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Gold(I)-catalyzed intermolecular hydroarylation of allenes with nucleophilic arenes: scope and limitations

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ABSTRACT

The addition of nucleophilic methoxyarenes to allenes proceeds at room temperature in dichloromethane with a catalytic amount of phosphite-gold(I) precatalyst and silver additive. The addition is regioselective for the allene terminus, and generates *E*-allylation products without the need for prefunctionalization of the synthons as organometallics or allyl bromides. Coordinating heteroaromatics and sterically hindered allenes do not participate in the reaction.

1. Introduction

A major goal of the last decade in organic chemistry has been the development of C–C bond-forming reactions that take place at room temperature without the prefunctionalization of either coupling partner.[1] These reactions ideally proceed with catalytic quantities of readily available metals at room temperature. This research details the development of an allene addition to electron-rich arenes catalyzed by gold(I), resulting in products normally accessed by deprotonation/allylation with an allylic halide.

Additions of pronucleophiles to allenes by gold catalysts have received much recent attention. *Intramolecular* cyclization of covalently linked allene nucleophiles by cationic gold(I) or gold(III) have been widely reported[2,3] (Scheme 1), but the corresponding intermolecular variants are rare. Widenhoefer recently reported an intermolecular hydroalkoxylation of allenes,[4] and Yamamoto an intermolecular hydroamination.[5] Intermolecular hydroarylations of alkynes were achieved by Reetz[6] and He[7] with gold(III) catalysts and Hashmi[8] with gold(I) (Scheme 2), but, with the exception of recent results by Widenhoefer with methylated indoles,[9] there have not been any reports on *gold-catalyzed intermolecular hydroarylation of allenes*.

Our group recently reported an intramolecular hydroarylation of allenes utilizing a triphenylphosphite-derived gold(I) catalyst.[10,11] One byproduct from a substrate intermediate was bis(allenyl)malonate,[12] which we discovered could react with electron-rich 1,3,5-trimethoxybenzene **1** under the aforementioned conditions (Scheme 3) to form a hydroarylative product in trace amounts (<10%).

Crude proton NMR and GC–MS analysis indicated that only one of the two allenes participated in the reaction, indicating that substrates possessing a single allene would participate. The commercially available 3-methyl-1,2-butadiene (dimethylallene, **2**) was chosen as a commercially available screening substrate, and the results of reaction optimization are shown in Table 1.

Entries 1–5 indicate a preference for dichloromethane as solvent in this reaction, with more coordinating or nonpolar solvents markedly slowing reactivity. Interestingly, gold(I) precatalysts that are found to be optimal in other gold-catalyzed reactions (entries 6[13] and 7[14]) were less active in this reaction. The trend toward more electrophilic phosphite ligands is evidenced when comparing entries 10, 11, and 13. The optimal system of $(4\text{-ClPhO})_3\text{P(AuCl)}$[15] and $AgBF_4$ reached full conversion after 1 h, when employing allene as the limiting reagent in the presence of 2 mol equiv of arene. Control experiments between **1** and ethyl-2,3-butadienoate or dimethylallene ruled out silver and acid-mediated catalysis in this reaction.[16] Another control indicated that gold(III)—either alone or with 3.0 equiv of silver cocatalyst—does not catalyze this reaction.

2. Substrate scope

The results indicate that small and relatively unsubstituted allenes work best in this chemistry. Functional groups such as esters, ethers, and enoates were well-tolerated, but more Lewis-basic heteroaromatic substrates did not function well (vide infra).

To probe how the electronics of the aryl system affected the ability to add an equivalent of allene, a variety of electron-rich methoxy-substitued arenes were tested. Shown in Table 2 are reactions utilizing allene **2**, which generates products of traditional prenylation. Arenes possessing constructively oriented *ortho*- and *para*-directing groups gave higher yields. A preference for allylation at unhindered positions on the arene, presumably due to steric

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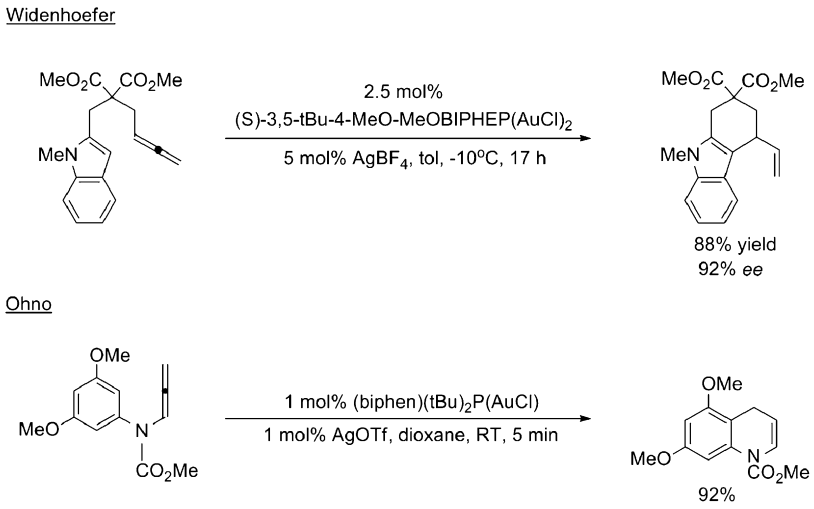
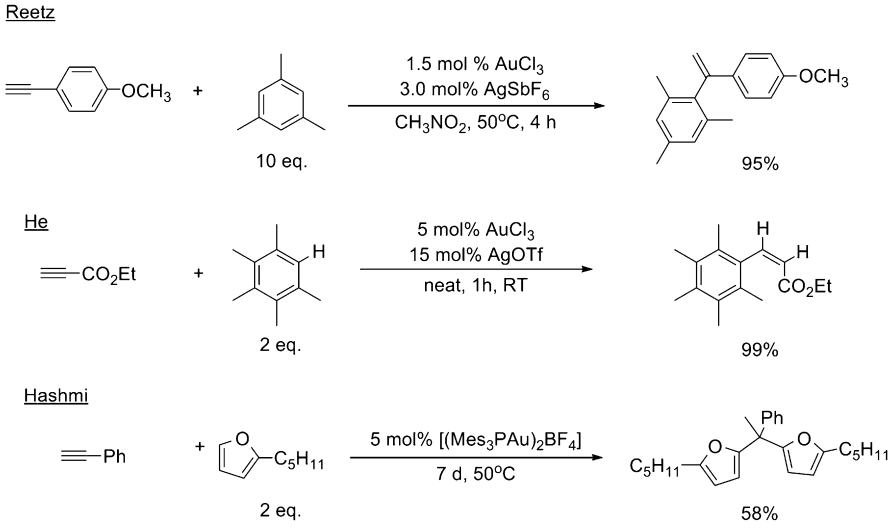
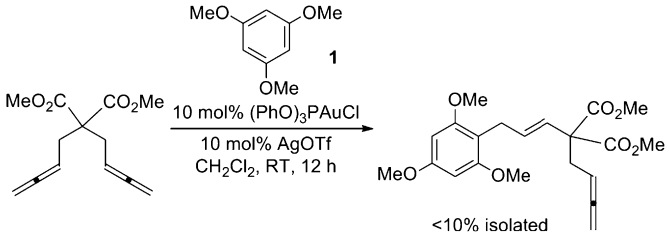


Scheme 1.



Scheme 2.



Scheme 3.

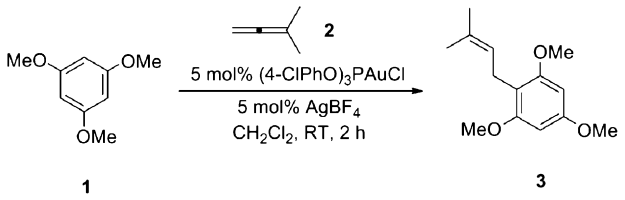
effects, is evidenced by the 6:1 ratio of products in **4** as well as the increased yield from **6** to **10**.

The allene scope was next examined using **1** or **4** as the aryl nucleophile. Table 3 presents allenes that are found to participate in this chemistry. Allylic products were formed with *E*-stereochemistry, indicated by the ^{1}H coupling constants of the isolated products.

3. Limitations

While highly nucleophilic methoxyarenes readily participate in this chemistry, it was envisioned that the method would become more practical if it was tolerant of heterocyclic rings, such as indoles, furans, and pyrroles. Unfortunately, these reactions could not be advanced with the arenes shown in Figure 1 using heat or acid

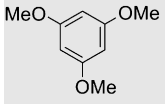
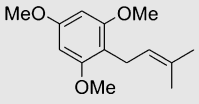
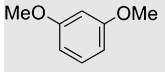
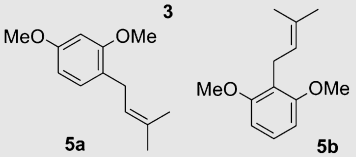
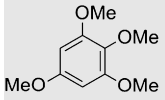
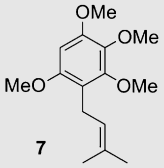
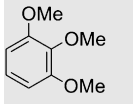
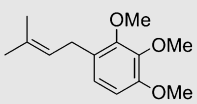
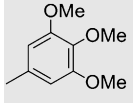
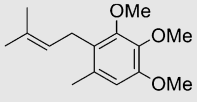
Table 1
Optimization of arene–allene hydroarylation reaction



Entry	Solvent[a]	Gold source	Silver source	Time	Conversion[b]
1[c]	THF	$(PhO)_3P(AuCl)$	AgOTf	0.5 h	2%
2	Toluene	$(PhO)_3P(AuCl)$	AgOTf	0.5 h	16%
3	Et_2O	$(PhO)_3P(AuCl)$	AgOTf	0.5 h	8%
4	**CH_2Cl_2**	$(PhO)_3P(AuCl)$	AgOTf	0.5 h	**54%**
5	MeCN	$(PhO)_3P(AuCl)$	AgOTf	0.5 h	<1%
6	CH_2Cl_2	(*t*-Bu_2-*o*-biphenyl)P(AuCl)[e]	AgOTf	48 h	52%
7	CH_2Cl_2	(IMes)AuCl[f]	AgOTf	20 h	55%
8[d]	CH_2Cl_2	$(PhO)_3P(AuCl)$	$AgSbF_6$	10 h	86%
9	CH_2Cl_2	$(PhO)_3P(AuCl)$	$AgNTf_2$[g]	10 h	79%
10	CH_2Cl_2	$(PhO)_3P(AuCl)$	**$AgBF_4$**	10 h	**92%**
11	CH_2Cl_2	(2,4-diMe-$PhO)_3P(AuCl)$	$AgBF_4$	1 h	88%
12	CH_2Cl_2	(2-Ph-$PhO)_3P(AuCl)$	$AgBF_4$	1 h	80%
13	CH_2Cl_2	**(4-Cl-$PhO)_3P(AuCl)$**	$AgBF_4$	1 h	**>95%**

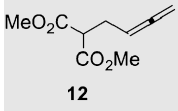
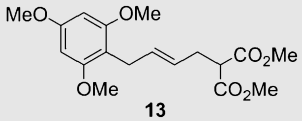
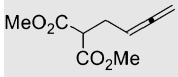
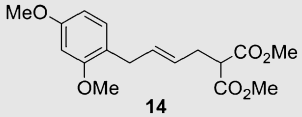
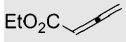
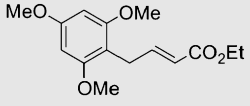
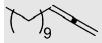
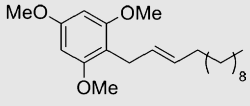
[a] Solvents dried by passage through alumina column with Ar (tol, Et_2O, CH_2Cl_2), or distilled from Na^0 (THF) or CaH_2 (MeCN).
[b] Integrated against remaining SM by GC.
[c] Entries 1–7 run with 1:1 arene to allene molar ratio.
[d] Entries 8–13 run with 2:1 arene to allene ratio.
[e] Ref. 4.
[f] Ref. 13.
[g] Ref. 15.

Table 2
Prenylation with dimethylallene

Arene	Time	Product	Yield[a,b]
 1	4 h	 3	67%
 4	4 h	 5a, 5b	71% (6:1[c])
 6	18 h	 7	53%
 8	16 h	 9	65%
 10	12 h	 11	75%

[a] General procedure: 2.0 equiv arene and 1.0 equiv allene were added to 5 mol % of preactivated gold catalyst in a 2-mL screwtop vial using anhydrous CH_2Cl_2 at room temperature for the time indicated.
[b] Isolated yield after silica gel chromatography in ethyl acetate/hexanes.
[c] Inseparable mixture.

Table 3
Reaction of **1** and **4** with substituted allenes

Allene	Time	Product	Yield
 12	14 h	 13	51%
	14 h	 14	58% (10:1 with 2-isomer)
 15	12 h	 16	90%
 17	16 h	 18	22%

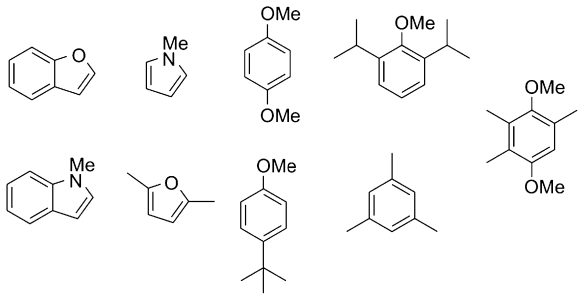
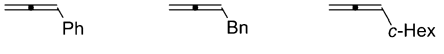


Figure 1. Arenes tested, which are unreactive under the specified conditions.

cocatalysts. Increasing the concentration of the reactants or even running the reaction in neat arene as solvent (methylpyrrole) did not result in useful conversion (<10%).

Unlike previously reported methods by Hashmi, furans did not participate in either addition or phenol-rearrangement chemistry, instead decomposing to >8 products. One hypothesis for the failure of these reactions is that the cationic gold(I) catalyst is simply deactivated by the excess coordinating arene in the reaction.[17]

Allenes with more sterically demanding α substituents were also unreactive in this chemistry. Scheme 4 lists allenes, which do not react under the examined conditions. Widenhoefer[4] has proposed a mechanism, which could rationalize such an observation.



Scheme 4. Allenes unreactive in the present system.

This mechanism might also explain the low reactivity of substrate **17** relative to the parent allene **2**; a σ-allyl gold species would be better stabilized by an internal 3° carbocation (**2**) or a nearby heteroatomic group (**12**, **15**). Oshima and co-workers have noted a similar effect on allene substitution in the Mn-catalyzed allene allylation.[18]

4. Conclusion

A method for the addition of methoxybenzenes to allenes by phosphite-gold(I) catalysts was reported. The reactions were stable to air and trace moisture, and were conducted on the benchtop in air. Electron-rich methoxybenzenes and unhindered monosubstituted allenes were found to be the best participants in these reactions.

5. Experimental section

5.1. General

All gold precatalysts were synthesized according to the published methods.[4,13,14] Silver bistriflimide ($AgNTf_2$) was formed according to the procedure of Gagosz.[19] All other silver salts were purchased from Strem Chemicals and stored in a nitrogen-atmosphere glovebox, then transferred to an oven-dried vial stored in a desiccator when used. All solvents were purified by alumina-packed columns under Ar or distillation from Na^0 or CaH_2. Arenes were purchased from Aldrich and used as received. Dimethylallene and ethyl-2,3-butadienoate were purchased from Aldrich; allenylmalonate was synthesized according to the literature procedure.[20]

5.2. General procedure for intermolecular hydroarylation

To a 5-mL vial charged with a stirbar were added $(4\text{-ClPhO})_3$-PAuCl (9.6 mg, 15 μmol) and $AgBF_4$ (3.0 mg, 15 μmol), and dichloromethane (1.0 mL) by syringe, resulting in a light gray suspension. After stirring for 2 min, 1,3,5-trimethoxybenzene (100 mg, 0.6 mmol) was added, resulting in a color change to light orange. After stirring for additional 2 min, dimethylallene (20.0 mg, 0.3 mmol) was added dropwise by microsyringe. Stirring was continued until GC/TLC (product R_f 0.5 in 1:7 ethyl acetate/hexanes) analysis indicated complete consumption of the allene. The reaction mixture was concentrated, loaded directly onto a silica flash column, and eluted with 1:10 to 1:8 ethyl acetate/hexanes to yield **3** (67% yield) as a clear oil. ^{1}H NMR (300 MHz): δ 6.13 (s, 2H), 5.16 (t, 1H), 3.79 (s, 9H), 3.26 (d, 2H), 1.75 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (100 MHz): 159.9, 158.7, 130.6, 123.5, 111.0, 90.9, 55.7, 55.3, 25.8, 21.8, 17.6.

5.3. Tri(4-chlorophenyl)phosphite gold(I) chloride

White crystalline solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (d, 2H, J=9 Hz), 7.12 (dd, 2H, J_1=9 Hz, J_2=1.8 Hz). ^{13}C NMR (100 MHz): δ 147.6, 132.5, 130.6, 122.3 (d). ^{31}P (121 MHz): δ 112.0.

5.4. 2-Methyl-4-(2,4-dimethoxyphenyl)-but-2-ene (5a) and 2-methyl-4-(2,6-dimethoxyphenyl)-but-2-ene (5b)

6:1 Mixture, inseparable by column chromatography. *Compound* ***5a***. ^{1}H NMR (400 MHz): 1.68 (s, 3H), 1.71 (s, 3H), 3.22 (d, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 5.26 (t, 1H), 6.42 (m, 2H), 7.01 (d, 1H). *Compound* ***5b***. ^{1}H NMR (400 MHz): 1.65 (s, 3H), 1.74 (s, 3H), 3.32 (d, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 5.19 (t, 1H), 6.53 (d, 2H), 7.09 (t, 1H). ^{13}C NMR (100 MHz) (mixture): 159.1, 158.1, 129.4, 123.3, 123.0, 122.6, 103.9, 98.6, 55.8, 55.3, 27.8, 25.8, 17.7.

5.5. 2-Methyl-4-(1,2,3,5-tetramethoxyphenyl)-but-2-ene (7)

^{1}H NMR (400 MHz): δ 6.24 (s, 1H), 5.11 (t, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.23 (d, 2H), 1.72 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (100 MHz): 153.6, 152.4, 151.6, 130.7, 123.6, 116.5, 100.0, 93.1, 60.9, 60.9, 56.3, 56.1, 25.7, 22.6, 17.7. HRMS (ESI^+): expected 289.1416, observed 289.1422 ($M+Na^+$).

5.6. 2-Methyl-4-(1,2,3-trimethoxyphenyl)-but-2-ene (9)

Clear oil. ^{1}H NMR (400 MHz): δ 6.80 (d, 1H), 6.59 (d, 1H), 5.24 (t, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.25 (d, 2H), 1.72 (s, 6H). ^{13}C NMR (100 MHz): 152.0, 151.8, 142.5, 131.9, 127.9, 123.5, 123.3, 107.5, 60.7, 56.0, 28.2, 25.7, 17.1.

5.7. 2-Methyl-4-(5-methyl-1,2,3-trimethoxyphenyl)-but-2-ene (11)

^{1}H NMR (400 MHz): 1.66 (s, 3H), 1.75 (s, 3H), 2.22 (s, 3H), 3.26 (d, 2H), 3.79–3.83 (m, 9H), 5.02 (t, 1H), 6.48 (s, 1H). ^{13}C NMR (100 MHz): 151.8, 151.1, 140.5, 131.8, 131.0, 126.3, 123.2, 109.6, 60.9, 60.8, 55.9, 25.6, 19.6, 17.8.

5.8. Dimethyl-2-(*E*-4-(1,3,5-trimethoxyphenyl)-but-2-enyl)malonate (13)

Clear oil. ^{1}H NMR (300 MHz): δ 6.09 (s, 2H), 5.58 (dt, 1H, J=15.3 Hz), 5.29 (dt, 1H, J=15.0 Hz), 3.78 (s, 3H), 3.75 (s, 6H), 3.65 (s, 6H), 3.35 (t, 1H, J=7.5 Hz), 3.20 (d, 2H, J=6 Hz), 2.51 (t, 2H, J=14.7 Hz). ^{13}C NMR (100 MHz): 169.4, 159.5, 158.7, 132.3, 124.5, 109.4, 90.8, 55.7, 55.3, 52.2, 52.1, 31.9, 25.6. HRMS (ESI^+): expected 375.1482, observed 375.1482 ($M+Na^+$).

5.9. Dimethyl-2-(*E*-4-(1,3-dimethoxyphenyl)-but-2-enyl)-malonate (14a) and dimethyl-2-(*E*-4-(2,5-dimethoxyphenyl)-but-2-enyl)malonate (14b)

6:1 mixture, inseparable by column chromatography. *Compound* ***14a***. ^{1}H NMR (300 MHz): δ 2.57 (t, 2H), 3.19 (d, 2H), 3.40 (t, 1H), 3.67 (s, 6H), 3.76 (s, 6H), 5.40 (dt, 1H, J=15.2 Hz), 5.63 (dt, 1H, J=15.2 Hz), 6.38 (m, 2H), 6.94 (d, 1H). ^{13}C NMR (100 MHz) (mixture): 169.4, 160.9, 159.4, 158.1, 132.4, 129.9, 129.8, 125.9, 124.9, 121.3, 106.2, 104.0, 102.9, 100.5, 98.5, 55.7, 55.3, 55.3, 55.2, 52.2, 51.9, 32.2, 31.9, 15.2. HRMS (ESI): expected 345.1314, observed 345.1329 ($M+Na^+$).

5.10. Ethyl-*E*-4-(1,3,5-trimethoxyphenyl)-but-2-enoate (16)

Clear oil. ^{1}H NMR (300 MHz): δ 7.01 (dt, 1H, J_1=15.6 Hz, J_2=6 Hz), 6.10 (s, 2H), 5.66 (dt, 1H, J=15.3 Hz), 4.11 (m, 2H), 3.79 (s, 3H), 3.76 (s, 6H), 3.42 (dd, 2H), 1.23 (t, 3H). ^{13}C NMR (100 MHz): 167.2, 160.1, 158.8, 148.1, 129.3, 120.6, 116.7, 106.6, 104.2, 90.6, 59.9, 55.3, 25.5, 14.3. HRMS (ESI^+): expected 281.1389, observed 281.1387 ($M+H^+$).

5.11. 1-(1,3,5-Trimethoxyphenyl)-2*E*-triskadecene (18)

Clear oil. ^{1}H NMR (400 MHz): δ 0.85 (t, 4H), 1.22 (m, 22H), 1.90 (m, 2H), 3.22 (d, 2H), 3.79 (m, 12H), 5.40 (m, 2H), 6.12 (s, 2H). ^{13}C NMR (100 MHz): 159.3, 158.8, 130.0, 128.3, 90.9, 55.8, 55.3, 32.5, 31.9, 29.6, 29.5, 29.3, 29.2, 25.7, 22.7, 14.1. HRMS (ESI^+): expected 371.2562, observed 371.2583 ($M+Na^+$).

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16. Catalysis with 2 mol % TfOH/CH_2Cl_2 or 5 mol % $AgBF_4$ in CH_2Cl_2 did not lead to any of the observed products. Addition of 5 mol % (4-ClTPOP)AuCl to silver control after 24 h allows reaction to proceed normally, indicating an authentic gold-catalyzed reaction.
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