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Synthesis of Benzonorcaradienes by Gold(I)-Catalyzed [4+3] Annulation

David J. Gorin, Pascal Dubé, and F. Dean Toste*
Department of Chemistry, University of California, Berkeley, California 94720

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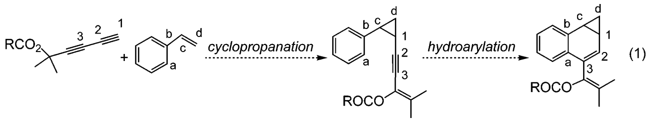
Transition metal-catalyzed sequential carbon−carbon bond-forming reactions provide a means to achieve increased synthetic efficiency.[1] To this end, we were drawn to the possibility of combining mechanistically distinct transition metal-catalyzed reactions of acetylenes, whereby an alkyne is generated as a result of the first reaction in a sequence. We envisioned that this might be accomplished by employing propargyl ester-containing diynes[2] in an intermolecular cyclopropanation[3]−intramolecular hydroarylation[4] cascade (eq 1). It is crucial that the catalyst control the timing of the sequential events, the regio- and diastereoselectivity of the cyclopropanation, and the regioselectivity of the hydroarylation step.[5] Herein we report the application of this concept to the development of an expedient synthesis of benzonorcaradienes[6] in which three carbon−carbon bonds and two rings are formed in a single operation.

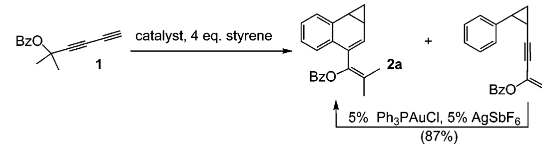


Recently, propargyl ester-containing diynes have been employed in a number of rearrangement reactions,[2] including the formation of cyclopropanes by an intramolecular cycloisomerization;[2c] however, intermolecular cyclopropanation by related diynes was not observed even in the presence of excess ethyl vinyl ether.[2a] We were therefore pleased to find that under the conditions developed for the gold(I)-catalyzed intermolecular cyclopropanation with propargyl esters,[3c] diyne **1** reacted smoothly with styrene to afford cyclopropane **2b** in 83% yield and with excellent cis-diastereo- and regioselectivity (Table 1, entry 1). Subsequently, treatment of **2b** under identical reaction conditions, but for 16 h, afforded benzonorcaradiene **2a** in 87% yield.

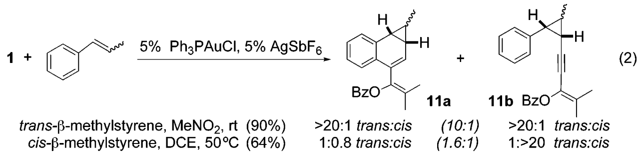
Consistent with these results, an increase in reaction time produced **2a** in 72% yield from diyne **1** and styrene in a single operation (entry 2).[7] While gold(I)chloride and gold(III)chloride also proved efficient catalysts for the cyclopropanation, they did not promote the intramolecular hydroarylation reaction (entries 3 and 4). Platinum complexes also catalyzed the cyclopropanation, albeit with modest diastereoselectivity (entries 5 and 6), and attempts to employ ruthenium-based catalysts resulted in poor conversion (entry 7) or formation of a complex mixture (entry 8). Finally, no reaction occurred in the presence of other cationic group 11 metal complexes (entries 9 and 10).

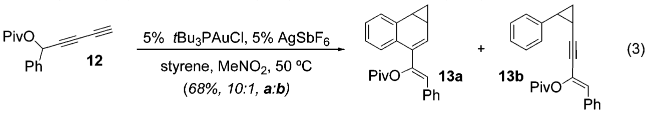
With a suitable catalyst in hand, the substrate scope of the benzonorcaradiene synthesis was examined (Table 2). A variety of styrene derivatives were tolerated in the reaction, although the hydroarylation step is particularly sensitive to electronic perturbation. For example, while alkyl substitution on the aryl ring resulted in good yields of the benzonorcaradiene (entries 2 and 3), halogenated styrenes required slightly elevated temperatures to produce the [4+3]-annulation products (entries 4 and 5). Tetracyclic norcaradienes (entries 6 and 7) were readily prepared from vinylnaphthylene or vinylindole in 74% and 54% yield, respectively. Notably, the regioselectivity of the hydroarylation reaction is excellent (entries 4−7). Quaternary centers can be formed from the gold(I)-catalyzed annulation of 1,1-disubstituted and trisubtituted olefins (entries 8 and 9). Gold(I)-catalyzed reaction of **1** with *trans*-β-methylstyrene proceeded at room temperature to afford **11a** as a single diastereomer (eq 2). In sharp contrast, the reaction with *cis*-β-methylstyrene afforded only *cis*-**11b** at room temperature and therefore required slightly elevated temperatures to furnish **11a** as a mixture of diastereomers.[8]

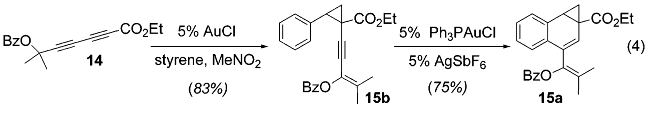
Table 1. Catalysts for [4+3] Annulation Reaction



entry	catalyst	conditions	**2a** (yield)	**2b** (yield, cis/trans)
1	5% Ph_3PAuCl, 5% $AgSbF_6$	$MeNO_2$, rt, 15 min		83% (>20:1 dr)
2	5% Ph_3PAuCl, 5% $AgSbF_6$	$MeNO_2$, rt, 16 h	72%	
3	5% AuCl	$MeNO_2$, rt, 16 h		71% (>20:1 dr)
4	5% $AuCl_3$	$MeNO_2$, rt, 16 h		66% (>20:1 dr)
5	5% $PtCl_2$	$PhCH_3$, 80 °C, 16 h		59% (1.2:1 dr)
6	5% $PtCl_2$, CO (1 atm)	$PhCH_3$, 80 °C, 16 h		33% (1.25:1 dr)
7	2.5% $[RuCl_2(CO)_3]_2$	DCE, 50 °C, 16 h		13% (>20:1 dr)
8	2.5% $[RuCl_2(CO)_3]_2$, 5% AgOTf	$PhCH_3$, 80 °C, 16 h		
9	5% $AgSbF_6$	$MeNO_2$, rt, 16 h		
10	5% $Cu(CH_3CN)_4PF_6$	DCE, 50 °C, 16 h		







The diyne component can also be varied. For example, the tri-*t*-butylphosphinegold(I)-catalyzed reaction of benzylic ester **12** afforded benzonorcaradiene **13a** as a 19:1 mixture of olefin isomers (eq 3). While nonterminal propargyl esters were not viable substrates for the intermolecular cyclopropanation,[3] we were pleased to find that ester-substituted diyne **14** could be employed in the gold(I)-catalyzed annulation reaction; however, sequential gold(I)chloride-catalyzed cyclopropanation and phosphinegold(I)-catalyzed hydroarylation proved most efficient for the preparation of ester-substituted norcaradiene **15a** (eq 4).

A mechanism involving sequential rearrangements proceeding via gold(I)-promoted alkyne activation is proposed (Scheme 1). Reaction of cationic phosphinegold(I) with diyne **1** generates Au−

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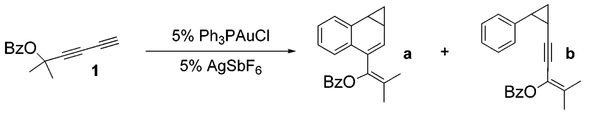
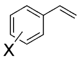
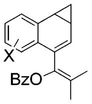
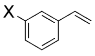
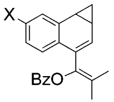
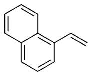
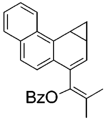
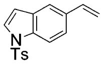
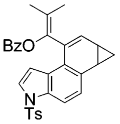
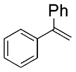
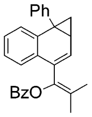
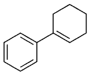
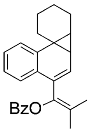
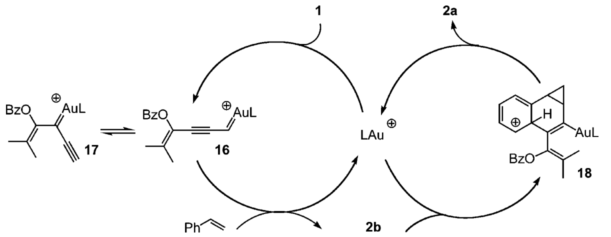
Table 2. Scope of Au(I)-Catalyzed [4+3] Annulation Reaction



entry	alkene		condition[a]	product		yield (**a** : **b**)
1		X = H	A		**2**	80% (>20:1)
2		X = 4-Me	A		**3**	85% (>20:1)
3		X = 2-Me	A		**4**	82% (>20:1)
4		X = Br	B		**5**	59% (1:1.2)
5		X = Cl	B		**6**	60% (2:1)
6			A		**7**	74% (>20:1)
7			A		**8**	54% (>20:1)[b]
8			B		**9**	71% (>20:1)
9			A		**10**	60% (>20:1)

[a] (A) propargyl ester (0.2 M in nitromethane), alkene (4 equiv), room temperature; (B) propargyl ester (0.2 M in dichloroethane), alkene (4 equiv), 50 °C. [b] Composed of a 10:1 mixture of regioisomers.

Scheme 1. Mechanistic Hypothesis



carbenoid intermediate **16**. The catalyst can reversibly coordinate to either alkyne in **1**, and thus two plausible pathways for the formation of **16** can be envisioned: one involving a 1,3-metallotropic rearrangement[2] of Au−carbene **17** and the other proceeding via a cumulene intermediate. Either way, cyclopropanation of styrene occurs selectively through carbenoid **16**, affording **2b** and regenerating the catalyst. Coordination of cationic phosphinegold(I) to the alkyne of **2b** induces nucleophilic trapping by the arene onto the alkyne. Proton transfer furnishes benzonorcaradiene **2a** from vinylgold(I) intermediate **18** and regenerates the catalyst.[9]

In conclusion, we have developed a cationic phosphinegold(I)-catalyzed tandem cyclopropanation/hydroarylation reaction,[10] which produces formal [4+3]-annulation products from vinyl arenes and propargyl esters. The cyclopropanation represents the first intermolecular reaction of diynyl esters and proceeds with excellent regio- and diastereocontrol.[11] The reaction provides access to a wide range of functionalized benzonorcaradienes with synthetic handles for further manipulation.[12] Further studies on the properties of these analogues and other reactions exploiting gold carbenoid intermediates will be reported in due course.

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

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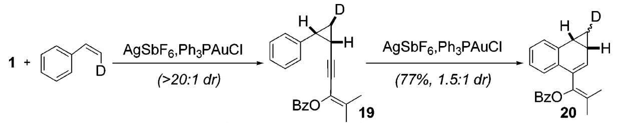
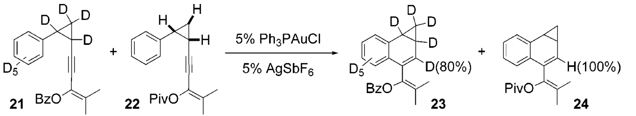
(7) The acetate (55%, 1.2:1, **a**/**b**) and pivaloate (73%, 7:1, **a**/**b**) analogs of **1** were also effective in the cycloisomerization. The acetate analog of **2a** was characterized by X-crystallography (see Supporting Information).

(8) The isomerization presumably occurs by a norcaradiene/cycloheptatriene rearrangement: (a) Vogel, E.; Wendisch, D.; Roth, W. R. *Angew. Chem., Int. Ed.* **1964**, *3*, 443. (b) Pomerantz, M.; Gruber, G. W. *J. Org. Chem.* **1968**, *33*, 4501. We also observed epimerization in the annulation of *cis-β-d*-styrene.



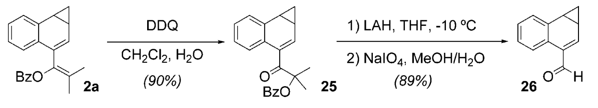
(9) The detailed mechanism of the proton transfers remains unclear. A double-labeled cross-over experiment showed very little scrambling in the hydroarylation reaction.



(10) For recent examples of Au-catalyzed tandem processes, see (a) Hashmi, A. S. K.; Grundl, L. *Tetrahedron* **2005**, *61*, 6231. (b) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925. (c) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804. (d) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436. (e) Sherry, B. D.; Maus, L.; Lafortezza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132. (f) Marion, M.; Diaz-González, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647. (g) Jung, H.-H.; Floreancig, P. E. *Org. Lett.* **2006**, *8*, 1949. (h) Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953. (i) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957. (j) Nguyen, R. V.; Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 2387. (k) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614.

(11) *trans*-Alkynylcyclopropane could only be observed as a minor product in a single case (Table 2, entry 9). See Supporting Information for additional examples of the cyclopropanation reaction.

(12) For example, the enol ester of **2a** was selectively oxidized to **25** and cleaved to give aldehyde **26**.



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