novel carbonyl-enamine reaction to yield 3,4dihydroquinoline derivatives. This system presents the first alkyl C-H reactivity of α -alkyl gold carbenes with an external substrate.

Introduction

Metal carbenes are versatile intermediates to implement a vast number of useful reactions including cyclopropanation, X-H insertion (X = C, N and O), skeletal rearrangement and annulation reactions (eqn (1)).1 Despite their widespread applications, applicable metal carbenes, derived from diazo precursors, are mainly restricted to donor/acceptor (D/A) types I (R = H, aryl and alkenyl; EWG = CN, ketones and esters)whereas highly desirable α-alkyl metal carbenes II are less efficient because of a competitive 1,2-hydrogen shift to form olefins (eqn (2)).1 This side reaction is particularly serious for gold carbenes because their LAu = C^+ carbons are highly cationic. Few intermolecular reactions involving Ar-Pd(II) catalysts focused on α-alkyl metal carbenes of D/A types.3 The limited utility of α-alkyl carbenoids features an unsolved and challenging task in metal carbene chemistry. We seek new α -alkyl carbenoids beyond commonly used D/A carbenes II, aiming at two objectives: (i) suppression of a 1,2-H shift and (ii) an alkyl C-H reaction with an external substrate.

Interest in the reactions of benzisoxazoles is rapidly growing in gold catalysis because of their various annulation modes with gold π -alkynes. 4-6 To explore the reactivity of benzisoxazoles toward gold carbenes,7 we first tested the reactions with D/Atype benzyl α -oxogold carbene II' (R = Ph and EWG = CO_2Et), yielding an olefin product III' efficiently (eqn (3)). We envisage that D/D type carbenes such as α -alkyl alkenylgold carbenes IV

Currently used carbenes: D/A types cyclopropanation, X-H insertion. rearrangement, annulation products `FWG M = Rh(II), Au(I), Cu(I)EWG = CN. ketone, este Ag(I), Zn(II), Pd(II) Our initial tests CO₂Et III' (>70%) reactive alkyl C-H bonds: no 1.2-hydrogen shift

might be viable species to achieve new annulations with benzisoxazoles because their gold-stabilized allyl cation character IV is unfavorable for a 1,2-H shift. According to this hypothesis, this work reports novel intermolecular (4 + 2)-annulations between α-alkyl vinylgold carbenes and benzisoxazoles, thus manifesting an unprecedented C-H reactivity of α-alkyl metal carbenes.

Results and discussion

As shown in eqn (5), we further tested the reaction of acyclic alkylgold carbenes A that were generated in situ from cyclopropene derivatives 1a-1b and gold catalysts.8 With IPrAuCl/ AgSbF₆, quinoline derivatives 3a and 3b were isolated in satisfactory yields (72-75%), together with enones 1a-O and 1b-O in minor proportions (17-19%). A 1,2-hydrogen shift was

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† Electronic supplementary information (ESI) available. CCDC 1819135-1819138. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8sc00986d

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effectively suppressed with vinylcarbenes A, supporting our hypothetic role of gold-stabilized allyl cations A.

Our primary interest is to construct complicated frameworks *via* cascade reactions. Fig. 1 depicts several bioactive compounds (VI-1)–(VI-6) bearing a common tricyclic framework VI, which can be easily constructed from cyclopentenylgold carbene A' and benzisoxazole. Indenoquinoline (VI-1) showed antiproliferative activities against breast (MCF-7) and lung epithelial (A-549) cells. 9a Species VI-2 and VI-3 served as 5HT2c agonists and CRTH₂ receptor modulators, respectively. 9b,c Compounds VI-4 and VI-5 were N-containing steroids found in higher plants. 9d,c Species VI-6 is a key intermediate for the total synthesis of naturally occurring (–)-isoschizogaline 9f and (–)-isoschizozygamine. 9g

In this new task, we optimized the annulation cascades between vinylallene **4a** and benzisoxazole **2a** in dichloromethane (DCM) using various gold catalysts; species **4a** serves as a precursor for cyclopentenylgold carbene **A'** (Table 1).¹⁰

An initial test of IPrAuCl/AgSbF₆ at a 5 mol% loading afforded a new azacyclic product 5a and cyclopentadiene 4a' in 62% and 25% yields, respectively (entry 1); the latter was derived from a 1,2-H shift of gold carbenes A' that was generated from cyclizations of gold-stabilized pentadienyl cation A-I. Notably, an increased gold loading (10 mol%) enhanced the yield of desired 5a up to 85%. Other gold catalysts LAuCl/AgSbF₆ (L = P(OPh)₃, PPh₃ and P(t-Bu)₂(obiphenyl)) gave 5a in 40-82% yields with $L = P(OPh)_3$ being the most effective (entries 3-5). For various silver salts as in IPrAuCl/AgX (X = OTf and NTf₂), resulting 5a was obtained in 65% and 71% yields, respectively (entries 6-7). AgNTf₂ was entirely inactive (entry 8). IPrAuCl/AgSbF₆ in various solvents gave 5a in the following yields: DCE 70%, MeCN 20% and 1,4dioxane 0 (entries 9-11). The molecular structure of compound 5a was characterized with X-ray diffraction,11 showing an anti-configuration between the alcohol and phenyl groups.

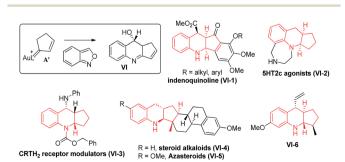


Fig. 1 Suitable alkylgold carbenes to access bioactive molecules.

Table 1 Catalytic reactions with various gold catalysts

				Yield ^b [%]		
Entry	Catalyst [mol%]	Solvent	t [h]	4a	5a	4a′
1	IPrAuCl/AgSbF ₆ (5)	DCM	12	8	62	25
2	IPrAuCl/AgSbF ₆ (10)	DCM	3	_	85	12
3	(PhO) ₃ PAuCl/AgSbF ₆ (10)	DCM	3	_	82	16
4	Ph ₃ PAuCl/AgSbF ₆ (10)	DCM	4	_	55	36
5	LAuCl/AgSbF ₆ (10) ^c	DCM	3	_	40	52
6	IPrAuCl/AgOTf (10)	DCM	4	_	65	26
7	IPrAuCl/AgNTf ₂ (10)	DCM	4	_	71	20
8	$AgSbF_6$ (10)	DCM	24	95	_	
9	IPrAuCl/AgSbF ₆ (10)	DCE	5	_	70	24
10	IPrAuCl/AgSbF ₆ (10)	MeCN	12	_	20	65
11	IPrAuCl/AgSbF ₆ (10)	Dioxane	10	_	_	90

 a [4a] = 0.05 M. b Product yields are reported after purification from a silica column. c L = $P(t\text{-Bu})_2(o\text{-biphenyl})$. IPr = 1,3-bis(diisopropylphenyl)imidazole-2-ylidene, DCE = 1,2-dichloroethane.

Table 2 assesses the generality of these gold-catalyzed reactions using various vinylallenes **4b–4t** catalyzed with IPrAuCl/AgSbF₆ (10 mol%) in DCM. All resulting products **5b–5t** assumed *anti*-configurations with the alcohol and R¹ groups being mutually *trans*. We tested the reaction of trisubstituted

Table 2 Catalytic annulations with various alkenylallenes

 $^a\left[4\right]=0.05$ M. b Product yields are reported after purification from a silica column.

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vinylallenes 4b-4f bearing R¹ = 4-MePh, 4-OMePh, 4-ClPh, 4-CF₃Ph and n-Bu, yielding desired 5b-5f in 78-88% yields (entries 1-5). For species 4g and 4h bearing 3-phenyl substituents (X = OMe and Cl), their corresponding products 5g and 5hwere obtained in 84% and 87% yields, respectively (entries 6 and 7). The reactions were extensible to other vinylallenes 4i-4k bearing 2-naphthyl, 2-furan and 2-thiophene, further delivering desired products 5i-5k in 82-84% yields (entries 8-10). We tested the reaction on vinylallene 4l bearing distinct $R^1 = Me$ and R^2 = Ph, which yielded compound 5l with an anticonfiguration in which the hydroxy and methyl groups are

mutually trans (entry 11); this configuration was established by the ¹H NOE effect. Additional alkyl-substituted vinylallenes 4m-4p yielded desired 5m-5p in satisfactory yields (80-85%, entries 12-15). Variations of the R^2 group with an *n*-butyl group as in species 4q gave expected product 5q in 86% yield (entry 16). We prepared species 4r bearing varied $R^2 = Ph$ and $R^3 = n$ -butyl, producing compound 5r in 80% yield (entry 17). For 1,3disubstituted vinylallenes 4s and 4t ($R^3 = H$), their resulting compounds 5s and 5t were obtained in 82-83% yields (entries

We tested these new annulations on distinct substrates such as enynyl acetates 6a-6g, bearing varied phenyl ($R = 4-XC_6H_4$, X = H, Cl, Br, Me, and OMe), 2-thienyl and isopropyl substituents; these enyne acetates can be catalyzed with the same gold catalyst to yield distinct α-alkylgold carbenes A' (see Table 3).¹² To our pleasure, new alkylgold carbenes A', generated from these enynyl acetates, were trapped efficiently with benzisoxazole 2a to afford the desired (4 + 2)-annulation products 7a-7g in satisfactory yields (61-74%), further manifesting the reaction generality (entries 1-7). For unsubstituted propargyl acetate 6h (R = H), its reaction led to a 68% recovery of initial **6h** (entry 8). Even if the reaction is successful, a dehydration of compound 7h would occur to give quinoline products. The molecular structure of compound 7a (R = Ph) was confirmed with

Table 3 Annulation reactions with enypyl acetates

 a 6 = 0.05 M. b Product yields are reported after purification from a silica column. ^c A 68% recovery of initial **6h** is found in entry 8.

Table 4 Catalytic annulations with various benzisoxazoles

 a 4a = 0.05. b Product yields are reported after purification from a silica column.

X-ray diffraction analysis that revealed an anti-configuration (Table 3).11

The scope of these catalytic reactions is further expanded with various applicable benzisoxazoles 2b-2j substituted with the C(3), C(5) and C(6) carbons. Other C(5)-substituted benzisoxazoles 2b-2f ($R^1 = Me$, OMe, Br, Cl, and $-OCO_2Et$) maintained high efficiencies to deliver anti-configured products 8b-8f in 80-90% yields (entries 1-5). High reaction efficiencies were maintained also for C(6)-substituted benzisoxazoles 2g-2i that furnished products 8g-8i in 86-92% yields (entries 6-8). A final applicable reaction with a C(3)-substituted benzisoxazole 2j enabled the production of a tertiary alcohol 8j, reflecting the reaction feasibility (entry 9). ¹H NOE spectra were recorded to verify the stereochemistry of compound 8j (Table 4).

Gold-catalyzed reactions of 3,5-dimethylisoxazole 2a' with vinylallenes 4a and 4u delivered 2-aminocyclopentadienes 9a and **9b** in 72% and 64% yields, respectively (eqn (6)). 5a,13,14 The molecular structure of compound 9b was characterized with Xray diffraction.11 Cyclizations of compounds 9a and 9b with a gold catalyst were unsuccessful because of the two different forms of the enol imines (eqn (6)). To rationalize the origin of the stereoselectivity, compound 5a was treated with Zn(OTf)2 (20 mol%) in refluxing DCE to examine the hydroxyl epimerization that turned out to be slow. An equilibrium, anti/syn = 4:1, was attained for species 5a after reflux in DCE for 48 h (eqn (7)).

Scheme 1 shows the stereoselective functionalizations of anti-5a via NaBH₄ reductions and m-CPBA oxidations,

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Scheme 1 Chemical functionalizations.

Scheme 2 A plausible reaction mechanism

respectively yielding compounds **5a-H** and **5a-O** as single diastereomeric products. The stereochemistries of compounds **5a-H** and **5a-O** were established with ¹H NOE spectra. Likewise, the acetate species **7a** was readily removed under basic conditions, yielding the enol form **7a'** as shown by its NMR in CD₃COCD₃ and CDCl₃. We also studied an O₃-induced oxidative cleavage of the acetate derivative **5a-OAc** to cleave the olefin group, yielding the peroxide **5a-O**₃ in 85% yield. The molecular structure of species **5a-O**₃ has been characterized by X-ray diffraction.¹¹

As depicted in Scheme 2, we postulate an initial formation of imines between alkylgold carbene **A** and benzisoxazole, yielding 2-iminoyl benzaldehyde **C**. This hypothesis is supported by our observation of 3,5-dimethylisoxazole, depicted in eqn (6). A tautomerization of imine species **C** is expected to form enamines **D** bearing an NH···O=C hydrogen bond. We believe that this enamine form, unlike other enamine-carbonyl couplings, ¹⁵ is stabilized with the NH···O=C bond to enable a concerted process, analogous to the well-known carbonyl-ene reactions. A boat-like conformation **D** is favorable to yield *anti-*5 stereoselectively.

Conclusions

This work reports novel gold-catalyzed (4 + 2)-annulations between alkylgold carbenes and benzisoxazoles 2 to form 3,4-dihydroquinoline derivatives. Gold carbenes in cyclic and acyclic forms are both applicable. In this reaction sequence, the gold complex catalyzes an initial formation of imines between alkylgold carbenes^{13,14} and benzisoxazoles; the resulting intermediates bear an enamine moiety that is bound to an aldehyde via a hydrogen bond to induce a carbonyl-enamine reaction. Control experiments with 3,5-dimethylisoxazoles supported this postulated mechanism. This new synthetic design involving α -

alkyl metal carbenes of **D/D** types will attract growing interest because of its distinct utility.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Ministry of Education (MOE 106N506CE1) and Ministry of Science and Technology (MOST 107-3017-F-007-002), Taiwan, for financial support of this work.

Notes and references

- 1 (a) H. M. L. Davies and E. G. Antoulinakis, *Intermolecular Metal-Catalyzed Carbenoid Cyclopropanations in Organic Reactions*, ed. L. E. Overman, John Wiley & Sons, Inc., New York, NY, 2001, vol. 57, pp. 1–326; (b) H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, 103, 2861; (c) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, 110, 704; (d) Q.-Q. Cheng, Y. Yu, J. Yedoyan and M. P. Doyle, *ChemCatChem*, 2018, 10, 488.
- For selected reviews for gold carbenes, see: (a) D. Qian and J. Zhang, Chem. Soc. Rev., 2015, 44, 677; (b) L. Liu and J. Zhang, Chem. Soc. Rev., 2016, 45, 506; (c) E. López, S. Gonzalez-Pelayo and L. A. López, Chem. Rec., 2017, 17, 312; (d) C. Obradors and A. M. Echavarren, Chem. Commun., 2014, 50, 16; (e) L. Zhang, Acc. Chem. Res., 2014, 47, 877; (f) D. P. Day and P. W. H. Chan, Adv. Synth. Catal., 2016, 358, 1368.
- 3 The reactions were only reported for Ar–Pd(II) species; see: (a) C. Peng, Y. Wang and J. Wang, *J. Am. Chem. Soc.*, 2008, **130**, 1566; (b) Z. Zhang, Y. Liu, M. Gong, X. Zhao, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2010, **49**, 1139.
- 4 (a) L. Li, T.-D. Tan, Y.-D. Tan, Y.-Q. Zhang, X. Liu and L.-W. Ye, *Org. Biomol. Chem.*, 2017, **15**, 8483; (b) D. B. Huple, S. Ghorpade and R.-S. Liu, *Adv. Synth. Catal.*, 2016, **358**, 1348; (c) S. S. Giri and R.-S. Liu, *Chem. Sci.*, 2018, **9**, 2991.
- 5 (a) A.-H. Zhou, Q. He, C. Shu, Y.-F. Yu, S. Liu, T. Zhao, W. Zhang, X. Lu and L.-W. Ye, Chem. Sci., 2015, 6, 1265; (b) X.-Y. Xiao, A.-H. Zhou, C. Shu, F. Pan, T. Li and L.-W. Ye, Chem.-Asian J., 2015, 10, 1854; (c) H. Jin, L. Huang, J. Xie, M. Rudolph, F. Rominger and A. S. K. Hashmi, Angew. Chem., Int. Ed., 2016, 55, 794; (d) H. Jin, B. Tian, X. Song, J. Xie, M. Rudolph, F. Rominger and A. S. K. Hashmi, Angew. Chem., Int. Ed., 2016, 55, 12688.
- 6 (a) Z. Zeng, H. Jin, J. Xie, B. Tian, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Org. Lett.*, 2017, 19, 1020; (b)
 M. Chen, N. Sun, H. Chen and Y. Liu, *Chem. Commun.*, 2016, 52, 6324; (c) W. Xu, G. Wang, N. Sun and Y. Liu, *Org. Lett.*, 2017, 19, 3307.
- 7 The reactions of isoxazoles with rhodium carbenes were noted by Davies' group; distinct [3 + 3]-annulations were reported for α-alkenylrhodium esters as shown below. (*a*) J. R. Manning and H. M. L. Davies, *Tetrahedron*, 2008, **64**,

6901; (b) J. R. Manning and H. M. L. Davies, *J. Am. Chem. Soc.*,

Chemical Science

2008, 130, 8602.

- 8 (a) A. Archambeau, F. Miege, J. Crossy and C. Meyer, in Patai's Chemistry of Functional Groups, ed. Z. Rappoport, J. F. Liebman and I. Marek, John Wiley & Sons Ltd., Hoboken, NJ, 2014, pp. 631-700; (b) Y. Deng and M. P. Doyle, Isr. J. Chem., 2016, 56, 399-408; (c) F. Miege, C. Meyer and J. Cossy, Org. Lett., 2010, 12, 4144; (d) F. Miege, C. Meyer and J. Cossy, Chem.-Eur. J., 2012, 18, 7810; (e) C. Li, Y. Zeng and J. Wang, Tetrahedron Lett., 2009, 50, 2956; (f) Z.-B. Zhu and M. Shi, Chem.-Eur. J., 2008, 14, 10219; (g) S. B. Wagh, Y.-C. Hsu and R.-S. Liu, ACS Catal., 2016, 6, 7160; (h) Z. Liu, Q. Li, P. Liao and X. Bi, Chem.-Eur. J., 2017, 23, 4756; (i) W. Rao, M. J. Koh, D. Li, H. Hirao and P. W. H. Chan, J. Am. Chem. Soc., 2013, 135, 7926; (i) W. Rao and P. W. H. Chan, Chem.-Eur. I., 2014, 20, 713; (k) J. Yan, G. L. Tay, C. Neo, B. R. Lee and P. W. H. Chan, Org. Lett., 2015, 17, 4176.
- 9 (a) S. Chakrabarty, M. S. Croft, M. G. Marko and G. Moyna, Bioorg. Med. Chem., 2013, 21, 1143; (b) Merck Sharp and Dohme Corp, WO 2012/174176 A1, 2012; (c) P. S. Ramamoorthy and R. E. McDevitt, US Pat., US 2004/0019040, 2004; (d) J. Wöfling, É. Frank, G. Schneider, M. T. Bes and L. F. Tietze, Synlett, 1998, 1205; (e) L. F. Tietze and A. Modi, Med. Res. Rev., 2000, 20, 304; (f) R. M. Kariba, P. J. Houghton and A. Yenesew, J. Nat. Prod., 2002, 65, 566; (g) J. L. Hubbs and C. H. Heathcock, Org. Lett., 1999, 1, 1315.
- 10 (a) S. Bhunia and R.-S. Liu, J. Am. Chem. Soc., 2008, 130, 16488; (b) J. H. Lee and F. D. Toste, Angew. Chem., Int. Ed., 2007, 46, 912; (c) H. Funami, H. Kasama and N. Iwasawa, Angew. Chem., Int. Ed., 2007, 46, 909; (d) G. Lemiere, V. Gandon, K. Cariou, T. Fukuyama, A. L. Dhimane,

- L. Fensterbank and M. Malacria, *Org. Lett.*, 2007, **9**, 2207; (e) V. Gandon, G. Lemiere, A. Hours, L. Fensterbank and M. Malacria, *Angew. Chem., Int. Ed.*, 2008, **47**, 7534; (f) M. R. Fructos, M. Besora, A. A. C. Braga, M. M. Díaz-Requejo, F. Maseras and P. J. Pérez, *Organometallics*, 2017, **36**, 172; (g) F.-Q. Shi, X. Li, Y. Xia, L. Zhang and Z.-X. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 15503; (h) W. Rao, D. Susanti, B. J. Ayers and P. W. H. Chan, *J. Am. Chem. Soc.*, 2015, **137**, 6350; (i) W. Rao, J. W. Boyle and P. W. H. Chan, *Chem. Eur. J.*, 2016, **22**, 6532.
- 11 Crystallographic data of compounds 5a, 5a-O₃, 7a, and 9b were deposited at the Cambridge Crystallographic Data Center: 5a (CCDC 1819135); 5a-O₃ (CCDC 1819137); 7a (CCDC 1819138); and 9b (CCDC 1819136).†
- 12 L. Zhang and S. Wang, J. Am. Chem. Soc., 2006, 128, 1442.
- 13 For gold-catalyzed nitrene reactions of alkynes; see selected examples: (a) D. J. Gorin, N. R. Davies and F. D. Toste, J. Am. Chem. Soc., 2005, 127, 11260; (b) A. Wetzel and F. Gagosz, Angew. Chem., Int. Ed., 2011, 50, 7354; (c) B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang and L. Zhang, Angew. Chem., Int. Ed., 2011, 50, 8358; (d) C. Shu, Y.-H. Wang, B. Zhou, X.-L. Li, Y.-L. Li, Y.-F. Ping, X. Lu and L.-W. Ye, J. Am. Chem. Soc., 2015, 137, 9567; (e) H.-H. Hung, Y.-C. Liao and R.-S. Liu, J. Org. Chem., 2013, 78, 7970.
- 14 Benzisoxazoles serve as nitrene sources in rhodium-catalyzed C-H functionalizations, see selected examples: (a) S. Yu, G. Tang, Y. Li, X. Zhou, Y. Lan and X. Li, Angew. Chem., Int. Ed., 2016, 55, 8696; (b) M. Zou, J. Liu, C. Tang and N. Jiao, Org. Lett., 2016, 18, 3030; (c) S. Yu, Y. Li, X. Zhou, H. Wang, L. Kong and X. Li, Org. Lett., 2016, 18, 2812.
- 15 The reactions of enamines and aldehydes are generally implemented with Lewis acids or a base, see: (a) R. Matsubara, N. Kawai and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2006, **45**, 3814; (b) T. Kochi, T. P. Tang and J. A. Ellman, *J. Am. Chem. Soc.*, 2003, **125**, 11276; (c) R. Matsubara, P. Vital, Y. Nakamura, H. Kiyohara and S. Kobayashi, *Tetrahedron*, 2004, **60**, 9769.