Gold(I)-catalysed synthesis of conjugated trienes[†]

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Gold(1)-catalysed reaction between cyclopropenes and furans produces functionalised conjugated trienes. The reaction is mild, facile and proceeds with very low catalyst loadings.

Conjugated trienes are important structural units in many biologically important polyene natural products such as antifungal macrolides and anticancer retinoids,¹ as well as π -extended materials.² As such, new synthetic methods towards such building blocks are of great interest to synthetic chemists.3 Current approaches towards functionalised, substituted trienes, however, often require several iterative steps and/or stoichiometric reagents.⁴ We recently initiated a programme to explore the diverse chemistry of gold-catalysed⁵ transformations with cyclopropenes.⁶⁻⁸ In this communication, we report an unprecedented gold(1)-catalysed reaction of cyclopropenes with furans to form a series of functionalised conjugated trienes in a single step (Scheme 1). The reaction is very mild, versatile, facile and proceeds with as little as 0.01 mol% of catalyst to produce differentially substituted trienes. We thus set out to explore the scope and selectivity of this novel, one-pot catalytic approach towards conjugated trienes.

We initiated our investigations with a catalyst screen on cyclopropene 1 (Table 1). Every gold(1) catalyst screened in Table 1 produced the conjugated triene in >70% yield (Entries 1–6). Reaction monitoring indicated that the initial gold(1)-catalysed ring-opening reaction is very fast (within minutes), however, the immediate product is a complex mixture of several E/Z isomer combinations of the triene product 3. Upon leaving the reaction for a further 24 h, the triene slowly isomerises, mainly to 3a and 3b in $\sim 1:1$ ratio. The cationic gold catalyst 4^9 produces by far the best isolated yield of 3 (Entry 5) and was thus adopted as the optimal catalyst.

In an effort to expedite the isomerisation process, a crystal of iodine was added to the reaction mixture after 15 min (Table 2).^{3d} Gratifyingly, this one-pot treatment with iodine successfully isomerises the triene product to a presumably thermodynamic ratio of stable isomers **3a** and **3b**, without affecting the isolated yield of the product (Entry 1, Table 2).



Scheme 1 Gold(I)-catalysed synthesis of conjugated trienes.

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^{*a*} Reaction conditions: cyclopropene **1** (1 equiv.), furan **2** (1.5 equiv.), catalyst (5 mol%), 0.3 M in CH₂Cl₂. ^{*b*} IPr = 1,3-bis(2,6-diisopropyl-phenyl)imidazolylidene. IMes = 1,3-bis(mesityl)imidazolylidene. ^{*c*} Isolated yield of 3a + 3b.

A variety of alkyl substituted cyclopropenes also react smoothly to produce the triene products in good yields (Entries 2–5, 82–91% yields). In fact, we were pleased to find that the (*EEE*)-triene can be isolated in good yields and excellent stereoselectivities using the gold(1)/iodine one-pot protocol when the substituents \mathbf{R}^1 and \mathbf{R}^2 are sterically or electronically differentiated (Entries 5–9, Table 2).

Successful intermolecular reaction of the cyclopropenes bearing aryl and/or ester functionalities is worthy of further mention (Entries 6-9). Previous investigations have shown that these cyclopropenes tend to undergo facile gold(I)-catalysed intramolecular rearrangement to indenes and/or butenolides and gold(I)-catalysed intermolecular reactions are, as a result, highly challenging with such substrates.^{6a,8a,b} It is thus very pleasing that, for example, the *intermolecular* reaction of cyclopropene 15 with furan 2 predominates over the intramolecular rearrangement in these reactions to produce the functionalised conjugated triene 16a in good yield (75%) and high selectivity (>95:5, Entry 7). Even the hindered trisubstituted cyclopropene 17 reacts smoothly to produce the (E, E, E) triene 18a in high selectivity (>95:5, 77%), albeit requiring a higher reaction temperature of 80 °C (Entry 8). When the phenyl substituents in 17 are replaced with alkyl substituents (19), the desired triene 20a is still formed stereoselectively, but only in moderate yield (37%, Entry 9). This is due to competition between the desired reaction and a different rearrangement to produce the diene 22 (see ESI). Successful reaction with cyclopropene carboxylate substrates such as 15, 17 and 19 is particularly pleasing as it produces conjugated trienes with a handle for functionalisation

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R ¹	$ \sum_{\substack{K^4 \\ K^4}} \frac{\text{catal}}{CH_2 \ell} $ ii) I ₂ (c	Me 2 yst 4 (5 mol%) Cl ₂ , RT, 15 min at.), 1 h	O Me O Me	R^{4} R^{2} R^{4} R^{2} R^{3} R^{4} R^{1}	[−] R ¹ a
Entry ^a	Cyclopropen	e	Product	Ratio of a : b	Yield ^b
1	Bn 1	R ¹ =Bn R ² =Me R ³ =R ⁴ =H	3a	2.2:1	91%
2	5	R ¹ -R ² =Cy R ³ =R ⁴ =H	6	N/A	83%
3	B B T F F F	R ¹ =(CH ₂₎₈ Me R ² =Me R ³ =R ⁴ =H	8a + 8b	1.5:1	82%
4	Bn 9	R ¹ = <i>i-</i> Pr R ² =Bn R ³ =R ⁴ =H	10a + 10b	3.5:1	91%
5		R ¹ = <i>t-</i> Bu R ² =Me R ³ =R ⁴ =H	12a	>95:5	85%
6	Ph	R ¹ =Ph R ² =Me R ³ =R ⁴ =H	14a	>95:5	64%
7		R ¹ =Ph ∕le R ² =CO₂Me R ³ =R ⁴ =H	16a	>95:5	75% ^c
8	Eto Ph 17	R ¹ =CO ₂ Et R ² =H R ³ =R ⁴ =Ph `Ph	18a	>95:5	77% ^d
9	Eto "Pr 19	R ¹ =CO ₂ Et ¹ R ² =H R ³ =R ⁴ = ⁿ Pr	20a + 5:1 0 ^{od} CO ₂ Et E:2 0 ⁿ Pr 22	>95:5	37% ^e

Table 2 Gold(1)-catalysed furan addition to a variety of cyclopropenes

^a Reaction conditions: cyclopropene (1 equiv.), furan 2 (1.5 equiv.), catalyst 4 (5 mol%) in CH₂Cl₂ (0.3 M), 15 min, followed by a crystal of I₂, 1 h, RT., unless otherwise stated. ^b Isolated yields. ^c Step i left for 16 h. ^d Reaction conditions for step (i): furan 2 (1.5 equiv.), catalyst 4 (15 mol%), DCE, 80 °C, 18 h. e Reaction conditions for step (i): furan 2 (12 equiv.), catalyst 4 (10 mol%), 15 °C, 24 h. By-product is diene 22.

at both ends of the triene (16a, 18a, 20a), allowing for potential incorporation of the triene unit into larger building blocks. Cyclopropene carboxylates are also very easy to access, for example, 17 and 19 are each synthesised in one step from commercially available ethyl diazoacetate.10

 Table 3
 Gold(I)-catalysed addition of a variety of furan nucleophiles
 to cyclopropene 11

11	$ \begin{array}{c} + \\ R^3 \\ 23 \end{array} $	i) 4 (5 mol%) CH ₂ Cl ₂ 15 min, RT ii) l ₂ , 1 h		2 R ³	K
Entry ^a	R ¹	R ²	R^3	Product	Yield ^b
1 2 3	H Me OMe	H H H	H H H	24 12a 25	61% 85% 70% ^c
4		Н	Н	26 27	71%
6	^t Bu	H H	н Н	27 28	89%
7	$(CH_2)_2CO_2$ $(CH_2)_2^i Pr$	Н	Н	29	89%
8 9 10	Me Me Me	H Me CO ₂ Me	Ме Н Н	30 31 32	82% 87% 75% ^d
11	Me		Me	N/A	Complex mixture

^a Reaction conditions: cyclopropene (1 equiv.), furan (1.5 equiv.), catalyst 4 (5 mol%) in CH₂Cl₂ (0.3 M), 15 min, followed by a crystal of I₂, 1 h, RT., unless otherwise stated. ^b Isolated yields; >95:5 selectivity of (E, E, E) isomer unless otherwise stated. ^c Step ii): I₂, 5 days, RT. ^d Conditions: cyclopropene (1 equiv.), furan (1 equiv.), catalyst 4 (3 mol%), 0.3 M in CH₂Cl₂. Ratio 1.5:1 Z/E around R² substituent (see ESI).

Having explored the scope of the cyclopropene substrates, we set out to explore the scope of the furan nucleophile (Table 3). The substituent R^1 on the furan 23 can be varied (e.g. H, Me, OMe) to produce the aldehyde, ketone and ester functionalised triene respectively (Entries 1-3). An acetal, CH₂OAc, bulky ^tBu and functionalised alkyl chain are also tolerated at the R¹ position, producing the corresponding trienes in good yields and selectivities (Entries 4-7). Next, we set out to investigate the reactivity and selectivity of disubstituted furans. Methyl substituents at R^1 and R^3 (Entry 8) as well as R^1 and R^2 (Entry 9) are not detrimental to the reactivity or selectivity, and is in fact a good way of introducing further substituents into the triene product. An electron withdrawing ester substituent is also tolerated at position R^2 (Entry 10). Trisubstituted furans, however, react less well, presumably due to selectivity issues. For example, the trisubstituted furan in Entry 11 provides a complex mixture of products under the standard reaction conditions.

Since the reaction appeared to be extremely facile, we were keen to investigate if the catalyst loading could be lowered. We were pleased to find that even with a 0.1 mol% loading of Au(I) catalyst, the reaction (step i) was complete in < 30 s with no drop in isolated yield (90%, Table 4, Entry 1). Encouraged by this result, the catalyst loading was lowered even further to 0.01 mol%. To our delight, the gold(I)-catalysed reaction was still complete within 2 min to yield the triene products 3a + 3bin 89% yield (Table 4, Entry 2). This corresponds to an impressive TON of 10000.

In an effort to ascertain if catalysts other than gold(I) can carry out the same reaction, a small screen of other transition

 Table 4
 Catalyst loading and further catalyst screening, and control reactions



^{*a*} Reaction conditions: cyclopropene **1** (1 equiv.), furan **2** (1.5 equiv.), in CH_2Cl_2 (0.3 M), 15 min, followed by a crystal of I_2 , 1 h, RT., unless otherwise stated. ^{*b*} Isolated yields.



Scheme 2 Plausible mechanism for the gold(t)-catalysed synthesis of conjugated trienes.

metal catalysts was carried out (Table 4). PtCl₂, a π -Lewis acid, ^{5f} successfully catalyses the reaction, but in a much slower reaction time and with a lower isolated yield (6 h, 77% yield, Entry 3).¹² [Ru(CO)₃Cl₂]₂^{3b} requires even longer reaction times (24 h) and produces the trienes in much lower yields (44%, Entry 4). Rh₂(OAc)₄ on the other hand, produced a complex mixture of products (Entry 5). By comparison, several different gold(1) catalysts shown in Table 1 successfully formed triene products within minutes. Finally, control reactions without catalyst (Entry 6) and with iodine (Entry 7) resulted in no reaction, thus confirming that the triene forming reaction in Entries 1 and 2 is indeed gold(1)-catalysed. It is also noteworthy that the gold(1)-catalysed reaction is not sensitive to air or moisture.

A plausible mechanism for the reaction is shown in Scheme 2. Gold(1) activates the ring opening of the cyclopropene to form intermediate I, which possesses both cation and carbene character.¹¹ Furan then reacts as a nucleophile^{13,14} and subsequent ring opening produces a mixture of triene isomers, which isomerises to the most stable triene (path A). A second possible pathway involves cyclopropanation of furan, followed by ring opening of II to form the triene (path B).

In conclusion, we have developed a mild and facile gold(i)-catalysed reaction of cyclopropenes and furans to form a series of functionalised trienes in high yields. As little as 0.01 mol% catalyst can be used and the trienes are formed

stereoselectively after treatment with iodine if the substituents on the cyclopropene are sterically or electronically differentiated. This novel reaction should be a useful addition to the toolkit of synthetic methods for polyene targets.

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Notes and references

- 1 C. Thirsk and A. Whiting, J. Chem. Soc., Perkin Trans. 1, 2002, 999.
- R. E. Martin and F. Diederich, Angew. Chem., Int. Ed., 1999, 38, 1350.
 Selected examples: (a) S. J. Lee, K. C. Gray, J. S. Paek and M. D. Burka, L. Am. Chem. Soc. 2009, 120, 444 (1); K. Milling, S. M. S. Marka, M. D. Burka, J. Am. Chem. Soc. 2009, 120, 444 (1); K. Milling, S. Mil
- M. D. Burke, J. Am. Chem. Soc., 2008, 130, 466; (b) K. Miki,
 M. Fujita, S. Uemura and K. Ohe, Org. Lett., 2006, 8, 1741;
 (c) Y. Ikeda, M. Murai, T. Abo, K. Miki and K. Ohe, Tetrahedron Lett., 2007, 48, 6651; (d) E. Wenkert, M. Guo, R. Lavilla,
 B. Porter, K. Ramachandran and J. H. Sheu, J. Org. Chem., 1990, 55, 6203; (e) P. Wipf and P. D. G. Coish, Tetrahedron Lett., 1997, 38, 5073; (f) K. Hemming and R. J. K. Taylor, J. Chem. Soc., Chem. Commun., 1993, 1409; (g) D. Frederico, P. M. Donate, M. G. Constantino, E. S. Bronze and M. I. Sairre, J. Org. Chem., 2003, 68, 9126; (h) Y. J. Zhao and T. P. Loh, Tetrahedron, 2008, 64, 4972; (i) A. G. M. Barrett, D. Hamprecht and M. Ohkubo, J. Org. Chem., 1997, 62, 9376; (f) B. H. Lipshutz and C. Lindsley, J. Am. Chem. Soc., 1997, 119, 4555.
- 4 S. Koo, in *Science of Synthesis*, Georg Thieme Verlag, 2010, vol. 45b, p. 1349.
- Selected reviews: (a) D. J. Gorin and F. D. Toste, *Nature*, 2007, 446, 395; (b) A. S. K. Hashmi, *Chem. Rev.*, 2007, 107, 3180; (c) E. Jimenez-Nunez and A. M. Echavarren, *Chem. Commun.*, 2007, 333; (d) Z. G. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, 108, 3239; (e) N. Marion and S. P. Nolan, *Chem. Soc. Rev.*, 2008, 37, 1776; (f) A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, 46, 3410; (g) A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2010, 49, 5232.
- 6 (a) J. T. Bauer, M. S. Hadfield and A. L. Lee, Chem. Commun., 2008, 6405; (b) M. S. Hadfield, J. T. Bauer, P. E. Glen and A. L. Lee, Org. Biomol. Chem., 2010, 8, 4090; (c) M. S. Hadfield and A. L. Lee, Org. Lett., 2010, 12, 484; (d) K. J. Kilpin, U. S. D. Paul, A. L. Lee and J. D. Crowley, Chem. Commun., 2010, DOI: 10.1039/c1030cc02185g.
- 7 Recent reviews on cyclopropene chemistry: (a) I. Marek, S. Simaan and A. Masarwa, Angew. Chem., Int. Ed., 2007, 46, 7364; (b) M. Rubin, M. Rubina and V. Gevorgyan, Synthesis, 2006, 1221; (c) M. Rubin, M. Rubina and V. Gevorgyan, Chem. Rev., 2007, 107, 3117; (d) J. M. Fox and N. Yan, Curr. Org. Chem., 2005, 9, 719.
- 8 For other reports on gold-catalysed reactions with cyclopropenes:
 (a) Z. B. Zhu and M. Shi, *Chem.-Eur. J.*, 2008, 14, 10219;
 (b) C. K. Li, Y. Zeng and J. B. Wang, *Tetrahedron Lett.*, 2009, 50, 2956;
 (c) C. K. Li, Y. Zeng, H. Zhang, J. Feng, Y. Zhang and J. B. Wang, *Angew. Chem., Int. Ed.*, 2010, 49, 6413;
 (d) F. Miege, C. Meyer and J. Cossy, *Org. Lett.*, 2010, 12, 4144.
- 9 C. Nieto-Oberhuber, S. Lopez, M. P. Munoz, D. J. Cardenas, E. Bunuel, C. Nevado and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2005, **44**, 6146.
- 10 C. Li, H. Zhang, J. Feng, Y. Zhang and J. Wang, *Org. Lett.*, 2010, **12**, 3082.
- 11 (a) D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. M. Wang, W. A. Goddard and F. D. Toste, *Nat. Chem.*, 2009, **1**, 482; (b) G. Seidel, R. Mynott and A. Fürstner, *Angew. Chem., Int. Ed.*, 2009, **48**, 2510; (c) A. M. Echavarren, *Nat. Chem.*, 2009, **1**, 431.
- 12 For a comparison of gold, Pt and Rh-catalysts for the synthesis of phenols from alkynes and furans, see: A. S. K. Hashmi, T. M. Frost and J. W. Bats, *Org. Lett.*, 2001, **3**, 3769.
- 13 For examples of carbene trigerred ring opening of furans, see ref. 3b-d.
- 14 For examples of gold-catalysed reactions of furans with alkynes to form phenols, see: (a) A. S. K. Hashmi, M. Rudolph, H.-U. Siehl, M. Tanaka, J. W. Bats and W. Frey, *Chem.–Eur. J.*, 2008, 14, 3703; (b) A. S. K. Hashmi, T. M. Frost and J. W. Bats, *J. Am. Chem. Soc.*, 2000, 122, 11553; (c) A. S. K. Hashmi, M. C. Blanco, E. Kurpejovic, W. Frey and J. W. Bats, *Adv. Synth. Catal.*, 2006, 348, 709.