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## Gold-catalyzed (4 + 2)-annulations between $\alpha$ -alkyl alkenylgold carbenes and benzisoxazoles with reactive alkyl groups†

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This work reports new (4 + 2)-annulations of  $\alpha$ -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  $\alpha$ -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.<sup>2</sup> Few intermolecular reactions involving Ar-Pd(II) catalysts focused on α-alkyl metal carbenes of D/A types.<sup>3</sup> The limited utility of α-alkyl carbenoids features an unsolved and challenging task in metal carbene chemistry. We seek new  $\alpha$ -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  $\pi$ -alkynes. 4-6 To explore the reactivity of benzisoxazoles toward gold carbenes,7 we first tested the reactions with D/Atype benzyl  $\alpha$ -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  $\alpha$ -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 CO<sub>2</sub>Et 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/ AgSbF<sub>6</sub>, 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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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. 94 Species VI-2 and VI-3 served as 5HT2c agonists and CRTH<sub>2</sub> receptor modulators, respectively. 9b,c Compounds VI-4 and VI-5 were N-containing steroids found in higher plants. 94,e 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).<sup>10</sup>

An initial test of IPrAuCl/AgSbF<sub>6</sub> 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/AgSbF<sub>6</sub> (L = P(OPh)<sub>3</sub>, PPh<sub>3</sub> and P(t-Bu)<sub>2</sub>(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 NTf<sub>2</sub>), resulting 5a was obtained in 65% and 71% yields, respectively (entries 6-7). AgNTf<sub>2</sub> was entirely inactive (entry 8). IPrAuCl/AgSbF<sub>6</sub> 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.

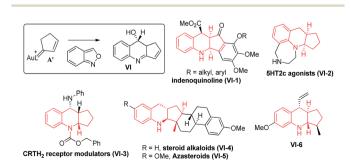


Fig. 1 Suitable alkylgold carbenes to access bioactive molecules.

Table 1 Catalytic reactions with various gold catalysts

				Yield <sup>b</sup> [%]		
Entry	Catalyst [mol%]	Solvent	<i>t</i> [h]	4a	5a	4a′
1	IPrAuCl/AgSbF <sub>6</sub> (5)	DCM	12	8	62	25
2	IPrAuCl/AgSbF <sub>6</sub> (10)	DCM	3	_	85	12
3	(PhO) <sub>3</sub> PAuCl/AgSbF <sub>6</sub> (10)	DCM	3	_	82	16
4	Ph <sub>3</sub> PAuCl/AgSbF <sub>6</sub> (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 <sub>2</sub> (10)	DCM	4	_	71	20
8	$AgSbF_6$ (10)	DCM	24	95	_	_
9	IPrAuCl/AgSbF <sub>6</sub> (10)	DCE	5	_	70	24
10	IPrAuCl/AgSbF <sub>6</sub> (10)	MeCN	12	_	20	65
11	IPrAuCl/AgSbF <sub>6</sub> (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/AgSbF<sub>6</sub> (10 mol%) in DCM. All resulting products **5b–5t** assumed *anti*-configurations with the alcohol and R<sup>1</sup> 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.

vinylallenes 4b-4f bearing R<sup>1</sup> = 4-MePh, 4-OMePh, 4-ClPh, 4-CF<sub>3</sub>Ph and n-Bu, vielding 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 <sup>1</sup>H 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 18 and 19).

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  $\alpha$ -alkylgold carbenes A' (see Table 3).<sup>12</sup> To our pleasure, new alkylgold carbenes A', generated from these enynyl acetates, were trapped efficiently with benzisox-azole 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 enynyl 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

 $^a$   ${\bf 4a}=0.05.$   $^b$  Product yields are reported after purification from a silica column.

X-ray diffraction analysis that revealed an *anti*-configuration (Table 3).<sup>11</sup>

The scope of these catalytic reactions is further expanded with various applicable benzisoxazoles  $2\mathbf{b}$ – $2\mathbf{j}$  substituted with the C(3), C(5) and C(6) carbons. Other C(5)-substituted benzisoxazoles  $2\mathbf{b}$ – $2\mathbf{f}$  ( $\mathbf{R}^1 = \mathbf{Me}$ , OMe, Br, Cl, and  $-\mathbf{OCO}_2\mathbf{E}\mathbf{t}$ ) maintained high efficiencies to deliver *anti*-configured products  $\mathbf{8b}$ – $\mathbf{8f}$  in 80–90% yields (entries 1–5). High reaction efficiencies were maintained also for C(6)-substituted benzisoxazoles  $2\mathbf{g}$ – $2\mathbf{i}$  that furnished products  $\mathbf{8g}$ – $\mathbf{8i}$  in 86–92% yields (entries 6–8). A final applicable reaction with a C(3)-substituted benzisoxazole  $2\mathbf{j}$  enabled the production of a tertiary alcohol  $\mathbf{8j}$ , reflecting the reaction feasibility (entry 9).  $^1$ H NOE spectra were recorded to verify the stereochemistry of compound  $\mathbf{8j}$  (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 X-ray diffraction. 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 NaBH<sub>4</sub> 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 <sup>1</sup>H NOE spectra. Likewise, the acetate species **7a** was readily removed under basic conditions, yielding the enol form **7a'** as shown by its NMR in CD<sub>3</sub>COCD<sub>3</sub> and CDCl<sub>3</sub>. We also studied an O<sub>3</sub>-induced oxidative cleavage of the acetate derivative **5a-OAc** to cleave the olefin group, yielding the peroxide **5a-O**<sub>3</sub> in 85% yield. The molecular structure of species **5a-O**<sub>3</sub> has been characterized by X-ray diffraction.<sup>11</sup>

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, 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<sup>13,14</sup> 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  $\alpha$ -

alkyl metal carbenes of  $\mathbf{D}/\mathbf{D}$  types will attract growing interest because of its distinct utility.

#### Conflicts of interest

There are no conflicts to declare.

### Acknowledgements

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$$CO_2R$$
  $Rh$  +  $NO$   $CO_2R$   $3,3-shift$   $N$   $CO_2R$ 

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