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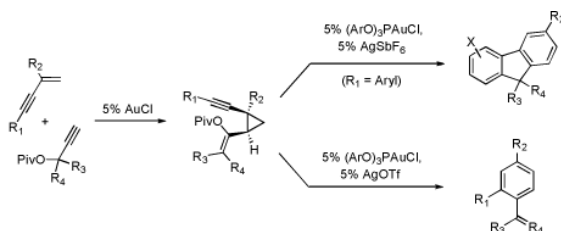
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Fluorenes and Styrenes by Au(I)-Catalyzed Annulation of Enynes and Alkynes

David J. Gorin, Iain D. G. Watson, and F. Dean Toste*

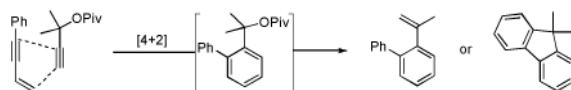
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Abstract



Intermolecular annulation of enynes and propargyl esters to selectively produce styrenes or fluorenes is reported. The divergent arene syntheses involve a Au-catalyzed, two-pot, multi-step process proceeding by *cis*-diastereoselective cyclopropanation, cycloisomerization, and, finally, annulation or elimination.

Metal-catalyzed cycloaddition reactions provide attractive and efficient methods for the synthesis of arenes, although regioselectivity presents a major challenge for intermolecular reactions.¹ The synthesis of polysubstituted benzenes by the [2+2+2] cyclotrimerization of alkynes² has been extensively studied, as has the Pd-catalyzed [4+2] cycloaddition of enynes and activated alkynes.³ We report herein a mechanistically distinct intermolecular annulation of enynes and alkynes to produce multiply substituted arenes (eq 1); styrene or fluorene products can be selectively accessed by judicious choice of reaction conditions.



(1)

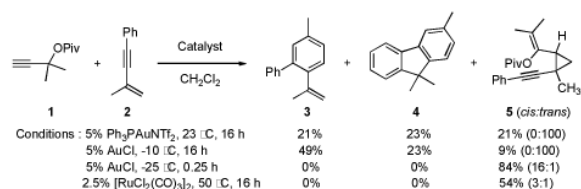
Given the synthetic utility of vinyl cyclopropanes,⁴ we anticipated that alkynyl cyclopropanes derived from the cyclopropanation of 1,3-enynes would provide similar opportunities for organic synthesis.⁵ In light of our previous work employing propargyl esters as carbene precursors in Au(I)-catalyzed cyclopropanation reactions of olefins,^{6,7} the reaction of **1** with enyne **2** was investigated.⁸

Initially, treatment of **1** and **2** with a cationic phosphinegold(I) complex resulted in a mixture of products, including styrene **3**, fluorene **4**, and cyclopropane *trans*-**5** (eq 2). The

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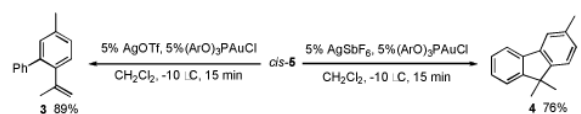
Supporting Information Available Experimental procedures and compound characterization data. This material is available free of charges at <http://pubs.acs.org>

unexpected products **3** and **4** were intriguing; **3** formally results from a completely regioselective [4+2] cross-dimerization of two different enynes, while compounds such as **4** are of interest due to the blue-light emitting properties of polyfluorenes.^{9,10}



(2)

Since cyclopropane **5** was obtained exclusively as the *trans*-diastereomer, we hypothesized that **3** and **4** arose from the *cis*-diastereomer. Therefore, we were pleased to find that the less reactive AuCl cleanly catalyzed the synthesis of cyclopropane **5** with high *cis*-diastereoselectivity and complete regioselectivity. With ready access to *cis*-**5**, we next investigated its transformation to **3** and **4**.



(3)

Gratifyingly, either compound could be selectively prepared simply by changing the silver salt co-catalyst in conjunction with triarylphosphitegold(I) chloride (Ar = 2,4-di-tert-butylphenyl).^{11,12} Thus, reaction of *cis*-**5** with the Au complex and AgOTf provided **3** in 89% yield, while the reaction with AgSbF₆ under otherwise identical conditions provided **4** in 76% yield (eq 3).¹³

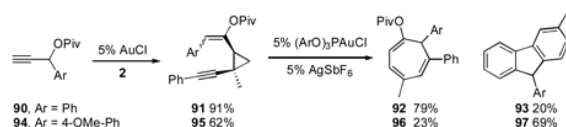
The substrate scope of the two-step, divergent syntheses of fluorenes and styrenes was investigated with other enynes (Table 1).¹⁴ Aryl enynes with a variety of substitution patterns and functional groups were tolerated, demonstrating the power of this method to prepare multiply substituted arenes from simple starting materials (entries 1-13). Moreover, both electron-rich and electron-poor enynes **14** and **18** undergo the cyclopropanation and arene syntheses; however, commensurate with the expected nucleophilicities of the aryl group, they demonstrated diametric preferences for styrenes versus fluorene formation (entries 3,4). Alkyl-substituted enynes are also tolerated in both the cyclopropanation and annulation steps (entries 14-16).

The carbene precursor was also varied (Table 2). The pivaloate ester provided the best selectivity in differentiating between the styrene and fluorene pathways (entries 1-3). [9,9]-Dibutyl-substituted fluorene **82** was prepared (entry 6); such hydrophobic solubilizing groups are often found in fluorenes designed for subsequent polymerization. Additionally, the use of unsymmetrical pivaloate **83** readily provided **85** or **86** (entries 7).

A mechanism accounting for the observed products begins with the formation of **5** by intermolecular cyclopropanation of enyne **2** via the gold carbenoid produced from rearrangement of propargyl ester **1**. Following coordination of the cationic gold catalyst to the resulting alkyne, the pendant olefin can participate in either a 5-*endo*-dig or 6-*endo*-dig cyclization (Scheme 1). When tertiary propargyl esters are employed in the gold-catalyzed

annulation, the 5-*endo*-dig cyclization to generate tertiary carbocation **87** dominates. Subsequent migration of the pivaloyloxy group gives allylic cation **88** that may be further stabilized by delocalization of the charge onto gold. Cyclopropyl ring opening *via* a pentadienyl cation leads to **89**, which is most likely converted to **3** and **4** by E1 and S_N1 mechanisms, respectively.^{15,16}

Use of secondary propargyl pivaloate **90** diverted the reaction pathway towards the 6-*endo*-dig cyclization and formation of cycloheptatriene **92** (eq 4). Selectivity for the 5-*endo*-dig pathway could be partially restored using **94**, which predominantly provided the fluorene **97**, suggesting that, for trisubstituted olefins, electronic factors govern the regioselectivity of the cycloisomerization.



(4)

In conclusion, readily available enynes and propargyl esters may be selectively transformed into styrenes or fluorenes under catalyst control *via* two new Au-catalyzed processes. Synthesized by a rarely investigated, highly selective cyclopropanation of 1,3 enynes, *cis*-vinyl-alkynyl-cyclopropanes undergo a novel cycloisomerization reaction, the outcome of which may be controlled simply through choice of catalyst counterion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

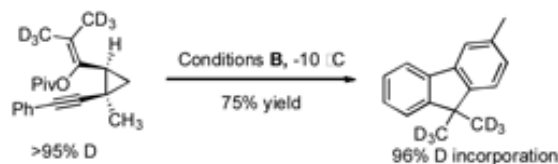
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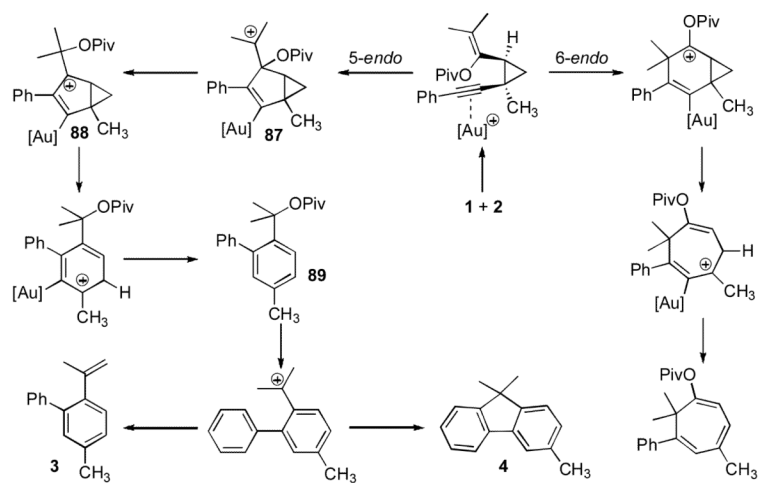
We gratefully acknowledge NIHGMS (RO1 GM073932), Merck Research Laboratories, Bristol-Myers Squibb, Amgen Inc., and Novartis for funding. D.J.G. thanks the ACS Organic Division (Merck) and Bristol Myers-Squibb for predoctoral fellowships. I.D.G.W. thanks NSERC for a postdoctoral fellowship.

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13. Other phosphine catalysts provided lower selectivity. For example, treatment of *cis*-**5** with PPh₃AuCl/AgSbF₆ resulted in 63% **4** and 34% **3**.
14. Optimization of the one-pot synthesis produced **4** in lower yield from **1** and **2**. See supporting information.
15. **89** was isolated and resubjected to the reaction conditions with and without the addition of triarylphosphitegold(I)chloride to afford the expected products, suggesting the possibility for silver or acid catalysis in the final step. Control experiments indicate that neither AgOTf nor HOTf catalyze the cycloisomerization of **5**. See Supporting Information.
16. Further experiments (see supporting information) indicate that **3** readily isomerizes to **4** under strongly acidic conditions. A deuterium-labeling experiment suggested that this is not a major pathway for the formation of **4** under our reaction conditions:

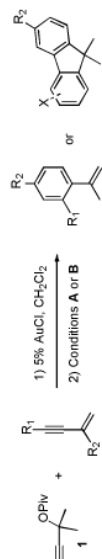




Scheme 1.
Proposed Mechanism for the Formation of **3** and **4**.

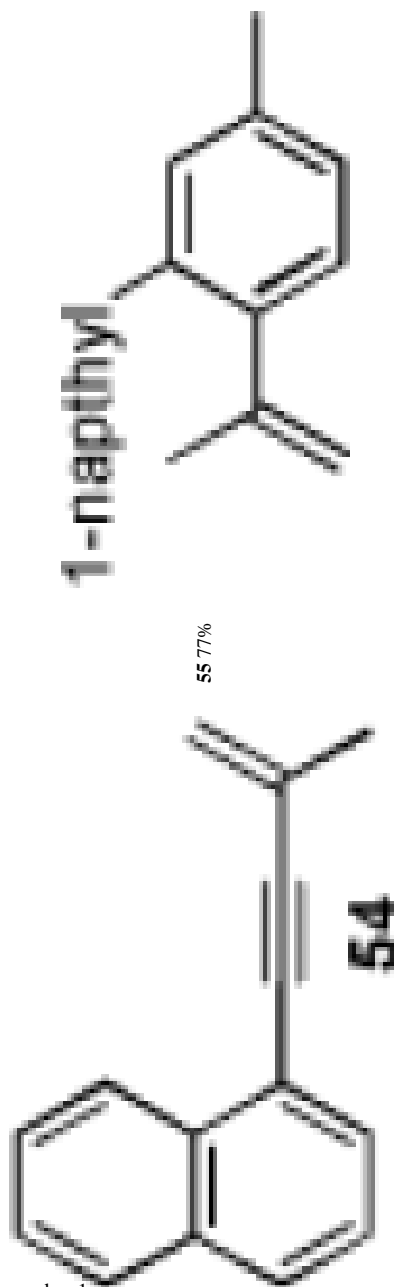
Au(I)-Catalyzed Arene Synthesis: Enyne Scope

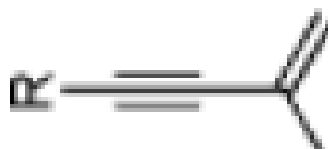
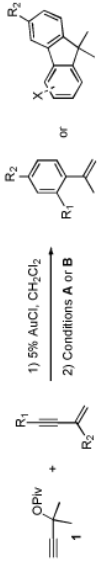
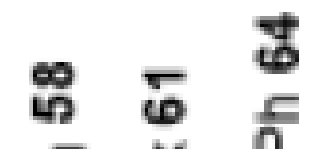
Table 1



entry	enyne	cp yield ^a	conditions A ^b	yield ^c	conditions B ^b	yield ^c
1		7.94%		8.81%		9.79%
2		11.83%		12.72%		13.66%

entry	enyne	cp yield ^a	conditions A ^b	yield ^c	conditions B ^b	yield ^c
3		15 82%		16 31% (+ 54% 17)		17 80% (15:1) ^d
4		19 72%		20 93%		21 25% (1:1) ^d (+ 62% 20)
5		23 75%		24 60%		25 85% (1.6:1) ^d
6		27 41%		28 58%		29 76%
7		31 62%		32 86%		33 93%
8		35 79%		36 83%		37 63%
9		39 79%		40 95%		41 59%
10		43 87%		44 71%		45 60%
11		47 73%		48 89%		49 71%
12		51 74%		52 64%		53 90%



entry	enyne	cp yield ^a	conditions A ^b	yield ^c	conditions B ^b	yield ^c
14		59		60		65%
15	R = C₅H₁₁ 58	62		63		53%
16	c-Hex 61	65		66	N/A ^e	66%
	C₃H₅Ph 64					

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^a Isolated yields of *cis*-cyclopropane Reactions run with 3:1 ratio of **1**:enyne.

^b **A**: 5% AgOTf, 5% (ArO)₃PAuCl, CH₂Cl₂. **B**: 5% AgSbF₆, 5% (ArO)₃PAuCl, CH₂Cl₂.

^c Isolated yields

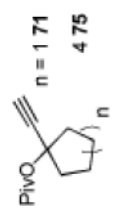
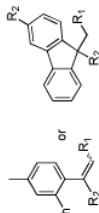
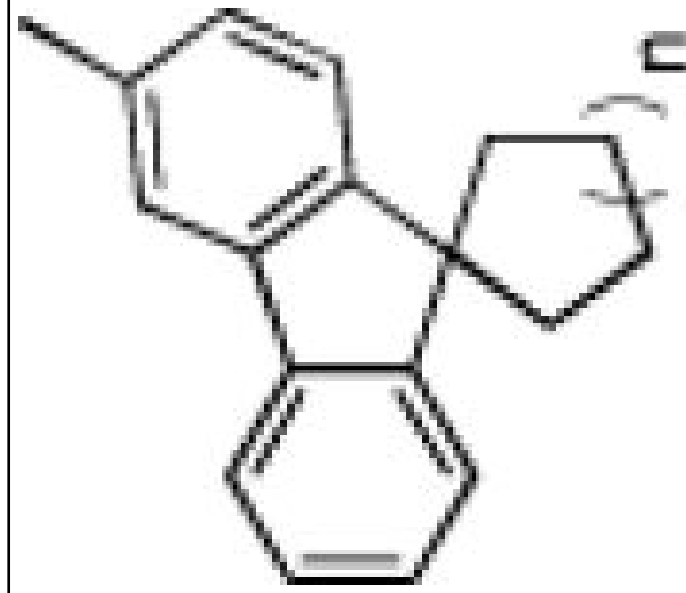
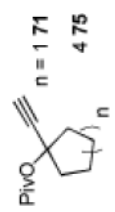
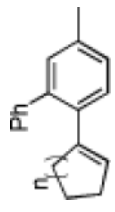
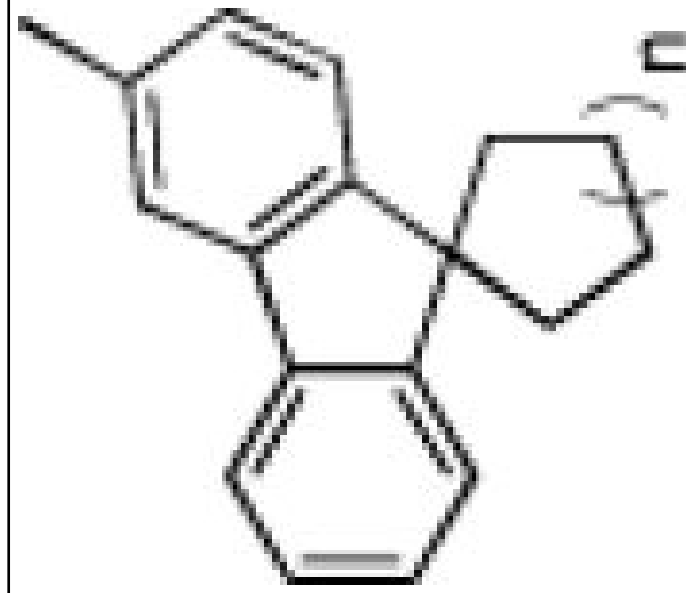
^d Ratio of regioisomers.

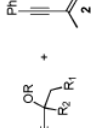
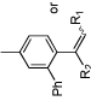
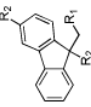

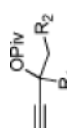
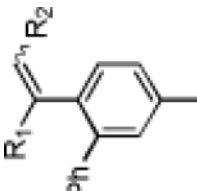
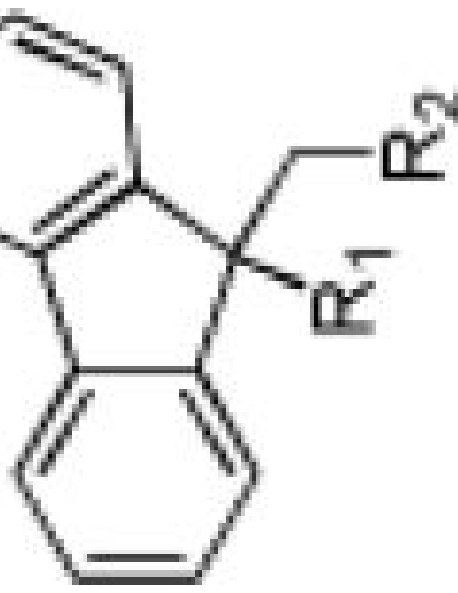
^e Conditions **B** were not investigated with **58**, **61** and **64**.

Table 2

Au(I)-Catalyzed Arene Synthesis: Propargyl Ester Scope

entry	propargyl ester	cp yield ^a	conditions A ^b	yield ^c	conditions B ^b	yield ^c
1		5 80%	1) 5% AuCl, CH ₂ Cl ₂ 2) Conditions A or B	89%		76%
2		68 82%		79%		19% (+ 53% 3)
3		70 60%	3	81%	4	57% (+ 32% 3)

entry	propargyl ester	cp yield ^a	conditions A ^b	yield ^c	conditions B ^b	yield ^c
4		72 80%	1) 5% AuCl ₃ , CH ₂ Cl ₂ 2) Conditions A or B			74 63%
5		76 83%				78 66%

entry	propargyl ester	cp yield ^a	conditions A ^b	yield ^c	conditions B ^b	yield ^c
6	  1) 5% AuCl, CH ₂ Cl ₂ 2) Conditions A or B	80 59%	 or	81 77% (8.3:1) ^d		82 84%
7	 R ₁ = n-Bu, R ₂ = n-Pr 79 R ₁ = c-Pr, R ₂ = H 83	84 79%		85 72%		86 84%

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^a Isolated yields of *cis*-cyclopropane. Reactions run with 3:1 ratio of propargyl ester:2

^b A: 5% AgOTf, 5% (AtO)₃PAuCl, CH₂Cl₂. B: 5% AgSbF₆, 5% (AtO)₃PAuCl, CH₂Cl₂.

^c Isolated yields

^d E:Z ratio.