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Gold Catalyzed Dehydrogenative Cycloisomerization of 1,4-Enyne Esters to 3,5-Disubstituted Phenol Derivatives

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Abstract. A method to prepare synthetically important 3,5-disubstituted phenol derivatives that relies on the sequential gold(I)-catalyzed dehydrogenative cycloisomerization of 1,4-enyne esters in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or *N*-fluorobenzenesulfonimide (NFSI) is described. The synthetic versatility of the methodology was exemplified by a gram-scale reaction of one example, the ease to realize subsequent functional transformations of an adduct, and the application of the method to the synthesis of the bioactive molecule LUF5771.

Keywords: 1,4-enyne esters; 3,5-disubstituted phenols; dehydrogenative cycloisomerization; gold; homogenous catalysis

Introduction

Phenols are important core structures and precursors for the construction of a wide variety of bioactive natural products, pharmaceutical compounds and polymers.[1–5] Representative of this are members of the family with a 3,5-disubstitution pattern that are found in a myriad of pharmacologically interesting compounds such as those illustrated in Figure 1.[2–5] For this reason, the development of synthetic approaches to construct 3,5-disubstituted phenols with selective control of substitution patterns efficiently is of considerable current interest. The regiospecific preparation of 3,5-disubstituted phenols via traditional electrophilic aromatic substitution of phenols, however, can be synthetically challenging due to the well-known strong *o*,*p*-directing effect of the hydroxyl functional group. Consequently, this has led to the establishment of a number of elegant synthetic methodologies in recent years.[6–11] Included in this have been synthetic approaches that have relied on the oxidative dehydrogenation,[6] base-promoted eliminative aromatization,[7] [3+3] annulation,[8] ring-closing olefin metathesis cascade,[9] and gold(I)-catalyzed annulation[10] of nonaromatic precursors. The transition-metal catalyzed template assisted C–H bond meta-functionalization of phenols has also been recently disclosed.[11] Despite these advances, there remains a need to realize new synthetic methods for the efficient preparation of 3,5-disubstituted phenols from readily accessible substrates under mild and practical conditions.

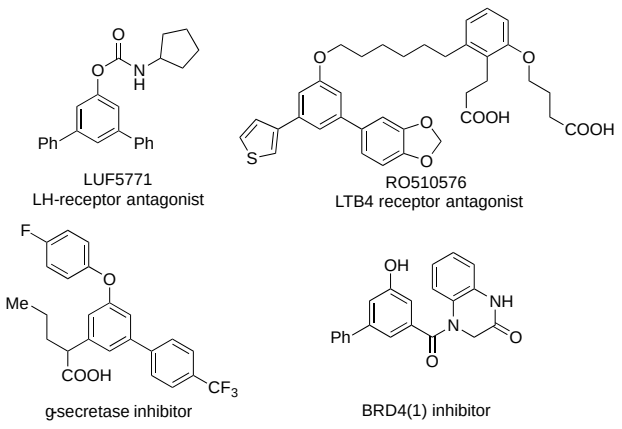
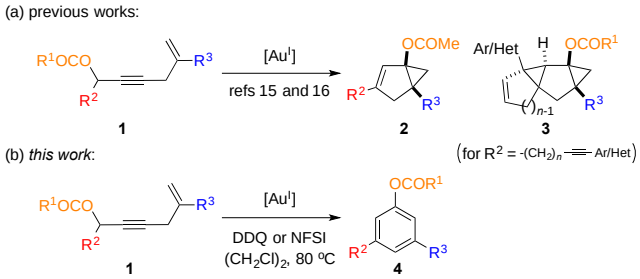


Figure 1. Selected examples of bioactive 3,5-disubstituted phenol derivatives.[2–5]

Gold-mediated cycloisomerization of 1,*n*-enynes and 1,*n*-enyne esters has become one of the most atom-economical and versatile synthetic strategies to rapidly increase molecular complexity in a single operation.[12–18] A recent notable example is the gold(I)-catalyzed cycloisomerization of 1,4-enyne acetates to bicyclo[3.1.0]hexenes (Scheme 1a).[15] Following this pioneering work, we reported the gold(I)-catalyzed tandem 1,3-acyloxy migration/double cyclopropanation of 1-ene-4,9-diyne and 1-ene-4,10-diyne esters to the architecturally challenging tetracyclodecenes and tetracycloundecenes *via* the bicyclic intermediate (Scheme 1a).[16] Inspired by these studies and as part of ongoing efforts in the field,[17] we were drawn to the potential reactivity of 1,4-enyne esters in the presence of an oxidant such as DDQ or NFSI (Scheme 1b).[18] We reasoned that such bicyclo[3.1.0]hexene adducts generated from gold(I)-catalyzed cycloisomerization of the substrate might be susceptible to a dehydrogenative/ring-opening pathway due to the oxidant to provide the 3,5-disubstituted aromatic ring system. Herein, we describe the details of this chemistry that provides an expedient and regioselective approach to the synthetically important phenolic ester derivative in good to excellent yields. The synthetic versatility of the methodology by demonstrating the ability to carry out a gram-scale reaction of one example and the ease to further functionalize the adduct along with the preparation of the LH-receptor antagonist LUF5771 in two steps is also presented.[2]

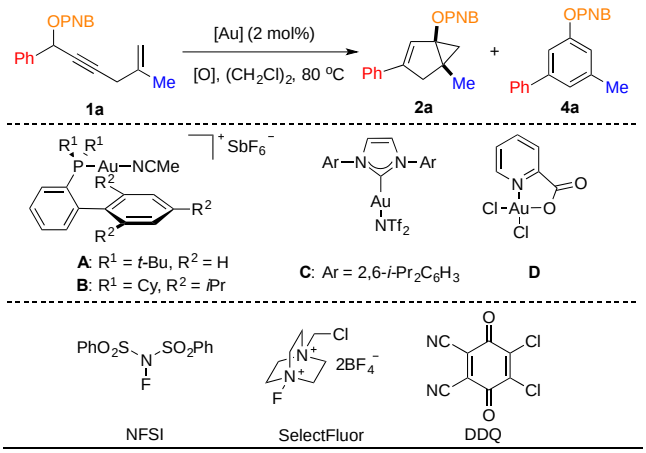


Scheme 1. Gold(I)-catalyzed reactivities of 1,4-enyne esters

Results and Discussion

The 1,4-enyne esters studied in this work were prepared from the corresponding aldehyde or carboxylic acid starting materials in three to four steps following literature procedures.[19] By choosing **1a** as the model substrate, we commenced our studies by examining the gold-catalyzed dehydrogenative rearrangement of the 1,4-enyne ester in the presence of an oxidant to establish the optimum reaction conditions (Table 1). This initially revealed that the anticipated phenol derivative **4a** could be obtained in 82% yield on treating the substrate with 2 mol % of gold(I) phosphine catalyst **A**[20a] and NFSI (2 equiv) in1,2-dichloroethane at 80 °C for 12 h (entry 1). More-

Table 1. Optimization of the reaction conditions[a]



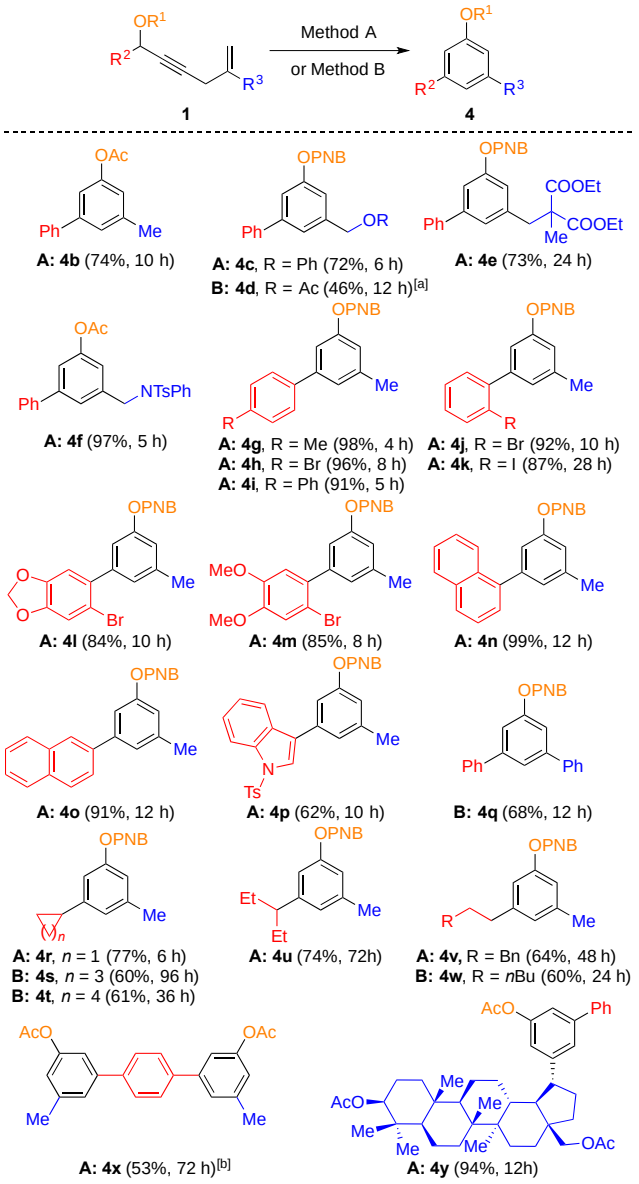
Entry	Catalyst	[O]	Reaction Time [h]	Yield [%]	
				2a	**4a**
1	**A**	NFSI	12	-	82
2	**A**	-[b]	24	99	-
3	**A**	SelectFluor	120	-	66
4	**A**	DDQ	4	-	99
5[c]	**A**	DDQ	120	-	87
6[d]	**A**	DDQ	4	-	99
7[d,e]	**A**	DDQ	4	-	97
8[d]	**B**	DDQ	3	-	85
9[d]	**C**	DDQ	16	-	97
10[d]	PPh_3AuNTf_2	DDQ	3	-	80
11[d]	**D**	DDQ	24	-	82

[a]All reactions were performed using 0.3 mmol of **1a**, 2 mol % of gold(I) or gold(III) catalyst and 0.6 mmol of oxidant in $(CH_2Cl)_2$ at 80 °C. [b]Reaction carried out in the absence of an oxidant. [c]Reaction carried out at room temperature. [d]Reaction performed with 0.36 mmol of DDQ. [e]Reaction performed in toluene.

over, a control experiment in the absence of NFSI was found to give the bicyclo[3.1.0]hexene adduct **2a** in 99% yield (entry 2). These promising results encouraged us to next examine other oxidants, which showed replacing NFSI with SelectFluor led to a lower product yield of 66% and the need of a reaction time of 5 days (entry 3). Changing the oxidant to DDQ, on the other hand, was found to increase the yield of **4a** to 99% after 4 h (entry 4). Repeating these reaction conditions at room temperature proceeded slowly and required a reaction time of 5 days to furnish a product yield of 87% (entry 5). Our investigations subsequently found a product yield 99% could also be achieved under the reaction conditions described in entry 4 and at a lower loading of DDQ of 1.2 equiv (entry 6). Under these latter conditions, a comparable product yield of 97% was obtained when the reaction was conducted in toluene instead of 1,2-dichloroethane as the solvent (entry 7). Likewise, control reactions with the more sterically crowded

Au(I) complex **B**,[20b] NHC−Au(I) (NHC = *N*-heterocyclic carbene) complex **C**,[20c] $Ph_3PAuNTf_2$[20c] or gold(III) complex **D**[20d] in place of **A** as the catalyst provided **4a** in 80−97% yield (entries 8−11). On the basis of the above results, reaction of **1a** in the presence of 2 mol % of Au(I) complex **A** as the catalyst and 1.2 equiv of DDQ (Method A) or 2 equiv of NFSI (Method B) as the oxidant in 1,2-dichloroethane at 80 °C for 4 or 12 h were deemed to provide the optimum conditions.

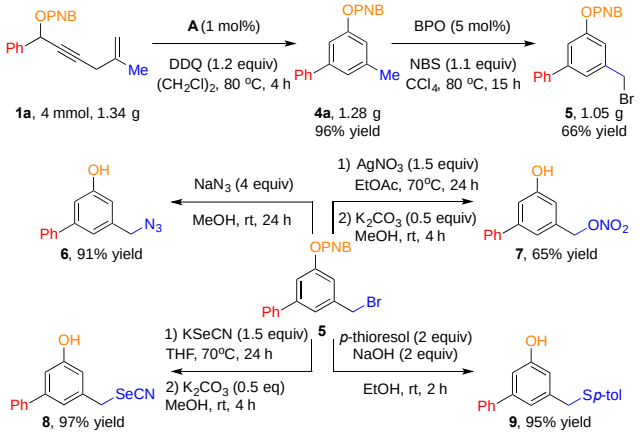
With the optimal conditions in hand, we next evaluated the generality of the present procedure with a series of 1,4-enyne esters, and the results are summarized in Scheme 2. Overall, the Au(I) complex **A**-catalyzed reaction conditions were found to be broad, providing a diverse set of 3,5-disubstituted phenol derivatives containing a variety of substitution patterns in 46–99% yield from the corresponding substrates **1a**–**y**. Under the conditions of Method A, the introduction of an acyl (**1b**) instead of a *p*-nitrobenzoyl (PNB) migrating group was found to proceed well, producing the corresponding 3,5-disubstituted phenol **4b** in 74% yield. Similarly, the reaction of substrates bearing a phenyl ether (**1c**), malonate (**1e**) and a tertiary sulfonamide (**1f**) group at the R^3 position were shown to give the corresponding 3,5-disubstituted phenols **4c** and **4e**–**f** in 72–97% yield. The dehydrogenative rearrangement of **1d** with a pendant methyl carbonate group was found to proceed best under the conditions of Method B, affording **4d** as well as **4a** as a byproduct in respective yields of 46 and 37%. The presence of an electron-donating (**1g**,**l** and **1m**) or electron-withdrawing (**1h**–**k**) substituent on the phenyl group at the R^2 position of the substrate was also found to have no appreciable effect on the outcome of the reaction. In these experiments, the corresponding phenol products **4g**–**m** were obtained in excellent yields of 84–98% under the conditions of Method A. Similarly, substrates containing a naphthyl (**1n**–**o**), or indolyl (**1p**) motif at the same position were well tolerated, furnishing the corresponding phenol derivatives **4n**–**p** in 62-99% yield. Under the reaction conditions of Method B, the diphenyl substituted substrate **1q** gave the corresponding phenolic ester adduct **4q** in 68% yield. Gratifyingly, the starting esters bearing an aliphatic substituent at both the R^2 and R^3 positions, as in **1r**–**w**, were also converted to the corresponding phenols **4r**–**w** in 60-77% yield using either Method **A** or **B** albeit requiring longer reaction times. Due to the importance of terphenyls and their derivatives in the fields of optical and conductive materials, as well as a wide range of biological applications,[2,21,22] the symmetrical 1,4-enyne ester **1x** was next examined. Under the reaction conditions of Method A at a catalyst loading of 4 mol % and 2.4 equiv of DDQ, this gave the expected terphenyl **4x** in 53% yield. The 1,4-enyne ester **1y**, which was prepared from the bioactive natural product betulin, was additionally shown to undergo dehydrogenative cycloisomerization to afford **4y** in an excellent yield of 94%.



Scheme 2. Gold(I)-catalyzed dehydrogenative cycloisomerization of 1,4-enyne esters **1b**–**y**. All reaction performed following: Method A: reaction performed with **1** (0.3 mmol), Au(I) complex **A** (2 mol%) and DDQ (0.36 mmol) in $(CH_2Cl)_2$ at 80 °C; or Method B: reaction performed with **1** (0.3 mmol), Au(I) complex **A** (2 mol%) and NFSI (0.6 mmol) in $(CH_2Cl)_2$ at 80 °C. Values in parentheses denote isolated product yields and reaction times. [a]Compound **4a** was isolated in 37% yield. [b]Reaction performed 4 mol % of Au(I) complex **A** and with 2.4 equiv of DDQ.

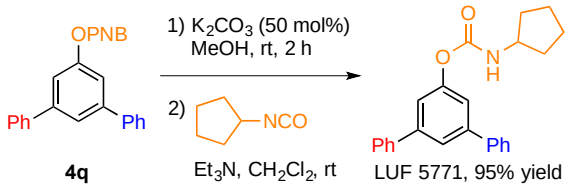
To demonstrate the scalability and practicality of the present protocol, a gram-scale reaction of **1a** (4 mmol, 1.34 g) was carried out in the presence of 1 mol % gold(I) catalyst **A**. Under the reaction conditions

described in Scheme 3, this provided **4a** in 96% yield (1.28 g). Accordingly, subjecting the adduct to 5 mol% benzoyl peroxide (BPO) and to *N*-bromosuccinimide (NBS, 1.1 equiv) in carbon tetrachloride at 80 °C for 15 h afforded the benzylic bromide **5** (1.05 g) in 66% yield. Subsequently, the synthetic versatility of **5** was demonstrated by its successfully conversion to the corresponding 3,5-disubstituted phenols with a range of functional groups (Scheme 3). By applying corresponding nucleophilic substitution reaction conditions, this included compounds with an azide (**6**), nitrate (**7**), selenocyanate (**8**) and thioether (**9**) motif in yields of 65–97%.



Scheme 3. Scale-up experiments and synthetic transformations.

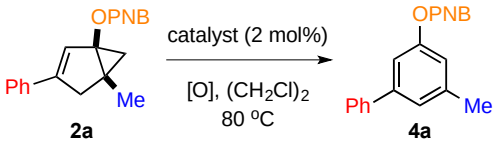
The synthetic application of the methodology was next demonstrated by the transformation of **4q** to the *O*-terphenylcarbamate LUF5771, a novel inhibitor of the human luteinizing hormone receptor.[2,6b,g,8c] As shown in Scheme 4, methanolysis of the 3,5-diphenyl-substituted substrate was achieved by subjecting it to K_2CO_3 in methanol at room temperature for 2 h. This was followed by treatment of the resultant crude mixture with cyclopentylisocyanate to furnish LUF5771 in 95% yield over two steps. This is comparable product yields obtained by previously reported synthetic methods to prepare the LH-receptor antagonist from a cyclic or acyclic precursor.[2,6b,8c]



Scheme 4. Synthesis of the LH-Receptor antagonist LUF5771.[2,6b,8c]

To gain an insight into the reaction mechanism, a number of control experiments were performed (Table 2 and Scheme 5). Our initial premise reasoned that the bicyclo[3.1.0]hexane adduct obtained from the gold catalysis step might be susceptible to a ring-opening/dehydrogenation process in the presence of an oxidant. With this mind, we first examined the reaction of **2a** in the presence and absence of the gold(I) catalyst **A** (2 mol %), 1.2 equiv of DDQ and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 2 equiv) under the conditions described in Table 2, entries 1 and 4. These tests was found to result in no reaction and, in both cases, the recovery of the starting material in 99% yield. Initially, this led us to consider a reaction mechanism involving the possible formation of a radical species as well as the bicyclic adduct as a key intermediate.[23] This was further supported by performing the reaction again for a third time in the absence of TEMPO and obtaining **4a** in 99% yield within 4 h (entry 2). Intriguingly, the transformation proceeded very slowly on repeating the reaction for a fourth time in the absence of gold catalyst **A**, requiring 5 days to furnish the product in 97% yield (entry 5). A similar outcome was observed when these latter set of two control experiments with **2a** was conducted with NFSI as the oxidant (entries 3 and 6). The possibility of an alternative competing pathway involving a hydride abstraction step, however, could not be ruled out based on findings obtained from control reactions of **2a** with $BF_3{\cdot}Et_2O$ or CuI in place of **A** as the catalyst.[24] Under the reaction conditions detailed in entries 7 and 8, these experiments gave the phenolic ester product in respective yields of 98 and 82%. Consistent with this are our findings in a control experiment treating **2a** to the conditions described in Scheme 5, which gave compound **10** in 21% yield and

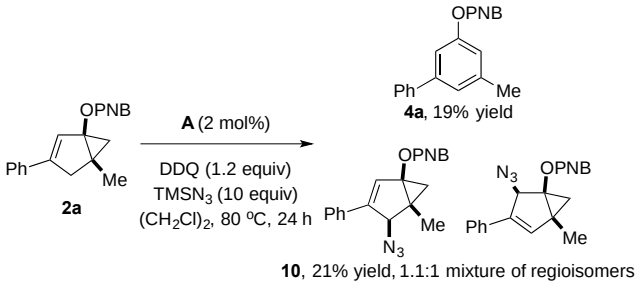
Table 2. Control experiments with **2a**[a]



Entry	Catalyst	[O]	Reaction Time [h]	Yield [%][b]
1[c]	**A**	DDQ	24	-[d]
2	**A**	DDQ	4	99
3	**A**	NFSI	12	83
4[c]	-	DDQ	24	-[d]
5	-	DDQ	120	97
6	-	NFSI	72	81
7	$BF_3{\cdot}Et_2O$	DDQ	6	98
8	CuI	DDQ	24	82

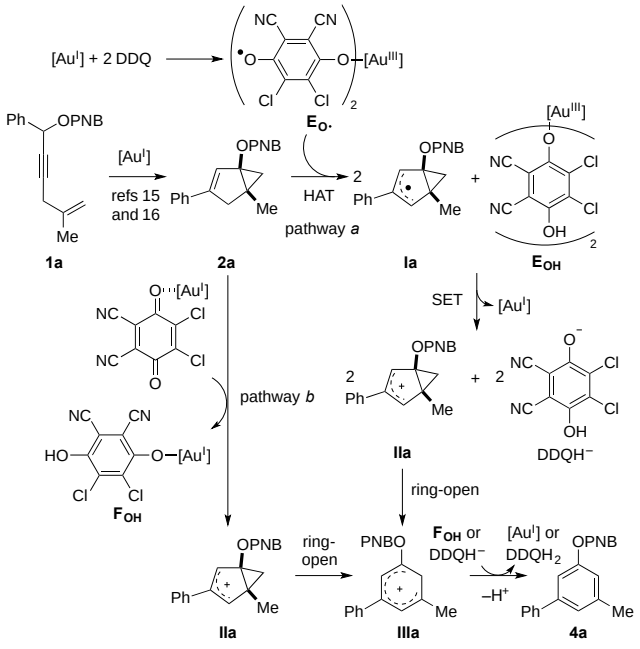
[a]All reactions were performed using 0.2 mmol of **2a**, in the presence or absence of 2 mol % of catalyst, DDQ (0.24 mmol) or NFSI (0.4 mmol) in $(CH_2Cl)_2$ at 80 °C. [b]Isolated product yield. [c]Reaction conducted in the presence of TEMPO (2 equiv). [d]Compound **2a** was recovered in 99% yield.

as a 1.1:1 mixture of regioisomers along with the substrate and **4a** in 31 and 19% yield, respectively.[25,26]



Scheme 5. Control experiment with **2a** in the presence of $TMSN_3$.

On the basis of the above observations, a tentative mechanism for the present Au(I)-catalyzed 1,4-enyne ester dehydrogenative cycloisomerization reaction in the presence of DDQ is illustrated in Scheme 6. With **1a** as a representative example, this initially involves Au(I)-catalyzed tandem [3,3]-rearrangement/ cyclopropanation to produce the bicyclo[3.1.0]hexene **2a**.[15,16] At this juncture, it is thought that the transformation of the bicyclic adduct to the phenolic ester product could proceed through possible competitive pathways *a* or *b*. While highly speculative, pathway *a* might begin with oxidation of the gold(I) catalyst by two molecules of DDQ to provide the gold(III) species $\mathbf{E_O}$..[27,28] As a consequence, this could lead to two molecules of the bicyclic adduct to undergo a hydrogen atom transfer (HAT) process with the *in situ* formed Au(III) complex to afford the



Scheme 6. Proposed mechanism for Au(I)-catalyzed dehydrogenative cycloisomerization of 1,4-enyne esters in the presence of DDQ represented by **1a**.

carboradical species **Ia**.[23] The gold(III) adduct $\mathbf{E_{OH}}$ also formed in this step may trigger further oxidation of **Ia** *via* a single-electron transfer (SET) event. This would give the allylic cation **IIa** and regenerate the Au(I) catalyst along with the two equivalents of $DDQH^-$, which would yield $DDQH_2$ on protonation. Alternatively, as shown in pathway *b* in Scheme 6, the bicyclic carbocation intermediate could be generated as a result of hydride abstraction of **2a** by DDQ.[24] The oxidizing ability of the quinone may be enhanced by the coordination of the Lewis acid to the oxygen center of the oxidant. Protodeauration of the ensuing gold(I) species $\mathbf{F_{OH}}$ would return the Au(I) catalyst and $DDQH_2$. Subsequent electrophilic ring-opening of **IIa** by either of these two possible routes might furnish the carbocationic species **IIIa**. Aromatization of this Wheland-type intermediate would then deliver the 3,5-disubstituted phenolic product **4a**.

Conclusion

In summary, we have developed a strategy for the assembly of a wide variety of 3,5-disubstituted phenol derivatives from gold(I)-catalyzed dehydrogenative cycloisomerization of 1,4-enyne esters in the presence of DDQ or NFSI. The utility of the present method was demonstrated by the scale-up conversion of one example followed by its transformation to the corresponding 3,5-disubstituted phenols with a range of functionalities, which are ubiquitous building blocks in a myriad of bioactive compounds.[2–5] The synthetic application of this approach was also exemplified by modifying one adduct obtained to the biologically active molecule LUF5771, a potent allosteric inhibitor of the human luteinizing hormone receptor.[2] Further exploration of the synthetic applications of the present reaction are currently underway and will be reported in due course.

Experimental Section

Representative Experimental Procedure for Gold(I) Complex A Catalyzed Dehydrogenative Cycloisomerization of 1,4-Enyne Esters (Method A with DDQ as the Oxidant):

To a solution of 1,4-enyne ester **1** (0.3 mmol) and DDQ (0.36 mmol) in 1,2-dichloroethane (6 mL) was added gold(I) catalyst **A** (6 μmol) under an argon atmosphere. The reaction mixture was stirred at 80 °C for 4 h. Upon completion, the reaction mixture was cooled to room temperature and filtered through Celite, washed with CH_2Cl_2 (10 mL) and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (petroleum ether:EtOAc:CH_2Cl_2 = 50:1:1 as eluent) to give the title compound.

Representative Experimental Procedure for Gold(I) Complex A Catalyzed Dehydrogenative Cycloisomerization of 1,4-Enyne Esters (Method B with NFSI as the Oxidant):

To a solution of 1,4-enyne ester **1** (0.3 mmol) and NFSI (0.6 mmol) in 1,2-dichloroethane (6 mL) was added gold(I) catalyst **A** (6 μmol) under an argon atmosphere. The reaction mixture was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (petroleum ether:EtOAc:CH_2Cl_2 = 50:1:1 as eluent) to give title compound.

5-methyl-[1,1'-biphenyl]-3-yl 4-nitrobenzoate (4a):

Yield: 99 mg, 99% (Method A). Colorless solid; mp 101-103 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.50 (s, 3H), 7.07 (s, 1H), 7.29 (d, 1H, J = 1.9 Hz), 7.38-7.42 (m, 2H), 7.46-7.49 (m, 2H), 7.62-7.64 (m, 2H), 8.37-8.44 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6, 117.3, 120.8, 123.8, 126.1, 127.2, 127.8, 128.9, 131.3, 135.0, 140.1, 140.2, 142.9, 150.8, 150.9, 163.5. IR (KBr) ν: 3109, 1735, 1528, 1266, 1085, 713 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{15}NO_4Na$ $[M+Na]^+$: 356.0899, found: 356.0894.

5-methyl-[1,1'-biphenyl]-3-yl acetate (4b):

Yield: 50.2 mg, 74% (Method A). Pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.33 (s, 3H), 2.43 (s, 3H), 6.91 (s, 1H), 7.12 (s, 1H), 7.29 (s, 1H), 7.35 (t, 1H, J = 7.3 Hz), 7.43 (t, 2H, J = 7.5 Hz), 7.57 (d, 2H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.2, 21.5, 117.5, 121.0, 125.6, 127.2, 127.6, 128.8, 139.9, 140.4, 142.6, 151.0, 169.6. IR (neat) ν: 3034, 2921, 1769, 1614, 1208, 1019, 762 cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1072, found: 227.1077.

5-(phenoxymethyl)-[1,1'-biphenyl]-3-yl 4-nitrobenzoate (4c):

Yield: 92 mg, 72% (Method A). Yellow solid; mp 80-82 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.18 (s, 2H), 7.01 (dt, 3H, J = 15.1, 4.1 Hz), 7.28-7.37 (m, 3H), 7.40 (m, 1H), 7.42-7.50 (m, 3H), 7.62 (dd, 3H, J = 5.6, 3.8 Hz), 8.34-8.45 (m, 4H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 69.3, 114.9, 119.0, 119.7, 121.3, 123.8, 123.9, 127.3, 128.0, 128.9, 129.6, 131.4, 134.9, 139.7, 139.8, 143.4, 151.0, 151.2, 158.6, 163.3. IR (KBr) ν: 3461, 3112, 1742, 1518, 1259, 1078, 715 cm^{-1}. HRMS (ESI) calcd for $C_{26}H_{19}NO_5Na$ $[M+Na]^+$: 448.1161, found: 448.1161.

5-(acetoxymethyl)-[1,1'-biphenyl]-3-yl 4-nitrobenzoate (4d):

Yield: 54 mg, 46% (Method B). Pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.14 (s, 3H), 5.21 (s, 2H), 7.24 (s, 1H), 7.35-7.49 (m, 4H), 7.53 (s, 1H), 7.56-7.64 (m, 2H), 8.33-8.45 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.0, 65.6, 119.8, 120.0, 123.8, 124.9, 127.2, 128.1, 129.0, 131.4, 134.8, 138.3, 139.6, 143.5, 151.0, 163.3, 170.8. IR (neat) ν: 3460, 3113, 1742, 1526, 1262, 1081, 716, 544 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{17}NO_6Na$ $[M+Na]^+$: 414.0954, found: 414.0959.

2-methyl-2-((5-((4-nitrobenzoyl)oxy)-[1,1'-biphenyl]-3-yl)methyl)malonate (4e):

Yield: 110.7 mg, 73% (Method A). Colorless solid; mp 75-76 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.25 (t, J = 7.1 Hz, 6H), 1.43 (s, 3H), 3.33 (s, 2H), 4.21 (q, 4H, J = 7.1 Hz), 7.04 (s, 1H), 7.31 (s, 1H), 7.32 (s, 1H),7.37 (t, 1H, J = 7.4 Hz), 7.44 (t, 2H, J = 7.6 Hz), 7.52-7.60 (m, 2H), 8.32-8.44 (m, 4H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.0, 20.0, 41.1, 54.9, 61.5, 118.7, 122.0, 123.8, 127.2, 127.9, 128.9, 131.3, 135.0, 142.8, 150.7, 151.0, 163.2, 171.8. IR (KBr) ν: 3413, 3116,1736, 1613, 1524, 1267, 1097, 711 cm^{-1}. HRMS (ESI) calcd for $C_{28}H_{28}NO_8$ $[M+H]^+$: 506.1815, found: 506.1822.

5-(((4-methyl-N-phenylphenyl)sulfonamido)methyl)-[1,1'-biphenyl]-3-yl acetate (4f):

Yield: 137.2 mg, 97% (Method A). Pale-yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.29 (s, 3H), 2.44 (s, 3H), 4.78 (s, 2H), 7.00-7.05 (m, 3H), 7.15 (t, 1H, J = 1.8 Hz), 7.22-7.25 (m, 3H), 7.28 (d, 3H, J = 1.4 Hz), 7.32-7.34 (m, 1H), 7.40 (t, 2H, J = 7.3 Hz), 7.42-7.46 (m, 2H), 7.56 (d, 2H, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.2, 21.6, 54.6, 119.6, 120.5, 124.6, 127.1, 127.8, 128.1, 128.8, 129.0, 129.1, 129.6, 135.5, 138.2, 139.0, 139.7, 142.7, 143.7, 151.1, 169.5. IR (neat) ν: 3131, 1766, 1595, 1400, 1206, 1163, 696 cm^{-1}. HRMS (ESI) calcd for $C_{28}H_{25}NO_4SNa$ $[M+Na]^+$: 494.1402, found: 494.1402.

4',5-dimethyl-[1,1'-biphenyl]-3-yl 4-nitrobenzoate (4g):

Yield: 102 mg, 98% (Method A). Pale-yellow solid; mp 124-126 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.43 (s, 3H), 2.49 (s, 3H), 7.04 (s, 1H), 7.28 (d, 3H, J = 8.4 Hz,), 7.37 (s, 1H), 7.52 (d, 2H, J = 8.1 Hz), 8.37-8.43 (m, 4H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.1, 21.5, 117.0, 120.5, 123.7, 125.9, 127.0, 129.6, 131.3, 135.1, 137.2, 137.6, 140.1, 142.8, 150.9, 150.9, 163.5. IR (KBr) ν: 3458, 3117, 1739, 1523, 1349, 1262, 1085, 711 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{17}NO_4Na$ $[M+Na]^+$: 370.1055, found: 370.1049.

4'-bromo-5-methyl-[1,1'-biphenyl]-3-yl 4-nitrobenzoate (4h):

Yield: 108.7 mg, 96% (Method A). Colorless solid; mp 105-107 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.47 (s, 3H), 7.06 (s, 1H), 7.22 (t, 1H, J = 1.5 Hz), 7.31 (d, 1H, J = 0.5 Hz), 7.42-7.48 (m, 2H), 7.52-7.60 (m, 2H), 8.32-8.42 (m, 4H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.5, 117.1, 121.2, 122.1, 123.8, 125.8, 128.8, 131.3, 132.0, 134.9, 139.0, 140.5, 141.6, 151.0, 163.4. IR (KBr) ν: 3450, 3166, 1736, 1527, 1265, 1091, 806, 712 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{14}NO_4{}^{79}BrNa$ $[M+Na]^+$: 434.0004, found: 434.0007.

5-methyl-[1,1':4',1''-terphenyl]-3-yl 4-nitrobenzoate (4i):

Yield: 111.8 mg, 91% (Method A). Yellow solid; mp 168-171 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.49 (s, 3H), 7.06 (s, 1H), 7.31 (s, 1H), 7.34-7.40 (m, 1H), 7.42 (s, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.61-7.72 (m, 6H), 8.34-8.44 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6, 117.1, 120.9, 123.8, 125.9, 127.1, 127.5, 127.6, 128.9, 131.3, 135.0, 139.0, 140.3, 140.5, 140.6, 142.4, 150.9, 163.5. IR (KBr) ν: 3116, 1729, 1525, 1261, 840, 712 cm^{-1}. HRMS (ESI) calcd for $C_{26}H_{20}NO_4$ $[M+H]^+$: 410.1392, found: 410.1392.

2'-bromo-5-methyl-[1,1'-biphenyl]-3-yl 4-nitrobenzoate (4j):

Yield: 113.8 mg, 92% (Method A). Colorless solid; mp 126-128 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.47 (s, 3H), 7.06 (s, 1H), 7.22 (t, 1H, J = 1.5 Hz), 7.31 (d, 1H, J = 0.5 Hz), 7.42-7.48 (m, 2H), 7.52-7.60 (m, 2H),8.32-8.42 (m, 4H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.5, 117.1, 121.2, 122.1, 123.8, 125.8, 128.8, 131.3, 132.0, 134.9, 139.0, 140.5, 141.6, 151.0, 163.4. IR (KBr) ν: 3449, 3166, 1736, 1527, 1336, 1265, 1092, 712 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{14}NO_4{}^{79}BrNa$ $[M+Na]^+$: 434.0004, found: 434.0011.

2'-iodo-5-methyl-[1,1'-biphenyl]-3-yl 4-nitrobenzoate (4k):

Yield: 120 mg, 87% (Method A). Colorless solid; mp 156-159 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.46 (s, 3H), 7.02-7.07 (m, 2H), 7.10 (s, 2H), 7.33 (dd, 1H, J = 7.6, 1.5 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.95 (d, 1H, J = 7.9 Hz), 8.37 (q, J = 8.9 Hz, 4H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.4, 98.2, 119.6, 121.2, 123.8, 128.2, 128.2, 129.1, 130.1, 131.3, 135.0, 139.6, 145.5, 145.5, 149.9, 150.9, 163.3. IR (KBr) ν: 3421, 3130, 1743, 1522, 1256, 1077, 764, 713 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{14}INO_4Na$ $[M+Na]^+$: 481.9865, found: 481.9871.

3-(6-bromobenzo[d][1,3]dioxol-5-yl)-5-methylphenyl 4-nitrobenzoate (4l):

Yield: 115 mg, 84% (Method A). Colorless solid; mp 150-152 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.44 (s, 3H), 6.02 (s, 2H), 6.83 (s, 1H), 7.06 (d, 2H, J = 0.7 Hz), 7.07-7.13 (m, 2H), 8.31-8.42 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 102.0, 110.8, 113.0, 113.0, 119.8, 121.1, 123.7, 128.4, 131.3, 134.7, 135.0, 139.6, 142.4, 147.4, 147.9, 150.0, 150.9, 163.3. IR (KBr) ν: 3109, 1743, 1519, 1260, 1233, 1081, 869, 716 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{15}NO_6{}^{79}Br$ $[M+H]^+$: 456.0083, found: 456.0088.

2'-bromo-4',5'-dimethoxy-5-methyl-[1,1'-biphenyl]-3-yl 4-nitrobenzoate (4m):

Yield: 120 mg, 85% (Method A). Colorless solid; mp 183-185 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.46 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 6.85 (s, 1H), 7.06 (s, 1H), 7.09 (s, 1H), 7.11 (s, 1H), 7.15 (d, 1H, J = 0.6 Hz), 8.33-8.41 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 56.2, 56.3, 112.4, 113.8, 115.8, 119.8, 121.0, 123.7, 128.4, 131.3, 133.6, 135.0, 139.6, 142.5, 148.3, 149.0, 150.0, 150.9, 163.4. IR (KBr) ν: 3413, 3109, 1741, 1524, 1248, 1139, 714 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{19}NO_6{}^{79}Br$ $[M+H]^+$: 472.0396, found: 472.0393.

3-methyl-5-(naphthalen-1-yl)phenyl 4-nitrobenzoate (4n):

Yield: 113.9 mg, 99% (Method A). Pale-yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.50 (s, 3H), 7.14 (s, 1H), 7.19 (s, 1H), 7.28 (s, 1H), 7.43-7.55 (m, 4H), 7.88 (d, 1H, J = 8.2 Hz), 7.91 (d, 1H, J = 7.7 Hz), 7.96 (d, 1H, J = 8.3 Hz), 8.32-8.37 (m, 2H), 8.37-8.42 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.5, 120.2, 120.9, 123.7, 125.3, 125.8, 125.9, 126.3, 127.0, 128.1, 128.4, 129.0, 131.3, 131.4, 133.8, 135.0, 139.1, 139.8, 142.3, 150.4, 150.9, 163.4; IR (neat) ν: 3114, 1741, 1526, 1397, 1263, 1082, 778, 714 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{17}NO_4Na$ $[M+Na]^+$: 406.1055, found: 406.1055.

3-methyl-5-(naphthalen-2-yl)phenyl 4-nitrobenzoate (4o):

Yield: 104.7 mg, 91% (Method A). Pale-yellow solid; mp 154-156 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.51 (s, 3H), 7.08 (s, 1H), 7.40 (s, 1H), 7.47-7.55 (m, 3H), 7.74 (dd, 1H, J = 8.5, 1.8 Hz), 7.85-7.95 (m, 3H), 8.06 (d, 1H, J = 1.1 Hz), 8.32-8.44 (m, 4H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.6, 117.5, 120.9, 123.8, 125.4, 126.0, 126.2, 126.3, 126.5, 127.7, 128.3, 128.6, 131.3, 132.8, 133.6, 135.0, 137.4, 140.3, 142.8, 150.9, 151.0, 163.5. IR (KBr) ν: 3125, 1741, 1523, 1256, 1080, 713 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{17}NO_4Na$ $[M+Na]^+$: 406.1055, found: 406.1057.

3-methyl-5-(1-tosyl-1*H*-indol-3-yl)phenyl 4-nitrobenzoate (4p):

Yield: 98 mg, 62% (Method A). Pale-yellow solid; mp 129-131 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.34 (s, 3H), 2.47 (s, 3H), 7.06 (s, 1H), 7.18-7.41 (m, 6H), 7.73 (s, 1H), 7.80 (t, 3H, J = 7.6 Hz), 8.06 (d, 1H, J = 8.2 Hz), 8.28-8.46 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 21.6, 113.9, 117.9, 120.3, 121.1, 122.9, 123.4, 123.7, 123.8, 125.1, 126.7, 126.9, 129.0, 130.0, 131.3, 134.6, 134.9, 135.1, 135.5, 140.5, 145.2, 150.9, 163.5. IR (KBr) ν: 3123, 1740, 1524, 1374, 1264, 1175, 682, 577 cm^{-1}. HRMS (ESI) calcd for $C_{29}H_{22}N_2O_6SNa$ $[M+Na]^+$: 549.1096, found: 549.1087.

[1,1':3',1''-terphenyl]-5'-yl 4-nitrobenzoate (4q):

Yield: 80.7 mg, 68% (Method B). Pale-yellow solid; mp 133-135 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.53 (m, 8H), 7.62-7.71 (m, 4H), 7.77 (t, 1H, J = 1.5 Hz), 8.34-8.48 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 118.9, 123.8, 124.1, 127.3, 128.0, 129.0, 131.4, 134.9, 140.0, 143.5, 151.0, 151.3, 163.4. IR (KBr) ν: 3108, 1744, 1521, 1258, 1082, 756 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{17}NO_4Na$ $[M+Na]^+$: 418.1055, found: 418.1055.

3-cyclopropyl-5-methylphenyl 4-nitrobenzoate (4r):

Yield: 68.7 mg, 77% (Method A). Colorless solid; mp 77-79 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.64-0.77 (m, 2H), 0.96-1.00 (m, 2H), 1.87-1.92 (m, 1H), 2.35 (s, 3H), 6.71 (s, 1H), 6.83 (d, 2H, J = 11.4 Hz), 8.28-8.41 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.4, 15.3, 21.4, 115.6, 119.0, 123.7, 124.8, 131.2, 135.2, 139.6, 146.1, 150.6, 150.9, 163.5. IR (KBr) ν: 3110, 1737, 1519, 1268, 1089, 715 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{15}NO_4Na$ $[M+Na]^+$: 320.0899, found: 320.0891.

3-cyclopentyl-5-methylphenyl 4-nitrobenzoate (4s):

Yield: 58.6 mg, 60% (Method B). Colorless solid; mp 103-105 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.89-1.54 (m, 6H), 2.02-2.13 (m, 2H), 2.37 (s, 3H), 2.92-3.06 (m, 1H), 6.86 (s, 1H), 6.89 (s, 1H), 7.00 (s, 1H), 8.31-8.42 (m, 4H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 25.5, 34.5, 45.7, 116.9, 119.2, 123.7, 126.2, 131.3, 135.2, 139.5, 148.5, 150.5, 150.9, 163.5. IR (KBr) ν: 2924, 1745, 1521, 1263, 1087, 871, 711 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{19}NO_4Na$ $[M+Na]^+$: 348.1212, found: 348.1215.

3-cyclohexyl-5-methylphenyl 4-nitrobenzoate (4t):

Yield: 62.1 mg, 61% (Method B). Colorless solid; mp 97-99 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.18-1.32 (m, 2H), 1.32-1.46 (m, 4H), 1.70-1.78 (m, 1H), 1.80-1.94 (m, 4H), 2.38 (s, 3H), 2.48-2.53 (m, 1H), 6.87 (d, 2H, J = 2.0 Hz), 6.97 (s, 1H), 8.29-8.42 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 26.1, 26.8, 34.4, 44.4, 76.7, 77.0, 77.4, 116.7, 119.3, 123.7, 125.9, 131.2, 135.3, 139.5, 149.9, 150.5, 150.9, 163.5. IR (KBr) ν: 3118, 2925, 1741, 1516, 1258, 1088, 712 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$: 340.1549, found: 340.1552.

3-methyl-5-(pentan-3-yl)phenyl 4-nitrobenzoate (4u):

Yield: 72.7 mg, 74% (Method A). Pale-yellow solid; mp 74-76 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.81 (t, 6H, J = 7.4 Hz), 1.52-1.60 (m, 2H), 1.66-1.73 (m, 2H), 2.30-2.35 (m, 1H), 2.38 (s, 3H), 6.80 (s, 1H), 6.88 (s, 1H), 6.90 (s, 1H), 8.33-8.41 (m, 4H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 12.2, 21.5, 29.2, 49.6, 117.5, 119.3, 123.7, 126.9, 131.2, 135.3, 139.4, 147.8, 150.5, 150.8, 163.4. IR (KBr) ν: 3115, 1733, 1529, 1348, 1267, 712 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{22}NO_4$ $[M+H]^+$: 328.1549, found: 328.1541.

3-methyl-5-(3-phenylpropyl)phenyl 4-nitrobenzoate (4v):

Yield: 72.1 mg, 64% (Method A). Pale-yellow solid; mp 53-55 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.92-2.08 (m, 2H), 2.69 (q, 4H, J =14.6 Hz), 6.90 (d, 2H, J = 5.2 Hz), 6.98 (s, 1H), 7.16-7.38 (m, 5H), 8.31-8.46 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 32.7, 35.2, 35.5, 118.3, 119.4, 123.7, 125.9, 127.5, 128.4, 128.5, 131.3, 135.2, 139.7, 142.1, 144.1, 150.6, 150.9, 163.5. IR (KBr) ν: 2932, 1731, 1522, 1264, 1087, 869, 714 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{21}NO_4Na$ $[M+Na]^+$: 398.1368, found: 398.1372.

3-hexyl-5-methylphenyl 4-nitrobenzoate (4w):

Yield: 61.5 mg, 60% (Method B). Pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, 3H, J = 6.7 Hz), 1.25-1.41 (m, 6H), 1.56-1.68 (m, 2H), 2.37 (s, 3H), 2.56-2.66 (m, 2H), 6.86 (d, 2H, J = 4.1 Hz), 6.95 (s, 1H), 8.32-8.40 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 21.4, 22.6, 29.0, 31.2, 31.7, 35.8, 118.2, 119.1, 123.7, 127.4, 131.2, 135.2, 139.5, 144.8, 150.5, 150.8, 163.5. IR (neat) ν: 3121, 2926, 1744,

1529, 1259, 1140, 712 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{23}NO_4Na$ $[M+Na]^+$: 364.1525, found: 364.1525.

5,5''-dimethyl-[1,1':4',1''-terphenyl]-3,3''-diyl diacetate (4x):

Yield: 59.5 mg, 53% (Method A). Pale-yellow solid; mp 174-176 °C. ^1H NMR ($CDCl_3$, 600 MHz): δ 2.33 (s, 6H), 2.44 (s, 6H), 6.92 (s, 2H), 7.16 (s, 2H), 7.32 (s, 2H), 7.63 (s, 4H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.2, 21.5, 117.3, 121.2, 125.4, 127.5, 139.5, 140.0, 142.0, 151.1, 169.7. IR (KBr) ν: 3128, 1752, 1587, 1399, 1216, 1144, 841 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{22}O_4Na$ $[M+Na]^+$: 397.1416, found: 397.1408.

((1*R*,3*aS*,5*aR*,5*bR*,7*aR*,9*S*,11*aR*,11*bR*,13*aR*,13*bR*)-9-acetoxy-1-(5-acetoxy-[1,1'-biphenyl]-3-yl)-5a,5b,8,8,11a-pentamethylicosahydro-3aH-cyclopenta[a]chrysen-3a-yl)methyl acetate (4y):

Yield: 196.5 mg, 94% (Method A). Pale-yellow solid; mp 161-163 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.52-0.67 (m, 1H), 0.67-0.92 (m, 10H), 0.93 (s, 3H), 0.99-1.29 (m, 9H), 1.29-1.46 (m, 6H), 1.47-1.83 (m, 6H), 1.86-1.95 (m, 3H), 2.03 (s, 3H), 2.10 (s, 3H), 2.32 (s, 4H), 2.87-2.94 (m, 1H), 3.95 (d, 1H, J = 11.0 Hz), 4.32 (d, 1H, J = 10.9 Hz), 4.42 (t, 1H, J = 7.6 Hz), 6.90 (s, 1H), 7.11 (t, 1H, J = 1.8 Hz), 7.27 (s, 1H), 7.33-7.37 (m, 1H), 7.43 (t, 2H, J = 7.5 Hz), 7.51-7.61 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.7, 16.0, 16.1, 18.2, 20.8, 21.1, 21.3, 21.3, 23.7, 27.0, 27.1, 28.0, 29.8, 34.1, 34.2, 34.8, 37.0, 37.5, 37.8, 38.3, 40.8, 42.6, 46.5, 46.7, 49.9, 54.2, 55.3, 62.8, 80.9, 117.6, 127.2, 127.6, 128.8, 140.5, 142.5, 150.9, 151.1, 169.4, 171.0, 171.6. IR (KBr) ν: 2948, 1769, 1735, 1455, 1366, 1243, 1029, 763, 701 cm^{-1}. HRMS (ESI) calcd for $C_{45}H_{61}O_6$ $[M+H]^+$: 697.4468, found: 697.4464.

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Gold Catalyzed Dehydrogenative Cycloisomerization of 1,4-Enyne Esters to 3,5-Disubstituted Phenol Derivatives

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