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Gold-Catalyzed Hydration of Haloalkynes to α-Halomethyl Ketones

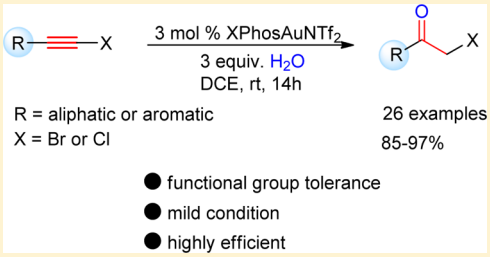
Longyong Xie,[†] Yundong Wu,[†] Weiguo Yi,[‡] Lei Zhu,[†] Jiannan Xiang,*[,†] and Weimin He*[,†]

[†]State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, People's Republic of China

[‡]Hunan Chemical Industry Vocation Technology Institute, Qingshi Road, Zhuzhou 412004, People's Republic of China

Supporting Information

ABSTRACT: A general atom-economical approach for the synthesis of α-halomethyl ketones is demonstrated through hydration of a wide range of haloalkynes. Other outstanding features include excellent yields from both alkyl- and aryl-substituted haloalkynes and wide functional group tolerance. This protocol is an alternative to conventional α-halogenation of ketones.



INTRODUCTION

Hydration of alkynes has emerged as a powerful method for synthesizing carbonyl compounds because of its 100% atom efficiency and its environmental advantages.[1] In spite of the great success achieved so far in this area, some important challenges still remain: the alkyne hydration is often limited to terminal alkynes, diarylalkynes, dialkylalkynes, or arylalkylalkynes,[2] and very little literature has been reported about hydration of heterosubstituted alkynes.[3] In addition, the functionalized terminal alkynes are not well tolerated in the chemoselective hydration reaction.

α-Halomethyl ketones are among the most versatile intermediates in organic synthesis, and their high reactivity makes them prone to react with a large number of nucleophiles to provide a variety of useful compounds.[4] In addition, many α-halomethyl ketones are biologically active molecules frequently used in medicine as drugs or diagnostic aids, such as enzyme inhibitors,[5] and therefore, their related chemistry has attracted broad interest. α-Halomethyl ketones are usually prepared from olefins[6] and ketones and their derivatives (enol silyl ethers[7] and β-ketoester[8]). Due to the difficulties in the synthesis and purification of enol silyl ethers and acetates, a number of methods for direct α-halogenation of ketones with different halogen-donating systems have been reported, including molecular halogen,[9] metal halides,[10] NXS,[11] and related or similar reagents.[12] However, most of these systems have drawbacks such as nonregiospecific halogenation and over-halogenation. Thus, the development of a mild, environmentally friendly, and highly efficient methodology for the synthesis of α-halomethyl ketones remains an intriguing challenge. In the continuing interest in gold catalysis,[13] we envisioned that the α-halomethyl ketones could be synthesized through gold-catalyzed hydration of haloalkynes,[14] which in turn can be easily prepared in one step from readily available terminal alkynes with NXS in almost quantitative yields.[15]

RESULTS AND DISCUSSION

To develop conditions that would be highly compatible with various functional groups, acidic additives and alkaline cocatalysts were avoided in the screening. As a preliminary study, 1-bromo-2-phenylacetylene was treated with 3 mol % $Ph_3PAuNTf_2$[16] and H_2O (3 equiv) in DCE (1 mL) at room temperature for 14 h (Table 1, entry 1). Pleasingly, α-bromoacetophenone (**2a**) was observed with 78% NMR yield via a gold-catalyzed hydration reaction. To increase the reaction efficiency, a series of gold catalysts (entries 2−8) were investigated. Among the catalysts tested, bulky gold catalysts, such as $MePhosAuNTf_2$, $XPhosAuNTf_2$, and $BrettPhosAuNTf_2$ (entries 6−8), showed higher reactivity than $Ph_3PAuNTf_2$. Though $XPhosAuNTf_2$ and $BrettPhosAuNTf_2$ worked equally well (92% isolated yield), we chose $XPhosAuNTf_2$ as the catalyst for economic reasons. To develop a catalyst efficient at low loadings, the amount of $XPhosAuNTf_2$ used was decreased to 2 mol % for the hydration of **1a**, and a promising 75% NMR yield of **2a** was obtained (entry 9). The solvent effect on this reaction was then examined, and it showed that solvents played a key role in the reaction outcome. Conducting the reaction in other common polar solvents such as CH_3OH, CH_3CN, THF, and DMF led to no product or trace amount of product (entries 11−14). The special catalytic role of gold in this reaction was substantiated by the inability of silver salts and $HNTf_2$ (entries 15−17) to catalyze this reaction.

Under the optimized reaction conditions (Table 1, entry 7), we then explored the scope and limitations of the hydrolytic reaction (Table 2). The reaction was highly efficient with a series of bromoalkynes, and the yields were all above 85%. Various functional groups were readily tolerated, including aryl groups having different electronic natures (**2a**−**2j**), an alkyl group (**2k**), alkyl halides (**2l** and **2m**), a variety of protected/

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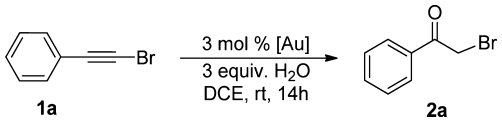
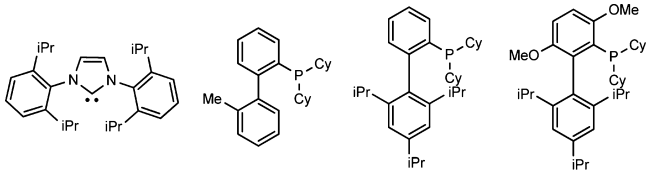
Table 1. Screening of Gold Catalysts and Reaction Conditions[a]



1a 2a

entry	catalyst[b]	solvent	yield[c] (%)
1	$Ph_3PAuNTf_2$	DCE	78
2	$(RO)_3PAuNTf_2$[d]	DCE	81
3	$Cy_3PAuNTf_2$	DCE	63
4	$Et_3PAuNTf_2$	DCE	37
5	$IPrAuNTf_2$	DCE	85
6	$MePhosAuNTf_2$	DCE	02
7	$XPhosAuNTf_2$	DCE	94
8	$BrettPhosAuNTf_2$	DCE	94
9	$XPhosAuNTf_2$	DCE	75[e]
10	$XPhosAuNTf_2$	DCM	66
11	$XPhosAuNTf_2$	CH_3OH	trace
12	$XPhosAuNTf_2$	CH_3CN	20
13	$XPhosAuNTf_2$	THF	18
14	$XPhosAuNTf_2$	DMF	15
15	$AgSbF_6$ (rt to 85 °C)[f]	DCE	
16	$AgNTf_2$ (rt to 85 °C)[f]	DCE	
17	$HNTf_9$ (rt to 85 °C)[f]	DCE	

[a]In vial. [1a] = 0.1 M. [b]Cy = cyclohexyl.



IPr MePhos XPhos BrettPhos

[c]Estimated by ^1H NMR spectroscopy using diethyl phthalate as an internal reference. [d]R = 2,4-(*t*-Bu)$_2$Ph. [e]2 mol % concentration of $XPhosAuNTf_2$ was used. [f]10 mol % concentration of catalyst was used.

functionalized OH groups (**2n**−**2s**), and protected amino groups such as benzamide (**2t**) and phthalimide (**2u**). It is noteworthy that 3-ethynylthiophene was also a suitable substrate for this reaction (**2j**). Reactions with substrates bearing a bulky group such as a cyclohexenyl group (**2v**) and a cyclohexyl group (**2w**) also proceeded smoothly. However, the *ortho*-substituted arylacetylenes such as 1-bromo-2-ethynylbenzene (**2x**) and 1-methyl-2-ethynylbenzene (**2y**) provided only trace amounts of target products, likely due to steric hindrance. By using chloroalkynes as the substrates, this alkyne hydration strategy could be extended to access the corresponding chloromethyl ketones in excellent yields (**2z**, **2aa**, and **2ab**). Unfortunately, 1-iodo-2-phenylacetylene afforded the corresponding iodomethyl ketone in less than 20% NMR yield presumably owing to steric hindrance.

To check the scalability of the present method, a gram-scale hydration of 1-bromo-2-phenylacetylene (**1a**) was carried out (Scheme 1). Hydration of **1a** (1.63g, 9 mmol) proceeded smoothly, giving the α-bromoacetophenone (**2a**) in 94% yield. In addition, the catalyst loading could be lowered to 2 mol % with little effect on the yield (Scheme 1).

This highly efficient synthesis of functionalized α-halomethyl ketones permits rapid access to various important heterocyclic compounds. For instance, the azaindolizine **3a** was isolated in 85% yield by the combination of the gold catalysis and a subsequent cyclocondensation of α-bromomethyl ketone with 2-aminopyridine in a one-pot process (Scheme 2, eq 1). Moreover, coupled with a subsequent Hantzsch thiazole synthesis upon simple workup, this reaction led to substituted thiazole **3b** in 88% overall yield (Scheme 2, eq 2).

■ CONCLUSIONS

In summary, we have developed a convenient protocol for the synthesis of α-halomethyl ketones from haloalkynes based on a gold-catalyzed hydration process. The presented methodology delivers an attractive alternative to classical procedures as nonregiospecific and environmental problems can be circumvented. A broad range of haloalkynes were tolerated in this method, and all the hydrolysis products could be obtained in excellent yields. Due to the easy availability of the starting materials, this work provides a simplified way to synthesize these important carbonyl compounds.

■ EXPERIMENTAL SECTION

General Information. Solvents, reagents, and gold catalysts were purchased as reagent grade and used without further purification. Column chromatography was performed on silica gel (200−300 mesh). ^1H NMR and ^{13}C NMR spectra were recorded using residue solvent peaks as internal standards ($CHCl_3$, δ = 7.26 ppm for ^1H; $CDCl_3$, δ = 77.0 ppm for ^{13}C; DMSO-d_6, δ = 2.50 ppm for ^1H; DMSO-d_6; δ = 39.5 ppm for ^{13}C). Coupling constants are given in hertz. Infrared spectra are reported in reciprocal centimeters (cm^{-1}). High-resolution mass spectrometry (HRMS) was performed on a Q-TOF microspectrometer. Melting points were determined on recrystallized solids and recorded on a national standard melting point apparatus and are uncorrected.

General Procedure for the Prepration of Alkynyl Bromides.[17] To a solution of alkyne (5 mmol, 1 equiv) in acetone (30 mL) were added NBS (980 mg, 5.5 mmol) and $AgNO_3$ (85 mg, 0.5 mmol) at room temperature with magnetic stirring for 6−8 h. After completion of the reaction, the mixture was filtered, and the filtrate was added to water (20 mL) and extracted with diethyl ether (20 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography by using ethyl acetate and petroleum ether as eluents to afford alkynyl bromides.

General Procedure for the Preparation of Alkynyl Chlorides.[18] To a solution of alkyne (5 mmol, 1 equiv) in THF (15 mL) was added a hexane solution of *n*-BuLi (2.4 M, 5.5 mmol) at −78 °C under argon; the reaction mixture was stirred at the same temperature for 1 h, and then a solution of *p*-toluenesulfonyl chloride (950 mg, 5 mmol) or NCS (668 mg, 5 mmol) in THF (5 mL) was added dropwise. The resulting reaction mixture was allowed to react at room temperature, hydrolyzed with water (10 mL), and extracted with ethyl acetate (20 mL × 3). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) to afford alkynyl chlorides.

Typical Experimental Procedure for the Prepration of α-Halomethyl Ketones. To a solution of haloalkyne (0.3 mmol) in CH_2ClCH_2Cl (3 mL) were added H_2O (0.9 mmol, 16.2 mg) and $XPhosAuNTf_2$ (0.009 mmol, 8.6 mg), the reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC. The reaction typically took 14 h. Upon completion, the mixture was concentrated, and the residue was purified by column chromatography on silica gel (eluent hexanes/ethyl acetate) to afford **2a**−**2w**, **2z**, **2aa**, and **2ab**.

Procedure for Gram-Scale Hydration of 1-Bromo-2-Phenylacetylene (1a). *Procedure A: Use of 3 mol % $XPhosAuNTf_2$ for Hydration of* ***1a****.* To a solution of **1a** (9 mmol, 1.63 g) in CH_2ClCH_2Cl (90 mL) were added H_2O (27 mmol, 0.49 g) and $XPhosAuNTf_2$ (0.27 mmol, 258 mg). The reaction mixture was stirred at room temperature for 13 h. Upon completion, the mixture was

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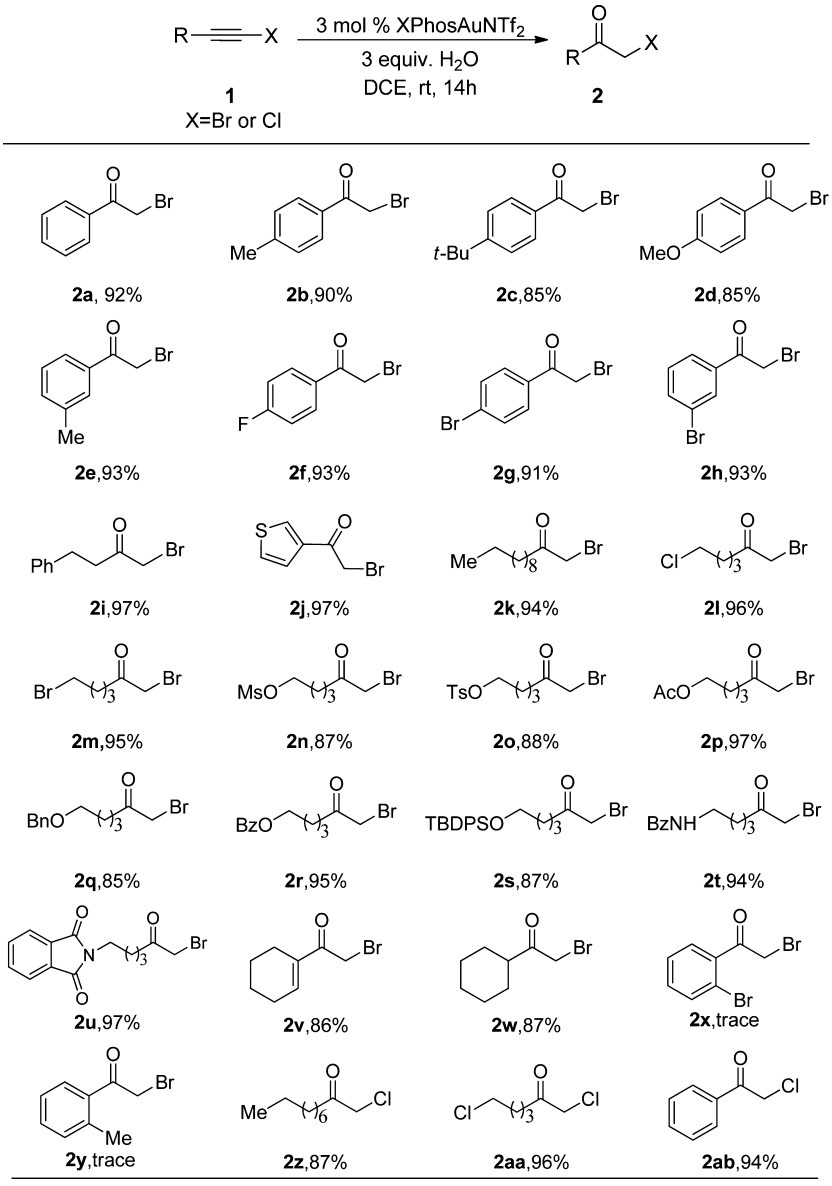
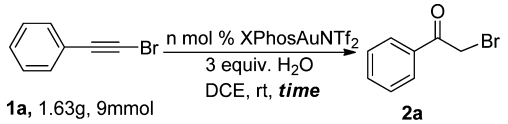
Table 2. Reaction Scope[a,b]



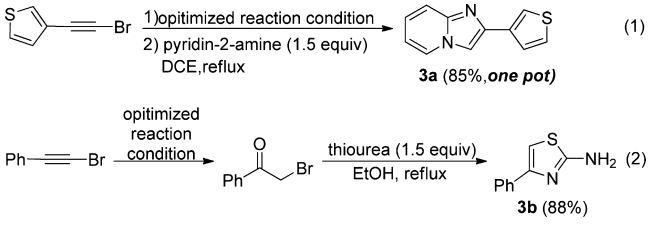
[a][1] = 0.1 M. [b]Isolated yields.

Scheme 1. Gram-Scale Hydration of 1-Bromo-2-phenylacetylene (1a)



n	*time*	*yield*
3	13	*94%, 1.68g*
2	16	*83%,1.49g*

Scheme 2



concentrated, and the residue was purified by column chromatography on silica gel (eluent hexanes/ethyl acetate, 20:1) to afford **2a** (1.68g, 94% yield).

*Procedure B: Use of 2 mol % XPhosAuNTf$_2$ for Hydration of **1a**.* To a solution of **1a** (9 mmol, 1.63 g) in CH_2ClCH_2Cl (90 mL) were added H_2O (27 mmol, 0.49 g) and XPhosAuNTf$_2$ (0.18 mmol, 172 mg). The reaction mixture was stirred at room temperature for 16 h. Upon completion, the mixture was concentrated, and the residue was purified by column chromatography on silica gel (eluent hexanes/ethyl acetate, 20:1) to afford **2a** (1.49 g, 83% yield).

Data for 2-bromo-1-phenylethanone (2a):[19] colorless solid (52.45 mg, 92% yield); mp 50−51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.2, 2H), 7.62 (t, J = 7.2, 1H), 7.50 (t, J = 8.0, 2H), 4.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.25, 133.94, 133.82, 128.86, 128.81, 31.00; IR (neat) 2965, 1710, 1576, 1187, 965, 695; HRMS (ESI) m/z calcd for C_8H_7BrO 198.9753 (M + H$^+$), found 198.9760.

Data for 2-bromo-1-(*p*-tolyl)ethanone (2b):[20] colorless solid (57.53 mg, 90% yield); mp 51−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ

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7.81 (d, J = 8.0, 2H), 7.21 (d, J = 8.0, 2H), 4.35 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.90, 144.99, 131.32, 129.50, 128.99, 31.01, 21.72; IR (neat) 2957, 1702, 1602, 1184, 802, 694; HRMS (ESI) m/z calcd for C_9H_9BrO 212.9910 (M + H^+), found 212.9921.

Data for 2-bromo-1-(4-(*tert*-butyl)phenyl)ethanone (2c):[21] colorless solid (65.06 mg, 85% yield); mp 51−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.8, 2H), 7.50 (d, J = 8.8, 2H), 4.44 (s, 2H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.87, 157.83, 131.23, 128.86, 125.78, 35.18, 30.98, 30.95; IR (neat) 2964, 1700, 1584, 1182, 802, 696; HRMS (ESI) m/z calcd for $C_{12}H_{15}BrO$ 255.0379 (M + H^+), found 255.0385.

Data for 2-bromo-1-(4-methoxyphenyl)ethanone (2d):[22] colorless solid (58.41 mg, 85% yield); mp 73−74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4, 2H), 6.95 (d, J = 8.4, 2H), 4.40 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.90, 164.05, 131.29, 126.76, 113.99, 55.52, 30.77; IR (neat) 2902, 1701, 1592, 1184, 802, 596; HRMS (ESI) m/z calcd for $C_9H_9BrO_2$ 228.9859 (M + H^+), found 228.9863.

Data for 2-bromo-1-(*m*-tolyl)ethanone (2e): colorless solid (59.45 mg, 93% yield); mp 47−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0, 2H), 7.34−7.30 (m, 2H), 4.38 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.43, 138.74, 134.73, 133.94, 129.32, 128.68,126.09, 31.08, 21.30; IR (neat) 2954, 1700, 1601, 1186, 802, 694; HRMS (ESI) m/z calcd for C_9H_9BrO 212.9910 (M + H^+), found 212.9917.

Data for 2-bromo-1-(4-fluorophenyl)ethanone (2f):[23] colorless solid (60.55 mg, 93% yield); mp 49−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 8.8, 5.6, 2H), 7.18 (t, J = 8.8, 2H), 4.43 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.80, 166.08 (d, J_{C-F} = 254), 131.69 (d, J_{C-F} = 9.6 Hz), 130.24, (d, J_{C-F} = 3.0 Hz), 116.06 (d, J_{C-F} = 22), 30.51; IR (neat) 2982, 1700, 1601, 1184, 988, 695; HRMS (ESI) m/z calcd for C_8H_6BrFO 216.9659 (M + H^+), found 216.9664.

Data for 2-bromo-1-(4-bromophenyl)ethanone (2g):[22] colorless solid (62.23 mg, 91% yield); mp 108−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.8, 2H), 7.64 (d, J = 8.8, 2H), 4.41 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.37, 132.50, 132.16, 130.37, 129.27, 30.44; IR (neat) 2944, 1699, 1582, 1184, 802, 700; HRMS (ESI) m/z calcd for $C_8H_6Br_2O$ 276.8858 (M + H^+), found 276.8866.

Data for 2-bromo-1-(3-bromophenyl)ethanone (2h): colorless solid (63.60 mg, 93% yield); mp 51−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.82 (d, J = 8.0, 1H), 7.65 (d, J = 5.0, 1H), 7.30 (t, J = 8.0, 1H), 4.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.95, 136.74, 135.55, 131.81, 130.36, 127.41,123.11, 30.44; IR (neat) 2944, 1699, 1582, 1184, 802, 700; HRMS (ESI) m/z calcd for $C_8H_6Br_2O$ 276.8858 (M + H^+), found 276.8864.

Data for 1-bromo-4-phenylbutan-2-one (2i):[24] colorless solid (66.09 mg, 97% yield); mp 38−39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.19 (m, J = 7.2, 2H), 7.13−7.10 (m, 3H), 3.76 (s, 2H), 2.90−2.86 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.17, 140.21, 128.51, 128.23, 126.27, 41.33, 34.37, 29.75; IR (neat) 2942, 1726, 1466, 1062, 782; HRMS (ESI) m/z calcd for $C_{10}H_{11}BrO$ 227.0066 (M + H^+), found 227.0072.

Data for 2-bromo-1-(thiophene-3-yl)ethanone (2j): colorless solid (57.83 mg, 94% yield); mp 62−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 2.8, 0.8, 1H), 7.58 (dd, J = 4.8, 0.8, 1H), 7.36 (dd, J = 4.8, 2.8, 1H), 4.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.53, 138.74, 133.76, 127.27, 126.87, 31.55; IR (neat) 2958, 1702, 1584, 1186, 804, 696; HRMS (ESI) m/z calcd for C_6H_5BrOS 204.9317 (M + H^+), found 204.9322.

Data for 1-bromododecan-2-one (2k):[25] colorless solid (74.23 mg, 94% yield); mp 40−41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 2H), 2.64 (t, J = 7.2, 2H), 1.61−1.58 (m, 2H), 1.33−1.22 (m, 14H), 0.88 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.24, 39.80, 34.36, 31.83, 29.49, 29.39, 29.26, 28.97, 23.80, 22.63, 14.08; IR (neat) 3706, 2919, 1708, 1466, 1045, 788; HRMS (ESI) m/z calcd for $C_{12}H_{23}BrO$ 263.1005 (M + H^+), found 263.1009.

Data for 1-bromo-6-chlorohexan-2-one (2l): colorless oil (61.49 mg, 96% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 2H), 3.53 (t, J = 6.4, 2H), 2.69 (t, J = 6.8, 2H), 1.78−1.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.47, 44.42, 38.69, 34.05, 31.52, 20.95; IR (neat) 3004, 2932, 1726, 1428, 1024, 732; HRMS (ESI) m/z calcd for $C_6H_{10}BrClO$ 212.9677 (M + H^+), found 212.9678.

Data for 1,6-dibromohexan-2-one (2m): colorless solid (73.52 mg, 95% yield); mp 54−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 2H), 3.41 (t, J = 6.4, 2H), 2.71 (t, J = 7.2, 2H), 1.91−1.84 (m, 2H), 1.81−1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.60, 38.62, 34.11, 33.11, 31.67, 22.20; IR (neat) 3002, 2928, 1726, 1428, 1026, 744; HRMS (ESI) m/z calcd for $C_6H_{10}Br_2O$ 256.9171 (M + H^+), found 256.9174.

Data for 6-bromo-5-oxohexyl methanesulfonate (2n): colorless oil (71.29 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (t, J = 5.8, 2H), 3.84 (s, 2H), 2.95 (s, 3H), 2.67 (t, J = 6.4, 2H), 1.76−1.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.34, 69.47, 38.63, 37.25, 34.16, 28.15, 19.58; IR (neat) 3746, 2943, 1732, 1346, 1176, 800; HRMS (ESI) m/z calcd for $C_7H_{13}BrO_4S$ 272.9791 (M + H^+), found 272.9797.

Data for 6-bromo-5-oxohexyl 4-methylbenzenesulfonate (2o): colorless oil (92.20 mg, 88% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4, 2H), 7.35 (d, J = 8.4, 2H), 4.01 (t, J = 5.8, 2H), 3.85 (s, 2H), 2.63 (t, J = 6.6, 2H), 2.44 (s, 3H), 1.66−1.64 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.31, 144.83, 132.69, 129.83, 127.77, 69.93, 38.57, 34.13, 27.81, 21.57, 19.58; IR (neat) 2932, 1744, 1600, 1358, 1104, 766; HRMS (ESI) m/z calcd for $C_{13}H_{17}BrO_4S$ 349.0104 (M + H^+), found 349.0106.

Data for 6-bromo-5-oxohexyl acetate (2p): colorless oil (68.99 mg, 97% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (t, J = 6.4, 2H), 3.83 (s, 2H), 2.64 (t, J = 6.6, 2H), 1.98 (s, 3H), 1.63−1.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.60, 171.06, 63.80, 39.01, 34.10, 27.72, 20.88, 20.11; IR (neat) 2941, 1764, 1596, 1336, 1056, 736; HRMS (ESI) m/z calcd for $C_8H_{13}BrO_3$ 237.0121 (M + H^+), found 237.0128.

Data for 6-(benzyloxy)-1-bromohexan-2-one (2q): colorless oil (72.72 mg, 85% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.42 (s, 2H), 3.79 (s, 2H), 3.41 (t, J = 6.6, 2H), 2.61 (t, J = 7.2, 2H), 1.68−1.64 (m, 2H), 1.58−1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.90, 138.37, 128.33, 127.61, 127.53, 72.88, 69.77, 39.40, 34.25, 28.88, 20.67; IR (neat) 2922, 1776, 1614, 1228, 1026, 742; HRMS (ESI) m/z calcd for $C_{13}H_{17}BrO_2$ 285.0485 (M + H^+), found 285.0493.

Data for 6-bromo-5-oxohexyl benzoate (2r): colorless oil (85.26 mg, 95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2, 2H), 7.54 (t, J = 7.6, 1H), 7.42 (t, J = 7.6, 2H), 4.32 (t, J = 6.0, 2H), 3.88 (s, 2H), 2.74 (t, J = 6.4, 2H), 1.80−1.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.57, 166.48, 132.87, 130.15, 129.45, 128.29, 64.28, 39.06, 34.10, 27.91, 20.24; IR (neat) 2944, 1740, 1594, 1356, 1122, 780; HRMS (ESI) m/z calcd for $C_{13}H_{15}BrO_3$ 299.0278 (M + H^+), found 299.0283.

Data for 1-bromo-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-one (2s): colorless oil (113.13 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 8.0, 1.6, 4H), 7.32−7.29 (m, 6H), 3.75 (s, 2H), 3.59 (t, J = 6.4, 2H), 2.54 (t, J = 7.2, 2H),1.69−1.61 (m, 2H), 1.53−1.47 (m, 2H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.93, 135.51, 133.80, 129.56, 127.60, 63.25, 39.40, 34.20, 31.61, 26.83, 20.25, 19.15; IR (neat) 3070, 2919, 1732, 1444, 1066, 766; HRMS (ESI) m/z calcd for $C_{22}H_{29}BrO_2Si$ 433.1193 (M + H^+), found 433.1198.

Data for *N*-(6-bromo-5-oxohexyl)benzamide (2t): colorless oil (84.09 mg, 94% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 7.2, 2H), 7.41 (t, J = 7.2, 1H), 7.33 (t, J = 7.4, 2H), 6.68 (br s, 1H), 3.82 (s, 2H), 3.35 (q, J = 6.4, 2H), 2.63 (t, J = 6.4, 2H), 1.63−1.54 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.04, 167.61, 134.44, 131.27, 128.40, 126.82, 39.31, 39.06, 34.23, 28.67, 20.66; IR (neat) 2970, 1772, 1474, 1383, 1081, 762; HRMS (ESI) m/z calcd for $C_{13}H_{16}BrNO_2$ 298.0437 (M + H^+), found 298.0441.

Data for 2-(6-bromo-5-oxohexyl)isoindoline-1,3-dione (2u):[26] colorless solid (94.33 mg, 97% yield); mp 112−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 5.2, 2.8, 2H), 7.72 (dd, J = 5.2, 2.8, 2H), 3.89 (s, 2H), 3.71 (t, J = 6.8, 2H), 2.75 (t, J = 6.8, 2H),1.73−1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.51,

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168.36, 133.93, 132.01, 123.20, 38.90, 37.27, 34.15, 27.71, 20.79; IR (neat) 2972, 1778, 1476, 1386, 1082, 760; HRMS (ESI) m/z calcd for $C_{14}H_{14}BrNO_3$ 324.0230 (M + H^+), found 324.0234.

Data for 2-bromo-1-(cyclohex-1-en-1-yl)ethanone (2v): colorless oil (52.39 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (t, J = 4.0, 1H), 4.11 (s, 2H), 2.24−2.19 (m, 4H), 1.60−1.57 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.16, 142.83, 136.79, 30.00, 26.19, 23.19, 21.64, 21.22; IR (neat) 2920, 1704, 1585, 1236, 1022, 758; HRMS (ESI) m/z calcd for $C_8H_{11}BrO$ 203.0066 (M + H^+), found 203.0072.

Data for 2-bromo-1-cyclohexylethanone (2w):[24] colorless oil (53.53 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 2H), 2.68−2.61 (m, 1H), 1.83−1.72 (m, 4H), 1.64−1.60 (m, 1H), 1.34−1.13(m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.60, 47.94, 33.44, 28.61, 25.54, 25.40; IR (neat) 2926, 2864, 1738, 1466, 784; HRMS (ESI) m/z calcd for $C_8H_{13}BrO$ 205.0223 (M + H^+), found 205.0229.

Data for 1-chlorodecan-2-one (2z):[27] colorless oil (49.78 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (s, 2H), 2.58 (t, J = 7.2, 2H), 1.63−1.57 (m, 2H), 1.33−1.18 (m, 10H), 0.87 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.80, 48.23, 39.68, 31.73, 29.22, 29.03, 28.99, 23.53, 22.58, 14.04; IR (neat) 3713, 2919, 1721, 1467, 1054, 784; HRMS (ESI) m/z calcd for $C_{10}H_{19}ClO$ 191.1197 (M + H^+), found 191.1199.

Data for 1,6-dichlorohexan-2-one (2aa):[28] colorless oil (48.69 mg, 96% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (s, 2H), 3.53 (t, J = 6.0, 2H), 2.64 (t, J = 6.4, 2H), 1.78−1.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.16, 48.07, 44.44, 38.64, 31.60, 20.73; IR (neat) 2934, 1716, 1476, 1332, 1034, 758; HRMS (ESI) m/z calcd for $C_6H_{10}Cl_2O$ 169.0182 (M + H^+), found 169.0188.

Data for 2-chloro-1-phenylethanone (2ab):[27] colorless solid (43.60 mg, 94% yield); mp 50−51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.2, 2H), 7.54 (t, J = 7.2, 1H), 7.42 (t, J = 7.6, 2H), 4.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.05, 134.17, 133.97, 128.85, 128.45, 46.00; IR (neat) 2986, 1700, 1452, 1198, 752, 691; HRMS (ESI) m/z calcd for C_8H_7ClO 155.0258 (M + H^+), found 155.0261.

One-Pot Synthesis of 2-(Thiophene-3-yl)imidazo[1,2-*a*]-pyridine (3a). To a solution of 3-(bromoethynyl)thiophene (0.3 mmol) in CH_2ClCH_2Cl (3 mL) were added H_2O (1.8 mmol, 32.4 mg) and $XPhosAuNTf_2$ (0.009 mmol, 8.3 mg). The reaction mixture was stirred at room temperature until the reaction was complete (monitored by TLC). After completion of the reaction, pyridin-2-amine (0.45 mmol, 42.3 mg) was added and stirring continued for a further 24 h. The reaction mixture was extracted with CH_2Cl_2 (2 × 8 mL), and the organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography to afford **3a**: yield 85%, 51.07 mg; colorless solid; mp 158−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 6.8, 1H), 7.81 (dd, J = 3.0, 1.3, 1H), 7.73 (s, 1H), 7.61 (d, J = 9.2, 1H), 7.52 (dd, J = 5.0,1.3, 1H), 7.38 (dd, J = 5.0, 3.0, 1H), 7.17 (ddd, J = 9.1, 6.8, 1.2, 1H), 6.77 (t, J = 6.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.45, 141.95, 135.47, 126.10, 125.90, 125.52, 124.78, 121.43, 117.29, 112.43, 108.05; IR (neat) 3126, 3085, 1632, 1507, 1493, 1304, 1270, 855; HRMS (ESI) m/z calcd for $C_{11}H_8N_2S$ 201.0481 (M + H^+), found 201.0489.

Synthesis of 4-Phenylthiazol-2-amine (3b). To a solution of (bromoethynyl)benzene (0.3 mmol) in CH_2ClCH_2Cl (3 mL) were added H_2O (1.8 mmol, 32.4 mg) and $XPhosAuNTf_2$ (0.009 mmol, 8.3 mg). The reaction mixture was stirred at room temperature until the reaction was complete (monitored by TLC). After completion of the reaction, the solution was concentrated under reduced pressure to remove CH_2ClCH_2Cl. Then a solution of pyridin-2-amine (0.45 mmol, 42.3 mg) in EtOH (2 mL) was added to the above residue, the reaction mixture was stirred at 80 °C overnight, the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL), and the organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent hexanes/ethyl acetate, 1:1) to afford **3b**:[29] yield 88%, 46.53 mg; colorless solid; mp 146−147 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 8.0, 2H), 7.36 (t, J = 7.6, 2H), 7.27 (t, J = 7.6, 1H), 7.09 (br s, 2H), 7.00 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.24, 149.63, 134.79, 128.47, 127.22, 125.53, 101.51; IR (neat) 3260, 2922, 1599, 1518, 1402, 1330, 1075; HRMS (ESI) m/z calcd for $C_9H_8N_2S$ 177.0481 (M + H^+), found 177.0486.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of compounds **2a−2w**, **2z**, **2aa**, **2ab**, **3a**, and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jnxiang@hnu.edu.cn.

*E-mail: wmhe@hnu.edu.cn.

Notes

The authors declare no competing financial interest.

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