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Synthesis of vinyl-substituted alcohols using acetylene as a C2 building block†

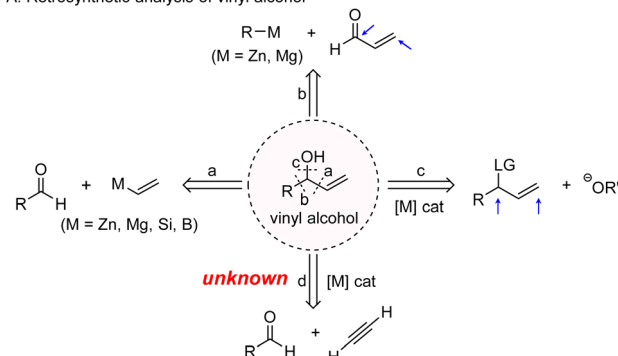
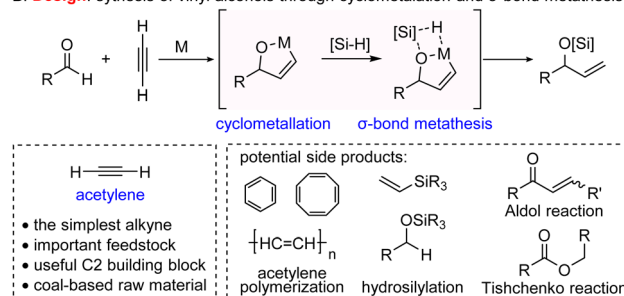
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Vinyl-substituted alcohols represent a highly useful class of molecular skeletons. The current method typically requires either stoichiometric metallic reagents or preformed precursors. Herein, we report a nickel catalysis-enabled synthesis of vinyl-substituted alcohols *via* a 5-membered oxa-metallacycle. In this protocol, acetylene, the simplest alkyne and abundant feedstock, is employed as an ideal C2 synthon. The reaction features mild conditions, good functional group tolerance and broad substrate scope. Mechanistic exploration implies that the oxa-metallacycle originated from the cyclometallation of aldehyde and acetylene is the key intermediate for this transformation, which is then terminated by a silane-mediated σ -bond metathesis and subsequent reductive elimination.

As a class of versatile motifs in organic synthesis, vinyl-substituted alcohols (abbreviated as vinyl alcohols) permit a myriad of opportunities for the manipulation and introduction of functional groups as well as construction of complex molecular architectures.¹ Therefore, numerous methods have been established to prepare such significant synthetic building blocks (Scheme 1A).² Among these approaches, alkenylation of aldehydes with vinyl metal is one of the most common strategies to deliver vinyl alcohols (Scheme 1A, path a).³ Despite widespread utilization of this method in organic synthesis, sensitive and stoichiometric organometallic reagents are often required under harsh conditions with poor functional group tolerance. In addition to the alkenylation of aldehydes, direct 1,2-addition of acrolein with organometallic compounds could give the desired vinyl alcohols as well (path b).⁴ However, the competition between 1,2- and 1,4-addition⁵ makes this method useless from a practical point of view. Apart from nucleophilic addition of metallic reagents, transition metal-catalyzed allylic substitution with O-nucleophiles represents another important route to obtain vinyl alcohols (path c),⁶ while it is often plagued with the control of regioselectivities and requirement of pre-synthesized allylic substrates. Taken together, syntheses of vinyl-substituted alcohols *via* these strategies are limited to either sensitive metallic reagents or allylic precursors. Therefore, developing alternative efficient approaches with easily available reagents to acquire vinyl-substituted alcohols and their derivatives under mild conditions is highly desirable.

As the simplest alkyne, acetylene is an inexpensive and abundant feedstock, which has been used as a raw material for bulk vinyl-containing monomer production in the chemical industry.⁷ While in the fine chemical field, catalytic transformation of this unique C2 unit into high value-added chemicals is underdeveloped.^{7e,8,9} Despite great efforts being devoted to the development of reductive coupling of substituted alkynes with aldehydes,¹⁰ incorporation of acetylene with aldehydes still

A. Retrosynthetic analysis of vinyl alcohol

B. Design: synthesis of vinyl alcohols through cyclometallation and σ -bond metathesis

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Scheme 1 Synthetic strategies of vinyl alcohols.



remains unknown (path d). This may be attributed to the unique properties of acetylene.¹¹ Moreover, the gaseous nature and flammable properties of acetylene make chemists stay away from it.¹²

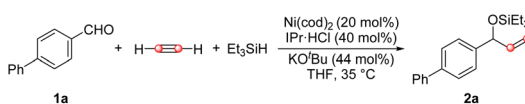
Inspired by the fact that substituted allylic alcohols could be provided by reductive coupling of aldehydes with substituted alkynes *via* an oxa-metallacycle intermediate,^{10a,h,j} we investigated whether it is feasible to employ acetylene and aldehyde through cyclometallation and subsequent silane-mediated σ -bond metathesis to construct silyl-protected vinyl alcohols (Scheme 1B). However, the cyclometallation of aldehyde with acetylene in the presence of silane to obtain key intermediate oxa-metallacycle is a really big challenge due to the following potential competitions: (1) self-polymerization of acetylene,^{11b,13} (2) direct hydrosilylation of aldehyde^{10c} or acetylene and (3) condensation or dimerization of aldehyde (Tischenko reaction and¹⁴ Aldol reaction¹⁵). More importantly, safety issues concerning explosive and flammable acetylene should not be ignored as well.^{12b,16}

Herein, we report the synthesis of vinyl-substituted alcohols enabled by a nickel-catalyzed reductive coupling of aldehyde with acetylene by utilizing hydrosilane as an efficient terminating reductant. Compared with the previously reported reductive coupling method requiring addition of an alkyne utilizing syringe pump, this protocol only needs slow addition of premixed solution of acetylene and aldehyde dropwise. Both aryl and aliphatic aldehydes with diverse functional groups react smoothly under mild conditions. The robustness of this strategy has also been exhibited by gram-scale reactions and further transformations of the resulting vinyl alcohols into diversely functionalized molecules. The mechanistic studies demonstrate that hydrogen comes from silane, which supports the postulation that the oxa-nickelacycle originated from cyclometallation is terminated by silane-mediated σ -bond metathesis.

Results and discussion

To start our investigation, 4-biphenylcarboxaldehyde **1a** and triethylsilane were chosen as model substrates along with acetylene as a vinyl synthon (Table 1). After optimization, we were pleased to find that the use of Ni(cod)₂ (20 mol%) and IPr·HCl (40 mol%) as precatalysts, KO^tBu (44 mol%) as the base, and triethylsilane (4 equiv.) as the terminating reductant successfully facilitated the formation of desired product **2a** in 74% yield at 35 °C (entry 1). No consumption of aldehyde **1a** was observed when utilizing Ni(0) generated from reduction of Ni(II) with Zn dust (entry 2). Among several Ni(0) precatalysts, Ni(cod)₂ was found to be the most efficient (entry 3, see the ESI for details[†]). The employment of the 20 mol% Ni(0) precatalyst might be attributed to the potential deactivation of Ni(0) species. The relatively unstable Ni(0) particles might agglomerate to form Ni black during the reaction.¹⁷ Ni black is devoid of catalytic activity which leads to the loss of catalytically active Ni(0) species.^{17a} When acetylene was charged in a balloon to conduct the reaction, low yield was afforded with vast amounts of insoluble black residue observed (entry 4), which might be attributed to the competing polymerization of acetylene. Most phosphine- and nitrogen-based ligands were ineffective for this process, while N-heterocyclic carbene (NHC) ligands proved to

Table 1 Optimization of reaction conditions^a

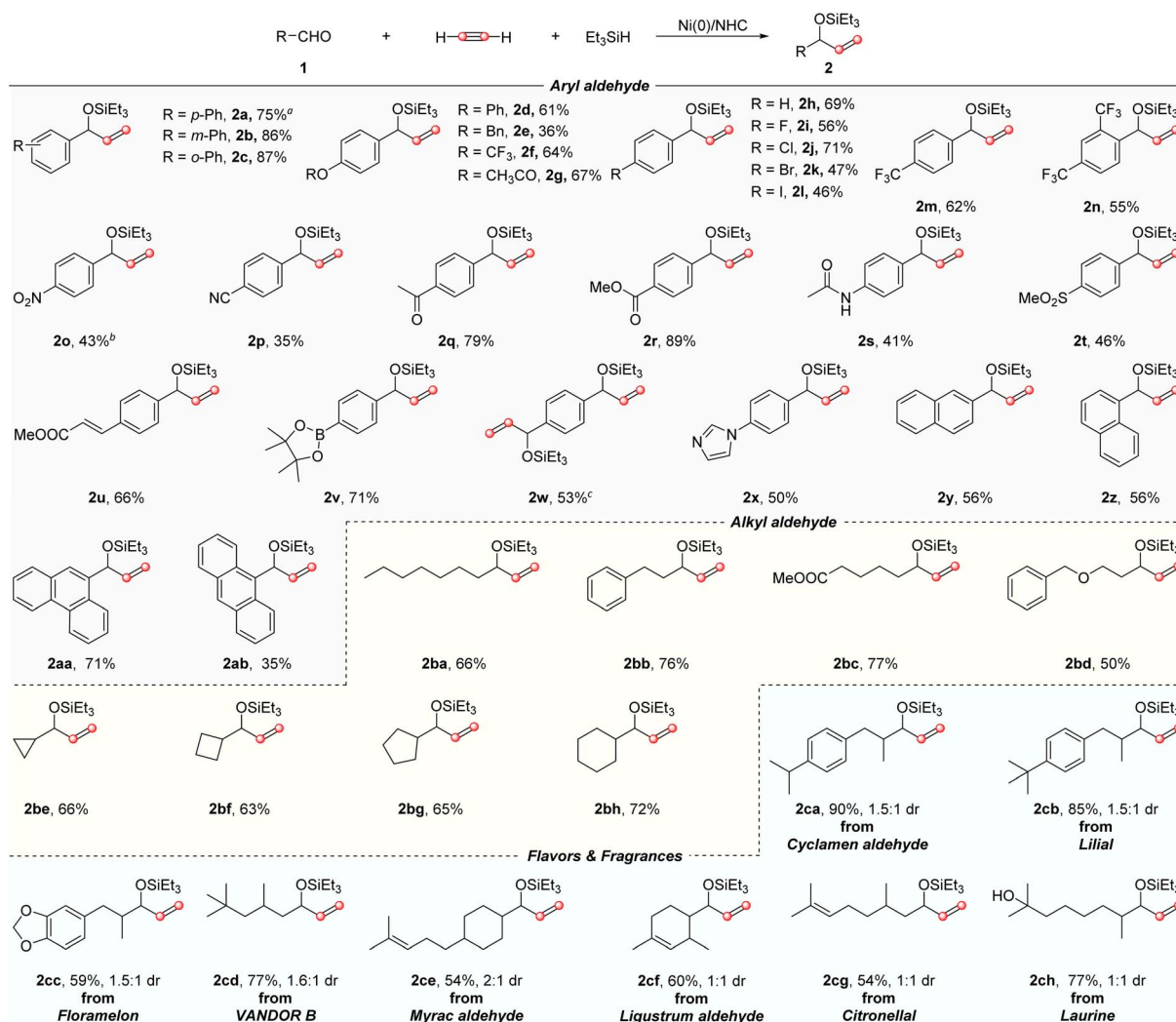
		
Entry	Deviation from the standard conditions	Yield (%)
1	None	74 (75) ^b
2	Ni(acac) ₂ /Zn instead of Ni(cod) ₂	0
3	Ni(cod)DQ instead of Ni(cod) ₂	13
4	A gaseous acetylene balloon instead of acetylene saturated solution in THF	18
5	IMes·HCl instead of IPr·HCl	17
6	IAd·HBF ₄ instead of IPr·HCl	40
7	NaO ^t Bu instead of KO ^t Bu	39
8	DCE instead of THF	21
9	Toluene instead of THF	32
10	10 mol% Ni(cod) ₂	34
11	1 equiv. acetylene	53
12	2 equiv. Et ₃ SiH	49
13	Room temperature instead of 35 °C	56

^a Reaction conditions: **1a** (0.3 mmol), saturated solution of acetylene in THF (0.6 mmol), Et₃SiH (1.2 mmol), Ni(cod)₂ (20 mol%), IPr·HCl (40 mol%), KO^tBu (44 mol%), THF (1.5 mL), 35 °C. The yield was determined by ¹H NMR spectroscopy with 4-nitrotoluene as the internal standard. ^b Isolated yield.

be effective (see the ESI for details[†]). Screening of various N-heterocyclic carbene (NHC) ligands showed that IPr provided the best result. It was supposed that the steric effect played a significant role in this reaction because both less sterically hindered ligand IMes and more crowded ligand IAd gave inferior results (entries 5 and 6). As for the base, KO^tBu was the best choice for this protocol (entry 7). Changing the solvent to DCE and toluene led to diminished yields (entries 8 and 9). The yield could not be further improved by varying other reaction parameters including the substrate ratio, catalyst loading and temperature (entries 10–13).

With the optimized reaction conditions in hand, the generality of this three-component reaction was then explored (Scheme 2). The reaction demonstrated broad substrate scope and excellent functional group tolerance. For example, in addition to 4-biphenylcarboxaldehyde **1a**, a variety of different aryl aldehydes were able to give the desired vinyl alcohols in 36–89% yields (**2a–2ab**). All the *para*-, *meso*-, and *ortho*-substituted phenyl aldehydes were converted into the corresponding products **2a–c** in 75–87% yields. Moderate yields could be obtained when the hydrogen was replaced by OBn or OPh groups (**2d–e**). The parent benzaldehyde was also a good substrate, providing the desired product **2h** in 69% yield. Aryl aldehydes bearing electron-withdrawing groups such as halogens, trifluoromethyl, and trifluoromethoxy were all well tolerated, giving the corresponding products in 46–71% yields (**2f**, **2i–n**). The decreased yields obtained from **2k–l** may be ascribed to the competing oxidative addition of the C–X bond (X = Br, I). The reaction offered excellent functional group tolerance; a broad range of synthetically valuable functional groups typically sensitive to the Grignard reagent could be well-tolerated,





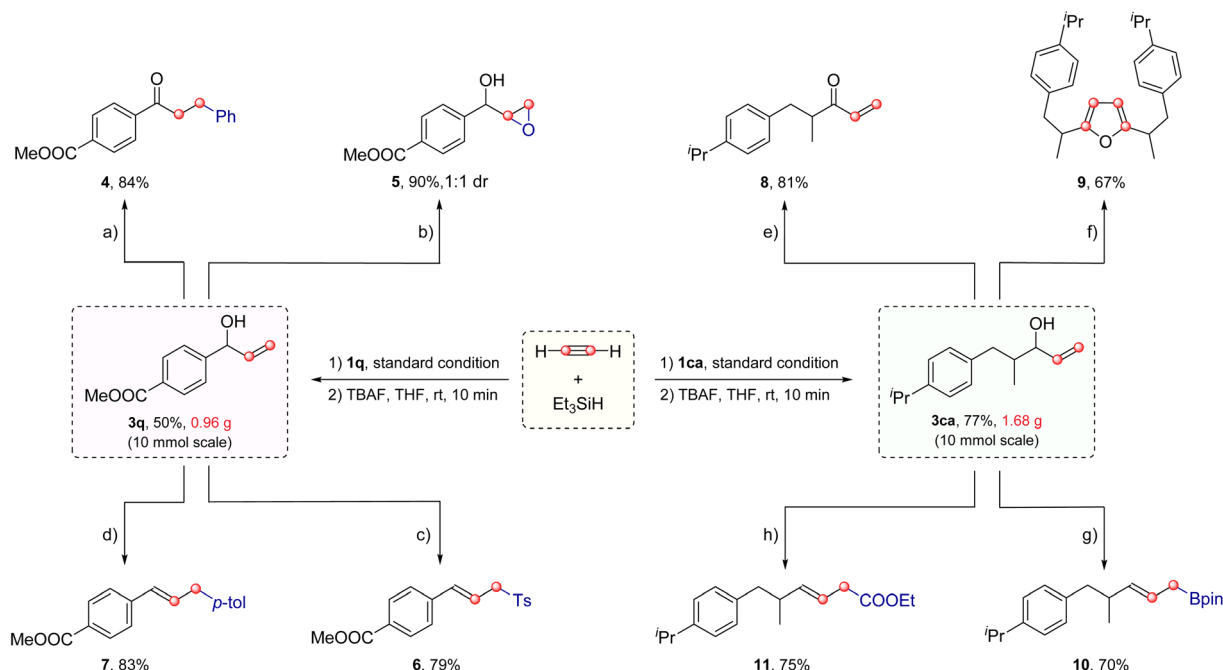
Scheme 2 Substrate scope. Reaction conditions: **1a** (0.2 mmol), acetylene (0.4 mmol), Et_3SiH (0.8 mmol), $\text{Ni}(\text{cod})_2$ (20 mol%), $\text{IPr}\cdot\text{HCl}$ (40 mol%), KO^tBu (44 mol%), THF (1.0 mL), 35°C . All yields shown are of isolated products. ^aOn a 0.3 mmol scale. ^bOn a 0.1 mmol scale. ^c40 mol% pre-catalyst, on a 0.1 mmol scale.

including ester, nitro, cyano, ketone, amide, and enoate furnishing the target products with functional groups that remained untouched in 35–89% yields (**2g**, **2o–s**, **2u**). Sulfone substituted arylaldehyde was also capable of participating in this reaction and gave the expected product **2t** as well. The strong affinity of nitrogen to $\text{Ni}(0)$ may be responsible for the modest yields obtained from nitrogen-containing aldehydes. It is noteworthy that *p*-pinacol boronate-substituted benzaldehyde could furnish the product **2v** in 71% yield. As pinacol boronate is a highly useful synthetic handle, it might permit access to diverse aryl vinyl alcohol derivatives. Interestingly, when terephthalaldehyde was employed in the reaction, bi-functionalization occurred smoothly to afford the expected di-substituted vinyl alcohol **2w** in 53% yield. Benzaldehyde substituted with imidazole was also a suitable substrate, giving the target product **2x** in 50% yield. Additionally, the fused aromatic aldehydes could be successfully applied in this transformation as well, leading to the corresponding products **2y–2ab** in 35–71% yields. Aliphatic aldehyde, which represents a type of challenging

substrate under basic conditions because of the potential self-aldol condensation, could also be converted to aryl vinyl alcohol derivatives successfully. Both primary and secondary aldehydes participated well in this allylation reaction, providing the corresponding products **2ba–bh** in 50–77% yields. To further demonstrate the feasibility of this protocol, late-stage modifications using some important aliphatic aldehydes applied for flavor and fragrance,¹⁸ such as cyclamen aldehyde,^{18b} lilial,^{18c} floramelon,^{18d} VANDOR B,^{18e} myrac aldehyde,^{18f} ligustrum aldehyde^{18g} and citronellal^{18h} were also successfully accomplished (**2ca–cg**). The coordination of the $\text{C}=\text{C}$ bond in the substrates with the Ni center might reduce the catalytic activity which led to relatively low yields. Notably, as a common food additive,¹⁸ⁱ laurine with a free hydroxyl could be tolerated as well, leading to the corresponding product **2ch** in 77% yield.

To showcase the robustness of this method, gram-scale preparation of the vinyl-substituted alcohols was then carried out. As shown in Scheme 3, both aryl vinyl alcohol **3q** and

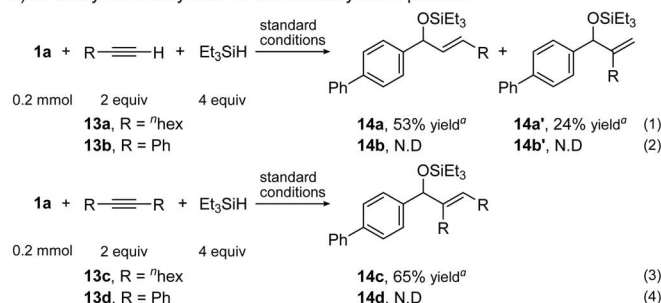




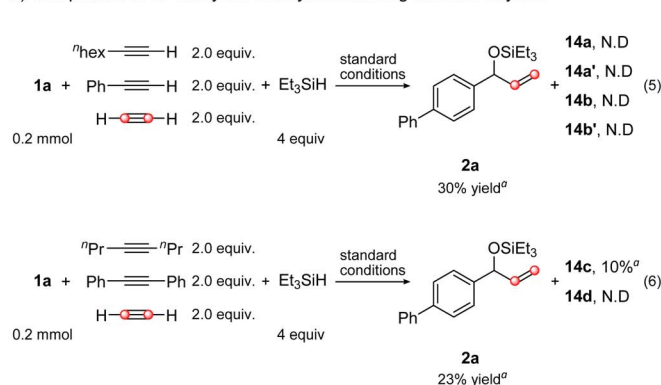
aliphatic vinyl alcohol **3ca** could be easily synthesized on a 10 mmol scale under slightly modified conditions followed by desilylation with TBAF.^{6a} With vinyl alcohols **3q** and **3ca** in hand, several further transformations were also performed. For

example, ketone **4** and epoxide **5** could be produced in 84% and 90% yields through the conventional Heck and epoxidation reactions, respectively. The dehydrative Tsuji–Trost reaction of **3q** with TsOH delivered allylic sulfone **6** in 79% yield.

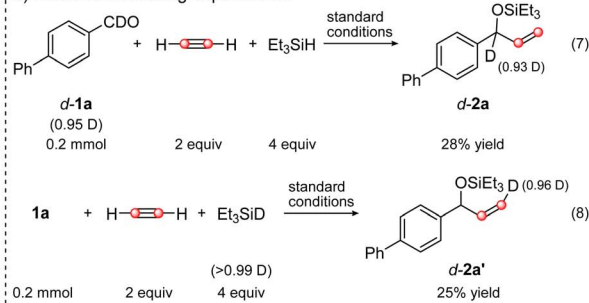
a) Ni-catalyzed alkenylation of different alkynes in parallel.



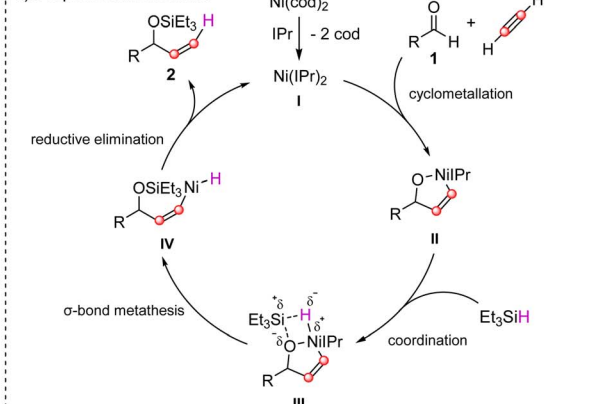
b) Competition of Ni-catalyzed alkenylation among different alkynes.



c) Deuterium-labelling experiments



d) Proposed mechanism



Scheme 4 Control experiments and proposed mechanism. ^aDetermined by ¹H NMR with 4-nitrotoluene as the internal standard.



Palladium-catalyzed allylation of **3q** with 4-tolylboronic acid afforded the coupling product **7**. Furthermore, oxidation of the vinyl alcohol **3ca** with DMP generated enone **8** in 81% yield which could then be a useful building block to assemble furan **9** in 67% yield *via* a tandem olefin cross metathesis/acid catalyzed isomerization/cyclization cascade reaction. It should be noticed that the four carbon atoms of furan all come from acetylene. Moreover, ester and boronate groups could also be introduced, furnishing *E*-homoallylic ester **10** and borate **11** in 70% and 75% yields, respectively.

To better understand this reaction, a series of control experiments were then performed. First, we wondered whether this nickel-catalyzed system was feasible for the substituted alkynes. As shown in Scheme 4a, when terminal aliphatic alkyne, 1-octyne was subjected to the standard conditions, the desired three-component reactions occurred smoothly but gave a mixture of regioisomers **14a** and **14a'** in 53% and 24% yield, respectively (eqn (1)). The attempt to assemble phenylacetylene turned out to be a failure and no desired three-component product **14b** or **14b'** was obtained (eqn (2)). In addition to the terminal alkynes, internal alkynes were also tested. Similarly, aliphatic 4-octyne was a suitable substrate for this catalytic system, leading to **14c** in 65% yield (eqn (3)), while the aromatic diphenylacetylene did not proceed in this catalytic system either (eqn (4)). These outcomes led us to conclude that this nickel-catalyzed three-component reaction seems to be only confined to acetylene or aliphatic alkyne, as both terminal and internal aromatic alkynes did not undergo the transformation. Furthermore, the competition reaction of different alkynes in one flask under standard conditions also suggested that the reaction of acetylene was faster than that of both internal and terminally substituted alkynes because the predominant product was **2a**, though 4-octyne-involved product **14c** was detected in 10% yield as well (Scheme 4b). To further elucidate the reaction mechanism, deuterium-labeling experiments were conducted (Scheme 4c). Initially, the deuterium (D)-labeled aldehyde *d*-**1a** was prepared and submitted to the reaction, and the desired deuterated product *d*-**2a** without observable loss of deuterium was isolated in 28% yield (eqn (7)). When deuterated triethylsilane (Et₃SiD) was employed in the model reaction, a deuterated product *d*-**2a'** was produced in 25% yield, with 96% D-incorporation at the terminal carbon of the C=C bond in *cis*-configuration (eqn (8)), which indicated that the silane was the hydrogen donor and validated our hypothesis on silane-mediated σ -bond metathesis.

Based on the above control experiments and previous reports,^{10a,c-i,k-m} a plausible mechanism for this protocol is proposed in Scheme 4d. Initial ligand exchange of precatalyst Ni(cod)₂ with IPr generates a stable low-valent bis-NHC-Ni species **I**, which then undergoes cyclometallation of aldehyde with acetylene, resulting in the formation of oxa-nickelacycle **II**. Subsequent coordination of triethylsilane with oxa-nickelacycle **II** delivers a transient four-center intermediate **III**. Cleavage of the Ni–O bond of **III** occurs *via* σ -bond metathesis, furnishing the alkenyl nickel intermediate **IV**. The following reductive elimination of **IV** produces the desired vinyl-substituted alcohol **2** and regenerates the active nickel species.

Conclusions

In conclusion, we have developed an efficient silane-mediated σ -bond metathesis-enabled synthesis of vinyl-substituted alcohols by nickel catalysis with readily available substrates and abundant acetylene. In this catalytic system, acetylene is incorporated into the vinyl alcohol as a useful C2 building block. This mild synthetic method features good functional tolerance and broad substrate scope, which can be achieved on a gram-scale. The resulting vinyl alcohols are important and versatile scaffolds in organic synthesis, which can be easily transformed into diversely functionalized molecules. Competition experiments between acetylene and other substituted alkynes exhibit the superior reactivity of acetylene. The deuterium-labelling experiments show that the *cis*-hydrogen at the terminal carbon of the C=C bond is created *via* silane-mediated σ -bond metathesis and subsequent reductive elimination. It is expected that the application of acetylene in this efficient catalytic transformation might spur interest in the development of novel methodologies employing acetylene as a C2 building block to assemble diverse high value-added molecules.

Data availability

All the data including experimental procedures, NMR, IR, and HRMS, are recorded in the ESI.†

Author contributions

Conceptualization, funding acquisition, resources and supervision were performed or provided by S. Zhu; project administration; investigation and formal analysis were performed by Z. Lin and B. L.; validation and data curation were performed by Z. Lin, Y. Wang and S. Li.; the conception of the experiments, discussion of the results and preparation of the manuscript were performed by Z. Lin, B. Liu. and S. Zhu.

Conflicts of interest

There are no conflicts to declare.

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