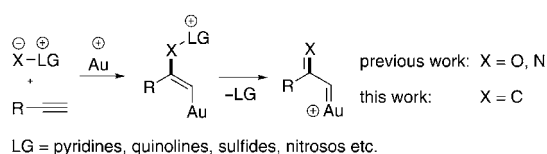


Gold-Catalyzed Carbene Transfer to Alkynes: Access to 2,4-Disubstituted Furans**

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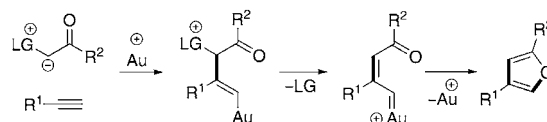
Furans are common motifs in biologically active compounds and therefore significant efforts have been made to synthesize this heteroaromatic ring.^[1] 2,4-Disubstituted furans possess an interesting substitution pattern, which is difficult to access synthetically, and the most common routes to such compounds rely on intramolecular rearrangements of complex motifs.^[2–4] The development of an intermolecular approach whereby the two substituents originate from different reagents that can combine in one step to form the aromatic core with complete regiocontrol would allow for a more direct route to the assembly of these furans, potentially with higher diversity.

Homogenous gold catalysis has been a rapidly growing field in synthetic organic chemistry within the last decade.^[5,6] The discovery of the formation of gold carbenes through intra- and intermolecular oxygen transfer has led to the development of a number of new synthetic transformations.^[7] The generation of α -oxo gold carbenes from alkynes is a promising alternative to the generation of α -oxo metal carbenes from hazardous α -diazo ketones. Few examples have been reported on the intramolecular nitrogen analogue,^[8] and the use of intermolecular nitrene transfer has only been recently demonstrated.^[9] On the other hand, there are no examples of the use of intermolecular carbene transfer to alkynes for the generation of gold carbenes. This reactivity would represent a considerable extension of this type of gold(I) chemistry because it would allow for highly valuable C–C bond formation (Scheme 1).



Scheme 1. General scheme for gold-catalyzed addition of ylides to alkynes. LG = leaving group.

We hypothesized that carbon ylides would represent the required carbene equivalent, and would be analogous to the oxygen and nitrogen ylides used for oxygen and nitrene transfer, respectively. A variety of carbon ylides are available. We decided to focus on ylides stabilized by a carbonyl group for two reasons: 1) their relatively high stability would facilitate the handling and storage of the ylide, and 2) the carbonyl group could potentially trap the generated gold carbene intramolecularly.^[10] We believed that the addition of the ylides to the terminal alkynes would be highly regioselective, and thus we envisaged the application of this carbene transfer/gold carbene formation as an entry to 2,4-disubstituted furans (Scheme 2).



Scheme 2. Gold carbene formation through carbene transfer for the synthesis of 2,4-disubstituted furans.

The treatment of a solution of 1-octyne (**1a**) in DCE with two equivalents of the sulfur ylide **2a** and 5 mol % of Gagosz's catalyst [(Ph₃P)AuNTf₂] afforded furan **3a** in 63 % yield after stirring at 60 °C for 22 hours (Table 1, entry 1).^[11–14] The reaction appeared to be unaffected by the concentration of the reagents because lowering the alkyne concentration from 0.4 M to 0.1 M had no effect on the product yield (Table 1, entry 2). When toluene or acetonitrile was used as the solvent, the yields were lower than that obtained with DCE (Table 1, entries 3 and 4). When the alkyne/ylide ratio was changed (Table 1, entries 5 and 6) or the reaction temperature was decreased or increased (Table 1, entries 7 and 8), the yield was also lowered. The use of the catalyst with the NTf₂ counter anion gave the furan product in better yield than the use of the catalyst with the OTf counter anion (Table 1, entries 1 and 9). However, the presence of silver chloride, which is generated when these catalysts were made in situ, appeared to be detrimental to the reaction (Table 1, entries 10 and 11). Indeed, the yield dropped significantly when 7 mol % of AgCl was added together with the otherwise active [(Ph₃P)AuNTf₂] (Table 1, entry 13). Other catalysts, including AgNTf₂, PtCl₂, [PicAuCl₂], [JohnPhosAu(MeCN)]SbF₆, [XPhosAuNTf₂], [SPhosAuNTf₂], and [IPrAuNTf₂] provided less than 5 % yield of the furan **3a**.^[15] The high sensitivity of the reaction toward the presence of a silver salt and variation of the ligand is intriguing.

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Table 1: Optimization of the catalytic system.

Entry	Modification	Yield [%] ^[a]
1	none	63
2	0.1 M	62
3	toluene	33
4	MeCN	39
5	1.5 equiv ylide	47
6	2.5 equiv ylide	56
7	50 °C	35
8	80 °C	49
9	[(Ph ₃ P)AuOTf]	39
10	[(Ph ₃ P)AuCl]/AgOTf	11
11	[(Ph ₃ P)AuCl]/AgNTf ₂	15
12	[(Ph ₃ P)AuCl]	6
13	[(Ph ₃ P)AuNTf ₂] (5 mol %)/AgCl (7 mol %)	4
14	no catalyst	0 ^[b]

[a] Yield of product after column chromatography. [b] Observed by ¹H NMR analysis of the crude reaction mixture. DCE = 1,2-dichloroethane, Hex = hexyl, Tf = trifluoromethylsulfonyl.

Table 2: Optimization of the sulfur ylide.

Entry	R	Yield [%] ^[a]
1	Me (2b)	24
2	4-MeOC ₆ H ₄ (2c)	50
3	C ₆ H ₅ (2a)	63
4	4-ClC ₆ H ₄ (2d)	64
5	4-FC ₆ H ₄ (2e)	67

[a] Yield of product after column chromatography.

With the optimized reaction conditions established, we turned our attention toward fine-tuning the sulfur ylide (Table 2). Reactions using aryl ylides (Table 2, entries 2–5) gave significantly better yields than those of the dimethyl ylide (Table 2, entry 1). Within the methyl aryl ylide series, the use of an ylide bearing an electron-donating group on the aryl substituent of the sulfur atom (Table 2, entry 2) led to a lower yield than the use of ylides bearing electron-withdrawing groups (Table 2, entries 4 and 5). Attempts to prepare the more electron poor pentafluorophenyl sulfur ylide derivative, the more sterically hindered 2,6-dimethylphenyl derivative, and the diphenyl sulfur ylide derivative were unsuccessful. Furthermore, the use of the corresponding pyridinium ylide, under the same reaction conditions, did not provide any of the furan. Although the use of *p*-fluorophenyl derivative **2e** gave slightly higher yields than the use of the simple phenyl derivative **2a**, variation of the latter was chosen as a means for investigating the substrate scope because of its significantly lower price (approximately 40 times cheaper).^[16]

The methyl phenyl ylides **2f–n** were easily prepared from the corresponding α -bromo ketones without the use of

column chromatography and they were significantly more stable than the dimethyl ylide **2b**.^[17]

A variety of substituents on the aryl moiety of the ylide were tolerated in this formal [3+2] cycloaddition (Table 3). The presence of a halide (Table 3, entries 2–4), a nitrile (Table 3, entry 5), a nitro (Table 3, entry 6), and an ester

Table 3: Furan synthesis with different sulfur ylides.

Entry	Ylide	Product	Yield [%] ^[a]
1	2a	3a	63
2	2f	3b	73
3	2g	3c	65
4	2h	3d	54
5	2i	3e	64
6	2j	3f	57
7	2k	3g	73
8	2l	3h	36
9	2m	3i	59
10	2n	3j	51 ^[b]

[a] Yield of product after column chromatography. [b] The reaction was performed at 84 °C.

group (Table 3, entry 7) were tolerated. Whereas the furan with a methyl substituent on the aryl moiety (Table 3, entry 8) was synthesized in relatively low yield, the naphthyl substituted furan was synthesized in good yield (Table 3, entry 9). Furthermore, the ylide derived from a *t*-butyl ketone, was also tolerated, however, a higher temperature was required for the reaction to occur (Table 3, entry 10).

The tolerance of the reaction toward variation of the substituent on the alkyne was then examined (Table 4). Variation of the alkyl length or the presence of cycloalkyl substituents did not adversely affect the yields (Table 4, entries 1–3). However, a small amount of the 2,5-substituted regioisomer was observed in the case of the cyclohexyl substituted alkyne **1d**, presumably because of the increased steric bulk (Table 4, entry 3). The presence of silyl and alkyl ethers was also tolerated (Table 4, entries 4 and 5). Surprisingly, a slight decrease in yield was observed when using an alkyne bearing an ester substituent (Table 4, entry 6); this result is in contrast to the relatively good yields that were obtained when ester substituents were part of the ylide

Table 4: Furan synthesis with different alkynes.

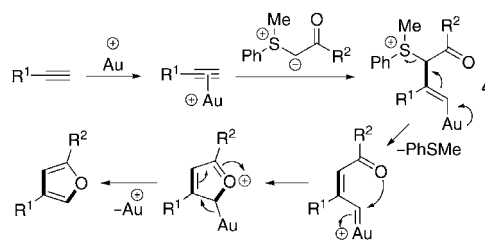
Entry	Alkyne	Product	Yield [%] ^[a]
1			62
2			82
3			61 ^[b]
4			67
5			78
6			48
7			57 ^[c]
8			69
9			30

[a] Yield of product after column chromatography. [b] Isolated as 96:4 mixture of regioisomers (2,4-substituted/2,5-substituted). [c] 2.5 equivalents of ylide. Bn = benzyl, Piv = pivaloyl, TIPS = triisopropylsilyl.

(Table 4, entries 2, 7, and 8, and Table 3, entry 7). The use of alkynes bearing a sulfonamide (Table 4, entry 7) or a carbamate (Table 4, entry 8) also provided the corresponding furan in high yields. Interestingly, for the sulfonamide derivative, when the standard 2.0 equivalents of ylide was used, the furan **3q** was obtained in 53% yield, however, 26% of alkyne **1h** was recovered. This amounts to a 72% yield based on recovered starting material. Increasing the amount of the ylide to 2.5 equivalents only increased the yield slightly to 57% (Table 4, entry 7).

The use of an alkyne bearing a primary chloride also afforded the desired furan, albeit in moderate yield (Table 4, entry 9). Under the same reaction conditions, however, the use of phenylacetylene or the internal alkynes, 2-octyne, and ethyl 3-phenylpropionate, did not lead to any of the corresponding furans. It would therefore appear that this transformation is selective for terminal alkynes over internal alkynes.

A mechanistic proposal for this furan synthesis is depicted in Scheme 3. Activation of the alkyne by gold(I) would be followed by a highly regioselective nucleophilic attack by the ylide to the vinyl gold intermediate **4**. Back donation from the gold center would lead to the liberation of



Scheme 3. Mechanistic proposal for the 2,4-disubstituted furan synthesis.

the leaving group with concurrent generation of an allylic gold carbene. This carbene would then be trapped intramolecularly by the carbonyl oxygen and a subsequent elimination of the gold catalyst would furnish the 2,4-disubstituted furan. A 5-endo-trig S_N2' cyclization of **4**, can also account for product formation, however, because it is a disfavored ring formation according to Baldwin's rules, we believe that this pathway is less likely.^[18]

In summary, we have developed a reaction involving the first example where a gold carbene is formed through carbene transfer to an alkyne. An ensuing intramolecular trapping of the gold carbene affords the nontrivial 2,4-disubstituted furans in good to high yields; the entire transformation represents a formal [3+2] cycloaddition. The use of carbon ylides as nucleophiles in this work represents a significant expansion of the intermolecular gold carbene formation chemistry, which previously included the use of oxygen and nitrogen ylides. Further studies on the addition of carbon ylides to alkynes using gold catalysis are underway.

Experimental Section

In an argon-filled glove box $[(\text{Ph}_3\text{P})\text{AuNTf}_2]^{-1/2}$ toluene (5 mol %, 5 μmol , 7.9 mg), sulfur ylide **2a** (2.0 equiv, 0.400 mmol, 96.9 mg), DCE (0.5 mL), and 1-octyne (**1a**; 1.0 equiv, 0.200 mmol, 29.8 μL) were added to a vial. The vial was sealed and the reaction mixture was stirred for 22 h at 60 °C. The reaction mixture was then cooled to room temperature and was directly purified by flash chromatography on silica gel using 100% pentane as the eluent, thus affording the desired furan (**3a**) in 63% yield (29 mg) as a colorless solid.

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