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## Au-Containing All-Carbon 1,4-Dipoles: Generation and [4 + 2] Annulation in the Formation of Carbo-/Heterocycles

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Au catalysis is a recent phenomenon that has attracted much attention and resulted in a variety of versatile synthetic methods.<sup>1</sup> Au-catalyzed cyclizations or cycloisomerizations have thus far been the major focus of this rapidly evolving research area, rendering a diverse range of functionalized cyclic structures. Intermolecular cycloaddition/annulation reactions are powerful methods for rapidly increasing molecular complexities and constructing polycyclic structures; however, Au complexes have been of limited use in catalyzing this versatile class of reactions except in a few studies.<sup>2</sup>

Our continued effort in exploring new Au chemistry and conceiving of novel Au catalysis has led to a new concept: Aucontaining all-carbon 1,n-dipoles. Charge-separated carbon chains, i.e., all-carbon 1,n-dipoles, are usually transient species and often difficult to harness toward cycloaddition/annulation reactions.<sup>3,4</sup> However, we envision that the negatively charged end of such a dipole can be masked by a Au complex, thus substantially tempering its nucleophilicity (i.e., intermediate A, Scheme 1). Consequently, the dipole becomes more stable and could participate in [n + m]annulation processes if the dipole chain is not long enough for selfcyclization.<sup>5</sup> We anticipate that the cationic end of such a dipole can initiate a bimolecular process by reacting with a dipolarophile, relaying the positive charge close to the Au-capped anionic end (i.e., the Au-C bond). The Au-C bond, preferably a  $Au-C(sp^2)$ bond, could then react with the cationic center,<sup>6</sup> forming a second bond and thus the cycloadduct (Scheme 1).

To put this concept into practice, we sought to generate Aucontaining all-carbon 1,4-dipoles, which would undergo favorable stepwise [4 + 2] annulation and at the same time minimize self-cyclization. One system that attracted our attention is the 1-(1-alkynyl)cyclopropyl ketones used previously by Zhang and Schmalz<sup>7</sup> for gold(I)-catalyzed formation of trisubstituted furans. While the mechanism was not completely defined in their study, we envisioned that furan intermediate **C** could be formed via oxocarbenium **B** from monocyclic substrates (Scheme 2). Importantly, intermediate **C** has charge separation and can serve as an example of the Aucontaining all-carbon 1,4-dipoles. Herein, we report our study in employing this type of novel dipoles in [4 + 2] annulations, which lead to the formation of not only 6-membered carbocycles but also oxygen-/nitrogen-containing heterocycles in good efficiencies and excellent regioselectivities.

We began by treating a mixture of cyclopropyl ketone **1** and 1-(2-ben-zenesulfonylethyl)-1H-indole (**2**)<sup>8</sup> with IPrAuNTf<sub>2</sub><sup>9</sup> [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidenegold(I) bis(trifluoromethanesulfonyl)imide, 5 mol %] at room temperature. Gratifyingly, the [4 + 2] annulation indeed happened, and tetracyclic furan **3**<sup>10</sup> was formed in 56% yield with 28% of ketone **1** left after 8 h (entry 1, Table 1). Optimization of the reaction conditions, as shown in Table 1, led to 87% yield of adduct **3** when 3 equiv of indole **2** was used and the reaction was run at 70 °C with 0.1 M of substrate concentration (entry 10). It is notable that TsOH did not catalyze the reaction (entry 5) and elevated reaction temperatures facilitated the conversion. **Scheme 1.** Au-Containing All-Carbon 1,*n*-Dipole: Concept and Reactivity



Scheme 2. Formation of Au-Containing All-Carbon 1,4-Dipoles from 1-(1-Alkynylcyclopropyl) Ketones



**Table 1.** [4 + 2] Annulation of Ketone 1 and Indole 2: Condition Optimization

Ph Me + Rear rear		catalyst tion conditions		$\overbrace{P_{r}AuNTf_{2}}^{ip_{r}} \xrightarrow{ip_{r}} \overbrace{P_{r}}^{ip_{r}} \xrightarrow{ip_{r}} \overbrace{P_{r}}^{ip_{r}} \xrightarrow{p_{r}} \overbrace{F_{3}Co_{2}s^{-N} \cdot so_{2}CF_{3}}^{ip_{r}}$	
				yield	conv.
entry	catalyst	conditions <sup>a</sup>	2/1	(%) <sup>b</sup>	(%)
1	5 mol % IPrAuNTf <sub>2</sub>	DCE, rt, 8 h	1.5	56	72
2	5 mol % PtCl <sub>2</sub>	toluene, 80 °C, 8 h	1.5	3	74
3	5 mol % AuCl	DCE, rt, 8 h	1.5	6	85
4	5 mol % Ph <sub>3</sub> PAuNTf <sub>2</sub>	DCE, rt, 8 h	1.5	19	74
5	5 mol % TsOH	DCE, rt, 8 h	1.5	С	С
6	5 mol % LAu $Cl_2^d$	DCE, rt, 8 h	1.5	2	11
7	5 mol % IPrAuNTf2	DCE, 50 °C, 12 h	1.5	59	100
8	5 mol % IPrAuNTf <sub>2</sub>	DCE, 50 °C, 2 h	3	69	100
9	5 mol % IPrAuNTf <sub>2</sub>	DCE, 70 °C, 15 min	3	78	100
10	5 mol % IPrAuNTf <sub>2</sub>	DCE, 70 °C, 15 min	3	87 <sup>e</sup>	100

<sup>*a*</sup> The concentration of **1** is 0.05 M except in entries 9 and 10, where 0.1 M was used. <sup>*b*</sup> Reaction run in vial; yield estimated by <sup>1</sup>H NMR using diethyl phthalate as internal standard. <sup>*c*</sup> No reaction. <sup>*d*</sup> L = pyridine-2-carboxylato. <sup>*e*</sup> Flask reaction; isolated yield.

The scope of this cycloaddition was then promptly studied, and the results are shown in Table 2. Various 1-(1-alkynyl)cyclopropyl ketones (i.e., 4) were allowed, and [4 + 2] annulations proceeded in mostly good to excellent efficiencies. Reaction of ketone 4 containing an additional substitution<sup>11</sup> at the cyclopropane ring (i.e.,  $R^3$  = Me or Ph) led to highly regioselective formation of the adduct with the substituent  $\alpha$  to the indoline ring (e.g., **5b**-**5g**) although the diastereoselectivities<sup>12</sup> were low. Tetracyclic indoles 5d and 5f were isolated in fairly good overall yield upon subsequent dehydrogenation with MnO<sub>2</sub> in order to simplify their characterization. Various substituents including cyclopropyl, cyclohexyl, phenyl, and oxygenated alkyl groups, were allowed at the alkyne terminus and at the carbonyl group, but a sterically demanding cyclohexyl group at the alkyne terminus led to only 47% yield of 5g along with a substantial amount of uncyclized indole 7. In addition to sulfonylethyl indole 2, PMB-protected indole 6 was also suitable (e.g., 5d).

Expanding the scope of this chemistry using ketones/aldehydes as the dipolarophile was surprisingly uneventful. As shown in Table 3, this [4 + 2] annulation worked well with carbonyl compounds

**Table 2.** [4 + 2] Annulation of Ketone 1 and Indole 2: Scope Study<sup>a</sup>



<sup>*a*</sup> The concentration of **4** was 0.1 M, and 3 equiv of **2** or **6** was used. <sup>*b*</sup> After reaction, the reaction mixture was treated with excess  $MnO_2$  at 70 °C for 3 h.





of various natures, including benzaldehyde, pivalaldehyde, anisaldehyde, cyclohexenone, acetophenone, and 3-(4-methoxyphenyl)propenal, and dihydropyran-fused, fully substituted furans **8** were isolated in fairly good to excellent yields. The tolerance of steric hindrance and the allowance of conjugated enal/enone substrates are noteworthy, and products containing quaternary carbon centers and functionalized substituents can be easily accessed. Similar to the indole cases, the [4 + 2] annulation of anisaldehyde with **4c** containing a methyl group at the cyclopropane ring also proceeded with excellent regioselectivity (eq 1).

To our delight, both imines and silyl enol ethers are suitable dipolarophiles as well, and two examples are shown in eqs 3 and 4. Further examination of other potential dipolarophiles revealed that furan, *N*-methylpyrrole, benzofuran, thiophene, and styrene did not participate in the [4 + 2] annulation reactions under the current reaction conditions.



The high regioselectivities observed with substituted cyclopropyl ketones suggest that the Au-containing all-carbon 1,4-dipole C

(Scheme 2) is most likely the reactive intermediate instead of oxocarbenium **B** for the subsequent [4 + 2] annulation as nucleophilic attack of the methine group of the cyclopropane ring in **B** is expected to be sterically disfavored. The cation-initiated nature of the [4 + 2] annulation is further supported by the observation that isomeric trisubstituted furan **11** was formed exclusively when cyclopropyl aldehyde **10** was used (eq 2). In this reaction, the oxocarbenium intermediate formed upon the nucleophilic attack by acetaldehyde selectively cyclized to the furan 2-position, favored sterically and likely electronically, suggesting the weak nucleophilic nature of the alkenylgold moiety.

In summary, a novel concept of Au-containing all-carbon 1,ndipoles is advanced, and its application in [4 + 2] annulation led to efficient formation of 6-membered carbo-/heterocycles. Polycyclic, fully substituted furans were easily accessible. Further applications of this novel concept are to be pursued.

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**Supporting Information Available:** Experimental procedures, compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

- For recent reviews on gold catalysis, see: (a) Zhang, L.; Sun, J.; Kozmin, S. A. Adv. Synth. Catal. 2006, 348, 2271–2296. (b) Jimenez-Nunez, E.; Echavarren, A. M. Chem. Commun. 2007, 333–346. (c) Gorin, D. J.; Toste, F. D. Nature 2007, 446, 395–403. (d) Fürstner, A.; Davis, P. W. Angew. Chem., Int. Ed. 2007, 46, 3410–3449. (e) Hashmi, A. S. K. Chem. Rev. 2007, 107, 3180–3211.
- (2) (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. J. Am. Chem. Soc. 2002, 124, 12650–12651. (b) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. J. Am. Chem. Soc. 2005, 127, 18002–18003. (c) Kusama, H.; Miyashita, Y.; Takaya, J.; Iwasawa, N. Org. Lett. 2006, 8, 289–292. (d) Gorin, D. J.; Dube, P.; Toste, F. D. J. Am. Chem. Soc. 2006, 128, 14480–14481. (e) Schelweis, M.; Dempwolff, A. L.; Rominger, F.; Helmchen, G. Angew. Chem., Int. Ed. 2007, 46, 5598–5601. (f) Hsu, Y.-C.; Datta, S.; Ting, C.-M.; Liu, R.-S. Org. Lett. 2008. 10, 521–524. For a review on [4 + 2] benzannulation, see: (g) Patil, N. T.; Yamamoto, Y. Arkivoc 2007, (v), 6–19.
- (3) For reviews on all-carbon 1,3-dipoles and their surrogates, see: (a) Yamago, S.; Nakamura, E. Org. React. 2002, 61, 1–217. (b) Little, R. D. Comprehensive Organic Synthesis, 1st ed.; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford; New York, 1991; Vol. 3, pp 239–270. (c) Chan, D. M. T. Comprehensive Organic Synthesis, 1st ed.; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford; New York, 1991; Vol. 3, pp 271–314. For our recent studies evoking all-carbon 1,3-dipoles, see: (d) Huang, X.; Zhang, L. J. Am. Chem. Soc. 2007, 129, 6398–6399.
- (4) For examples of surrogates of all carbon 1,4-dipoles, see: (a) Zhu, X.-F.; Lan, J.; Kwon, O. J. Am. Chem. Soc. 2003, 125, 4716–4717. (b) Wurz, R. P.; Fu, G. C. J. Am. Chem. Soc. 2005, 127, 12234–12235. (c) Hauser, F. M.; Rhee, R. P. J. Org. Chem. 1978, 43, 178.
- (5) We have previously reported a study involving the generation and cyclization of Au-containing all-carbon 1,6-dipoles, see: Wang, S.; Zhang, L. J. Am. Chem. Soc. 2006, 128, 14274–14275.
- (6) The reaction between an electrophile and an alkenylgold is most likely involving the attack of the electrophile by the alkene π-electrons accompanied by simultaneous Au–C bond cleavage. For selected examples, see: (a) Shi, Z.; He, C. J. Am. Chem. Soc. 2004, 126, 5964–5965. (b) Zhang, L. J. Am. Chem. Soc. 2005, 127, 16804–16805. (c) Reference 5. (d) Jimenez-Nunez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. Angew. Chem., Int. Ed. 2006, 45, 5452–5455.
- (7) Zhang, J. L.; Schmalz, H. G. Angew. Chem., Int. Ed. 2006, 45, 6704–6707. For the first study of Au-catalyzed cyclization of propargylic ketones, see: Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. Angew. Chem., Int. Ed. 2000, 39, 2285–2288.
- (8) The use of the polar 2-benzenesulfonylethyl group to protect indole is to facilitate product purification.
- (9) (a) Li, G.; Zhang, L. Angew. Chem., Int. Ed. 2007, 46, 5156-5159. (b) Ricard, L.; Gagosz, F. Organometallics 2007, 26, 4704-4707.
- (10) The expected *cis* ring fusion of **3** was supported by 1D NOESY.
- (11) These substituted ketones **4** were prepared diastereomerically pure; see the Supporting Information for details.
- (12) The diastereomers were not separable. In the case of 5c, 1D NOESY studies indicated that the isomer with the Me group residing on the concave side of the tetracycle was the major one.

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