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Synthetic Methods

Gold-Catalyzed Oxidation/C–H Functionalization of Ynones: Efficient and Rapid Access to Functionalized Polycyclic Salicyl Ketones

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Abstract: An efficient strategy to construct salicyl ketones through gold-catalyzed oxidation/C–H functionalization of ynones is reported. A variety of functionalized salicyl ketones are readily accessed by utilizing this non-diazo approach, thus providing a viable alternative to synthetically useful salicyl ketones with a yield up to 98%. The α-oxo gold carbenes generated in situ through gold-catalyzed oxidation of ynones can be trapped effectively by internal aryl and heteroaromatic groups. Electronic and steric effects were also investigated in this reaction. The anticancer activity of one salicyl ketone analogue was investigated and its cytotoxicity assays against the PC-3 prostate cancer cell line and SKOV-3 human ovarian carcinoma cell line yield IC_{50} were 0.81 ± 0.05 and 0.87 ± 0.15 μM, respectively, demonstrating that salicyl ketone analogues showed good anticancer activity.

Introduction

The salicyl group is an important motif in natural products and biologically active molecules (Figure 1).[1] Salicyl analogues as pharmocologically interesting compounds are also potentially useful precursors for a variety of functional group transformations and drug discovery programs. In this context, the development of efficient methods to synthesis functionalized aromatic salicyl derivatives with selective control of substitution patterns continues to be actively pursued.

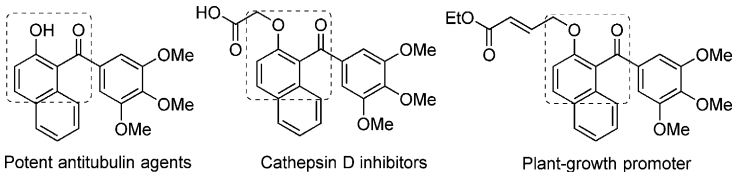

Figure 1. Biologically active molecules containing the salicyl group

Recently, gold-catalyzed alkyne oxidations using pyridine/quinoline *N*-oxides as oxidants for the generation of α-oxo gold-carbene/carbenoid intermediates to synthesize various useful molecules were reported.[2] This strategy is safe, green, and represents a promising alternative to the generation of α-oxo metal carbenes from the hazardous and potentially explosive α-diazo ketone precursors.[3–11] Ynones are electron-deficient alkynes in which the C≡C triple bond is polarized substantially by the carbonyl group, which causes the distal end of the ynone to be significantly more electron-deficient than the proximal end, thereby inviting preferential attack by approaching nucleophiles (Scheme 1, Eq. (1)).[6,12,13] The strategy of gold-catalyzed oxidation of ynones has also been developed with the generated α-oxo gold carbene intermediates trapped in situ by relatively electron-rich nucleophiles, such as oxygen and C=C double bonds.[12] Recently, Zhang and co-workers reported gold(I)-catalyzed intramolecular oxidation-cyclopropanation of 1,6-enynes to [*n*.1.0]bicycloalkanes with the C=C double bonds trapping the α-oxo gold carbene intermediates (Scheme 1, Eq. (2)).[6a,c] Later, Yang and co-workers reported the gold-catalyzed oxidation of ynones to dihydrofuran-3-ones with the oxygen atom trapping the α-oxo gold carbene intermediates using 1.1 equiv of $Yb(OTf)_3$ as co-catalyst (Scheme 1, Eq. (3)).[12a] In contrast, the use of an unactivated aryl sp^2 carbon as a nucleophile to trap the α-oxo gold carbene intermediates efficiently proved to be challenging because of the double oxidation of ynones and other intractable side reactions.[12c] Thus, reports on the successful use of unactivated aryl sp^2 carbon to trap the α-oxo gold carbene generated in situ from ynones are limited. To further develop ynones as surrogates of hazardous α-diazo ketones in gold catalysis, we focused here on expanding the scope of suitable internal nucleophiles such as aryl groups. Our first target was *o*-aryl ynones (Scheme 1, Eq. (4)). Notably, the reaction would offer efficient and rapid access to functionalized polycyclic salicyl ketone analogues under mild conditions.

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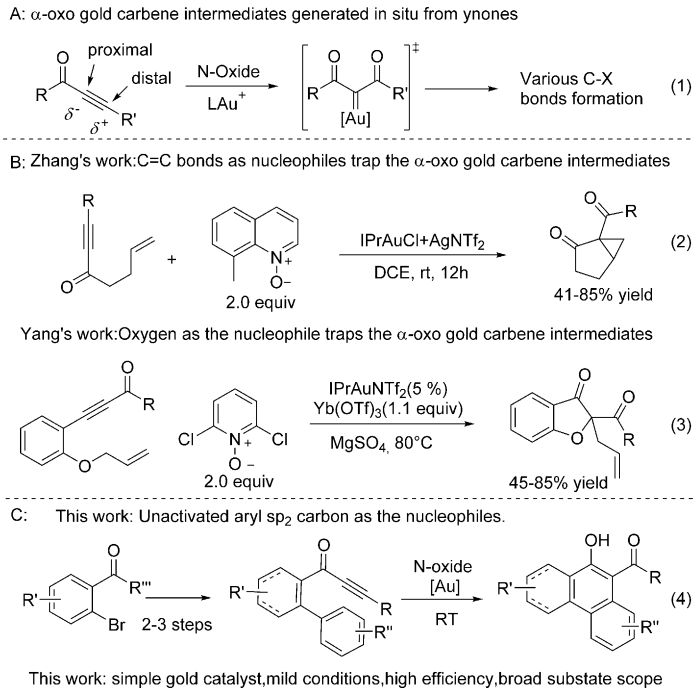


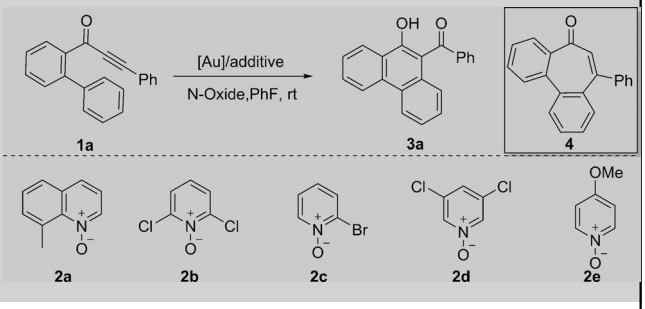
Scheme 1. Design of the reaction from ynones.

Results and Discussion

At the outset, we used *o*-phenyl ynone **1a** and pyridine 1-oxide as the oxidant; the results of optimization studies are shown in Table 1. Initially, we used 0.15 mmol **1a** and *N*-oxide **2a** (1.5 equiv) with $Ph_3PAuNTf_2$ (5 mol%) as catalyst; to our delight, the desired product (10-hydroxyphenanthren-9-yl)(phenyl)methanone (**3a**) was obtained in 98% isolated yield after 3 h in fluorobenzene (PhF) at room temperature, and no 7-phenyl-5*H*-dibenzo[*a*,*c*][7]annulen-5-one (**4**) was observed (entry 1). An alternative *N*-oxide, 2,6-dichloropyridine *N*-oxide (**2b**), was also investigated and this provided a similar result (entry 2). *N*-Oxides **2c**–**e** were also tested, but the results were not improved even after longer reaction time (entries 3–5). Other cationic gold complexes derived from typical ligands such as X-Phos, IPr were less effective (entries 6 and 7). The use of Mor-DalPhosAuNTf$_2$ (5 mol%) also promoted the reaction and gave an excellent yield (entry 8). Gold(III) complexes such as $AuCl_3$ were largely ineffective, resulting in ynone **1a** remaining with little desired product. Other catalysts such as $AgNTf_2$, $Zn(OTf)_2$, $Hg(OTf)_2$, and $PtCl_2$ were also investigated, but were ineffective. Solvent effects were considered through the use of tetrahydrofuran (THF), 1,2-dichloroethane (DCE), and toluene, but no effective solvent was found. Upon decreasing the gold catalyst loading to 2 mol%, an acceptable result (74% yield) was observed after 7 h. No reaction occurred in the absence of $Ph_3PAuNTf_2$.

With the optimized reaction conditions established (Table 1, entry 1), the scope of the transformation was examined with various *o*-phenyl ynones, as shown in Table 2. Thus, a tandem gold-catalyzed oxidation/C–H functionalization of ynones **1a**–**s** proceeded smoothly to provide the corresponding products **3a**–**s** in moderate to excellent yield. The reaction worked well with aromatic R groups. Various electron-donating and electron-withdrawing R groups were tolerated (**1b**–**d**). Steric effects of the R aryl groups was also considered. By installing a methyl or bromide group in the *ortho* position (**1e** vs. **1f**) it was found that the substrate with the *o*-methyl aryl group gave better yield than that with an *o*-bromide aryl group. *O*-Phenyl ynone **1h**, with a heteroaromatic R group, afforded the desired product **3h** in 91% yield. Furthermore, substrates such as **1i**–**j**, with an aliphatic R group, also gave the desired product **3i**–**j** in good yield. Other ynones such as **1k**–**o**, with different R′ group, were also investigated. Substrates such as **1k**, with the methyl R′ group at the *meta*-position, showed excellent selectivity, giving the corresponding product **3k** in 92% yield by selective C–H functionalization of the *para*-sp^2 carbon of the methyl on the phenyl moiety. The relative configuration of the product **3k** was unambiguously assigned by X-ray crystallographic analysis (Figure 2).[14] Other ynones such as **1l**–**m**, with an electron-donating or electron-withdrawing R′ group on the *para*-position, also gave the desired product **3l**–**m** in acceptable yield. Interestingly, instead of *o*-phenyl ynones, ynones

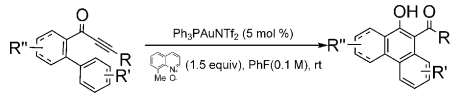
Table 1. Screening conditions.[a]

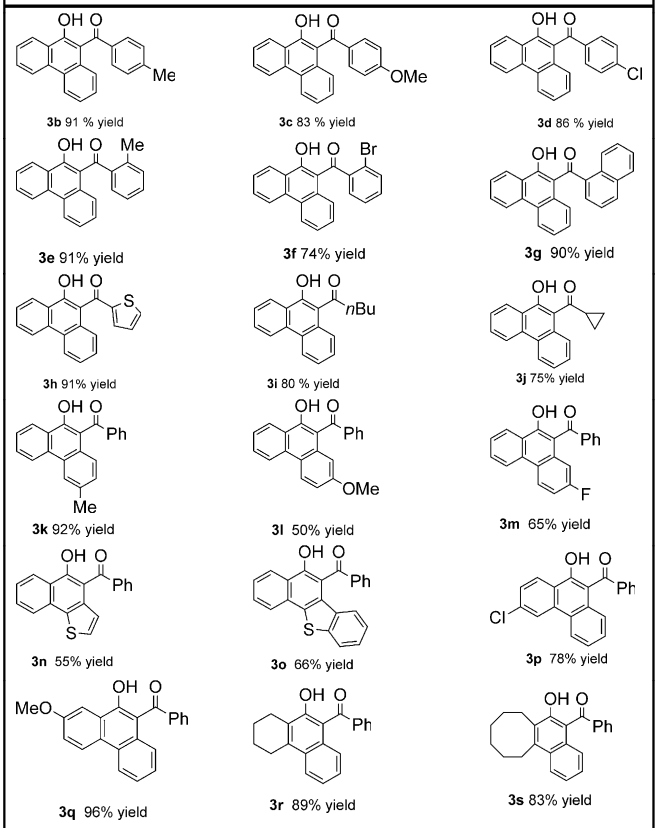


Entry	N-Oxide [equiv]	Catalyst [mol%]	Yield [%][b]
1	**2a** (1.5)	$Ph_3PAuNTf_2$ (5)	98
2	**2b** (1.5)	$Ph_3PAuNTf_2$ (5)	97
3	**2c** (1.5)	$Ph_3PAuNTf_2$ (5)	68
4	**2d** (1.5)	$Ph_3PAuNTf_2$ (5)	70
5	**2e** (1.5)	$Ph_3PAuNTf_2$ (5)	NR
6	**2a** (1.5)	XPhosAuCl (5) + $AgNTf_2$ (5)	81
7	**2a** (1.5)	IPrAuCl (5) + $AgNTf_2$ (5)	62
8	**2a** (1.5)	Mor-DelPhosAuNTf$_2$ (5)	92
9	**2a** (1.5)	$AuCl_3$ (5)	<10[c]
10	**2a** (1.5)	$AgNTf_2$ (5)	NR
11	**2a** (1.5)	$Ph_3PAuNTf_2$ (5)	71[d]
12	**2a** (1.5)	$Ph_3PAuNTf_2$ (5)	79[e]
13	**2a** (1.5)	$Ph_3PAuNTf_2$ (5)	64[f]
14	**2a** (1.5)	$Ph_3PAuNTf_2$ (2)	74[g]
15	**2a** (1.5)	–	NR
16	**2a** (1.5)	$Zn(OTf)_2$ (5)	NR
17	**2a** (1.5)	$Hg(OTf)_2$ (5)	trace
18	**2a** (1.5)	$PtCl_2$ (5)	NR

[a] Reaction was run with everything in a vial capped with a septum; initially, [**1a**] = 0.1 M. [b] Isolated yield. [c] 30% Conversion based on SM. [d] Solvent DCE. [e] Solvent toluene. [f] Solvent THF. [g] Reaction time 7 h.

Table 2. Scope of polycyclic salicyl ketones **3**.[a]





[a] Initially, [**1**] = 0.1 M. The reactions were run under the standard conditions, unless otherwise specified. [b] Yields of isolated products are shown.

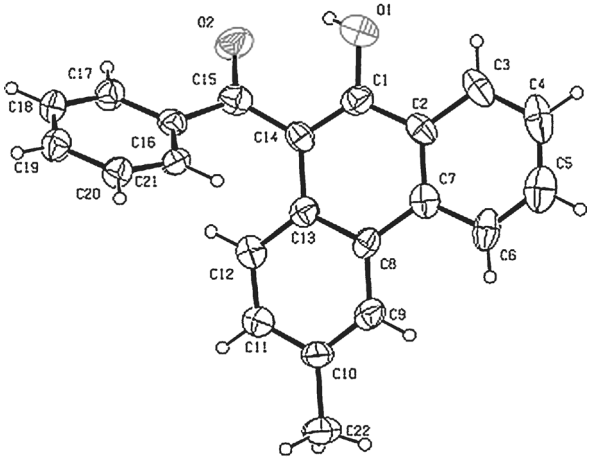
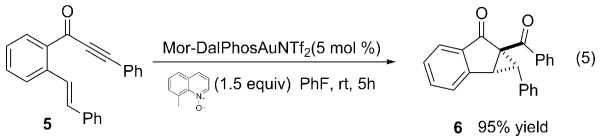


Figure 2. X-ray structure of **3k**.[14]

1n–o, with a heteroaromatic group such as thiophene andbenzo[*b*]thiophene on the *ortho*-position, were also C–H functionalized selectively to afford the corresponding products **3n–o** in acceptable yield. Ynones such as **1p–q**, with different R′′ group were also studied and the substrates with different electron-donating and electron-withdrawing R′′ groups proceeded smoothly to provide the corresponding products **3p–q** in moderate to excellent yield. Considering other synthetically useful transformations, ynones such as **1r–s**, with different aliphatic groups, were also tested and the reaction worked well to afford **3r–s** in good yield.

To gather additional experimental evidence for the mechanism, we examined the direct conversion of ynone **5** by installing an alkene group on the *ortho*-position in the presence of 5 mol% of Mor-DalPhosAuNTf$_2$. To our delight, this reaction worked well and afforded 6a-benzoyl-1-phenyl-1a,6a-dihydrocyclopropa[*a*]inden-6(1*H*)-one (**6**) in 95% yield with the C=C double bond trapping the α-oxo gold carbene intermediate (Eq. (5)).



(5)

On the basis of the above observations, we propose the following plausible mechanisms for this transformation (Figure 3). 1) Coordination of the ynone moiety with the cationic gold complex and attack of the N-oxide on the distal end of the ynone gives complex A. 2) Gold complex back donation of an electron removes the pyridine to give the α-oxo gold carbene intermediate B, followed by internal aryl sp^2 carbon trapping to afford intermediate C. 3) Intermediate C releases the cationic gold complex to afford product **3** through aryl isomerization.

The anticancer activity of salicyl ketone analogue **3c** was investigated and its cytotoxicity assays against the PC-3 prostate cancer cell line and SKOV-3 human ovarian carcinoma cell line

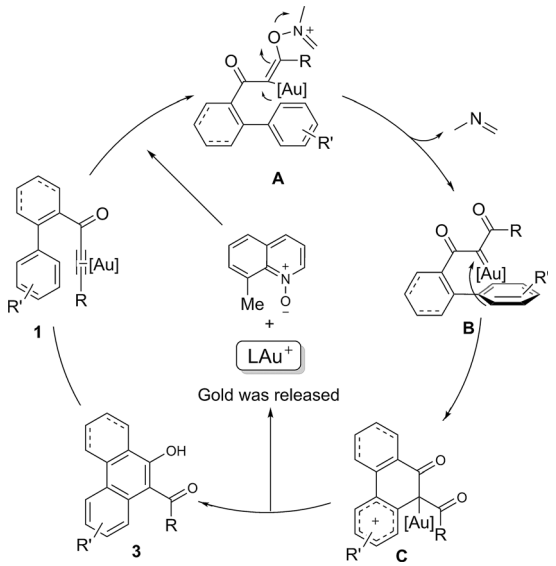


Figure 3. Proposed mechanism.

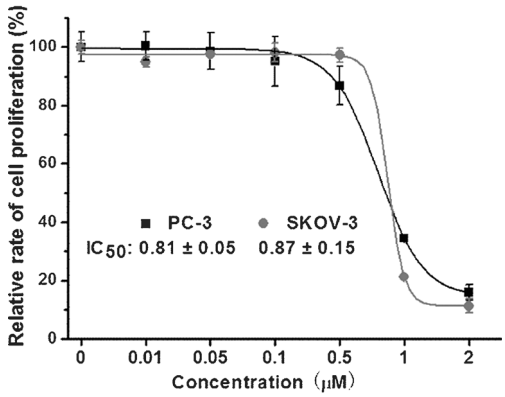


Figure 4. Salicyl ketone analogue **3c** reduces the proliferation of cancer cells. The IC_{50} values represent the concentration resulting in 50% inhibition of cell proliferation. Cells were grown and treated with **3c** at 0–2 μM, PC-3 cells for 48 h, and SKOV-3 cells for 72 h. All data (mean ± SD) are the average of three determinations.

indicated IC_{50} values of 0.81 ± 0.05 and 0.87 ± 0.15 μM, respectively, demonstrating that the salicyl ketone analogues exhibit good anticancer activity (Figure 4).

Conclusion

We have described an efficient strategy to construct salicyl ketones through gold-catalyzed oxidation/C–H functionalization of ynones. A variety of functionalized salicyl ketones are readily accessed by utilizing this non-diazo approach, thus providing a viable alternative route to synthetically useful salicyl ketones. The anticancer activity of salicyl ketone analogue **3c** against the PC-3 and prostate cancer cell line and SKOV-3 human ovarian carcinoma cell line was also investigated and showed good biological activity.

Experimental Section

General experimental details: Column chromatography was carried out on silica gel. Unless noted, ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$ with trimethylsilane (TMS) as internal standard. IR spectra were recorded with a FTIR spectrometer, and only the major peaks are reported (in cm^{-1}). Melting points were determined with a microscopic apparatus and are uncorrected. All new compounds were further characterized by elemental analysis or high-resolution mass spectrometry (HRMS); copies of their ^{1}H and ^{13}C NMR spectra are provided in the Supporting Information. Detailed data of **3k** and X-ray crystallographic studies of **3k** are also provided. Commercially available reagents and solvents were used without further purification. THF was distilled immediately prior to use.

General procedure A: Gold-catalyzed oxidation/C–H functionalization of ynones to functionalized polycyclic salicyl ketones **3**. To a 3 dram vial containing 3 mL of PhF were added sequentially ynone **1a–s** (0.15 mmol), 8-methylquinoline *N*-oxide **2a** (29 mg, 0.225 mmol, 1.2 equiv), and $Ph_3PAuNTf_2$ (5.5 mg, 0.003 mmol). The resulting mixture was stirred at 25 °C or the indicated temperature, and the progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated under vacuum. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate) to afford the desired (10-hydroxyphenanthren-9-yl)(phenyl)methanone **3a–s**.

(10-Hydroxyphenanthren-9-yl)(phenyl)methanone (3a): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.75 (s, 1H), 8.60 (dd, J = 11.2, 4.3 Hz, 2H), 8.53 (d, J = 8.2 Hz, 1H), 7.86–7.76 (m, 1H), 7.69 (dd, J = 11.6, 4.5 Hz, 1H), 7.66–7.61 (m, 2H), 7.56–7.51 (m, 1H), 7.42–7.33 (m, 4H), 7.18 ppm (qd, J = 7.0, 3.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 200.19, 160.64, 140.34, 133.99, 132.41, 130.59, 130.25, 129.42, 128.45, 127.65, 127.08, 126.13, 125.89, 125.21, 125.05, 124.40, 122.83, 122.59, 110.97 ppm; IR (neat): $\tilde{\nu}$ = 1617, 1447, 1305, 1010, 753, 722 cm^{-1}; HRMS: *m/z* calcd for $C_{21}H_{15}O_2^+$: 299.1067 [*M*+H$^+$]; found: 299.1069.

General procedure B: Gold-catalyzed oxidation/cyclopropanation of ynone **5** to 6a-benzoyl-1-phenyl-1a, 6a-dihydrocyclopropa[*a*]inden-6(1*H*)-one (**6**). To a 3 dram vial containing 3 mL of PhF were added sequentially the ynone **5** (0.15 mmol), 8-methylquinoline *N*-oxide *N*-oxide **2a** (29 mg, 0.225 mmol, 1.2 equiv), and Mor-DalPhosAuNTf$_2$ (6.9 mg, 0.003 mmol). The resulting mixture was stirred at 25 °C and the progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated under vacuum. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate) to afford the desired 6a-benzoyl-1-phenyl-1a, 6a-dihydrocyclopropa[*a*]inden-6(1*H*)-one (**6**).

6a-Benzoyl-1-phenyl-1a,6a-dihydrocyclopropa[*a*]inden-6(1*H*)-one (6): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92–7.86 (m, 2H), 7.75 (d, J = 7.6 Hz, 1H), 7.61–7.55 (m, 2H), 7.49–7.44 (m, 1H), 7.41–7.33 (m, 3H), 7.17–7.09 (m, 5H), 4.13 (d, J = 4.3 Hz, 1H), 3.24 ppm (d, J = 4.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 195.36, 191.42, 151.67, 136.72, 134.43, 134.08, 133.98, 133.37, 130.25, 128.36, 127.94, 127.81, 127.71, 127.36, 125.62, 125.01, 57.17, 53.83, 30.73 ppm. IR (neat): $\tilde{\nu}$ = 1711, 1658, 1347, 1009, 752, 684 cm^{-1}; HRMS: *m/z* calcd for $C_{23}H_{17}O_2^+$: 325.1223 [*M*+H$^+$]; found: 325.1225.

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Keywords: antitumor agents · carbenes · C–H activation · gold · oxidation

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[14] CCDC 1443325 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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FULL PAPER

Synthetic Methods

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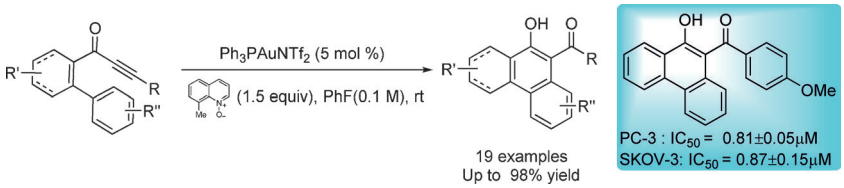
Gold-Catalyzed Oxidation/C–H Functionalization of Ynones: Efficient and Rapid Access to Functionalized Polycyclic Salicyl Ketones



A golden route: An efficient strategy to construct salicyl ketones through gold-catalyzed oxidation/C–H functionalization of ynones is reported (see scheme). A variety of functionalized salicyl ketones are readily accessed by utilizing this non-diazo approach, thus providing a viable alternative to synthetically useful salicyl ketones.