A Reactivity Switch in the Gold-Catalysed Coupling of Allyl Sulfides with Propargylic Carboxylates

Paul W. Davies,* Sebastien J.-C. Albrecht

School of Chemistry, University of Birmingham, Edgbaston, B15 2TT, Birmingham, UK Fax +44(121)4144403; E-mail: p.w.davies@bham.ac.uk *Received 7 September 2011*

Abstract: The gold-catalysed coupling of allyl sulfides with propargylic carboxylates follows different pathways depending upon the choice of nonmigrating group on the sulfur and the aromatic group at the propargylic position of the alkyne substrate.

Key words: gold, sulfur ylides, alkynes, propargylic carboxylates, coupling

The rearrangement of propargylic carboxylates by activation of the alkyne with a π -acid has proven to be a privileged process in the development of novel and diverse efficient synthetic methodologies.¹ As part of a programme to access sulfur ylides from alkynes, to bypass prior installation of sacrificial functionality such as a diazo unit, we demonstrated an intramolecular coupling of propargylic carboxylates such as **1a** with allyl sulfides **2a** to afford **3aa** (Scheme 1).^{2–5}



Scheme 1 Gold-catalysed intermolecular coupling of allyl sulfides with propargylic carboxylates

The coupling proceeded through the widely encountered 1,2-rearrangement pathway to generate the vinyl carbenoid 4 (Scheme 2). Though such systems had been very successfully employed as one-centre reactive intermediates in intermolecular reactions such as cyclopropanation,^{6,7} this reactivity should afford product **6aa** from a [2,3]-sigmatropic rearrangement.⁸ Instead, overall twocentre 1,3-C,C-dipole reactivity of 4 was observed in this process: On formation of ylide 5 the newly installed adjacent enol acetate was involved in the subsequent reaction evolution to give 3 as a single isomer. Such incorporation of the three-carbon unit of propargylic carboxylates has been observed in other reactions, for instance in the intermolecular sense with α , β -unsaturated imines⁹ or alkenes¹⁰ or intramolecularly with allyl ethers.¹¹ As allyl sulfur ylides generated from gold carbenoids have been shown

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to react normally and undergo [2,3]-sigmatropic rearrangement,³ the absence of isomer **6** suggests either a fast subsequent evolution of **6** by [3,3]-sigmatropic rearrangement or that direct S–C allyl transfer from **5** to afford **3** is preferred.



Scheme 2 Proposed mechanism in the gold-catalysed coupling reaction

This reaction provides efficient access to a structural motif populated with functional groups suited for subsequent orthogonal activation. In order to pursue the synthetic opportunities that this motif offered, we were interested in exploring whether the phenyl unit in the propargylic carboxylate could be replaced with a heteroaromatic group that would have greater use in subsequent synthetic application.¹² Propargylic carboxylates incorporating a furan or thiophene, 1b and 1c, were therefore prepared and tested in the catalysis reaction with allyl phenyl sulfide. However, only trace conversion was observed (Table 1, entries 1 and 2). p-Methoxybenzene-derived substrate 1d was then employed to assess whether the unproductive reaction system stemmed from the electron-rich character of the heteroaromatic units. This was borne out when 1d proved similarly unreactive (Table 1, entry 3). In contrast, the para-carboxylate 1e reacted smoothly with allyl sulfide to afford the desired product 3ea in high yield (Table 1, entry 4).

Following this trend, the use of a deactivated heteroaryl unit seemed appropriate, and the conjugated furan derivative **1f** was prepared from known aldehyde 7^{13} to continue the study (Scheme 3). The enolizable carbonyl unit in **1f** has two functions: to render the heteroaromatic ring electron-deficient, and to test the functional-group compati-

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^a AuCl (5%) was added to a solution of **1** and **2a** (1.1 equiv) in DCE (0.1 M), the flask was sealed and heated at 70 $^{\circ}$ C.

^b Yield of isolated product after flash column chromatography.



Scheme 3 Preparation of 1f and its use in the gold-catalysed coupling with 2a

bility of this sulfur ylide preparation. Pleasingly, under the standard conditions, the coupling of **1f** with **2a** proceeded smoothly to afford the coupling product **3fa** in high yield as a single isomer.

With a heteroaryl unit now accommodated in this coupling, attention turned to exploring the nature of the nonmigrating group on the sulfur (Table 2). Surprisingly, the switch from S-phenyl- to S-benzyl allyl sulfide resulted in the formation of the expected coupling product **3fb** in small quantities only. The major product was instead isomer **6fb**, isolated predominantly as the *E* isomer, which is expected from a [2,3]-sigmatropic rearrangement of the sulfur ylide intermediate. The use of Au(I) or Au(III) precatalysts gave consistent results for either benzyl allyl sulfide or allyl phenyl sulfide (Table 2, entries 1 vs. 2 and 3 vs. 4). Diallyl sulfide **2c** was then employed in the reaction and gave isomer **6fc** as the major product, again with **3fc** identified in low yield (Table 2, entry 5). The use of methyl allyl sulfide **2d** gave **6fd** in excellent yield as a ca. 2:1 mix of geometric isomers (Table 2, entry 6) with none of isomer **3fd** observed. A complete switch in reaction outcome is therefore observed relative to the use of phenyl allyl sulfide.

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Table 2 The Impact of the Nonmigrating Sulfur Substituent in the Coupling Reaction



Entry ^a	\mathbb{R}^1	Catalyst	Product, yield (%) ^b
1	Ph	AuCl	3fa 81
2	Ph	AuCl ₃	3fa 74
3	Bn	AuCl	(<i>E</i>)- 6fb 63 3fb /(<i>Z</i>)- 6fb (1:0.6) 19 ^c
4	Bn	AuBr ₃	(<i>E</i>)- 6fb 67 ^d
5	Allyl	AuCl	(<i>E</i>)-6fc 57 3fc/(<i>Z</i>)-6fc/1f (1:0.6:0.3) 25°
6	Me	AuCl	(<i>E</i>)-6fd 66 (<i>Z</i>)-6fd 30

^a Catalyst (5%) was added to a solution of **1f** and **2a–d** (1.1 equiv) in DCE (0.1 M), the flask was sealed and heated at 70 °C for 14 h. ^b Yield of isolated product after flash column chromatography.

⁶ Potio determined from ¹H NMP spectroscopy

^c Ratio determined from ¹H NMR spectroscopy.

^d A mixture of other product isomers alongside unreacted starting material was also observed.

The impact of the nonmigrating group on the reaction pathway was subsequently examined in the reactions of phenyl-substituted propargylic carboxylates (Scheme 4). Only isomer **3ab** was observed from the reaction of **1a** with benzyl allyl sulfide. Similarly, **3gd** was formed from the pivalate **1g**. However, when using allyl methyl sulfide **2d**, the product from [2,3]-sigmatropic rearrangement of the sulfur ylide **6gd** was observed as the major product alongside **3gd**.

To study whether isomer **3** results from a fast rearrangement of **6**, or vice versa, the structural isomers **3gd** and **6gd** were separated by HPLC and heated independently in 1,2-dichloroethane at 70 °C with: (i) no catalyst; (ii) AuCl (10 mol%); (iii) AuCl₃ (10 mol%). No interconversion between isomers or other reaction was observed under any



Scheme 4 Coupling of methyl and benzyl allyl sulfides

of these conditions. To rule out an active catalyst for the Cope rearrangement only being formed during a coupling reaction, (E/Z)-**6gd** was also added to a reaction between **1a** and **2e** and was recovered unaffected alongside the expected product **3ae** (Scheme 5).¹⁴



Scheme 5 Control reaction to assess interconversion of isomers

This lack of interconversion between isomers is consistent with the formation of **3** directly from **5** by transfer of the allyl cation from sulfur to the nucleophilic C-3 carbon. Though generally a facile process in sulfur ylide chemistry, the [2,3]-sigmatropic rearrangement of ylide **5** appears to be disfavored in this specific process in the presence of a competing S–C allyl migration pathway. Steric congestion between the nonmigrating S-substituent and the enol acetate unit may affect the ability of **5** to adopt the conformation about the S–C bond that is required for sigmatropic rearrangement. It is notable that increasing quantities of [2,3]-sigmatropic rearrangement product **6** are observed as the steric environment directly at sulfur decreases, going from C_{aromatic}, benzylic, and allylic to methyl, presumably allowing greater rotational freedom around the ylidic S–C bond.

The difference in reactivity between **1a** and **1f**, with the latter more likely to afford the product of [2,3]-sigmatropic rearrangement, may result from the smaller furan unit aiding the sigmatropic pathway on steric grounds. However, the effect of the conjugated carbonyl unit on reducing the localised anionic character at C-3 could well decrease the relative rate of the allyl cation migration onto this position.

In summary, a heteroaromatic unit can be incorporated into the gold-catalysed intermolecular coupling reaction between a propargylic carboxylate and an allyl sulfide. Sulfur ylides can even be installed by this method in the presence of an enolizable carbonyl group. The [2,3] rearrangement of sulfur ylides prepared directly from propargylic carboxylates is observed for the first time, and the outcome of this reaction is highly dependent upon the choice of the nonmigrating sulfur substituent. The structurally isomeric products are formed by divergent pathways from the sulfur ylide and a complete switch in reaction outcome was observed when using *S*-phenyl and *S*-methyl allyl sulfide.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

- Reviews: (a) Fürstner, A.; Davies, P. W. Angew. Chem. Int. Ed. 2007, 46, 3410. (b) Hashmi, A. S. K.; Hutchings, G. J. Angew. Chem. Int. Ed. 2006, 45, 7896. (c) Gorin, D. J.; Toste, F. D. Nature (London) 2007, 446, 395. (d) Marion, N.; Nolan, S. P. Angew. Chem. Int. Ed. 2007, 46, 2750. (e) Marco-Contelles, J.; Soriano, E. Chem. Eur. J. 2007, 13, 1350.
- (2) Davies, P. W.; Albrecht, S. J.-C. Chem. Commun. 2008, 238.
- (3) For our further studies into the formation of sulfur ylides from alkynes, see: (a) Davies, P. W.; Albrecht, S. J. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 8372. (b) Davies, P. W. *Pure Appl. Chem.* **2010**, *82*, 1537.
- (4) For a diazo-free transition-metal-catalysed cyclisation– aromatisation approach to generate sulfur ylides, see: Kato, Y.; Miki, K.; Nishino, K. F.; Ohe, K.; Uemura, S. *Org. Lett.* 2003, *5*, 2619.
- (5) For examples of low-valent sulfur employed alongside effective gold-catalysed organic synthesis, see:
 (a) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* 2006, 45, 4473. (b) Nakamura, I.; Bajracharya, G. B.; Wu, H.; Oishi, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* 2004, *126*, 15423.
 (c) Peng, L.; Zhang, X.; Zhang, S.; Wang, J. *J. Org. Chem.* 2007, *72*, 1192. (d) Morita, N.; Krause, N. *Angew. Chem.*

Int. Ed. 2006, 45, 1897. (e) Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F. Green Chem. 2003, 5, 64. (f) Hashmi, A. S. K.; Rudolph, M.; Huck, J.; Frey, W.; Bats, J. W.; Hamzić, M. Angew. Chem. Int. Ed. 2009, 48, 5848. (g) Hashmi, A. S. K.; Yang, W.; Rominger, F. Angew. Chem. Int. Ed. 2011, 50, 5762.

- (6) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. J. Am. Chem. Soc. 2005, 127, 18002.
- (7) We observed cyclopropanation as the major pathway when allyl sulfides bearing greater substitution at the alkene were employed.
- (8) (a) Kirmse, W.; Kapps, M. Chem. Ber. 1968, 101, 994. (b) Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; van Leusen, D. J. Org. Chem. 1984, 49, 1917. (c) Reggelin, M. Sulfur-Mediated Rearrangements II, In Topics in Current Chemistry, Vol. 275; Schaumann, E., Ed.; Springer: Berlin, 2007, 1-65. For a recent study of a transition-metalcatalysed Doyle-Kirmse reaction, see: (d) Davies, P. W.; Albrecht, S. J.-C.; Assanelli, G. Org. Biomol. Chem. 2009, 7, 1276; and references cited therein.
- (9) Shapiro, N. D.; Toste, F. D. J. Am. Chem. Soc. 2008, 130, 9244.
- (10) (a) Garavalde, D.; Kruger, K.; Nevado, C. Angew. Chem. Int. Ed. 2011, 50, 911. (b) Sperger, C. A.; Tungen, J. E.; Fiksdahl, A. Eur. J. Org. Chem. 2011, 3719.

(11) Uemura, M.; Watson, I. D. G.; Katsukawa, M.; Toste, F. D. J. Am. Chem. Soc. 2009, 131, 3464.

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Only very limited success has been observed with aliphatic (12)substituents at the propargylic position. Aldehyde-derived systems are observed to give only trace amounts of conversion or undergo degradation. Ketone derivative A-1 proceeds sluggishly to give the desired coupling product A-3a in low yield (Scheme 6).



Scheme 6

- (13) Hashmi, A. S. K.; Kurpejović, E.; Wölfle, M.; Frey, W.; Bats, J. W. Adv. Synth. Catal. 2007, 349, 1743.
- (14)Similarly, neither (E)- or (Z)-6gd were observed when 3gd was added to an ongoing reaction.

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