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Organocatalytic Synthesis of Alkynes

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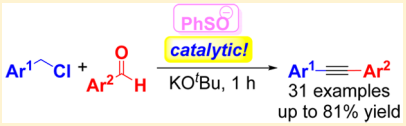
Supporting Information

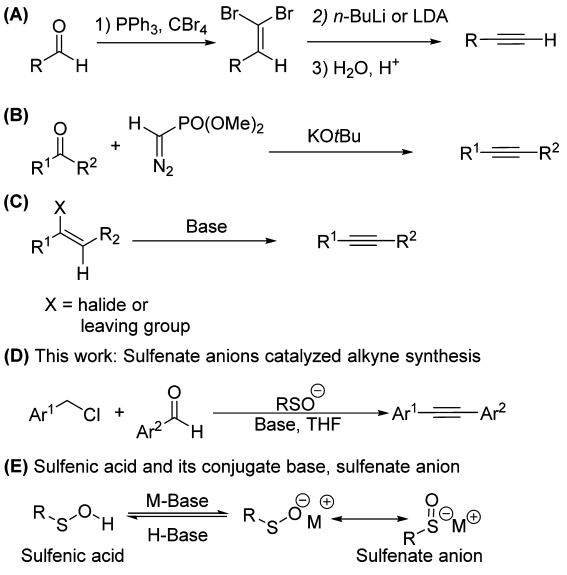
ABSTRACT: Carbon−carbon triple bonds of alkynes are ubiquitous. They serve as valuable starting materials that can be transformed into a vast array of diverse materials, with applications ranging from medicinal chemistry to electronic materials. The methods used to prepare alkynes involve stoichiometric reactions and the most popular install only a single carbon rather than uniting larger fragments. These methods are useful, but they are limited by harsh conditions or the need to prepare reagents. Introduced herein is the first catalytic method to prepare carbon−carbon triple bonds from precursors that do not contain such linkages. By coupling benzaldehyde and benzyl chloride derivatives under basic conditions with an organocatalyst, good yields of alkynes are obtained. The catalyst, a highly reactive sulfenate anion, is readily generated under the reaction conditions from air-stable precursors. This method represents an attractive organocatalytic alternative to well-established stoichiometric approaches to alkynes and to transition-metal-based alkyne functionalization methods in various applications.



The carbon−carbon triple bond of alkynes is among the most useful functional groups in chemistry and plays a significant role in modern society. Alkynes occur in natural products and marketed pharmaceuticals. For example, naturally occurring calicheamicin[1] is a highly reactive antitumor agent while norethynodrel was the first oral contraceptive, and Efazirenz is an antiretroviral introduced by Merck. Alkynes can be transformed into a vast array of value added organic compounds by well-established stoichiometric methods or in the presence of metal catalysts or organocatalysts.[2] A renewed interest in alkyne chemistry stems from emerging applications in organic materials. Alkynes are vital in the synthesis of π-conjugated oligomers and polymers with applications in photonics, optoelectronics, and molecular electronics, to name a few.[3] As a result of the long-standing interest in the reactions of alkynes, their synthesis is of fundamental importance.

The majority of alkyne syntheses can be categorized by three general approaches. The first forms the triple bond from isolated reagents, which include the pioneering and very useful Corey−Fuchs reaction with aldehyde substrates (Scheme 1A).[4] Similarly, the Seyferth−Gilbert and Bestmann−Ohira homologations employ aldehydes or ketones for terminal/internal alkyne generation (Scheme 1B).[5] Although these methods are reliable, they are stoichiometric and use harsh (*n*-BuLi) or potentially explosive reagents (diazo) or precursors (TsN_3). The second approach involves elimination reactions that form one or two π-bonds of the alkyne (Scheme 1C).[6] These methods employ starting materials with the carbon−carbon framework already in place, making them more labor intensive and less attractive. Finally, beautiful work to elaborate existing carbon−carbon triple bonds is well documented, most notably the Sonogashira cross-coupling[7] and alkyne metathesis.[8] Notably absent from known approaches are methods to directly convert readily available starting materials into functionalized alkynes *under catalytic conditions*. Such transformations would form all three bonds of the alkyne from substrates that do not possess preexisting triple bonds. Herein we introduce the first organocatalytic method to prepare a variety of diaryl alkynes from simple aryl or heteroaryl aldehydes and benzyl halide derivatives. Advantages of this catalytic approach over well-established methods include avoidance of transition metal catalysts and the issues associated

Scheme 1. Synthetic Approaches to Alkynes (A−D) and Sulfenate Anions (E)



Received: June 12, 2015
Published: July 24, 2015

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DOI: 10.1021/jacs.5b06137
J. Am. Chem. Soc. 2015, 137, 10346−10350

with metal residues, mild conditions, and use of readily available and inexpensive reagents.

We envisioned sulfenate anions as novel catalysts potentially suitable for the synthesis of alkynes. Sulfenate anions and their conjugate acids, sulfenic acids (Scheme 1E), are relatively unexplored, highly reactive species proposed to be transient intermediates in organic[9] and biochemistry.[10] We,[11] and others,[12] observed that sulfenate anions possess the ability to act as both nucleophiles and leaving groups in palladium catalyzed arylation reactions. This observation inspired us to hypothesize that they could also behave as catalysts. As proof-of-concept we developed the first sulfenate anion catalyzed reaction, the coupling of benzyl halides to afford *trans*-stilbenes (Figure 1, cycle A).[13] To access higher value alkynes, we

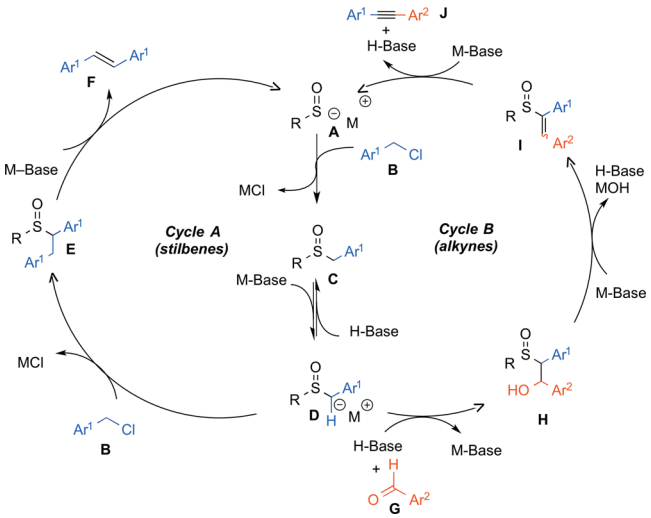
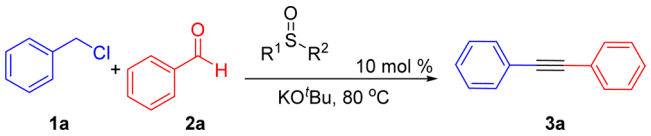


Figure 1. Proposed mechanism of the sulfenate anion catalyzed generation of *trans*-stilbenes (Cycle A) and diaryl acetylenes (Cycle B).

envisioned the catalytic coupling of benzaldehyde derivatives with benzyl halides, as depicted in a proposed catalytic cycle (Figure 1, cycle B). Generation of the sulfenate anions **A** under basic conditions in the presence of benzyl halides (**B**) will result in benzylation to give sulfoxide **C** via an SN^2 reaction pathway. Deprotonation of the sulfoxide by base generates a nucleophile (**D**). Key to the success of this process is control of the relative rates of reaction of the deprotonated sulfoxide **D** with the two electrophilic coupling partners. The reaction with benzyl chloride leads to stilbenes and consumes 2 equiv of starting material (Figure 1, cycle A). In the presence of benzaldehyde derivatives, addition of the deprotonated sulfoxide to the aldehyde **G** provides *β*-hydroxy sulfoxide **H** after proton transfer. Base promoted elimination of hydroxide from **H** is proposed to generate the vinyl sulfoxide **I**, which can undergo a second elimination to produce the desired alkyne, regenerate the sulfenate anion, and close cycle B.

To explore the viability of the proposed catalytic cycle B in Figure 1, we initiated the reaction discovery process with the coupling of benzaldehyde and benzyl chloride to form diphenyl acetylene in the presence of six bases [LiO^{t}Bu, NaO^{t}Bu, KO^{t}Bu, LiN(SiMe$_3$)$_2$, NaN(SiMe$_3$)$_2$, and KN(SiMe$_3$)$_2$] in four different solvents [THF, DME, dioxane, and cyclopentyl methyl ether (CPME)] for 10 h at 80 °C. To simplify the screening we chose 10 mol % benzyl phenyl sulfoxide as the catalyst (**C**, Ar^1 = Ph) rather than entering the catalytic cycle by generating the sulfenate anion (**A**). In this initial screen the combination of 3 equiv of KO^{t}Bu in THF was the most promising. When conducted on lab scale (0.1 mmol) diphenyl acetylene was generated in 20% assay yield (AY, as determined by GC, Table 1, entry 1). Byproducts identified from this reaction include

Table 1. Optimization of Diaryl Acetylene Synthesis of Benzyl Chloride (1a) and Benzaldehyde (2a)[a]



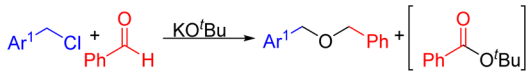
1a 2a 3a

entry	1a:2a:base	R^1/R^2	*t* (h)	3a (%)[b]
1[c]	1:2:3	Ph/CH$_2$Ph	10	20
2[d]	1:2:3	Ph/CH$_2$Ph	10	41
3	1:2:3	Ph/CH$_2$Ph	10	65
4[e]	1:2:3	Ph/CH$_2$Ph	10	62
5	1:2:3	4-C$_6$H$_4$-OMe/CH$_2$Ph	10	64
6	1:2:3	4-C$_6$H$_4$-Me/CH$_2$Ph	10	55
7	1:2:3	4-C$_6$H$_4$-F/CH$_2$Ph	10	64
8	1:2:3	4-C$_6$H$_4$-CF$_3$/CH$_2$Ph	10	11
9	1:2:3	1-Naphthyl/CH$_2$Ph	10	37
10	1:2:3	2-Pyridyl/CH$_2$Ph	10	5
11	1:2:3	Cyclohexyl/CH$_2$Ph	10	18
12	1:2:3	Ph/CH$_2$Ph	1	67
13	1:2:3	Ph/CH$_2$Ph	0.5	55
14[f]	1:2:3.1	Ph/*tert*-butyl	1	55
15[f]	1:2:3.1	Ph/CH$_2$CH$_2$COOEt	1	48
16[f]	1:2:3.1	Ph/CH$_2$CH$_2$Ph	1	68
17[f,g]	1:2:3.2	Ph/CH$_2$CH$_2$Ph	1	73(72[h])

[a]Reactions performed using 10 mol % catalyst, 3.0 equiv of base with a stock solution of 1.0 equiv of benzyl chloride **1a**, and 2.0 equiv of benzaldehyde **2a** on a 0.5 mmol scale. One tenth of the stock solution was added to reaction mixture every one tenth of reaction time. [b]Determined by GC analysis of the crude reaction mixture. [c]Reactions performed without slow addition on a 0.1 mmol scale. [d]0.1 mmol scale. [e]1.0 mmol scale. [f]Extra base added for catalyst activation. [g]20 mol % catalyst loading. [h]Isolated yield.

trans-stilbene, derived from coupling of benzyl chloride (8%), and dibenzyl ether (62%). Dibenzyl ether was presumably generated from benzyl chloride and benzyl alcohol, the latter of which could arise from a Cannizzaro reaction with benzaldehyde promoted by KO^{t}Bu (Scheme 2). Consistent with this hypothesis, use of 3-methyl benzyl chloride (Ar^1 = 3-Tol) generated the unsymmetrical dibenzyl ether, 3-TolCH$_2$OCH$_2$Ph.

Scheme 2. Proposed Reaction for Generation of Dibenzyl Ether Byproducts via the Cannizzaro Reaction



Based on these observations, we decided to limit the exposure of the substrates to the base by slow addition of a 2:1 ratio of benzaldehyde to benzyl chloride. Slow addition of the substrates to the catalyst and KO^{t}Bu mixture led to 41% AY of diphenyl acetylene (entry 2). Increasing the substrates stock solution concentration to 0.5 M benzyl chloride resulted in a 65% assay yield (entry 3). Further increasing the concentration of the substrates solution to 1.0 M resulted in reduced AY

DOI: 10.1021/jacs.5b06137
J. Am. Chem. Soc. 2015, 137, 10346−10350

(entry 4). It should be noted that although the slow addition decreased the formation of byproducts *trans*-stilbene and dibenzyl ether, we have been unable to eliminate their formation.

We next examined the influence of the catalyst structure on performance, as judged by the assay yield. Employing Ar–S(O)CH_2Ph with the Ar supporting 4-OMe, 4-Me, 4-F, 4-CF_3, 1-naphthyl, and 2-pyridyl indicated that the parent phenyl was as good or better than the other catalysts (entry 3 vs 5–10). Use of the aliphatic *c*-Hex-S(O)CH_2Ph led to 18% AY (entry 11). Thus, the parent *S*-Ph-based catalyst was used for the remainder of this study.

With the optimized catalyst, the reaction time was examined. It was found that the reaction using benzyl phenyl sulfoxide reached completion in 1 h at 80 °C, giving 67% conversion (entries 12–13). Changing the ratios of benzyl chloride, benzaldehyde, and base revealed the optimal conditions employed 3.0 equiv of KO^{t}Bu with a 1:2 ratio of benzyl chloride to benzaldehyde (see Supporting Information).

Although benzyl sulfoxide proved to be a good catalyst, its use is problematic in combination with other benzyl chloride derivatives. Benzyl sulfoxide will lead to a phenyl-substituted alkyne in the first turnover, PhC≡CAr^2, which is difficult to separate from the desired product, Ar^1C≡CAr^2 (Figure 2). To

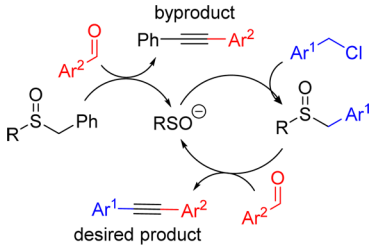
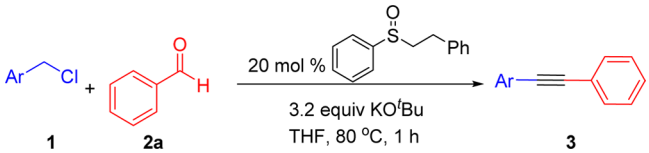


Figure 2. Byproduct formation using benzyl sulfoxide as catalyst.

avoid this problem, a better strategy is to enter the catalytic cycle at the sulfenate anion **A**. We therefore examined different precatalysts to generate the sulfenate anion through E2 elimination and found 2-phenylethyl phenyl sulfoxide outperformed (AY = 68%) other sulfenate anion precatalysts (48–55% AY, entries 14–16). Raising the catalyst loading to 20 mol % rendered 73% diphenyl acetylene AY (entry 17). To compensate for the 0.2 equiv base consumed in conversion of the precatalyst to the catalyst, 3.2 equiv of base were employed. Thus, our standard conditions involve 20 mol % 2-phenylethyl phenyl sulfoxide precatalyst and 3.2 equiv of KO^{t}Bu with slow addition of coupling partners as a stock solution containing 0.5 M benzyl chloride (limiting reagent) and 2.0 equiv of aldehyde to 20 mol % sulfenate anion precursor in THF at 80 °C for 1 h.

With the optimized conditions, we next investigated the scope of the alkyne synthesis with a series of benzyl chlorides (Table 2). Electron-donating groups on the benzyl chloride, such as 4-Me, 4-^{t}Bu, and 4-OMe, provided 61–77% isolated yields (**3b–3d**, entries 2–4). Substrates bearing 4-F, 4-Cl, and 4-Br afforded the corresponding products in 69–73% yield (**3e–3g**, entries 5–7). The bulkier 2-TolCH_2Cl (**3h**) was a poor substrate (23% yield, entry 8) due to steric hindrance. Smaller substituents, such as 2-F (**3i**, 63%) or 1-naphthyl (**3j**, 68%) derived benzyl halides, exhibited better reactivity. Benzyl chlorides substituted at the 3-position with Me, F, or CF_3

Table 2. Substrate Scope of Benzyl Chlorides in Diaryl Acetylene Synthesis



1 2a 3

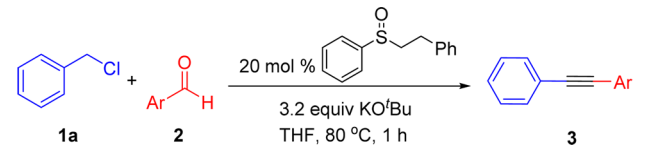
entry	prod.	Ar	yield (%)[a]
1[c]	**3a**	Ph	72
2	**3b**	4-C_6H_4-Me	61
3	**3c**	4-C_6H_4-^{t}Bu	69
4	**3d**	4-C_6H_4-OMe	77
5	**3e**	4-C_6H_4-F	70
6	**3f**	4-C_6H_4-Cl	69
7	**3g**	4-C_6H_4-Br	73
8	**3h**	2-C_6H_4-Me	23
9	**3i**	2-C_6H_4-F	63
10	**3j**	1-naphthyl	68
11	**3k**	3-C_6H_4-Me	65
12	**3l**	3-C_6H_4-F	62
13	**3m**	3-C_6H_4-CF_3	53

[a]Isolated yields.

furnished alkyne products in 53–65% yield (**3k–3m**, entries 11–13).

Aldehyde coupling partners were examined next (Table 3). Benzaldehydes with electron-donating (4-OMe and 4-SMe,

Table 3. Substrate Scope of Benzaldehydes in Diaryl Acetylene Synthesis



1a 2 3

entry	prod.	Ar	yield (%)[a]
1	**3d**	4-C_6H_4-OMe	61
2	**3n**	4-C_6H_4-SMe	70
3	**3e**	4-C_6H_4-F	67
4	**3f**	4-C_6H_4-Cl	74
5	**3g**	4-C_6H_4-Br	76
6	**3o**	4-C_6H_4-CF_3	72
7	**3p**	4-C_6H_4-CO_2Me	31
8	**3j**	1-naphthyl	81
9	**3q**	2-naphthyl	75
10	**3r**	3-C_6H_4-(1-pyrrolyl)	76
11	**3s**[b]	3-C_6H_4-OH	66
12	**3t**	3-C_6H_4-CN	68
13	**3u**	2-pyridyl	54
14	**3v**	3-pyridyl	70
15	**3w**	5-isoquinolinyl	73
16	**3x**	2-furanyl	80
17	**3y**	2-thienyl	77

[a]Isolated yield. [b]5.2 equiv of base.

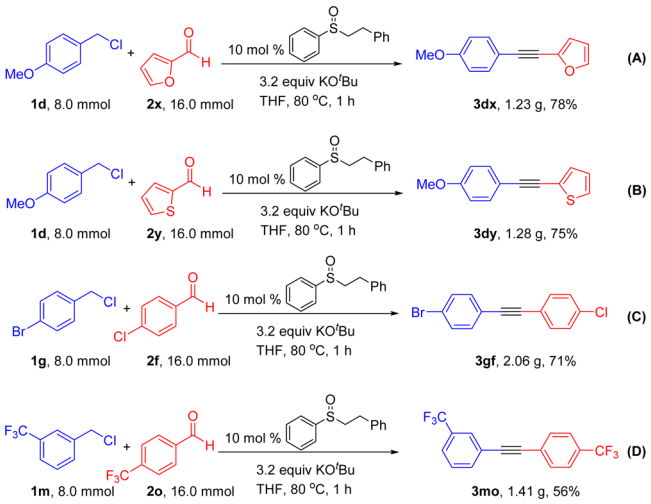
61–70% yield, **3d** and **3n**) and -withdrawing substituents (4-F, 4-Cl, 4-Br, 4-CF_3, 67–76%, **3e–3g**, **3o**) readily furnished alkyne products. However, 4-CO_2Me benzaldehyde resulted in a poor yield, due to the basic reaction conditions. With 1- and 2-naphthyl aldehydes, 81% and 75% yields (**3j** and **3q**),

DOI: 10.1021/jacs.5b06137
J. Am. Chem. Soc. 2015, 137, 10346–10350

respectively, were obtained. Heterocyclic 3-(1-pyrrolyl) benzaldehyde gave the corresponding alkyne in 76% yield (**3r**). Interestingly, a 3-hydroxy group was tolerated, providing alkyne (**3s**) in 66% yield without formation of the benzyl ether. Base-sensitive 3-cyano benzaldehyde also gave the desired product in 68% yield. We were particularly interested in applying our method to heterocycles. We were pleased to find that 2-pyridyl, 3-pyridyl, 5-isoquinilinyl, 2-furanyl, and 2-thienyl substituted alkynes could be accessed in moderate to good yields (54–80%). Under our current conditions, 4-NO_2-benzaldehyde, indole-5-carboxaldehyde, and 4-imidazolecarboxaldehyde were not tolerated.

The scalability of this novel alkyne synthesis was evaluated by performing four reactions with 8 mmol of benzyl chlorides and 10 mol % precatalyst (Scheme 3). The reaction with 4-methoxy

Scheme 3. Gram Scale Reactions

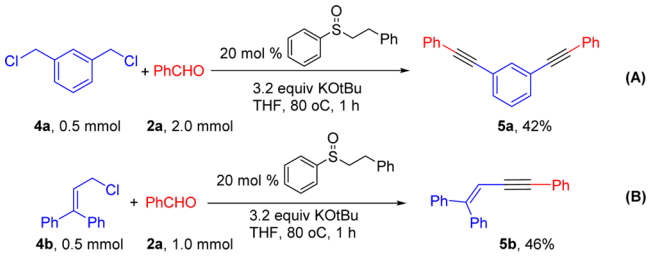


benzyl chloride and 2-furaldehyde resulted in formation of the desired product in 78% yield (**3dx**, 1.23 g). Very similar results were obtained with the 2-thienyl derivative (**3dy**, 75% yield, 1.28 g). Coupling of 4-bromobenzyl chloride with 4-chlorobenzaldehyde proceeded smoothly in 71% yield (**3gf**, 2.06 g). Synthesis of this alkyne by a Sonogashira coupling reaction could be complicated by the presence of the aryl bromide. Product **3gf** could be easily elaborated using cross-coupling chemistry. With the more challenging 3-trifluoromethyl benzyl chloride coupling under the standard conditions with 4-trifluoromethyl benzaldehyde provided the alkyne product in 56% yield (**3mo**, 1.41 g). These results indicate the reactions perform better on scale.

Diynes are important precursors to polycyclic aromatic hydrocarbons.[14] We therefore applied our method to α,α'-dichloro-*m*-xylene **4a**, which gave the double-coupling product **5a** in 42% yield (Scheme 4A). In addition to benzyl chlorides, preliminary studies with the allyl chloride derivative 1,1-diphenyl-3-chloro-1-propene **4b** were undertaken. In combination with benzaldehyde under conditions optimized for benzyl chlorides, the desired enyne **5b** was generated in 46% yield (Scheme 4B).

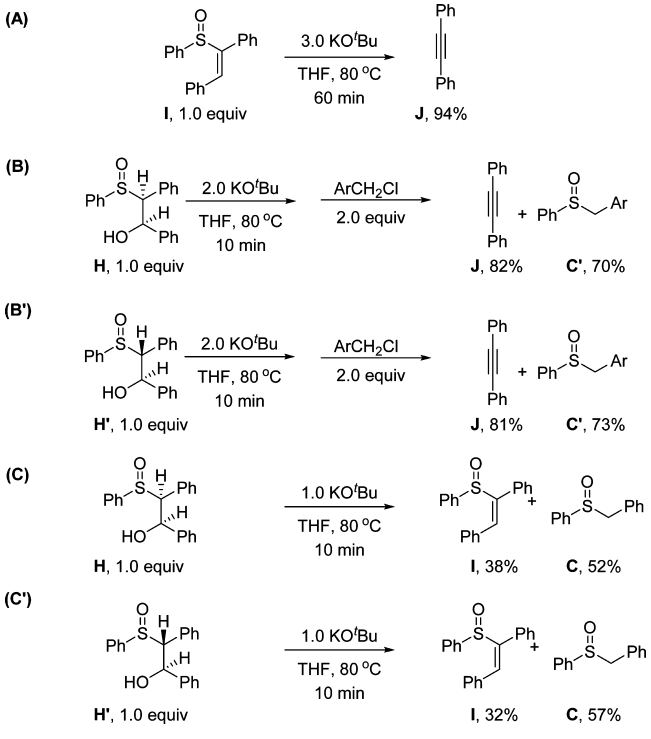
To gain insight into the mechanism of the catalytic alkyne synthesis, we set out to investigate the catalyst resting state. The reaction between benzyl chloride and benzaldehyde was performed under the standard conditions except the reaction was quenched with H_2O after only 15 min. Among the sulfur-

Scheme 4. Special Substrates Applied in Sulfenate-Anion-Catalyzed Alkyne Synthesis



containing compounds, the (*Z*)-vinyl sulfoxide **I** (Figure 1) was isolated in 62% yield as a single diastereomer (see Supporting Information). Benzyl phenyl sulfoxide (33%, Figure 1, **C**) was also observed by ^{1}H NMR. Based on these findings, the vinyl sulfoxide **I** is the most likely resting state for the catalyst. Independently synthesized vinyl sulfoxide (**I**) was shown to generate diphenyl acetylene under basic conditions in 94% yield (Scheme 5A).

Scheme 5. Preliminary Mechanistic Study of Sulfenate Anion-Catalyzed Diaryl Acetylene Formation



To probe the water elimination step of the proposed mechanism, both *threo*- and *erythro*-2-phenylsulfinyl-1,2-diphenyl-1-ethanol (**H**) were synthesized by reaction of thiophenoxide with either *cis*- or *trans*-stilbene oxide followed by oxidation.[15] When *threo*- or *erythro*-2-phenylsulfinyl-1,2-diphenyl-1-ethanol (**H**) were treated with 2 equiv of base and quenched with 4-methoxy benzyl chloride, diphenyl acetylene (**J**) was generated via elimination in 81–82% yield (Scheme 5B and 5B'. 4-Methoxy benzyl phenyl sulfoxide (**C**′) was also isolated in 70–73% yield, suggesting the sulfenate anion was generated during the reactions. Treatment of either *threo*- or *erythro*-2-phenylsulfinyl-1,2-diphenyl-1-ethanol (**H**) with only 1.0 equiv of KO^{t}Bu resulted in 32–38% conversion to vinyl

DOI: 10.1021/jacs.5b06137
J. Am. Chem. Soc. 2015, 137, 10346–10350

sulfoxide (**I**) and 52−57% benzyl phenyl sulfoxide (**C**). Formation of benzyl phenyl sulfoxide suggests that the condensation between the deprotonated sulfoxide and the aldehyde is reversible (Scheme 5C). The reversible condensation between the deprotonated sulfoxide and benzaldehyde derivative suggests that the preferred diastereomer leading to elimination to generate the vinyl sulfoxide can be accessed. These results lend credence to the proposed reaction mechanism in Figure 1.

In conclusion, despite the long history of the alkyne functional group and its utility in modern society, we are unaware of catalytic methods that generate all three bonds that make up the alkyne from nonacetylinic precursors. Herein, we developed the first organocatalytic approach to synthesize alkynes from benzyl chlorides and benzaldehyde derivatives. The reaction is catalyzed by sulfenate anions and leads to diaryl and heteroaryl aryl alkynes in moderate to good yields. The method is scalable and can be conducted with a reduced loading of the organocatalysts. Preliminary mechanism studies demonstrate that the catalyst resting state is (*Z*)-vinyl sulfoxide. It is particularly noteworthy that this method provides diaryl acetylenes, which are usually synthesized by the Sonogashira coupling of terminal alkynes. The advantage of our method over this well-known cross-coupling reaction is that it does not employ costly transition metals or designer phosphine ligands, does not require the synthesis of terminal alkyne precursors, and circumvents problems associated with metal residues that can be problematic in the pharmaceutical and electronics industries.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06137.

Procedures and full characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation [CHE-1152488] for the financial support.

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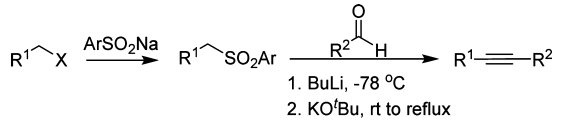

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DOI: 10.1021/jacs.5b06137
J. Am. Chem. Soc. 2015, 137, 10346−10350