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COMMUNICATIONS

Published on Web 08/28/2008

Au-Containing All-Carbon 1,3-Dipoles: Generation and [3+2] Cycloaddition Reactions

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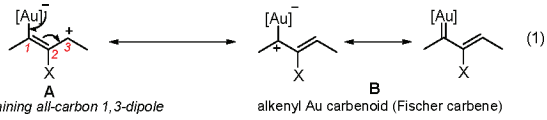
Received June 19, 2008; E-mail: lzhang@ unr.edu

We have recently advanced a concept of "*Au-containing all-carbon 1,n-dipole*" and applied it in a versatile [4+2] annulation process.[1] To further implement this concept and expand the scope of Au-catalyzed[2] annulation/cycloaddition reactions, we have developed and herein report the generation of Au-containing all-carbon 1,3-dipoles and their applications in [3+2] cycloadditions.



(1)

The difficulty in studying a Au-containing all-carbon 1,3-dipole such as **A**[3] (eq 1) is to avoid the reactivities derived from its resonance form, alkenyl Au carbenoid **B**. In fact, carbenoid **B** (X = RCO_2 or RS), accessible via a 1,2-migration of acyloxy[4a−d] or alkylthio[5] groups in propargylic substrates, has been reported to undergo facile inter-[4a,c]/intramolecular[4b,d,e] cyclopropanation reactions and cyclizations,[4] while no cycloaddition via its 1,3-dipole resonance form **A** has ever been reported.[6] However, we envision that the resonance form **B** could be destabilized by direct substitution of an electron-withdrawing group (EWG) at the carbene center and consequently reactivities of 1,3-dipole **A** may be harnessed (Scheme 1). In addition, such an EWG can facilitate regioselective migration of acyloxy[7] or alkylthio groups due to electronic polarization of the C−C triple bond.

However, no [3+2] cycloaddition between substrate **1** (X = OAc or SPh, EWG = CO_2Me, R = ^{n}Pr) and anisaldehyde was observed under various reaction conditions. We speculated that this lack of reactivity might be due to the decreased nucleophilicity of the alkenylgold moiety in dipole **C** in the presence of an EWG group and reasoned that it could be overcome by replacing known migrating groups (i.e., X = RCO_2[4] or RS[5]) with a more electron-donating alkoxy group. However, substrate **1** with X = OMe again did not work, as MeO 1,2-migration appeared difficult. We envisioned that a novel migration−fragmentation sequence of a ketal substrate[8] could deliver such a 1,3-dipole [i.e., intermediate **C** (X = OR), Scheme 1]. Notable in this design is the fragmentation of the ketal moiety into a migrated alkoxy group and a ketone which behaves as a good leaving group.

To our delight, the expected 4-methoxy-2,5-dihydrofuran **4** was indeed formed when a mixture of ketal ester **3** and anisaldehyde was treated with $Ph_3PAuNTf_2$ (5 mol %) in 15 min (entry 1, Table 1). Moreover, this annulation is highly diastereoselective as only *cis*-**4** was observed. Optimization of reaction conditions (Table 1) revealed

Scheme 1. Design

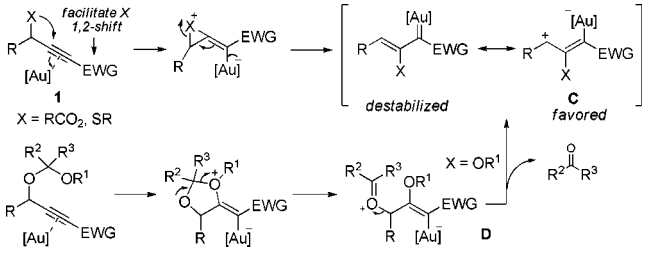
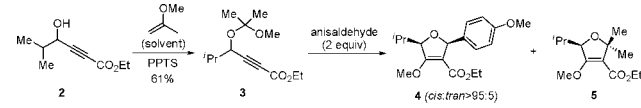


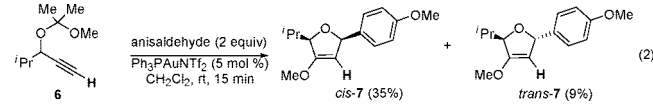
Table 1. Initial Results and Reaction Conditions Optimization



entry	catalyst	conditions[a]	yield of **4** (**2**, **5**) (%)[b]
1	5 mol % $Ph_3PAuNTf_2$	CH_2Cl_2 (0.2 M), rt, 15 min	55 (25, <5)
2	**5 mol % $Ph_3PAuNTf_2$**	**CH_2Cl_2 (0.05 M), rt, 15 min**	**82 (12, <5)**[c]
3	5 mol % $Ph_3PAuNTf_2$	CH_2Cl_2 (0.05 M), 0 °C, 15 min	41 (40, <5)
4	5 mol % $Ph_3PAuNTf_2$	THF (0.05 M), rt, 15 min	2 (70, -)
5	5 mol % $Ph_3PAuNTf_2$	CH_3CN (0.05 M), rt, 8 h	5 (50, <5)
6	5 mol % $Ph_3PAuNTf_2$	CH_3NO_2 (0.05 M), rt, 15 min	2 (80, -)
7	5 mol % $IPrAuNTf_2$	CH_2Cl_2 (0.05 M), rt, 15 min	77 (10, -)
8	5 mol % $PtCl_2$	toluene, 80 °C, 8 h	-
9	5 mol % $AuCl_3$	CH_2Cl_2 (0.05 M), rt, 15 min	- (50, -)
10	5 mol % TsOH	CH_2Cl_2 (0.05 M), rt, 15 min	- (95, -)
11	5 mol % BF_3.Me_2O	CH_2Cl_2 (0.05 M), rt, 15 min	- (95, -)

[a] Anhydrous solvent used. [b] Estimated by ^{1}H NMR. [c] 75% isolated yield.

that $Ph_3PAuNTf_2$ (entry 2) is a slightly better catalyst than $IPrAuNTf_2$[9] (entry 7). The major side reaction was hydrolysis of **3** back to alcohol **2**, which could not be prevented under various conditions. Interestingly, dihydrofuran **5**, formed via direct cyclization of **D** (R = ^{i}Pr; R^1, R^2, R^3 = Me; EWG = CO_2Et), was also isolated in small amounts, offering strong support for the initial alkoxy migration. No product **4** was observed when alcohol **2**, MeOH, and anisaldehyde were treated with $Ph_3PAuNTf_2$ for 1 h.[10] Without anisaldehyde, treatment of **3** with $Ph_3PAuNTf_2$, as expected, led to mostly hydrolysis and the formation of <5% of **5**.

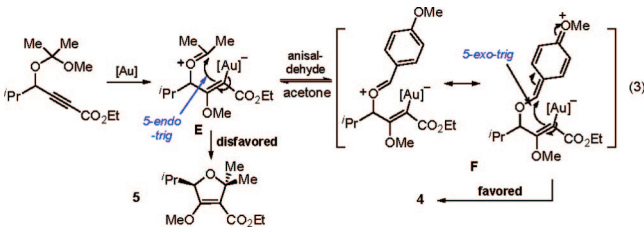


(2)

The success of this reaction is worth commenting on: (a) the terminal carboxylate group was important as ketal **6** with a terminal alkyne reacted rather poorly and with a low diastereoselectivity (eq 2); (b) there is a facile exchange of the leaving acetone and anisaldehyde likely via 1,3-dipole intermediate **C**, and the highly selective formation of **4** can not be explained simply by sterics (*vide infra*) but rather by stereoelectronic considerations (eq 3): 5-*endo-trig* cyclization[11] of **E** is disfavored according to the Baldwin's rule,[12] but for anisaldehyde-substituted intermediate **F**, its significant quinone methide resonance form can undergo favored and facile 5-*exo-trig* cyclization.[11]

The reaction scope study is shown in Table 2. First, we examined the dipolarophiles.[13] Both enals (entries 1, 2, and 5) and electron-rich aromatic aldehydes (entries 3 and 4) reacted well. In all these cases, excellent diastereoselectivities were again observed as only the *cis*-isomers were isolated. Particularly noteworthy is the case of cyclohex-1-enecarbaldehyde (entry 5), indicating that a simple double bond is sufficient to facilitate the 5-*exo-trig* cyclization (eq 3). Not surprisingly, hexanal or cyclohexanone did not react well, and the corresponding

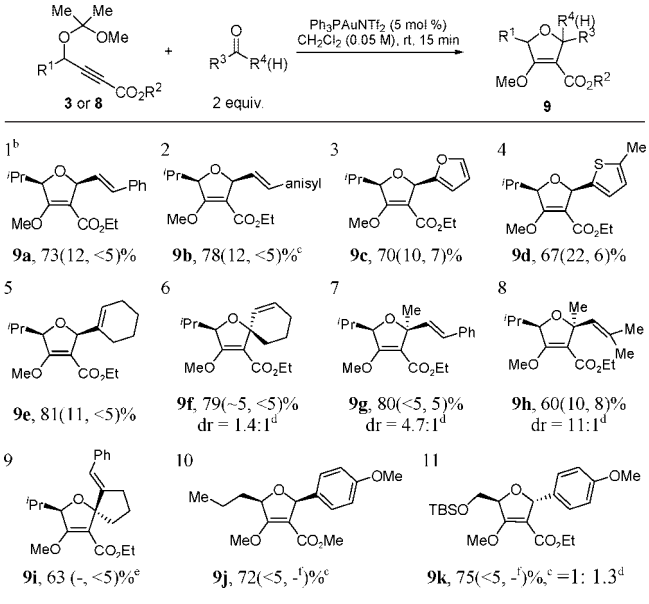
10.1021/ja804690u CCC: $40.75



cycloadducts were formed in 8% and 15% yield, respectively. To our surprise, benzaldehyde reacted poorly (<5% yield). In addition, electron-rich furan and thiophene rings did not notably interfere with the cycloaddition. In contrast to acetone, simple enones (entries 6 and 8) and aryl enones (entries 7 and 9) underwent this cycloaddition smoothly, and dihydrofurans with quaternary carbon centers were obtained in moderate to good yields. Asymmetric ketones with large steric biases showed good to excellent diastereoselectivity (entries 8 and 9). In the case of 2-benzylidenecyclopentanone (entry 9), *spiro*-**9i** was isolated as a single diastereomer in 63% yield along with 25% of the enone recovered. For the Au-containing 1,3-dipole precursor, besides **3**, esters with R^1 = *n*-propyl (entry 10) or siloxymethyl (entry 11) reacted smoothly although the latter case displayed surprisingly low and opposite diastereoselectivity. In most cases except entries 2, 10, and 11, $Ph_3PAuNTf_2$ worked better than $IPrAuNTf_2$, and hydrolysis was a notable side reaction for some cases.

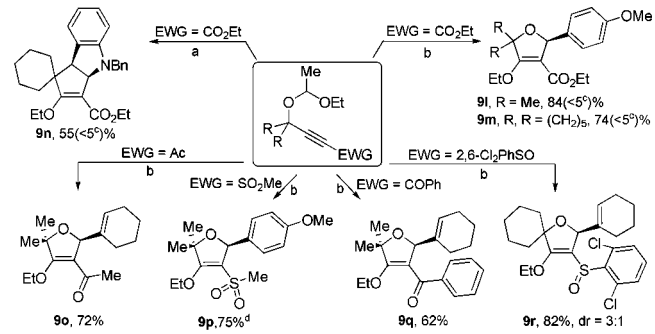
Ester substrates with fully substituted γ-positions also underwent smooth cycloadditions, yielding highly substituted **9l** and **9m** efficiently (Scheme 2). In these substrates, ethyl acetals were employed for the migration−fragmentation process as the corresponding ketal derivatives were difficult to prepare due to steric congestion. Besides carbonyl compounds, *N*-benzylindole reacted as dipolarophile as well, forming the cyclopentene ring in **9n** and allowing expedient functionalization of indole. Moreover, the ester group can be readily replaced with other EWGs[14,15] including acetyl, mesyl, benzoyl, and 2,6-dichlorobenzenesulfinyl groups,[16] yielding products (i.e., **9o**−**9r**) with diverse functionalizations at the dihydrofuran 3-position in fair to good yields.[17] Interestingly, the last example could allow chiral sulfoxide-controlled stereoselective construction of dihydrofurans.

Table 2. Efficient Formation of Functionalized 2,5-Dihydrofurans[a]



[a] The amounts of alcohols and **5** were estimated by ^{1}H NMR and shown in parentheses, respectively. [b] Entry number. [c] $IPrAuNTf_2$ (5 mol %) was used. [d] The major isomer is shown. [e] **3** was used in excess instead (2 equiv), and two batches of 5 mol % of $Ph_3PAuNTf_2$ were added; time, 1 h; 25% of the enone was recovered. [f] The corresponding 2,2-dimethyldihydrofuran was not identified.

Scheme 2. Further Scope Study



[a] *N*-Benylindole (2 equiv.), $Ph_3PAuNTf_2$ (5 mol %), CH_2Cl_2, rt, 40 min. [b] Aldehyde (2 equiv.), $Ph_3PAuNTf_2$ (5 mol %), CH_2Cl_2, rt, 15 min. [c] For compound **5**. [d] $IPrAuNTf_2$ (5 mol %) was used.

In summary, we have developed a novel approach to generate Au-containing all-carbon 1,3-dipoles via an unprecedented migration−fragmentation of ketals/acetals. These in situ generated dipoles undergo facile [3+2] cycloaddition with various enones/enals, electron-rich aromatic aldehydes, and *N*-benzylindole at room temperature, leading to rapid formation of highly functionalized 2,5-dihydrofurans[17] and cyclopentenes with good efficiencies.

Acknowledgment. Generous financial support from ACS PRF (43905-G1), ORAU, and Merck are appreciated. The NMR spectrometers are funded by NSF CHE-0521191.

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

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(10) <5% of **4** was formed if the reaction was stirred overnight at rt.
(11) This step likely proceeds via cyclization of the π electrons to the electron-deficient center with concurrent Au−C bond fragmentation.
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(13) Preliminary studies using imines, styrene, and ethyl vinyl ether as dipolarophile did not yield desired [3+2] cycloadducts.
(14) Using H instead of an EWG led to rather poor cycloaddition (26% yield, 60% conv.). For details, please see the Supporting Information.
(15) Other EWG groups such as Br, Cl, and CN led to no product.
(16) Using benzenesulfinyl instead led to signficant acetal hydrolysis.
(17) For substrates not fully substituted at the γ-positions, replacing CO_2R with these EWGs led to significant hydrolysis and <50% yields.

JA804690U