Carboxylate catalyzed silylation of alkynes

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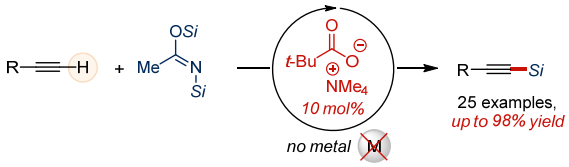
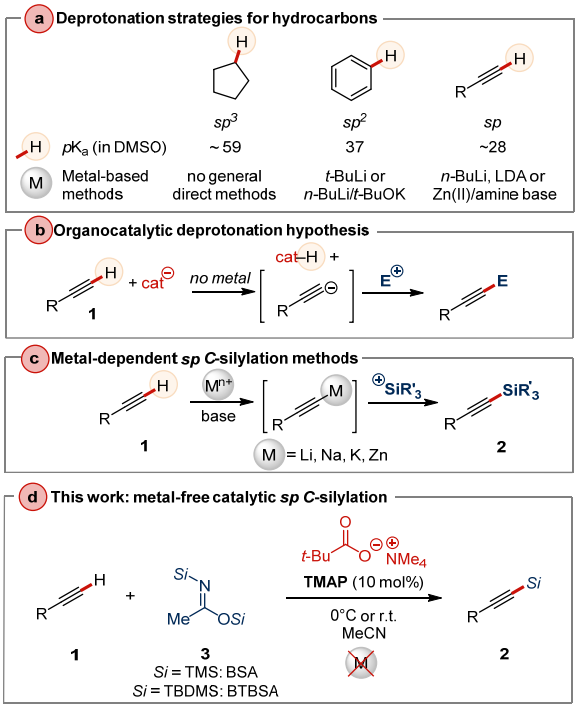
Deprotonation, carboxylate catalysis, silylation, alkynes



ABSTRACT: A carboxylate-catalyzed, metal-free *C*-silylation protocol for terminal alkynes is reported using a quaternary ammonium pivalate as the catalyst and commercially available *N,O*-bis(silyl)acetamides as silylating agents. The reaction proceeds under mild conditions, tolerates a range of functionalities, and enables concomitant *O*- or *N*-silylation of acidic OH or NH groups. A Hammett ϱ value of +1.4±0.1 obtained for *p*-substituted 2-arylalkynes is consistent with the proposed catalytic cycle involving turnover-determining deprotonation step.

Metal-free deprotonation of hydrocarbons is challenging due to the high pK_a values of most hydrocarbons,[1] and typical methods to generate carbanions with strong organometallic bases result in the formation of another organometallic species. For example, aromatic hydrocarbons can be deprotonated only by strong bases (e.g. Schlosser reagent)[2–4] unless they activated by a directing group.[5–7] With a pK_a of ca 28 (in DMSO), terminal alkynes might be an exception to this rule, but in practice even they require the use of strong organometallic bases and/or more electropositive, π-coordinating metals such as Zn.[8,9] Catalytic deprotonation reactions of alkynes without metals are presumed to be highly challenging[10] although reactions with aldehydes and ketones (Favorskii reaction) have been realized with strong metal-free bases such as quaternary ammonium hydroxides.[11–13]

We have previously shown that metal-free catalytic enoyl isomerization[14] and silylative aldol reactions[15] are possible with simple carboxylate salt catalysts, without the need of metal or strong (and potentially nucleophilic) hydroxide bases. In the aldol reaction, the combination of tetramethylamonia pivalate (TMAP) and neutral silylating agent *N,O*-bis(trimethylsilyl)acetamide (BSA) was required for rapid turnover rates. Herein we show that catalytic deprotonation of terminal alkynes with concomitant *C*-silylation can be achieved under very mild conditions using metal-free carboxylate catalyst (Scheme 1) and silylamides as the silyl source.



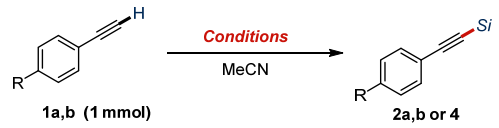
Scheme 1. Deprotonation of hydrocarbons: concept of metal-free deprotonation-silylation sequence.

Silylated terminal alkynes are versatile precursors of alkynyl nucleophiles in synthetic organic chemistry,[16–18] and the silyl group also plays a role of a protecting group. Typical approaches to the synthesis of *C*-silylated alkynes in-

clude deprotonation of terminal alkynes with stoichiometric amount of organolithium compounds (e.g. *n*-BuLi) and the use of halosilanes as the silylating agent.[19] An alternative silylation method with stoichiometric Lewis acid ($ZnCl_2$) has been reported using silylamines,[20] and the more reactive $Zn(OTf)_2$ has been used as a Lewis acid in stoichiometric and catalytic variants employing halosilanes[21] and silyltriflates,[22] respectively. More recent catalytic versions of TMS protection employing the Ruppert-Prakash reagent ($TMSCF_3$)[23] and bis(trimethylsilyl)acetylene as the electrophilic TMS donor[24] with strong bases, NaH and KHMDS, have also been reported recently. Silyl hydrides can also be used as silylating agents with alkali metal hydroxides as catalysts.[25]

We initiated our study by using phenylacetylene **1a** and *p*-CF_3-phenylacetylene **2a** as a model substrate and exposing these alkynes to a catalytic amount of TMAP and 1.5 equiv of BSA. To our delight, both substrates were converted to the desired TMS–acetylenes (R = H, **2a** or R = CF_3, **2b**) in high yields (Table 1, entries 1 and 2). With **1b**, the reaction proceeded at –10 °C with nearly quantitative yield (94%was obtained **2b**. Deviations in catalyst loading or the quantity of the BSA did not lead to any improvement (Table 1, entries 3-5), but the absence of the catalyst (TMAP), no **2a** was detected (Table 1, Entry 6). Interestingly, replacing the silylating agent with BSTFA gave no reaction (Table 1, Entry 7), but a bulkier *t*-butyldimethylsilylating agent BTBSA afforded the corresponding TBDMS-protected alkyne **4** in 65 % yield.

Table 1. Optimization table of the TMAP-catalyzed silylation of alkynes.



1a,b (1 mmol) **2a,b or 4**

Entry	Conditions	Yield, %
1	**1a** (R = H), TMAP (0.1 equiv.), BSA (1.5 equiv.), r.t., 5 h	**85**
2	**1b** (R = CF_3), TMAP (0.1 equiv.), BSA (1.5 equiv.), -10 °C, 1 h	**94**
	Deviations from above	
3	R = CF_3, TMAP (0.05 equiv.), BSA (1.5 equiv.), r.t., 5 h	50[1]
4	R = H, TMAP (0.1 equiv.), BSA (1.3 equiv.), r.t., 5 h	82[1]
5	R = CF_3, TMAP (0.1 equiv.), BSA (1.5 equiv.), r.t., 5 h	90[1]
6	R = H, TMAP (0.1 equiv.), BSTFA (1.5 equiv.), r.t., 5 h	n.d.[2]
7	R = H, TMAP (0 equiv.), BSA (1.5 equiv.), r.t., 24 h	n.d.[2]
8	R = H, TMAP (0.1 equiv.), BTBSA (1.5 equiv.), r.t., 5 h	65

TMAP **BSA** **BSTFA** **BTBSA**

[1] Conversion based ^{1}H NMR based on the crude reaction mixture
[2] Run as an ^{1}H NMR experimnent in MeCN-*d3*

The utility of the carboxylate-BSA silylating protocol was then explored with a range of substrates. Substituted phenylacetylenes **1a-i** gave the TMS-protected alkynes in excellent, even nearly quantitative yields, with both electron-donating as well as electron withdrawing groups (EWGs) **2a-i**. Typically, the reactions proceeded to quantitative conversions as judged by ^{1}H NMR and/or TLC analysis of the crude reaction mixture. In general, EWG-substituted substrates **2b, 2f** and **2i** gave better yields when the reaction was conducted at –10 or 0 ℃. Double silylation of **1u** was also readily achieved using 3 equiv of BSA, giving **2u** in 98% yield. Heterocyclic and other aromatic terminal alkynes **2j-m** also gave high yields of the TMS-protected alkynes. The reaction also tolerated enynes and propargylic substrates bearing different functionalities and protecting groups **2n-2q**. With **2o**, a gram-scale experiment demonstrated that the process is scalable (91% yield at 10 mmol scale vs. 97% at 1 mmol scale).

The process also tolerates aliphatic alkynes **1r-1t**, but with these, the reaction is more sluggish. With these substrates, reactions typically reached ca. 90% conversion, requiring additional purification. The desired TMS-protected alkynes **2r-2t** can nevertheless be obtained in moderate isolated yields (52-70%) after purification.

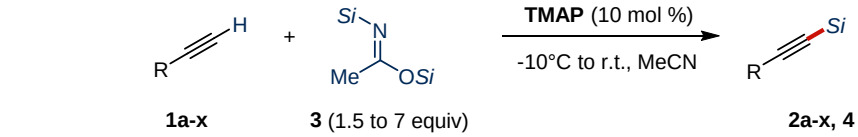
The current catalytic BSA-TMAP system can also readily protect other hydroxy and amine groups in situ. To demonstrate the applicability of the silylation protocol with a complex substrate, we carried out a reaction with ethynylestradiol **1v** using excess of BSA (7 equiv). The triply silylated product **2v**, with the TMS-protected phenol, ter-

tiary alcohol, and terminal alkyne, was obtained in 84 % yield (based on 90 % sample purity). The triple silylation was unambiguously confirmed by scXRD (see the SI).

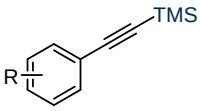
In addition, double *N*,*C*-silylation of propargylamine **1w** could be achieved in 95% yield. *N*-silylated compounds, especially those bearing a N-TMS group, are known to be relatively unstable,[26,27] and indeed, spontaneous hydrolysis of *N*-TMS group of **2w** during storage (4 ℃) led to slow crystallization of the *C*-silylated carbamate **2x** (see Scheme 2). The scXRD of **2x** also confirmed the position of the *C*-silyl group.

Limitations of the present *C*-silylation method include the following examples. *N*-tosyl-protected *N*-methylpropargyl amine **1y** underwent to partial isomerization provide a poorly separable mixture of allene **5** and the desired TMS-protected alkyne **2y**. Attempts to perform double silylation for primary hydroxy group and terminal alkyne (**1z,** derived from 5-(hydroxymethyl)furfural) gave a mixture of mono **5z'** and bis-silylated **5z** products with 25:75 ratio, respectively, with total yield 50%. Finally, we noted that the phthalimide protecting group is not tolerated under the reaction conditions, and only decomposition of starting material **1aa, ab** was observed.

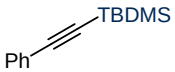
Since control experiments without the TMAP catalyst (Table 1, entry 7) or with the alternative CF_3-substituted silylating agent BSTFA (Table 1, entry 6) resulted in no reaction, the catalytic cycle appears to require both species. We propose a probase mechanisms involving an initial silyl transfer from BSA to the pivalate anion of TMAP,[15] leading to formation of anionic species[28–31] (**I**, Scheme 4) with subsequent deprotonation of the alkyne (Scheme 4). This mechanism is supported by the inertness of BSTFA, which should give rise to a weaker base. Furthermore, this mechanistic scenario also corroborated by the Hammett plot with different aryl-conjugated alkynes (**2a, 2c-2g**), which resulted in a ϱ value of +1.4±0.1 (see SI). This value is consistent with the formation of carbanionic-like species in the turnover-determining deprotonation step, and agrees with our initial mechanistic blueprint for the reaction.[32–34,20] In the proposed catalytic cycle, the alkyne anion-Me_4N^+ ion pair[10–12] (**II**, Scheme 4) is silylated by BSA, generating the probase and completing the cycle. In the kinetic experiments with phenylacetylenes, 1 mol% of TMAP catalyst was sufficient to give reasonable rates in ^{1}H NMR studies (see SI), but in preparative experiments we found that using 10 mol% TMAP was a safer option to cover a broad range of substrates.



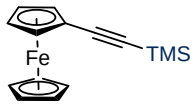
Aromatic and heteroaromatic



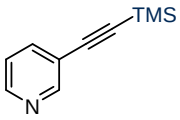
2a, R=H, 5h, 85%
2b, R= *p*-CF_3, 3h, 94%[a]
2c, R= *p*-OMe, 5h, 85%
2d, R= *p*-NMe_2, 5h, 92%
2e, R= *p*-Me, 5h, 86%
2f, R= *p*-F, 3h, 87%[b]
2g, R= *p*-Cl, 5h, 91%
2h, R= *o*-Cl, 3h, 91%
2i, R= 3,5-CF_3, 3h, 94%[a]



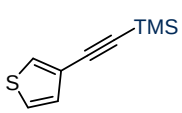
4, 5h, 65%[f]



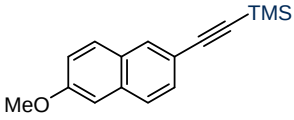
2j
3h, 92%



2k
3h, 69%

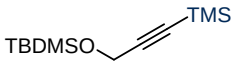


2l
3h, 98%[c]

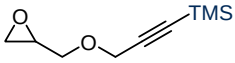


2m
5h, 87%[c]

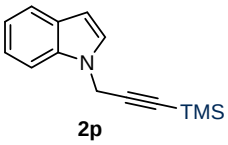
Propargylic and enyne systems



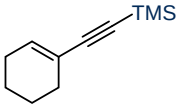
2n
5h, 87%



2o
3h, 97%[b]
(gram scale: 91%[b])

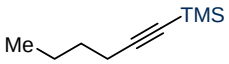


2p
3h, 75%

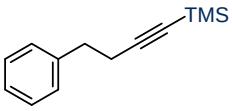


2q
3h, 71%

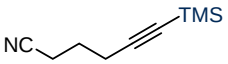
Aliphatic substrates



2r
3 days, 54%

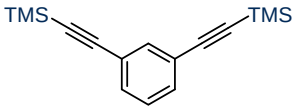


2s
48h, 52%

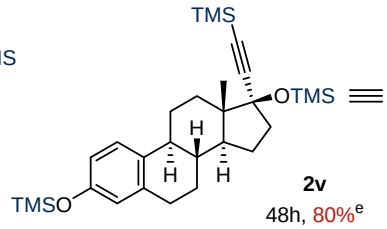


2t
48h, 70%

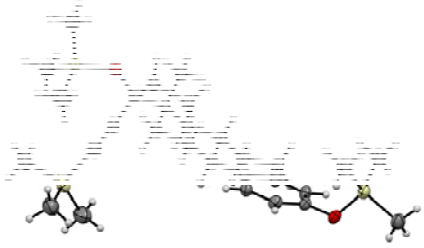
Multiple *in situ* silylation



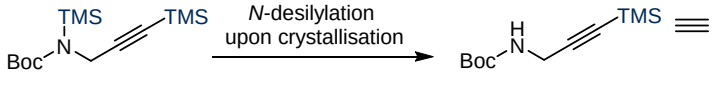
2u
5h, 98%[c]



2v
48h, 80%[e]

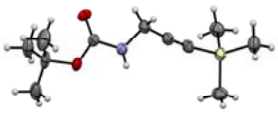


CCDC 2313380



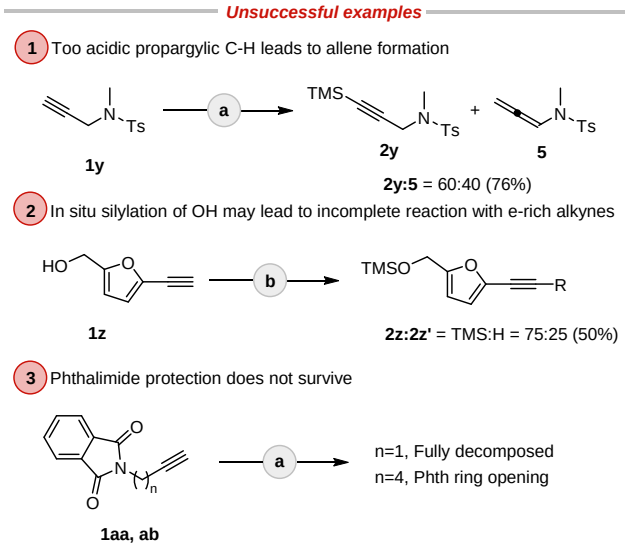
2w
5h, 95%[d]

2x

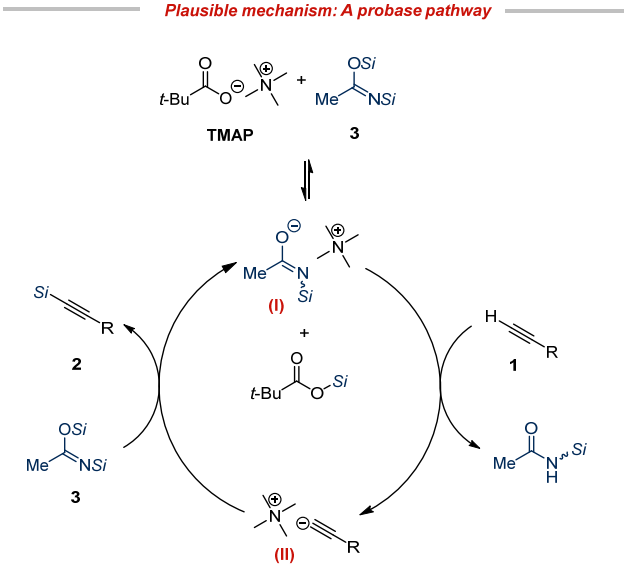


CCDC 2313373

Scheme 2. Methodology scope. Reactions carried out at r.t. with 1.5 equiv of BSA, unless otherwise noted. (a) run at –10 ℃; (b) run at 0 ℃ (c) 3 equiv of BSA was used; (d) 5 equiv of BSA was used; (e) 7 equiv of BSA and MeCN-THF (1:1) mixture were used; (f) 1.5 equiv of BTBSA was used.



Scheme 3. Unsuccessful examples. Reaction conditions: (a) TMAP (10 mol%), BSA (1.5 equiv), MeCN, 0 °C to r.t.; (b) TMAP (10 mol%), BSA (5 equiv), MeCN, 0 °C to r.t.



Scheme 4. Plausible reaction mechanism.

In conclusion, we report a new carboxylate-catalyzed, metal-free protocol for silylation of terminal alkynes. A bench-stable, inexpensive catalyst (TMAP) and commercially available, noncorrosive silylating agents BSA (or BTBSA) can be employed. The protocol tolerates a range of substrates and has the added benefit of concomitant in situ silylation of OH and NH groups if necessary.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, copies of NMR spectra, kinetics experiments, crystallographic data (PDF)

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