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Sequential protocol for C(sp)–H carboxylation with CO_2: KO^{t}Bu-catalyzed C(sp)–H silylation and KO^{t}Bu-mediated carboxylation

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CO_2 incorporation into C–H bonds is an important and interesting topic. Herein a sequential protocol for C(sp)–H carboxylation by employing a metal-free C–H activation/catalytic silylation reaction in conjunction with KO^{t}Bu-mediated carboxylation with CO_2 was established, in which KO^{t}Bu catalyzes silylation of terminal alkynes to form alkynylsilanes at low temperature, and simultaneously mediates carboxylation of the alkynesilanes with atmospheric CO_2. Importantly, the carboxylation further promotes the silylation, which makes the whole reaction proceed very rapidly. Moreover, this methodology is simple and scalable, which is characterized by short reaction time, wide substrate scope, excellent functional-group tolerance and mild reaction conditions, affording a range of corresponding propiolic acid products in excellent yields in most cases. In addition, it also allows for a convenient ^{13}C-labeling through the use of $^{13}CO_2$.

CO_2 incorporation, carboxylation, propiolic acid, KO^{t}Bu, C(sp)–H silylation

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1 Introduction

Due to the abundance and inherent synthetic potential of carbon dioxide as a renewable C1 source, the use of CO_2 in organic synthesis is of actual interest and continues to attract the attention of the scientific community. Therefore, considerable efforts have recently been made for the development of effective CO_2 incorporation reacitons [1–7]. Among these technologies, the direct carboxylation of alkynes with CO_2 offers atom-economic routes for the synthesis of propiolic acids [8–13], which is an important kind of organic intermediates with versatile applications in organic synthesis and preparation of functional materials [14–19]. Although the significant advancements made in this area, there is still room for the development of carboxylation of a C(sp)–H bond with CO_2, which should provide a new entry to CO_2 incorporation chemistry.

We recently reported that alkynesilanes, which can be *in situ* prepared from reaction of terminal alkynes with timethylsilyacetylene, can be easily carboxylated in the presence of CsF and atmospheric CO_2 gas to afford the corresponding propiolic acids at room temperature [20]. As part of our ongoing interest in metal-free carboxylation of terminal alkynes with CO_2, we suppose that if alkynylsilanes could be *in-situ* produced from the reaction of terminal alkynes with hydrosilanes, the coorsponding propiolic acid could also become available following activation of alkynylsilanes with CO_2. To achieve this goal, it involves the activation of C–H bond, the formation of C–Si bond, and subsequent

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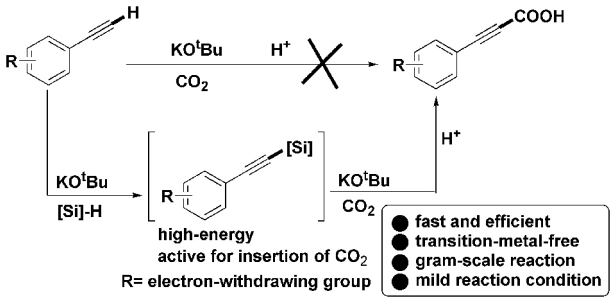
incoporation of CO_2 into the C–Si bond. Therefore, a suitable reaction system is the key and highly required to combine these processes together.

Recently, potassium tertbutoxide (KO^{t}Bu) has been presented an efficient reagent in C–H bond functionalization, and widely applied in the synthesis of various chemicals [21–26]. Zhang and coworkers [26] showed that propiolic acid derivatives could be obtained by direact carboxylation with CO_2 (2.5 atm) in the presence of Cs_2CO_3 at 120 °C. In the case of KO^{t}Bu, the reaction could proceed at ambient temperature. However, in our preliminary experiments, we discovered that the propiolic acids containing electron-withdrawing groups could not be obtained and propiolic acids containing electron-donating groups could be obtained with poor yield in the presence of KO^{t}Bu under mild condition. Then we found that KO^{t}Bu could activate the C(sp)–H bond of phenylacetylene and further catalyze the silylation of phenylacetyne with diethoxymethylsilane ($HSi(OEt)_2Me$) to give 1-phenyl-2-diethoxymethylsilylacetylene, meanwhile it was also able to promote the direct carboxylation of the phenylkynylsilane with atmospheric CO_2.

Inspired by such progress, together with our interest in the development of new practical methods for C–C bond formation using CO_2 as C1 source [27,28], herein we present a novel and highly effective sequential protocol for C(sp)–H carboxylation under mild condition by employing KO^{t}Bu-catalyzed C–H silylation in conjunction with KO^{t}Bu-mediated carboxylation with ambient CO_2 (Scheme 1). In this approach, KO^{t}Bu catalyzed the dehydrogenative cross-coupling of terminal alkynes with hydrosilanes leading to alkynylsilanes intermediate under mild condition, and simultaneously mediated the carboxylation of the *in-situ* generated alkynylslianes with atmospheric CO_2. Importantly, the carboxylation of alkynylsilanes further promotes the C(sp)–H silylation, which makes the C(sp)–H carboxylation proceed very rapidly. This approach has the merits of short reaction time, wide substrate scope and excellent functional-group tolerance, which could afford various functionalized propiolic acids in excellent yields in most cases. Moreover, it is scalable that the propiolic acids could be readily produced in gram scale with high yield. During the submission of our manuscript, an elegant study was reported by Grubbs and co workers [29], which detailed the similar alkali metal-hydroxide-catalyzed C(sp)–H bond silylation process.



Scheme 1 Sequential protocol for C(sp)–H carboxylation by employing KO^{t}Bu-catalyzed C–H silylation in conjunction with KO^{t}Bu-mediated carboxylation with ambient CO_2.

2 Experimental

2.1 General information

Carbon dioxide (99.999%), ^{13}C-labled carbon dioxide (purity>99.9%, ^{13}C 99%, ^{18}O<1%) was purchased from Beijing Analytical Instrument Company (China). All terminal alkynes, KO^{t}Bu and other salts were purchased from J&K (China) or Innochem (China) and were used as received without further purification. PMHS (poly(methylhydrosiloxane), M ~1900), and other hydrosilanes were purchased from Alfa Aesar (USA) and used without purification.

All reactions were monitored by thin-layer chromatography (TLC) analysis, which was performed on silica gel 60 F254 (China) and the spots were visualized under UV light at 254 nm or by exposure to iodine vapor. Column chromatography was performed with 200–400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AvanceII 400M type (^{1}H NMR, 400 MHz; ^{13}C NMR, 101 MHz; Germany) spectrometer at ambient temperature. ^{29}Si NMR spectra were recorded on a Bruker Avance 300M type (Germany). Their peak frequencies were referenced versus an internal standard (TMS) shifts at 0 ppm for ^{1}H NMR and against the solvent ($CDCl_3$, 77.0 ppm) for ^{13}C NMR, respectively. Multiplicity abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Coupling constants (J, Hz).

2.2 General procedure for silylation/carboxylation tandem reaction and characterization data

The terminal alkyne (1.0 mmol) was added to a mixture of $HSi(OEt)_2Me$ (5.0 mmol) and KO^{t}Bu (1.5 mmol) in a 10 mL Schlenk tube with a magnetic stirrer. The Schlenk tube was evacuated and back-filled with CO_2 for 3 times. After a CO_2 ballon was connected, the reactor was moved to a water bath of 40 °C. After being stirred for 2 h, the reaction mixture was diluted with water (30 mL), and was extracted with CH_2Cl_2 (3×10 mL). The aqueous layer was acidified with aqueous HCl (6 M) and then extracted with diethyl ether (5×20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the pure propiolic acid (such as compound 3-phenylpropiolic acid (**3a**): 98%).

3-Phenylpropiolic acid (**3a**): 143.1 mg, 98%, white solid. ^{1}H NMR (400 MHz, DMSO) δ 7.68–7.62 (m, 2H), 7.55 (d, J=7.4 Hz, 1H), 7.49 (t, J=7.4 Hz, 2H). ^{13}C NMR

(101 MHz, DMSO) δ 154.81, 133.07, 131.36, 129.50, 119.53, 119.51, 85.03, 81.68.

3-(*p*-Tolyl)propiolic acid (**3b**): 142.4 mg, 89%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J*=8.1 Hz, 2H), 7.21 (t, *J*=17.4 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.48, 141.61, 133.19, 129.40, 116.31, 88.54, 80.17, 21.72.

3-(4-Methoxyphenyl)propiolic acid (**3c**): 154.8 mg, 88%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J*=8.8 Hz, 2H), 6.89 (d, *J*=8.8 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.85, 157.84, 135.25, 114.38, 111.06, 89.51, 79.80, 55.41.

3-(4-Fluorophenyl)propiolic acid (**3d**): 216 mg, 96%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.44 (m, 2H), 7.41–7.35 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.40, 134.21, 131.90, 125.08, 118.92, 84.23, 82.33.

3-(3-Chlorophenyl)propiolic acid (**3e**): 178.4 mg, 98%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.56 (m, 1H), 7.51–7.42 (m, 2H), 7.32 (t, *J*=7.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.87, 134.58, 132.78, 131.18, 129.90, 121.14, 85.94, 81.16.

3-(4-Chlorophenyl)propiolic acid (**3f**): 175.1 mg, 97%, white solid. ^{1}H NMR (400 MHz, DMSO) δ 7.36 (dd, *J*=16.1, 4.6 Hz, 1H), 7.28–7.19 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 154.92, 136.35, 133.79, 128.76, 118.23, 83.58, 82.15.

3-(2-Chlorophenyl)propiolic acid (**3g**): 176.2 mg, 97%, white solid. ^{1}H NMR (400 MHz, DMSO) δ 7.75 (dd, *J*=7.7, 1.5 Hz, 1H), 7.64 (dd, *J*=8.1, 0.9 Hz, 1H), 7.56 (td, *J*=7.8, 1.6 Hz, 1H), 7.45 (td, *J*=7.6, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 153.49, 135.14, 134.15, 131.86, 129.12, 127.09, 118.49, 85.50, 79.89.

3-(4-Fluorophenyl)propiolic acid (**3h**): 160.7 mg, 98%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J*=8.8, 5.3 Hz, 2H), 7.07 (t, *J*=8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.25, 162.73, 156.67, 156.62, 140.02, 135.43, 135.34, 133.41, 133.33, 127.98, 127.90, 116.24, 116.02, 86.25, 86.19, 80.67.

3-(3-Fluorophenyl)propiolic acid (**3i**): 159.1 mg, 97%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 2H), 7.21 (ddd, *J*=3.8, 2.1, 1.2 Hz, 1H), 7.10 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.45, 160.98, 156.86, 130.42, 130.34, 129.03, 129.00, 121.26, 121.17, 119.88, 119.65, 118.47, 118.26, 86.06, 86.03, 80.92.

3-(2-Fluorophenyl)propiolic acid (**3j**): 160.2 mg, 97%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.55 (m, 1H), 7.47 (ddd, *J*=15.4, 5.3, 1.7 Hz, 1H), 7.21–7.10 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.12, 161.57, 156.50, 133.78, 132.10, 132.02, 123.35, 123.31, 115.05, 114.85, 107.28, 107.13, 83.66, 81.00.

3-(4-Hydroxymethylphenyl)propiolic acid (**3k**): 150.1 mg, 85%, white solid. ^{1}H NMR (400 MHz, DMSO) δ 13.62 (s, 1H), 7.45 (d, *J*=7.9 Hz, 2H), 7.27 (d, *J*=8.1 Hz, 2H), 4.41 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 154.79, 146.37, 132.94, 127.19, 117.47, 85.28, 81.89, 62.85.

3-(Biphenyl-4-yl)propiolic acid (**3l**): 204.2 mg, 92%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J*=8.3 Hz, 2H), 7.65–7.57 (m, 4H), 7.47 (t, *J*=7.4 Hz, 2H), 7.39 (t, *J*=7.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.93, 143.80, 139.76, 133.68, 128.97, 128.20, 127.28, 127.14, 118.05, 88.27, 80.85.

3-(Nitrophenyl)propiolic acid (**3m**): 118.4 mg, 62%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J*=8.8 Hz, 2H), 7.74 (d, *J*=8.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.58, 153.77, 148.53, 133.68, 130.65, 126.42, 126.23, 123.71, 84.34, 83.22.

3-(4-Cyanophenyl)propiolic acid (**3n**): 137.2 mg, 80%, white solid. ^{1}H NMR (400 MHz, DMSO) δ 14.03 (s, 1H), 7.93 (d, *J*=8.4 Hz, 2H), 7.85 (d, *J*=8.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 154.29, 133.65, 133.22, 124.32, 118.72, 113.50, 85.47, 82.50.

3-(2-(Trifluoromethyl)phenyl)propiolic acid (**3o**): 207.6 mg, 97%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J*=8.2 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.87, 154.84, 133.20, 132.36, 132.03, 131.79, 126.56, 125.57, 125.54, 125.50, 125.46, 124.89, 123.51, 122.19, 84.60, 82.42.

3-(3-(Methoxycarbonyl)phenyl)propiolic acid (**3p**): 195.8 mg, 96%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J*=8.4 Hz, 1H), 7.65 (d, *J*=8.4 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.10, 155.15, 140.43, 132.81, 132.15, 131.66, 130.61, 129.59, 125.70, 124.30, 90.29, 82.86, 52.39

3-(Thiophen-2-yl)propiolic acid (**3q**): 144.4 mg, 95%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J*=3.7, 1.0 Hz, 1H), 7.48 (dd, *J*=5.1, 1.0 Hz, 1H), 7.06 (dd, *J*=5.0, 3.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.84, 136.97, 131.59, 127.60, 119.24, 84.82, 81.88.

3-(Thiophen-3-yl)propiolic acid (**3r**): 146.1 mg, 96%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J*=2.8, 0.9 Hz, 1H), 7.34 (dd, *J*=5.0, 3.0 Hz, 1H), 7.28–7.23 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.70, 134.60, 130.29, 126.25, 118.53, 84.14, 80.26.

3,3′-(1,4-Phenylene)dipropiolic acid (**3u**): 181.9 mg, 85%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.44, 133.41, 121.62, 84.29, 83.51.

3,3′,3″-(1,3,5-Phenylene)tripropiolic acid (**3v**): 248.1 mg, 88%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.26, 137.97, 121.54, 83.63, 81.65.

Methyl 3-pyridylpropiolate (**3s′**): 115.6 mg, 78%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J*=1.3 Hz, 1H), 8.63 (dd, *J*=4.9, 1.5 Hz, 1H), 7.85 (dt, *J*=7.9, 1.8 Hz, 1H), 7.31 (dd, *J*=7.9, 4.9 Hz, 1H), 3.83 (s, 3H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.84, 153.25, 150.67, 139.74, 123.12,

116.90, 83.15, 82.67, 52.89.

Methyl 2-pyridylpropiolate (**3t′**): 112.5 mg, 76%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J=4.3 Hz, 1H), 7.72 (td, J=7.7, 1.7 Hz, 1H), 7.59 (d, J=7.8 Hz, 1H), 7.35 (ddd, J=7.6, 4.8, 1.1 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.37, 150.18, 140.17, 135.99, 128.18, 124.33, 83.76, 78.40, 52.39.

Cyclopropylpropiolic acid (**3w**): 91.2 mg, 82%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (tt, J=7.9, 5.2 Hz, 1H), 0.97–0.89 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.68, 96.04, 68.13, 9.39, −0.61.

Cyclohexylpropiolic acid (**3x**): 142.8 mg, 92%, colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (td, J=9.0, 4.5 Hz, 1H), 1.86–1.76 (m, 2H), 1.74–1.63 (m, 2H), 1.51 (dd, J=8.9, 3.4 Hz, 3H), 1.30 (dd, J=14.3, 4.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.16, 95.60, 72.66, 31.24, 28.84, 25.48, 24.48.

2.3 Synthesis of alkynylsilane 4a

Phenylacetylene (1.0 mmol) was added to a mixture of $HSi(OEt)_2Me$ (5.0 mmol) and KO^{t}Bu (0.2 mmol) in a 10 mL Schlenk tube with a magnetic stirrer. The Schlenk tube was evacuated and back-filled with N_2 for 3 times. Then a N_2 ballon was connected to the reactor, which was then moved to a water bath of 40 °C. After being stirred for 5 h, the reaction mixture was diluted with water (30 mL), and was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude mixture, which then analyzed by ^{13}C NMR (Figure S2(b), Supporting Information online) spectroscopy. The residue was purified by silica gel flash column chromatography (petroleum ether/EtOAc, 10:1–5:1) to give the pure desired product as pale yellow liquid in 70% yield. pale yellow liquid, ^{1}H NMR (400 MHz, DMSO) δ 7.47–7.49 (dd, J=7.5, 1.9 Hz, 2H), 7.38–7.41 (dd, J=12.1, 7.1 Hz, 3H), 3.75–3.69 (m, 4H), 1.13–1.16 (td, J=6.9, 2.1 Hz, 6H), 0.06 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 132.10, 129.37, 129.09, 122.20, 83.88, 81.10, 55.31, 18.51, −2.75.

2.4 Synthesis of product 6

Phenylacetylene (1.0 mmol) was added to a mixture of $HSi(OEt)_2Me$ (5.0 mmol) and KO^{t}Bu (1.5 mmol) in a 10 mL Schlenk tube with a magnetic stirrer. The Schlenk tube was evacuated and back-filled with CO_2 for 3 times. Then a CO_2 ballon was connected to the reactor, which was then moved to a water bath of 40 °C. After being stirred for 2 h, the solution of MeI (1.2 mmol MeI in 2 mL anhydrous DMSO) was added via syringe. After 2 h, the reaction mixture was diluted with water (30 mL), and was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude mixture, which was purified by silica gel flash column chromatography (petroleum ether/EtOAc, 5:1) to give pure **6** as light yellow liquid in 89% yield [30]. Colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.41 (m, 2H), 7.37–7.32 (m, 1H), 7.24 (t, J=7.4 Hz, 2H), 3.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.26, 132.83, 130.60, 128.52, 119.45, 86.27, 80.32, 52.57.

2.5 Synthesis of product 7

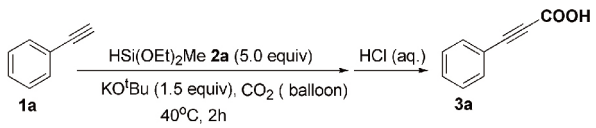
Phenylacetylene (1.0 mmol) was added to a mixture of $HSi(OEt)_2Me$ (5.0 mmol) and KO^{t}Bu (1.5 mmol) in a 10 mL Schlenk tube with a magnetic stirrer. The Schlenk tube was evacuated and back-filled with CO_2 for 3 times. Then a CO_2 ballon was connected to the reactor, which was then moved to a water bath of 40 °C. After being stirred for 2 h, the solution of morpholine (1.1 mmol morpholine and 1.2 mmol HBTU (*O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) in 3 mL anhydrous dimethyl formamide (DMF)) was added via syringe. After 5 h, the reaction mixture was diluted with water (30 mL), and was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude mixture, which was purified by silica gel flash column chromatography (petroleum ether/EtOAc, 5:1) to give pure **7** as light yellow powder in 67% yield [31]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2H), 7.35 (ddd, J=16.0, 11.7, 4.5 Hz, 3H), 3.83–3.79 (m, 2H), 3.75–3.70 (m, 2H), 3.67 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.22, 132.35, 130.16, 128.52, 120.25, 91.23, 80.74, 47.32, 41.99.

3 Results and discussion

3.1 Optimization of the reaction conditions

At the outset of this investigation, the reaction conditions were explored using phenylacetylene (**1a**) as the model substrate, and the optimal conditions were obtained (for 1.0 mmol **1a**, 5 equiv. $HSi(OEt)_2Me$ (**2a**), 1.5 equiv. KO^{t}Bu, 1 atm CO_2, 40 °C, 2 h). The carboxylation reaction of **1a** with CO_2 in the presence of **2a** occurred smoothly under the optimized conditions, affording **3a** in an isolated yield of 98% at 100% conversion of **1a** (Table 1, entry 1). The reaction did not proceed at all in the absence of KO^{t}Bu (entry 2), indicating that KO^{t}Bu was indispensable for the carboxylation. For comparison, other bases instead of KO^{t}Bu were tested, and it was demonstrated that KF, CsF, and K_2CO_3 gave rise to the desired product in declined yields (entries 3–5). In the next set of experiments, various hydrosilanes were examined, and it was found that all the tested hydrosilianes were effective for the reaction and diethoxymethylsilane **2a** displayed the best performance under the other identical conditions, affording the propiolic acid in highest yield (entries 1 and 6–12). Remarkably, the yield of propiolic acid

Table 1 Optimization of the reaction conditions [a]



Entry	Catalyst system: change from standard reaction conditions	Yield (%) [b]
1	None	98
2	no KO^{t}Bu	0
3	KF instead of KO^{t}Bu	67
4	CsF instead of KO^{t}Bu	72
5	K_2CO_3 instead of KO^{t}Bu	48
6	Et_3SiH **2b** instead of **2a**	40
7	Et_2SiH_2 **2c** instead of **2a**	56
8	$(EtO)_3SiH$ **2d** instead of **2a**	86
9	PMHS **2e** instead of **2a**	90
10	$PhMe_2SiH$ **2f** instead of **2a**	35
11	Ph_2MeSiH **2g** instead of **2a**	23
12	$PhSiH_3$ **2h** instead of **2a**	82
13	**2a** (1.0 equiv.)	24
14	**2a** (3.0 equiv.)	69
15	**2a** (6.0 equiv.)	98

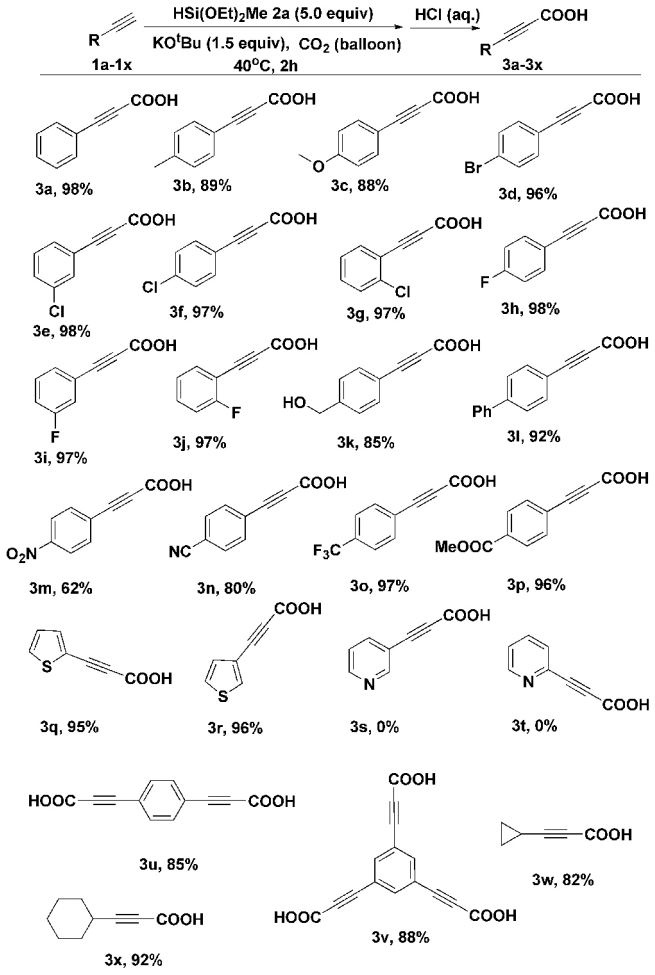
a) Standard reaction conditions: phenylacetylene (**1a**, 1.0 mmol), $HSi(OEt)_2Me$ (**2a**, 5.0 mmol), KO^{t}Bu (1.5 mmol, 1.5 equiv.), at 40 °C for 2 h; b) isolated yield.

product increased with the increasing of Si–H amount, reaching a maximum yield of 98% and then unchanged with further increase of the Si–H amount (entries 13–15).

3.2 The scope of substrate

To demonstrate the general applicability of the proposed approach, the domino reaction of various terminal alkynes (**1a**–**1v**) was carried out under the optimized reaction conditions (Table 2). Excitingly, all substrates with electron-donating as well as electron-withdrawing substituents in different positions were well carboxylated, producing corresponding carboxylic acids in excellent yields after acidification in most cases (**3a**–**3v**). Notably, in the case of halo-substituted aromatic alkynes, no dehalogenated products were detectable, suggesting that the reaction system had excellent tolerence to functional groups of the substrates. The isomers of the alkynes (e.g., 2-, 3-, and 4-ethynylhalobenzenes) had similar reactive activity (**3e**–**3j**), suggesting that the steric effect of substituents in aromatic rings was negligible. In addition, in the case of the substrates with reducible substituents (e.g., $-NO_2$, –C≡N, –COOMe), the desired propiolic acids were obtained without reduction of the reducible groups. Remarkably, the domino reaction of heteroaromatic alkynes (**1q** and **1r**) with CO_2 also efficiently proceeded, affording the corresponding products in excellent yields (**3q** and **3r**).

Table 2 Sequential C(sp)–H carboxylation for synthesis of various functionalized propiolic acids (**3a**–**3x**) [a,b]



a) Reaction conditions: terminal alkynes (**1a**–**1v**, 1.0 mmol), **2a** (5.0 mmol), KO^{t}Bu (1.5 mmol, 1.5 equiv.), 40 °C, 2 h; b) yield of isolated products.

However, 2- and 3-ethynylpyridine did not give the desired acid products after acidification (**3s** and **3t**). They indeed are formed, as demonstrated by the methyl ester formation, but difficult to be isolated as the salts (Scheme S1, Supporting Information online). This also demonstrated the successful carboxylation of 2- and 3-ethynylpyridine with CO_2. The protocol presented in this work was also capable of the carboxylation of multiple alkynes. For example, 3,3′-(1,4-phenylene)-di-propiolic acid and 3,3′,3″-(1,3,5-phenylene)-tri-propiolic acid that are useful building blocks for functional materials, were successfully obtained in very good yields (**3u**–**3v**). Excitingly, the reaction system was also effective for terminal aliphatic alkynes providing corresponding propiolic acids in high yields (**3w**–**3x**).

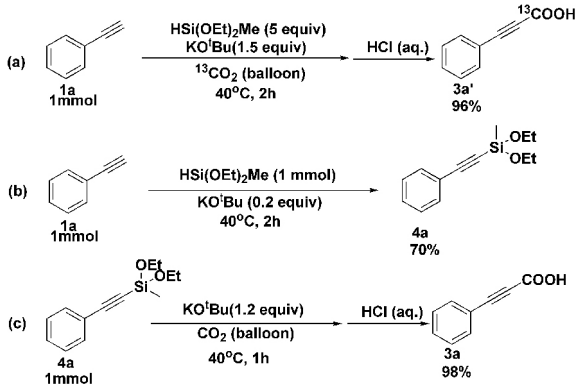
3.3 Control experiments and NMR analysis

To gain insight into the possible reaction pathway, several control experiments were carried out as illustrated in

Scheme 2. First, the reaction was conducted with isotopically labled $^{13}CO_2$ (balloon) as the carboxylative reagent under the standard reaction conditions (Scheme 2(a)), and ^{13}C labeled phenylpropiolic acid was obtained in a yield of 96% determined by ^{13}C NMR analysis (Figure S1), indicating that CO_2 involved the carboxylation of terminal alkynes. Next, the reaction of phenylacetylene **1a** with $HSi(OEt)_2Me$ **2a** was performed in the presence of KO^{t}Bu (0.2 equiv.), and alkynylsilane **4a** was obtained in an isolated yield of 70% within 5 h, confirmed by ^{13}C NMR (Figure S2(b)) analysis. This result indicated that KO^{t}Bu could catalyze the silylation of terminal alkynes to form alkynylsilane, similar to a recent report [25]. As described above, the same amount of phenylacetylene **1a** (i.e., 1 mmol) could convert completely into the carboxylated compound in an isolated yield of 98% via a tandem reaction within 2 h. Thus, it can be deduced that the carboxylation of alkynylsilane intermediate further promoted the silylation of terminal alkynes, which made the tandem process proceed very rapidly.

In the spectrum of alkynylsilane **4a** as shown in Figure 1(b), besides the signal at −44.79 ppm assigning to the Si of **4a**, there existed a small signal at −49.59 ppm, which became intenser as more KO^{t}Bu, e.g., excess of 1 mmol, was added into the alkynylsilane **4a** solution (Figure 1(c)). This signal may be ascribed to a pentavalent silicon intermediate (**II**) from **4a** and KO^{t}Bu [32], which also could be deduced from the intensity decline of the signal at −49.59 ppm with the addition of more KO^{t}Bu. These results suggest that KO^{t}Bu could efficiently activate alkynylsilane **4a**. Bubbling CO_2 gas into the *in-situ* generated intermediate (**II**) solution, and the solution was examined by ^{29}Si NMR spectroscopy at desired time. As shown in Figure 1(d), a new and intense signal appeared at −36.48 ppm accompanied with other two small peaks at −28.02 and−36.86 ppm in ^{29}Si NMR spectrum of the reaction solution obtained after 10 min, and this signal still remained with disappearance of the other two in spectrum of the solution reacting for 1 h (Figure 1(e)). These findings indicated the formation and further transformation of Si-containing species in the reaction process. The signals at −28.02 and −36.86 ppm were assigned to intermediates **III** and **IV**, while the signal at −36.48 ppm maybe belonged to the product from silane in the form of $CH_3Si(OEt)_2(O^tBu)$ (donated as **V**), which was confirmed by ^{13}C NMR analysis (Figure S2(c)). From the reaction solution acidified with HCl aqueous solution, a product in an isolated yield of 98% was obtained, which was confirmed to be phenylpropiolic acid by ^{13}C NMR analysis (Figure S2(c)). It is demonstrated that KO^{t}Bu activated the C–Si bond of **4a** and promoted the insertion of CO_2, finally giving carboxylated product (Scheme 2(c)).

Based on the above results and previous studies [32–35], a possible reaction pathway was proposed as illustrated in Scheme 3. This tandem reaction involves two processes: (1) KO^{t}Bu-catalyzed silylation of terminal alkynes to alkynylsilanes; (2) KO^{t}Bu-mediated carboxylation of *in-situ* formed alkynylsilane, which promoted former process. In the silylation step, alkynyl anion is generated from alkynes catalyzed by KO^{t}Bu, which then nucleophilically attacks to Si atom of hydrosilane, leading to the formation of new Si–C bond to afford alkynylsilane **4a**. In the second step, the addition of Lewis base **(LB)** KO^{t}Bu to **4a** affords a pentavalent silicon intermediate (**II**), which converts to a hexacoordinate



Scheme 2 Control experiments for mechanistic studies.

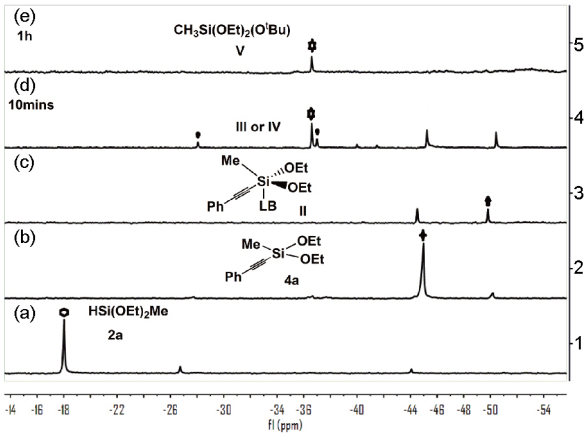
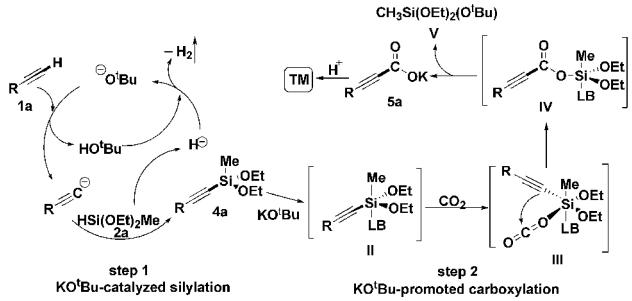


Figure 1 ^{29}Si NMR spectra. (a) **2a**; (b) the reaction solution of **1a** (1 mmol) with **2a**(1 mmol) in the presence of KO^{t}Bu (0.2 equiv.) at 40 °C for 12 h; (c) the mixture of **4a** and KO^{t}Bu (1.2 mmol); (d) the solution of intermediate **II** bubbled with CO_2 at 40 °C for 10 min; (e) the solution of intermediate **II** bubbled with CO_2 at 40 °C for 1 h.



Scheme 3 Possible reaction mechanism. LB=Lewis base, i.e., KO^{t}Bu.

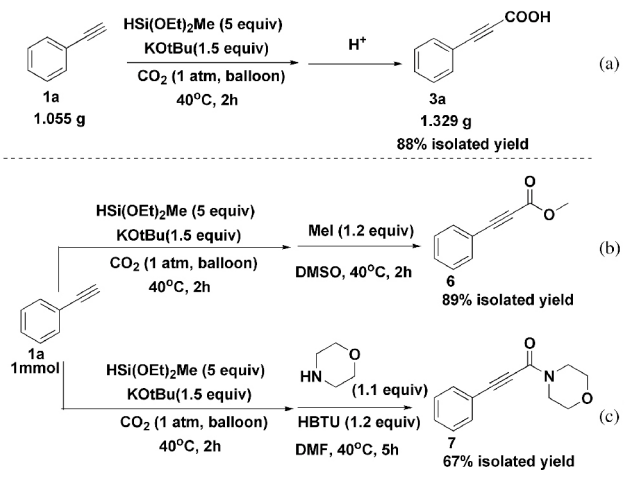
intermediate (**III**) as CO_2 is introduced [32]. Then alkynyl nucleophile attacks to CO_2 resulting in the formation of an alkyne-addition intermediate (**IV**), followed by generation of carboxylate **5a**. The target product is finally obtained after acidification of **5a**.

3.4 Gram-scale synthesis and applications of this method

In order to demonstrate the synthetic utility of the above approach, we also performed the reaction on a gram scale, and a satisfactory isolated yield (88%) was obtained (Scheme 4(a)). This indicates that the protocol presented in this work is scalable and may have promising and practical application in the production of propiolic acids. This protocol could also be applied to produce other value-added chemicals derived from proliolic acids. For example, methyl ester of phenylpropiolic acid was obtained in an isolated yield of 89% via treating the carboxylated compound with methyl iodide (Scheme 4(b)). Alkynylamides is a kind of valuable intermediates in organic and pharmaceutical synthesis [36–38]. The carboxylated compound from phenylacetylene with CO_2 could be further converted into alkynylamide in a 67% isolated yield via its reaction with amine (Scheme 4(c)).

4 Conclusions

In summary, based on the construction of high-energy alkynylsilanes, we have successfully developed a novel and highly effective sequential strategy for mild carboxylation of terminal alkynes with ambient CO_2 in the presence of KO^{t}Bu, which plays dual roles in this sequential protocol, catalyzing the dehydrogenative cross-coupling reaction of terminal alkynes with hydrosilanes and promoting carboxylation of the *in-situ* generated alkynylsilanes with ambient CO_2. Remarkably, the carboxylation further promotes the silylation, which makes the domino reaction proceed very rapidly. Various kinds of structurally diverse propiolic acids and their derivatives could be obtained in excellent yields in most cases. This sequential protocol features short reaction time, a broad substrate scope, good functional-group tolerance, facial scalability, solvent-free and mild conditions, which may have promising practical application in the production of propiolic acids. Further work on construction of C–C bond with CO_2 as C1 building is currently underway in our lab.



Scheme 4 Gram-scale synthesis and applications in synthsis of alkynotes and alkynylamides.

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Conflict of interest The authors declare that they have no conflict of interest.

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