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Selectivity, Compatibility, Downstream Functionalization, and Silver Effect in the Gold and Palladium Dual-Catalytic Synthesis of Lactones

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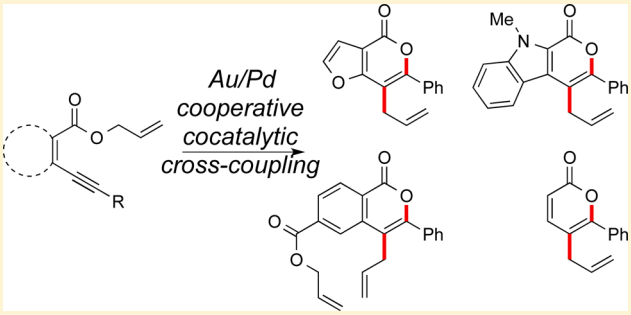
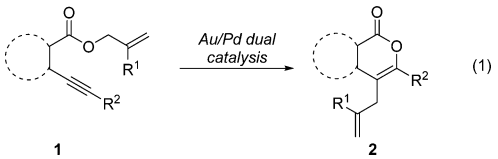
Supporting Information

ABSTRACT: The chemo- and regioselectivity and functional group compatibility in gold and palladium cooperatively catalyzed cross-coupling reactions were determined in the synthesis of lactones; the selectivity in the gold and palladium dual-metal catalysis system was distinct from that available for the same class of substrates in systems with only gold catalysis or only palladium catalysis rather than dual catalysis. The dual-catalytic rearrangement reaction selectively promoted oxidative addition at the C−O bond over the C−Br bond, providing a useful C−Br bond handle for downstream functionalization showcased via Suzuki−Miyaura and Sonogashira coupling reactions. Product classes were expanded from isocoumarins to three previously unpublished ring classes: pyrone, indolepyrone, and furopyrone.



INTRODUCTION

When two metals cooperate in catalysis, it creates the opportunity for chemo-, regio-, and diastereoselectivities that are unique to the system with *both* metals—distinct from those available to either metal alone.[1,2] Significantly less is known about the selectivities available to cooperative metal systems than is known about single metal systems.[1] This limited knowledge restricts the application of such reactions in synthesis. We previously reported dual-catalytic cross-coupling reactions with gold and palladium that access novel reactivity[3−9] unavailable to single metal systems (eq 1).[10−20]



(1)

Our group and the Hashmi, Gagné, and Sarandeses groups also reported stoichiometric and/or monocatalytic mechanistic studies related to these dual-catalytic systems.[21−27] We herein closely examine the chemo-, diastereo-, and regioselectivity in the gold and palladium dual-catalytic synthesis of lactones through cross-coupling reactions that interrogate the unique selectivities available in this dual-catalytic system. The reaction chemoselectivity is then harnessed to expand the substrate scope and showcase downstream functionalization reactions of interest in synthetic chemistry.

RESULTS AND DISCUSSION

In order to compare the chemoselectivity of the three catalytic systems—the gold and palladium cooperative system, the gold-alone system, and the palladium-alone system—we first turned our attention to the reaction of diallyl terephthalate **1a** (Scheme 1). This compound was chosen due to its potential for different modes of chemoselectivity. Gold(I) and palladium(II) are both independently well-established as π Lewis acids and cyclization catalysts.[28,29] Therefore, **1a** in theory could undergo allyl ester activation at the 1-position with concomitant cyclization onto the alkyne in all three systems.[30,31] In addition, the second allyl ester group at the 4-position could also be activated, albeit without inducing cyclization due to its position further from the alkyne. Finally, as both 5-exo and 6-endo cyclizations are known for gold and palladium catalytic systems separately, the potential for regioisomeric ring products exists.

Treatment of **1a** with our standard gold and palladium dual-catalyzed rearrangement reaction conditions[5] with 5 mol % PPh_3AuCl, 5 mol % AgOTf, and 5 mol % Pd_2dba_3 yielded exclusively the product **2a** from activation of the allyl ester at the 2-position, cyclization, and cross-coupling transfer of this allyl group onto the carbon skeleton (Scheme 1). The allyl ester at the 4-position remained intact, and the reaction was highly regioselective with the formation of the 6-membered ring exclusively. This reaction, therefore, provided regioselective cyclization with the chemoselective monoallyl group transfer.

In contrast, compound **1a** exhibited no reaction under similar conditions with gold only.[5] Therefore, reaction of **1a** under gold-only catalysis was reexamined in the presence of 2-phenylethanol as an allyl scavenger. These conditions induced deallylation and cyclization to form isocoumarin **3**, but with no

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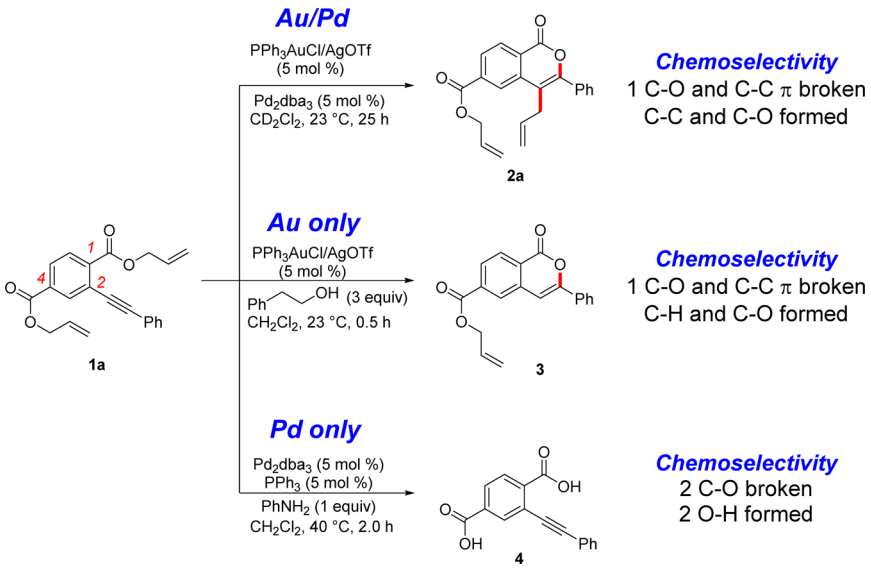
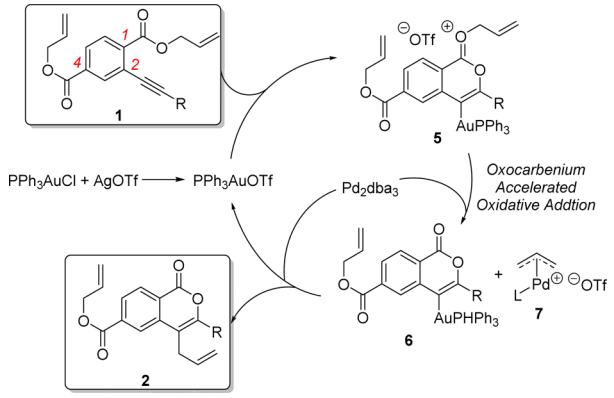
Scheme 1. Chemoselectivity of the Gold/Palladium Dual-Catalytic System Is Distinct from Gold-Only or Palladium-Only Catalytic Systems with Substrate 1a



allyl transfer to the carbon skeleton (Scheme 1). These results are consistent with gold-only catalysis that terminates in protodeauration of the final carbon−gold bond to create a new carbon−hydrogen bond, which is one of the well-established reactivity modes for gold(I).[32] Exclusively, the allyl ester at the 1-position was deallylated, despite the use of 3 equiv of 2-phenylethanol as an allyl scavenger. Thus, the catalysis is selective in this system for the allyl group that becomes an enhanced electrophile via oxocarbenium formation upon gold-induced cyclization (**5**, Scheme 2).

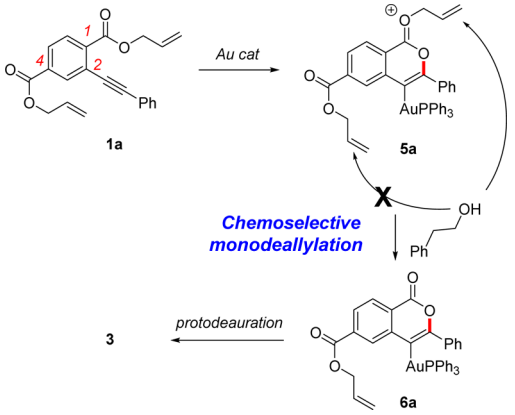
Scheme 2. Dual-Catalytic Cycle Consistent with Previous Mechanistic Studies, Showing Origin of Chemoselectivity in This Study[a]



[a]Gold lowers the barrier for oxidative addition to palladium by cyclizing substrate **1** to generate electrophilic oxocarbenium ion **5** with enhanced reactivity toward oxidative addition.

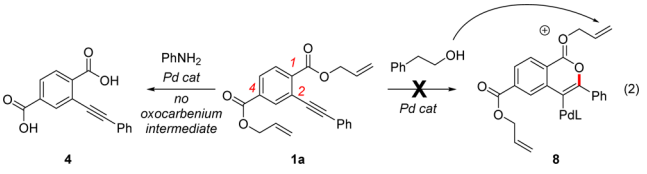
Interestingly, the exclusive selectivity for the 6-membered ring formation was similar in this gold-only system as in the Au/Pd dual system (Scheme 3). This similarity suggests that the gold dictates the regioselectivity in the dual-metal system, rather than palladium, although both potential alkynophilic Lewis acids are present in the same pot.

Scheme 3. Origin of Chemoselectivity in Gold-Catalyst-Only Reaction[a]



[a]Gold-induced cyclization generates oxocarbenium ion **5a**, which increases the electrophilicity of the allyl group at the 1-position, but not at the 4-position.

Next, the reactivity of diallyl terephthalate **1a** under conditions with palladium alone was monitored. Palladium(0)-catalyzed selective deallylation of diallyl terephthalate **1a** is of particular interest because both of the allyl groups in **1a** have the possibility of undergoing oxidative addition with palladium(0).[30,31] In contrast to the gold-only system, 2-phenylethanol was not a sufficiently strong nucleophile to serve as an allyl scavenger with palladium alone. When **1a** was treated with Pd_2dba_3 and 5 mol % PPh_3 at 40 °C and 3 equiv of 2-phenylethanol, only slow deallylation occurred (eq 2). These



results are consistent with a scenario wherein the palladium does not activate the alkyne toward cyclization; thus,

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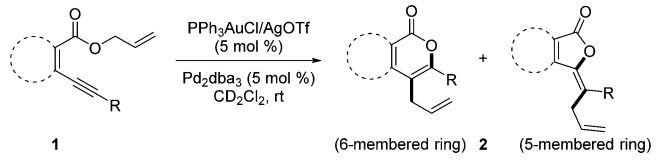
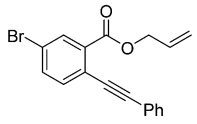
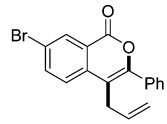
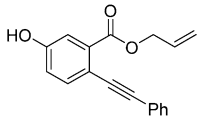
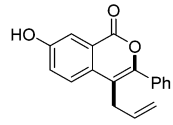
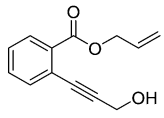
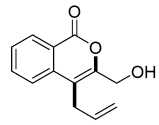
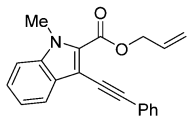
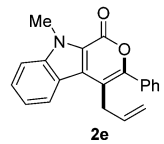
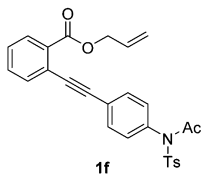
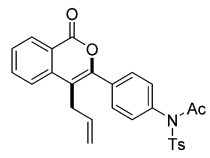
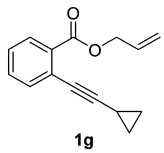
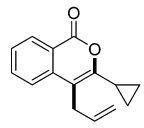
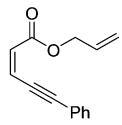
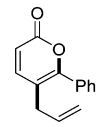
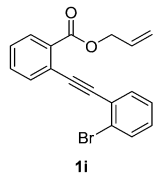
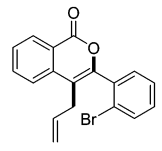
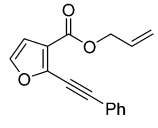
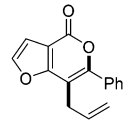
Table 1. Gold and Palladium Dual-Catalytic Synthesis of Lactones 2b−2i[a,b,c,d,e,f]



Entry	Starting material	Product	Isolated yield (%)	Product ratio (6-:5-membered ring)
1	 **1b**	 **2b**	88	16:1
2[b]	 **1c**	 **2c**	24	11:1
3	 **1d**	 **2d**	84	Only 6-membered ring
4[c]	 **1e**	 **2e**	79	Only 6-membered ring
5[b]	 **1f**	 **2f**	50	16:1
6	 **1g**	 **2g**	71	12:1
7	 **1h**	 **2h**	88	Only 6-membered ring
8	 **1i**	 **2i**	(50)[d]	Only 6-membered ring
9[e]	 **1j**	 **2j**	83	Only 6-membered ring

[a]Unless otherwise noted, reaction conditions: substrate **1** (1.0 equiv), PPh_3AuCl (5 mol %), AgOTf (5 mol %), and Pd_2dba_3 (5 mol %) in dry CD_2Cl_2 (0.1 M substrate) were stirred at ambient temperature. [b]Reaction was carried out at 60 °C in DCE-d_4. [c]Catalysts loading: PPh_3AuCl (10 mol %), AgOTf (10 mol %), and Pd_2dba_3 (10 mol %). [d]^1H NMR yield and was determined based on the ratio of product **2i** relative to mesitylene, which was used as an internal standard. [e]Reaction was carried out at 50 °C in DCE-d_4. [f]Bonds formed are denoted with bold.

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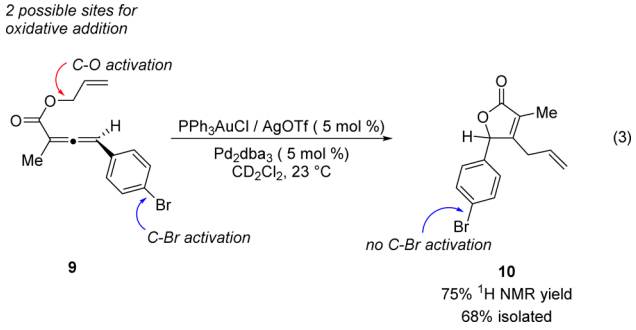
organopalladium oxocarbenium intermediate **8** does not form (or does not form sufficiently) to generate an adequately electrophilic allyl group for nucleophilic deallylation by the weak nucleophile 2-phenylethanol (or by another equivalent of Pd(0) via oxidative addition).

Deallylation, however, could be induced by switching to the stronger nucleophile aniline as the allyl scavenger (eq 2). Palladium(0) generally requires addition of a phosphine ligand to promote allyl acetate oxidative addition;[33] thus, treatment of **1a** with 1 equiv of aniline in dichloromethane in the presence of 5 mol % Pd_2dba_3 and 5 mol % PPh_3 at 40 °C caused elimination of the two allyl groups to give a quantitative yield of dicarboxylic acid **4** (with generation of coproduct *N*,*N*-diallylaniline). Thus, the chemoselectivity in the system with palladium alone was distinct from the dual-catalytic system and the gold-only system: no cyclization or new C−C bond formation occurred, and both esters were deallylated.

We next examined the chemoselectivity and compatibility of the gold and palladium dual-catalytic system for a variety of functional groups (Table 1). The substrates in this study have functional groups that could react with one or more of the catalysts and/or putative intermediates in ways that would inhibit catalysis (e.g., with lone pairs that could bind to gold or palladium, with protic functional groups that could protodeaurate the proposed organogold intermediates, with electrophilic cross-coupling partners that could undergo competitive oxidative addition, with alkenes that could undergo diastereomerization, or with other sensitive groups).

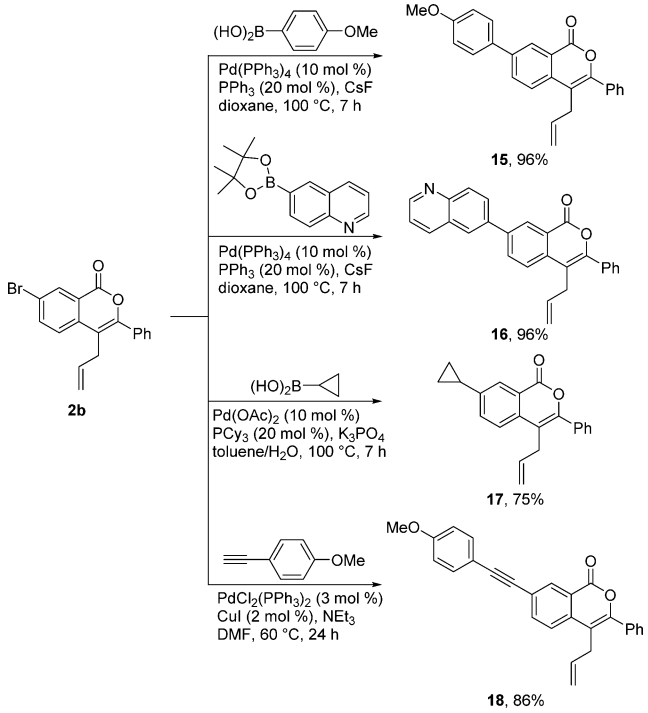
These studies were inspired by our previous observation that the Au/Pd dual-catalytic system was chemoselective for oxidative addition of the allylester **9** rather than the aryl bromide in allenoate rearrangements to form butelnolides **10** (eq 3, reproduced here for clarity).[5] Specifically, substrate **9**



contained both an allylic carbon−oxygen bond and an aryl bromide bond, both of which are susceptible to oxidative addition by palladium(0).[34−38] The gold and palladium dual-catalytic reaction produced solely the butenolide cyclization product from C−O activation **9**[5] while avoiding potential side reactions[39,40] or catalyst death[41] from oxidative addition by palladium(0) into the aryl bromide bond.[34−37] This chemoselectivity result encouraged us to think about substrates with a variety of potentially competing functional groups.

Thus, initial studies examined the gold and palladium rearrangement reaction to aryl bromide containing benzoate **1b** with the standard reaction conditions.[5] Benzoate **1b** contained an allylic carbon−oxygen bond and an aryl bromide bond, both of which are susceptible to oxidative addition by palladium(0).[42] The gold and palladium dual-catalytic reaction produced exclusively the product from the carbon−oxygen bond activation **2b** while the aryl bromide bond remained untouched (Table 1, entry 1). The chemoselectivity enabled downstream functionalization of the untouched aryl bromide bond, as will be described in detail later (Scheme 4; vida infra).

Scheme 4. Suzuki−Miyaura and Sonogashira Cross-Coupling Reactions with Isocoumarin 2b



The next study examined the phenol motif of compound **1c**, which could bind with cationic gold(I) catalyst.[43] This binding could inhibit catalysis by taking up a coordination site or by generating a sufficiently strong acid to lead to protodeauration[32] of reaction intermediates due to acidification of the O−H bond upon binding to the Lewis acidic gold cation. When performing the gold and palladium dual-catalytic reaction with this substrate at either ambient temperature or 40 °C, no conversion to product was observed by ^{1}H NMR spectroscopy. Gold-catalyzed reactions in the presence of phenols have been reported at higher temperature (presumably to overcome alcohol-binding catalyst inhibition);[43,44] consistent with those reports, changing the solvent to DCE-d_4 at 60 °C resulted in 24% isolated yield of product **2c** after 8 h (Table 1, entry 2). Thus, from a reactivity standpoint, in this example, the dual-catalytic Au/Pd conditions respond similarly to temperature as gold-only literature conditions for other rearrangement reactions.

The acidic phenol promoted protodeauration in this system at 60 °C;[32] ca. 35% of the mass balance was accounted for through this competitive protodeauration process. Protodeauration is the common catalysts turnover steps in previously reported gold catalysis on phenolic substrates. From a chemoselectivity standpoint, the addition of palladium, therefore, bifurcates the pathway between protodeauration to cross-coupling, apparently by outcompeting protodeauration via a similar rate C−C bond forming reaction. This diversion produces the observed allylated product.

Compatibility with an alcohol group to the propargylic position was next examined (**1d**). Under gold and palladium dual-catalysis conditions, substrate **1d** produced the isocoumar-

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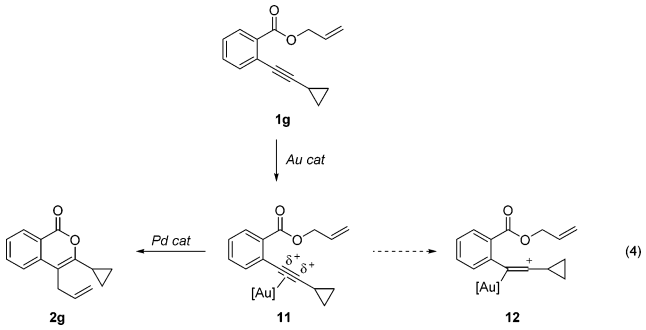
in **2d** in 84% yield after 17 h at ambient temperature (Table 1, entry 3). Thus, the original reaction conditions tolerated a free alcohol but were slowed by free phenols (vida supra). This difference underscores the subtlety of chemoselectivity in this dual-catalytic system.

Indole rings are the key structures in drug development.[45−50] Thus, the synthesis of **2e** from **1e** was next examined. Under the gold and palladium dual-catalytic conditions, substrate **1e** yielded the corresponding indolepyrone **2e** with 79% yield (Table 1, entry 4) without the need to change the standard reaction conditions.

Substrate **1f** has a resonance-hybridized nitrogen atom that may bind with gold[6,51] and decelerate or fully inhibit catalysis to the corresponding desired product **2f**. Indeed, in this case, the dual-metal catalytic reaction proceeded very slowly at ambient temperature. However, after raising the temperature to 60 °C in DCE-d_4 for 9 h, 50% of product **2f** was isolated (Table 1, entry 5).

Binding of the alkyne **1g** to gold(I) induces a partial positive charge on the digonal carbon (**11**, eq 4). The cyclo-

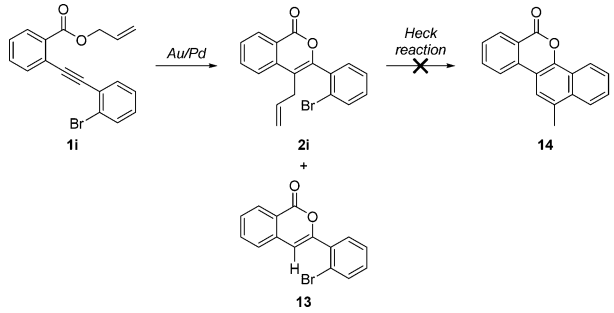


(4)

propylcarbinyl cations are known to isomerize to the cyclobutyl and homoallylic cations in certain cases.[52] Nevertheless, the gold and palladium dual-catalyzed reaction resulted in a 71% isolated yield of **2g** with the cyclopropyl group intact (Table 1, entry 6).[53−55]

We next examined the applicability of the current gold and palladium dual-metal methodology to *Z*-alkene substrate **1h**. This substrate was chosen to examine the selectivity toward cyclization/cross-coupling relative to metal-catalyzed E/Z isomerization. Cyclization directly from the E isomer would not be possible due to geometrical constraints. Thus, if irreversible isomerization to the E isomer occurred, the cyclization would be suppressed. When substrate **1h** was subjected to the gold and palladium dual-catalytic conditions, however, the corresponding pyrane **2h** was obtained within 10 min in 88% isolated yield (Table 1, entry 7), indicating that the conditions were selective for cyclization/cross-coupling over isomerization.

Next, we aimed to test the gold and palladium dual-catalytic reaction with the substrate **1i** to yield the product isocoumarin **2i** (Table 1, entry 8). Isocoumarin **2i** has the possibility for a downstream Pd-catalyzed intramolecular Heck reaction onto the untouched aryl bromide[21,56,57] in one pot. When the gold and palladium dual-catalytic reaction was carried out at ambient temperature in dry CD_2Cl_2, the rate of formation of isocoumarin **2i** was slow. Raising the temperature to 40 °C yielded isocoumarin **2i** with the formation of protodeaurated product **13** in a 1:1 ratio. Changing of solvents to DCE-d_4 at 60 °C also resulted in formation of isocoumarin **2i** and protodeaurated product **13** in a 1:1 ratio. The protodeaurated product **13** was also observed even when the reaction was carried out in the presence of molecular sieves as a scavenger for water (a potential source of proton for protodeauration). Lowering the temperature produced higher chemoselectivity for the desired product: The reaction proceeded in DCE-d_4 at ambient temperature with 100% consumption of starting material after 48 h, as observed by ^{1}H NMR spectroscopy with yields of 50% and 23% for isocoumarin **2i** and protodeaurated product **13**, respectively, as determined relative to mesitylene internal standard. The subsequent one-pot Heck reaction did not proceed (eq 5), however, perhaps due to the crowded steric environment of the aryl bromide or due to the absence of sufficient base.



(5)

Finally, the gold and palladium dual-catalytic reaction was studied by using the furan ring containing substrate **1j** to yield furopyranone product **2j**. Natural products consisting of a furopyranone core moiety lead to important biological activities, including antilymphoma activity.[58−60] We were also interested in the substrate **1j** from the view of chemoselectivity, because the furan ring could undergo a Lewis-acid/Lewis-base reaction with the gold(I) catalyst to produce an electrophilic aromatic substitution reaction.[61] However, when compound **1j** was applied to the gold and palladium dual-catalytic system, only the rearrangement product **2j** was obtained avoiding any competing substitution reaction (83% isolated yield, Table 1, entry 9).

Next, the possibility of employing the chemoselectivity generated aryl bromide functional group handle for downstream functionalization was explored (Scheme 4). First, we studied the Suzuki−Miyaura cross-coupling reaction[62−64] using isocoumarin **2b** with different boronic acids or esters. When **2b** was treated with 4-methoxyphenylboronic acid in dioxane with $Pd(PPh_3)_4$ and CsF at 100 °C for 7 h, the corresponding coupling product **15** was produced in 96% isolated yield.

This result encouraged us to use other boronic esters for the Suzuki−Miyaura coupling reactions to obtain the products that constitute important classes of compounds for drug discovery. For instance, when **2b** and 6-quinolineboronic acid pinacol ester were employed, maintaining the same cross-coupling conditions, Suzuki−Miyaura coupling product **16** was generated in 96% yield. Cyclopropyl-containing structures have significant importance in the field of pharmaceutical sciences.[65] The Suzuki−Miyaura cross-coupling reaction of **2b** and cyclopropylboronic acid in the presence of $Pd(OAc)_2$ and K_3PO_4 in toluene/H_2O proceeded at 100 °C to afford the corresponding coupled product **17** with 75% yield.

The Sonogashira cross-coupling reaction is a powerful method for generating complex molecules via Pd catalysis.[66] We were thus interested to see whether chemoselectively synthesized bromoisocoumarin **2b** would be a viable Sonoga-

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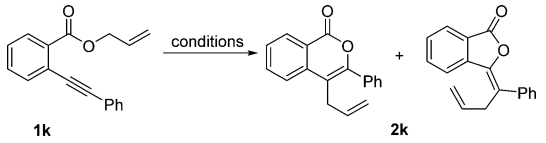
shira reaction partner. When **2b** was treated with *p*-methoxyphenylacetylene in the presence of $PdCl_2(PPh_3)_2$, CuI, and NEt_3 in DMF at 60 °C, the corresponding coupling product **18** was obtained in 86% yield (Scheme 4).

Because salt metathesis with AgOTf is employed to generate the active PPh_3AuOTf catalyst in situ, the residual silver could influence the reaction selectivity. An influence on reaction conversion with residual silver in gold catalysis was reported previously by our group and Shi's group,[3,67] but its effect on selectivity had not yet been reported. A study of the effect of silver(I) in the reaction[3,67] (Table 2) showed that silver influenced the regioselectivity in the rearrangement of substrate **1k** to **2k**.

Table 2. Effect of Silver(I) in the Reaction



1k **2k**

entry	conditions[a]	^{1}H NMR yield (%)[b]	product ratio (6-:5-membered ring)
1	Ag(I) filtered[c]	96	8:1−16:1
2	Ag(I) unfiltered	98	8:1−>20:1
3	AgOTf only[d]	20	>20:1

[a]PPh_3AuCl (5 mol %), AgOTf (5 mol %), and Pd_2dba_3 (5 mol %) in CD_2Cl_2 at rt. [b]^{1}H NMR spectroscopy yield was determined after 24 h, based on the ratio of product **2k** relative to mesitylene, which was used as an internal standard. [c]AgCl and AgOTf were removed via filtration through Celite or glass fiber paper. [d]In the absence of PPh_3AuCl.

The experiments in Table 2 are presented in order of increasing amount of silver. Specifically, in entry 1, the precipitated silver salts (presumably AgCl) after metathesis between AgOTf and PPh_3AuCl were removed by Celite or glass-fiber filtration prior to addition of substrate. Entry 2 is the normal dual-catalytic conditions. These conditions resulted in variable regioselectivity between experiments, demonstrating high sensitivity of the outcome to the filtration conditions (e.g., Celite vs glass fiber filtration medium, exact time of filtration of the mixture, and its concentration at the moment of filtration or at the moment of addition to substrate). These observations regarding the sensitivity of the regioselectivity to experimental conditions underscore the conclusion that the reaction mixture formed by gold and silver salt metathesis is not equivalent to that from gold catalysts generated in the absence of silver.[3,67] Entry 3 is the reaction run without gold. These experiments are consistent with a silver(I)/palladium(0) catalyzed pathway that proceeds in conjunction with the gold(I)/palladium(0) pathway. This silver pathway then has higher regioselectivity for the 6-membered ring but lower reactivity overall.

CONCLUSION

The chemo- and regioselectivities, functional group compatibilities, and downstream functionalization in the gold and palladium dual-catalytic synthesis of isocoumarins and related ring systems have been investigated. Chemoselectivity distinct to the gold and palladium dual-catalytic system was identified—this chemoselectivity is different than in the gold-only or palladium-only catalysis systems with the same substrate. This chemoselectivity was applied when harnessing the untouched aryl bromide of isocoumarin in the successful functionalization in Suzuki−Miyaura and Sonogashira couplings to access molecules with increased complexity. It is also noteworthy that silver had an effect on the regioselectivity of the reaction, which may be a more general effect in the field due to the prevalence of generating active gold catalysts via in situ salt metathesis with gold.[68,69] Finally, the revealed reaction selectivities were harnessed to expand the substrate scope to include pyrone, indolepyrone, and furopyrone cores relevant to drug discovery.

EXPERIMENTAL SECTION

General Information. All chemicals were used as received from commercial suppliers unless otherwise noted. Precatalysts PPh_3AuCl, AgOTf, and Pd_2dba_3 were purchased from Strem Chemical Co. Dichlorobis(triphenylphosphine)palladium(II) was purchased from Alfa Aesar. Dichloromethane-d_2 and DCE-d_4 were dried over CaH_2, degassed using three freeze, pump, thaw cycles, and vacuum transferred prior to use. All manipulations were conducted in a glovebox under a nitrogen atmosphere or using standard Schlenk techniques unless otherwise noted. Analytical and preparatory TLC was performed on Merck F_{250} TLC plates. Plates were visualized under UV irradiation (254 nm) and/or using a basic aqueous solution of potassium permanganate. Flash column chromatography was performed using 35−70 μm silica gel. All proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a 400 MHz spectrometer, a 500 MHz spectrometer outfitted with a cryoprobe, or a 600 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane and referenced to the residual protiated solvent peak (δ = 7.26 ppm for $CDCl_3$, δ = 5.32 ppm for CD_2Cl_2, and δ = 3.73 ppm for DCE-d_4 in ^{1}H NMR spectroscopy experiments; δ = 77.16 ppm for $CDCl_3$, δ = 53.84 ppm for CD_2Cl_2, and δ = 43.50 ppm for DCE-d_4 in ^{13}C NMR spectroscopy experiments). High-resolution mass spectrometry (HRMS) data were obtained at the facility operated by the University of California, Irvine.

General Procedure for Allyl Ester Rearrangements. For consistency, the reagents were always added in the same order. In the golvebox, PPh_3AuCl (5 mol %), AgOTf (5 mol %), Pd_2dba_3 (5 mol %), and the rearrangement substrate (allyl ester, 1.0 equiv) were weighed in separate dram vials. Dry CD_2Cl_2 was added via syringe to the vial containing PPh_3AuCl. The solution was transferred to the vial containing AgOTf. Dry CD_2Cl_2 was used as a rinse. Next, PPh_3AuCl/AgOTf solution was added to the vial containing the allyl ester substrate. Dry CD_2Cl_2 was used as a rinse. The solution was transferred to the vial containing Pd_2dba_3. Dry CD_2Cl_2 was used as a rinse. Now, the dram vial containing the solution of substrate and all reagents was capped and allowed to stir for a specified amount of time depending on the substrate. Note that the total amount of dry CD_2Cl_2 was used based on the concentration of 0.1 M substrate. Reaction progress was monitored by checking TLC of the reaction mixture at different time intervals. The product was purified by using an automated flash chromatography system.

Chemoselectivity Studies Using Diallyl Terephthalate 1a. *With PPh_3AuCl/AgOTf and Pd_2dba_3 in Dry CD_2Cl_2.* By following the same general procedure for allyl ester rearrangements, the reaction was conducted using diallyl-2-(phenylethynyl) terephthalate **1a** (60 mg, 0.17 mmol), PPh_3AuCl (4.2 mg, 0.0085 mmol), AgOTf (2.2 mg, 0.0085 mmol), Pd_2dba_3 (7.8 mg, 0.0085 mmol), and dry CD_2Cl_2 (1.7 mL) and was allowed to proceed for 25 h at ambient temperature. Purification by flash chromatography gave **2a** (52.8 mg, 88%) as a colorless solid of 6-membered ring product. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.51 (d, J = 2.5 Hz, 2H), 4.89 (d, J = 5.5 Hz, 2H), 5.11 (d, J = 17.5 Hz, 1H), 5.25 (d, J = 10.0 Hz, 1H), 5.34 (d, J = 10.5 Hz, 1H), 5.45 (d, J = 17 Hz, 1H), 6.02−6.17 (m, 2H), 7.47 (s, 3H), 7.64 (d, J = 3.5 Hz, 2H), 8.15 (d, J = 8.0 Hz, 1H), 8.31 (s, 1H), 8.44 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 31.7, 66.6, 111.0, 117.8, 119.2, 124.3, 126.3, 128.5, 128.7, 129.1, 130.2, 130.4, 132.0, 133.0, 135.7, 135.9, 138.4, 153.6, 162.0, 165.5. HRMS (ESI): $[M + Na]^+$ calcd for $C_{12}H_{18}O_4$, 369.1103; found, 369.1102.

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With $PPh_3AuCl/AgOTf$ and 2-Phenylethanol in Wet CH_2Cl_2. In a glovebox, PPh_3AuCl (1.5 mg, 0.0029 mmol) and AgOTf (0.8 mg, 0.003 mmol) were weighed in separate dram vials and pumped out from the glovebox. Wet CH_2Cl_2 (0.1 mL) was added via syringe to the vial containing PPh_3AuCl. The solution was transferred to the vial containing AgOTf. Wet CH_2Cl_2 (0.1 mL) was used as a rinse. Next, diallyl-2-(phenylethynyl) terephthalate **1a** (20 mg, 0.058 mmol) was added via glass Pasteur pipet to the solution of PPh_3AuCl and AgOTf containing vial. Wet CH_2Cl_2 (0.3 mL) was used to wash the Pasteur pipet. Then, 2-phenylethanol (21 mg, 21 μL, 0.17 mmol) was added via gastight syringe to the above vial. The reaction mixture was stirred at ambient temperature and was monitored by checking TLC at different time intervals. After 0.5 h, when no more diallyl terephthalate remained, concentration at reduced pressure gave the residue, which was purified by flash chromatography to give the product **3** (15.2 mg, 86%) as a colorless solid of 6-membered ring product. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.89 (d, *J* = 6.0 Hz, 2H), 5.35 (d, *J* = 10.5 Hz, 1H), 5.46 (d, *J* = 17.0 Hz, 1H), 6.03−6.11 (m, 1H), 7.02 (s, 1H), 7.44−7.49 (m, 3H), 7.89 (d, *J* = 6.5 Hz, 2H), 8.11 (d, *J* = 8.5 Hz, 1H), 8.20 (s, 1H), 8.37 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 66.5, 101.7, 119.2, 123.6, 125.5, 127.7, 128.5, 129.1, 130.1, 130.5, 131.7, 131.8, 135.9, 137.7, 154.6, 161.7, 165.1. HRMS (ESI): [M + Na]$^+$ calcd for $C_{19}H_{14}O_4$, 329.0790; found, 329.0797.

With Pd_2dba_3/PPh_3 and Aniline in Wet CH_2Cl_2. In a glovebox, Pd_2dba_3 (2.7 mg, 0.0029 mmol) and PPh_3 (0.8 mg, 0.003 mmol) were weighed in separate dram vials and pumped out from the glovebox. Wet CH_2Cl_2 (0.1 mL) was added via syringe to the vial containing PPh_3. The solution was transferred to the vial containing Pd_2dba_3. Wet CH_2Cl_2 (0.1 mL) was used as a rinse. Next, diallyl-2-(phenylethynyl) terephthalate **1a** (20 mg, 0.058 mmol) was added via glass Pasteur pipet to the solution of Pd_2dba_3 and PPh_3 containing vial. Wet CH_2Cl_2 (0.3 mL) was used to wash the Pasteur pipet. Then, aniline (5.4 mg, 5.3 μL, 0.058 mmol) was added via gastight syringe to the above vial. The reaction mixture was stirred at 40 °C and was monitored by checking TLC at different time intervals. After 0.5 h, when no more diallyl terephthalate remained, concentration at reduced pressure gave the residue, which was purified by flash chromatography to give the dicarboxylic acid **4** (15.3 mg, quantitative yield) as a yellowish solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.37−7.42 (m, 3H), 7.55−7.59 (m, 3H), 8.03 (d, *J* = 8.5 Hz, 1H), 8.22 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (CD_3OD, 125 MHz): δ 88.2, 95.9, 124.4, 124.9, 129.5, 129.9, 131.5, 132.8, 134.9, 135.6, 135.8, 137.8, 168.1, 169.0. HRMS (ESI): [M − H]$^-$calcd for $C_{16}H_9O_4$, 265.0501; found, 265.0497.

Allyl Ester Rearrangements. *4-Allyl-7-bromo-3-phenyl-1H-isochromen-1-one* ***2b***. By following the same general procedure for allyl ester rearrangements, the reaction was conducted using allyl-5-bromo-2-(phenylethynyl) benzoate **1b** (99 mg, 0.29 mmol), PPh_3AuCl (7.4 mg, 0.015 mmol), AgOTf (3.9 mg, 0.015 mmol), Pd_2dba_3 (14 mg, 0.015 mmol), and dry CD_2Cl_2 (2.9 mL) and was allowed to proceed for 22 h at ambient temperature. Purification by flash chromatography gave **2b** (87 mg, 88%) as a colorless solid in the ratio of 16:1 of 6- and 5-membered ring products. Characterization for the major 6-membered ring product **2b**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.45 (t, *J* = 2.5 Hz, 2H), 5.07 (d, *J* = 17.5 Hz, 1H), 5.24 (d, *J* = 15.5 Hz, 1H), 6.06−6.14 (m, 1H), 7.45−7.48 (m, 4H), 7.62 (dd, *J* = 3.5, 2.0 Hz, 2H), 7.84 (dd, *J* = 2.0, 2.0 Hz, 1H), 8.50 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 31.4, 110.4, 117.6, 121.8, 122.6, 126.3, 128.5, 128.8, 130.0, 132.4, 132.8, 135.5, 136.9, 137.9, 153.1, 161.2. HRMS (ESI): [M + Na]$^+$ calcd for $C_{18}H_{13}BrO_2$, 362.9997; found, 362.9995.

4-Allyl-7-hydroxy-3-phenyl-1H-isochromen-1-one ***2c***. By following the same general procedure for allyl ester rearrangements, the reaction was conducted using allyl-5-hydroxy-2-(phenylethynyl)-benzoate **1c** (21 mg, 0.076 mmol), PPh_3AuCl (1.9 mg, 0.0038 mmol), AgOTf (1.0 mg, 0.0038 mmol), Pd_2dba_3 (3.5 mg, 0.0038 mmol), and dry DCE-d_4 (0.96 mL) and was allowed to proceed for 8 h at 60 °C. Purification by flash chromatography gave **2c** (5.1 mg, 24%) as a colorless solid in the ratio of 11:1 of 6- and 5-membered ring products. Characterization for the major 6-membered ring product **2c**: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.45 (d, *J* = 3.5 Hz, 2H), 5.09 (d, *J* = 17.8 Hz, 1H), 5.22 (d, *J* = 10.1 Hz, 1H), 6.10 (ddt, *J* = 17.8, 10.1, 3.5 Hz, 1H), 6.71 (s, br, 1H), 7.35 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.44 (m, 3H), 7.54 (d, *J* = 8.9 Hz, 1H), 7.62 (m, 2H), 7.98 (d, *J* = 2.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 31.6, 111.3, 114.3, 117.4, 122.3, 124.3, 126.6, 128.5, 125.9, 129.7, 131.5, 133.2, 136.0, 150.5, 156.4, 163.3. HRMS (ESI): [M + Na]$^+$ calcd for $C_{18}H_{14}O_3$, 301.0841; found, 301.0840.

4-Allyl-3-(hydroxymethyl)-1H-isochromen-6-carboxylate ***2d***. By following the same general procedure for allyl ester rearrangements, the reaction was conducted using allyl-2-(3-hydroxypropynyl) benzoate **1d** (70 mg, 0.32 mmol), PPh_3AuCl (7.9 mg, 0.016 mmol), AgOTf (4.1 mg, 0.016 mmol), Pd_2dba_3 (15 mg, 0.016 mmol), and dry CD_2Cl_2 (3.2 mL) and was allowed to proceed for 17 h at ambient temperature. Purification by flash chromatography gave **2d** (58.8 mg, 84%) as a colorless solid, consisting solely of the 6-membered ring product. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.07 (br, 1H), 3.47 (d, *J* = 5.0 Hz, 2H), 4.55 (s, 2H), 5.02−5.10 (m, 2H), 5.91−5.99 (m, 1H), 7.49 (t, *J* = 8 Hz, 1H), 7.55 (d, *J* = 8 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 30.0, 59.7, 112.2, 117.1, 121.5, 124.0, 128.5, 130.2, 135.0, 135.1, 137.5, 152.2, 162.7. HRMS (ESI): [M + Na]$^+$ calcd for $C_{13}H_{12}O_3$, 239.0684; found, 239.0685.

4-Allyl-9-methyl-3-phenylpyrano[3,4-b]indol-1(9H)-one ***2e***. By following the same general procedure for allyl ester rearrangements, the reaction was conducted using allyl-1-methyl-3-(phenylethynyl)-1*H*-indole-2-carboxylate **1e** (70 mg, 0.22 mmol), PPh_3AuCl (11 mg, 0.022 mmol), AgOTf (5.7 mg, 0.022 mmol), Pd_2dba_3 (20 mg, 0.022 mmol), and dry CD_2Cl_2 (2.2 mL) and was allowed to proceed for 7 h at ambient temperature. Purification by flash chromatography gave **2e** (55.3 mg, 79%) as a yellow solid, consisting solely of the 6-membered ring product. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.71 (d, *J* = 5.0 Hz, 2H), 4.29 (s, 3H), 5.14 (d, *J* = 17.5 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 6.28−6.33 (m, 1H), 7.27 (d, *J* = 9.0 Hz, 2H), 7.44 (d, *J* = 7.0 Hz, 3H), 7.50−7.67 (m, 2H), 7.66 (d, *J* = 7.0 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 31.8, 32.7, 111.0, 111.5, 117.5, 121.3, 121.8, 124.1, 126.3, 127.7, 128.6, 129.1, 129.4, 133.4, 136.0, 141.9, 151.1, 157.6. HRMS (ESI): [M + Na]$^+$ calcd for $C_{21}H_{17}NO_2$, 338.1157; found, 338.1164.

N-(4-(4-Allyl-1-oxo-1H-isochromen-3-yl)phenyl)-N-tosylacetamide ***2f***. By following the same general procedure for allyl ester rearrangements, the reaction was conducted using allyl-2-((4-((*N*,4-dimethylphenyl)sulfonamide)phenyl)ethynyl)benzoate **1f** (30 mg, 0.064 mmol), PPh_3AuCl (1.5 mg, 0.0032 mmol), AgOTf (0.9 mg, 0.003 mmol), Pd_2dba_3 (3.0 mg, 0.0032 mmol), and dry DCE-d_4 (0.74 mL) and was allowed to proceed for 6 h at 60 °C. Purification by flash chromatography gave **2f** (15 mg, 50%) as a colorless solid in the ratio of 16:1 of 6- and 5-membered ring products. Characterization for the major 6-membered ring product **2f**: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.92 (s, 3H), 2.47 (s, 3H), 3.53 (d, *J* = 2.4 Hz, 2H), 5.10 (d, *J* = 17.5 Hz, 1H), 5.28 (d, *J* = 10.1 Hz, 1H), 6.17 (ddt, *J* = 17.5, 10.1, 2.4 Hz, 1H), 7.36 (app-t, *J* = 7.2, 4H), 7.58 (app-t, *J* = 7.4 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.79 (m, 3H), 7.93 (d, *J* = 8.1 Hz, 2H), 8.40 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.7, 25.1, 31.3, 116.6, 117.5, 121.0, 124.4, 128.4, 129.2, 129.4, 129.5, 129.8, 129.9, 130.1, 134.5, 134.8, 135.3, 135.8, 137.5, 137.7, 145.2, 150.7, 162.0, 169.7. HRMS (ESI): [M + Na]$^+$ calcd for $C_{27}H_{23}NO_5S$, 496.1195; found, 496.1194.

4-Allyl-3-cyclopropyl-1H-isochromen-1-one ***2g***. By following the same general procedure for allyl ester rearrangements, the reaction was conducted using allyl-2-(cyclopropylethynyl)benzoate **1g** (23 mg, 0.10 mmol), PPh_3AuCl (2 mg, 0.005 mmol), AgOTf (1.3 mg, 0.0049 mmol), Pd_2dba_3 (5 mg, 0.005 mmol), and dry CD_2Cl_2 (1.0 mL) and was allowed to proceed for 24 h at ambient temperature. Purification by flash chromatography gave **2g** (16 mg, 71%) as a colorless solid in the ratio of 12:1 of 6- and 5-membered ring products. Characterization for the major 6-membered ring product **2g**: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.94 (m, 2H), 1.18 (m, 2H), 1.97 (m, 1H), 3.53 (app-dt, *J* = 5.6, 1.3, 2H), 5.10 (app-dq, *J* = 17.2, 1.4 Hz, 1H), 5.12 (app-dq, *J* = 10.5, 1.3 Hz, 1H), 5.99 (ddt, *J* = 17.1, 10.4, 5.7 Hz, 1H), 7.42 (app-td, *J* = 7.2, 1.3 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.70 (app-td, *J* = 7.4, 1.4

Hz, 1H), 8.28 (dd, J = 7.9, 1.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 7.3, 11.1, 29.8, 109.2, 116.5, 122.6, 126.9, 130.0, 134.8, 134.9, 138.3, 154.5, 162.6. HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_{14}O_2$, 227.1072; found, 227.1076.

5-Allyl-6-phenyl-2H-pyran-2-one ***2h***. By following the same general procedure for allyl ester rearrangements, the reaction was conducted using allyl(*Z*)-5-phenylpent-2-en-4-ynoate **1h** (70 mg, 0.33 mmol), PPh_3AuCl (8.4 mg, 0.017 mmol), AgOTf (4.4 mg, 0.017 mmol), Pd_2dba_3 (16 mg, 0.017 mmol), and dry CD_2Cl_2 (3.3 mL) and was allowed to proceed for 10 min at ambient temperature. Purification by flash chromatography gave **2h** (61 mg, 88%) as a colorless solid, consisting solely of the 6-membered ring product. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.19 (d, J = 5.5 Hz, 2H), 5.10 (d, J = 17 Hz, 1H), 5.21 (d, J = 10.5 Hz, 1H), 5.89–5.96 (m, 1H), 6.31 (d, J = 9.5 Hz, 1H), 7.30 (d, J = 9.5 Hz, 1H), 7.44 (t, J = 8.5 Hz, 3H), 7.55–7.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 34.2, 113.4, 114.9, 117.7, 128.7, 128.8, 130.4, 132.4, 135.7, 147.8, 159.0, 162.4. HRMS (ESI): $[M + Na]^+$ calcd for $C_{14}H_{12}O_2$, 235.0735; found, 235.0735.

4-Allyl-3-(2-bromophenyl)-1H-isochromen-1-one ***2i***. By following the same general procedure for allyl ester rearrangements, the reaction was conducted using allyl-2-((2-bromophenyl)ethynyl)benzoate **1i** (30 mg, 0.088 mmol), PPh_3AuCl (2.2 mg, 0.0044 mmol), AgOTf (1.1 mg, 0.0044 mmol), Pd_2dba_3 (4.0 mg, 0.0044 mmol), and dry DCE-d_4 (0.5 mL) in a J. Young tube and was allowed to proceed for 48 h at ambient temperature. When no more starting material remained, as was observed by ^{1}H NMR spectroscopy, mesitylene was used as an internal standard to measure the yield of product, and we found 50% and 23% yields of desired isocoumarin **2i** and the protodeaurated product **13**, respectively, as an inseparable mixture.

7-Allyl-6-phenyl-4H-furo[3.2-c]pyran-4-one ***2j***. By following the same general procedure for allyl ester rearrangements, the reaction was conducted using allyl-2-(phenylethynyl)furan-3-carboxylate **1j** (17 mg, 0.066 mmol), PPh_3AuCl (1.6 mg, 0.0033 mmol), AgOTf (0.9 mg, 0.003 mmol), Pd_2dba_3 (3.0 mg, 0.0033 mmol), and dry DCE-d_4 (0.76 mL) and was allowed to proceed for 6 h at 50 °C. Then, an excess of dimethylaminoethanethiol and triethylamine was added to the reaction mixture, and the mixture was stirred at ambient temperature for overnight to remove dba from the reaction mixture. Purification by flash chromatography gave **2j** (13.9 mg, 83%) as a colorless solid, consisting solely of the 6-membered ring product. ^{1}H NMR (DCE-d_4, 600 MHz): δ 3.42 (d, J = 5.7 Hz, 2H), 5.09 (d, J = 17.3 Hz, 1H), 5.16 (d, J = 11.0, 1H), 6.07 (ddt, J = 17.3, 11.0, 5.7 Hz, 1H), 6.91 (d, J = 1.8 Hz, 1H), 7.47 (m, 3H), 7.61 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 29.5, 106.5, 107.8, 109.8, 116.6, 125.6, 128.7, 129.2, 130.1, 132.3, 135.0, 144.8, 156.1, 158.7, 162.3. HRMS (ESI): $[M + Na]^+$ calcd for $C_{16}H_{12}O_3$, 275.0684; found, 275.0693.

Suzuki–Miyaura Cross-Coupling Reaction. *4-Allyl-7-(4-methoxyphenyl)-3-phenyl-1H-isochromen-1-one* ***15***. To a stirred solution of isocoumarin **2b** (22 mg, 0.064 mmol) in dioxane (2.0 mL) was added 4-methoxyphenylboronic acid (29 mg, 0.19 mmol), $Pd(PPh_3)_4$ (6 mg, 0.006 mmol), PPh_3 (3.4 mg, 0.013), and CsF (39 mg, 0.26 mmol) at ambient temperature. The reaction mixture was stirred at 100 °C for 7 h and then cooled to ambient temperature, followed by filtration through a pad of Celite. Concentration at reduced pressure gave the residue, which was purified by flash chromatography to give the corresponding coupling product **15** (23 mg, 96%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.49 (t, J = 2.5 Hz, 2H), 3.87 (s, 3H), 5.12 (d, J = 17.5 Hz, 1H), 5.25 (d, J = 10.5 Hz, 1H), 6.12–6.17 (m, 1H), 7.02 (d, J = 8.5 Hz, 2H), 7.45 (t, J = 3.5 Hz, 3H), 7.64 (dd, J = 8.5, 9.0 Hz, 5H), 7.96 (dd, J = 8.5, 8.5 Hz, 1H), 8.57 (d, J = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 31.5, 55.5, 110.8, 114.6, 117.4, 121.5, 125.0, 127.1, 128.3, 128.4, 128.9, 129.7, 131.7, 133.0, 133.2, 135.9, 136.3, 140.5, 152.3, 159.9, 162.8. HRMS (ESI): $[M + Na]^+$ calcd for $C_{25}H_{20}O_3$, 391.1310; found, 391.1327.

4-Allyl-3-phenyl-7-(quinolin-6-yl)-1H-isochromen-1-one ***16***. To a stirred solution of isocoumarin **2b** (30 mg, 0.088 mmol) in dioxane (3.0 mL) was added 6-quinolineboronic acid pinacol ester (67 mg, 0.26 mmol), $Pd(PPh_3)_4$ (10 mg, 0.0088 mmol), PPh_3 (4.7 mg, 0.018 mmol), and CsF (53 mg, 0.35 mmol) at ambient temperature. The reaction mixture was stirred at 100 °C for 7 h and then cooled to ambient temperature, followed by filtration through a pad of Celite. Concentration at reduced pressure gave the residue, which was purified by flash chromatography to give the corresponding coupling product **16** (33 mg, 96%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.52 (d, J = 2.5 Hz, 2H), 5.14 (d, J = 17.0 Hz, 1H), 5.28 (d, J = 10.5 Hz, 1H), 6.14–6.19 (m, 1H), 7.47 (s, 4H), 7.67 (d, J = 7.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 10.5 Hz, 2H), 8.23 (t, J = 10.0 Hz, 2H), 8,76 (s, 1H), 8.95 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 31.5, 110.8, 117.5, 121.7, 121.9, 125.3, 126.0, 128.2, 128.5, 128.6, 128.7, 128.9, 129.9, 130.5, 133.0, 133.6, 135.8, 136.5, 137.3, 137.4, 139.9, 148.0, 151.0, 152.9, 162.6. HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{19}NO_2$, 390.1494; found, 390.1486.

4-Allyl-7-cyclopropyl-3-phenyl-1H-isochromen-1-one ***17***. To a stirred solution of isocoumarin **2b** (10 mg, 0.029 mmol) in toluene/H_2O (1.5:1) was added cyclopropylboronic acid (7.4 mg, 0.087 mmol), $Pd(OAc)_2$ (2 mg, 0.003 mmol), PCy_3 (1.6 mg, 0.0058), and K_3PO_4 (21.5 mg, 0.102 mmol) at ambient temperature. The reaction mixture was stirred at 100 °C for 7 h and then cooled to ambient temperature, followed by filtration through a pad of Celite. Concentration at reduced pressure gave the residue, which was purified by flash chromatography to give the corresponding coupling product **17** (6.7 mg, 75%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.82 (q, J = 5.0 Hz, 2H), 1.08 (q, J = 6.5 Hz, 2H), 2.0–2.03 (m, 1H), 3.45 (d, J = 2.5 Hz, 2H), 5.07 (d, J = 17.0 Hz, 1H), 5.21 (d, J = 10.5 Hz, 1H), 6.08–6.14 (m, 1H), 7.43 (d, J = 7.0 Hz, 3H), 7.49 (s, 2H), 7.62 (t, J = 7.5 Hz, 2H), 8.04 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.1, 15.6, 31.5, 110.9, 117.2, 121.1, 124.4, 125.8, 128.4, 128.9, 129.6, 133.0, 133.2, 135.5, 136.00, 144.9, 151.7, 162.8. HRMS (ESI): $[M + Na]^+$ calcd for $C_{21}H_{18}O_2$, 325.1205; found, 325.1210.

Sonogashira Cross-Coupling Reaction. *4-Allyl-7-((4-methoxyphenyl)ethynyl)-3-phenyl-1H-isochromen-1-one* ***18***. To a stirred solution of isocoumarin **2b** (45 mg, 0.029 mmol) in degassed DMF (1.0 mL) were added $PdCl_2(PPh_3)_2$ (2.8 mg, 0.039 mmol) and CuI (0.5 mg, 0.03 mmol) at ambient temperature. Then, *p*-ethynylanisole (19 μL, 0.15 mmol) and NEt_3 (0.33 mL) were added to the reaction mixture at the same temperature. The reaction mixture was allowed to stir under nitrogen at 60 °C for 24 h. After the completion of the reaction, as indicated by TLC, brine was added to the reaction mixture and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure to give a residue, which was directly crystallized to give the coupled product **18** (42 mg, 86%) as a colorless solid. ^{1}H NMR (CD_2Cl_2, 600 MHz): δ 3.46 (app-dt, J = 5.6, 1.3 Hz, 2H), 3.83 (s, 3H), 5.08 (app-dq, J = 17.2, 1.3 Hz, 1H), 5.22 (app-dq, J = 10.4, 1.3 Hz, 1H), 6.1238 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 6.92 (d, J = 8.9 Hz, 2H), 7.48 (m, 3H), 7.51 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.64 (m, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 8.44 (d, J = 1.7 Hz, 1H). ^{13}C NMR (CD_2Cl_2, 125 MHz): δ 31.2, 55.4, 86.8, 91.5, 110.7, 114.1, 114.6, 116.9, 121.2, 123.4, 124.6, 128.3, 128.6, 129.7, 132.0, 133.0, 133.1, 135.6, 136.8, 137.1, 152.9, 160.1, 161.3. HRMS (ESI): $[M + Na]^+$ calcd for $C_{27}H_{20}O_3$, 415.1310; found, 415.1302.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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