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Silver catalyzed proto- and sila-Nakamura-type α -vinylation of silyl enol ethers with dichloroacetylene. Divergent formation of stereochemically pure tri- and tetrasubstituted olefins.

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Abstract

The silver-catalyzed reaction of silyl enol ethers with dichloroacetylene (DCA) is described. When DCA was used as a solution in diethyl ether, we found that the silyl group was transferred to the vinyl group, resulting in stereochemically pure tetrasubstituted olefins. However, when DCA was used as a solution in the more polar acetonitrile, protonation was the major pathway, and trisubstituted olefins were the dominant products.

Graphical Abstract

Tri- and tetrasubstituted alkenes are ubiquitous structures in organic chemistry, thus a significant amount of research has gone into developing synthetic routes towards alkenes. However, the stereocontrolled synthesis of multi-substituted alkenes remains a significant challenge in organic synthesis.¹ Traditional methods of olefin syntheses, including Wittig,² Julia,³ and Peterson olefinations,⁴ require prefunctionalized reagents, produce significant amounts of byproducts, and often lead to mixtures of isomers. More recent approaches minimize preactivation by “building out” from suitable C₂ building blocks, either *via* the hydro- and carbometalation of alkynes⁵ or *via* the synthesis of stereodefined vinyl halides

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Author Contributions

The manuscript was written through contributions of all authors.

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Supporting Information

The Supporting Information is available free of charge on the internet. Further catalyst optimization screening data, synthetic details and characterization data, and crystallographic data (PDF). Copies of ¹H and ¹³C NMR spectra (PDF).

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

and vinyl silanes that can be sequentially functionalized *via* transition metal cross-coupling reactions.⁶

Organ⁷ and others⁸ have developed modular syntheses of polysubstituted olefins from commercially available or easily accessible 1,1- and 1,2-dihaloalkenes. Trichloroethylene has also been identified as an inexpensive and useful C₂ building block for constructing polysubstituted olefins. Trichloroethylene can be converted into dichloroacetylene (DCA) *in situ*, and reacted with alcohols and amines to generate dichlorovinyl ethers and amides that could be further elaborated *via* palladium-catalyzed cross coupling reactions.⁹

We imagined that if DCA could be engaged in cycloaddition chemistry, we could access a wide variety of dichlorinated (hetero)cycles. The electron-rich Danishefsky's diene has been frequently used in the synthesis of oxygen-substituted six-membered rings *via* Diels-Alder cycloadditions with olefins.¹⁰ Hilt and co-workers have described a series of cobalt-catalyzed reactions of simple 1,3-butadienes¹¹ and mono-*O*-functionalized 1,3-butadienes¹² with alkynes that yielded six-membered Diels-Alder adducts as either the 1,4-hexadiene or benzene, depending on the location of the oxygen substituent (Scheme 1, A). We therefore sought to develop an analogous benzannulation reaction of dichloroacetylene (DCA) *via* a Diels-Alder cycloaddition with Danishefsky's and related dienes to synthesize substituted *o*-dichlorobenzenes (Scheme 1, B). However, while we were only able to detect a trace amount of the targeted dichlorobenzene derivative by GC-MS, we were pleased to observe the addition of the enol ether across DCA to yield tri- and tetrasubstituted olefins **3a** and **3b**.

DCA has been previously shown to react with lithium enolates only under strongly basic conditions.¹³ An alternate approach to the reaction of enolates with alkynes is the Nakamura reaction (Scheme 1, C, right). This process however, is also very limited as it requires a highly activated carbonyl compounds and monosubstituted alkynes.¹⁴ Other methods of synthesizing α -vinyl carbonyl compounds include palladium¹⁵ or base¹⁶ catalyzed cross-coupling with vinyl electrophiles. Dihalosilylolefins are highly useful synthetic intermediates, generally prepared by the addition of dihalides¹⁷ to or dihalide equivalents¹⁸ to silylacetylenes (Scheme 1, C, left).

Our serendipitous discovery that silyl enol ethers added across DCA in the presence of a catalyst to generate β,γ -unsaturated ketones both with and without silyl transfer inspired us to develop conditions that could selectively generate either protonated or silylated dichloroalkenes. We began our optimization process by evaluating the performance of several Lewis acids in the reaction between the silyl enol ether of acetophenone, **1b**, and DCA **2** (Table 1). For the convenience and safety of using DCA,¹⁹ we prepared DCA as an ether solution (~1 M), which can be stored in a freezer for one week.²⁰ To our surprise, the copper complex that we discovered the reaction with failed to catalyze the reaction between **1b** and **2** (Entry 1). Extensive screening of more than 40 catalysts (see Electronic Supporting Information (ESI) for additional details) revealed that copper triflate (Entry 2) and silver triflate (Entry 3) both led to moderate isolated yields for the product **3a** (30% and 28% yield, respectively) after 24 hours; most of the screened catalysts were ineffective, and only unreacted **1b** and/or acetophenone **5** could be detected. When copper triflate was employed as the catalyst, increasing the reaction time from 24 to 48 hours was ineffective (Entry 4);

this is attributed to the rapid copper catalyzed decomposition of silyl enol ether **1b**. However, when silver triflate was employed as the catalyst, decomposition of **1b** was slower, and thus increasing the reaction time from 24 to 48 hours improved the isolated yield of **3b** from 28% to 40% (Entry 3 versus 5) as determined by ¹H NMR analysis. We also detected a third byproduct, **3b'**, by ¹H NMR spectroscopy.²¹

Continuing with silver triflate as our optimum catalyst, we turned to screening other reaction variables. Changing the solvent to a mixture of diethyl ether with other solvents did not improve the yield (see ESI for additional solvent screening details). The application of nonpolar solvents, such as toluene (Entry 6) and hexane (Entry 7), gave only 17% and 10% conversion to **3b**, and increased production of **3b'**. A slightly more polar solvent, CH₂Cl₂, gave a better result (30% yield of **3b** and comparable production of **3b'**, entry 8). More polar solvents, such as MeCN (Entry 9) and DMF (Entry 10), were much less effective. In most of the screening conditions, acetophenone **5** was the major component in the crude reaction mixture, which was presumably produced *via* the decomposition of silyl enol ether **1b**.

As changing the solvent led to no improvement in the conversion to **3b**, we next screened several additives to evaluate their effectiveness in both reducing the decomposition of **1b** and the formation of **3b'** (see ESI for additional details). When substoichiometric amounts of exogenous TMSCl were used as an additive,²² the yield of product **3b** was increased to 50% (Entry 11). More significantly, **3b'** was no longer detected by ¹H NMR analysis. Because acetophenone **5** was still observed as the major byproduct, we next decreased the reaction temperature in an attempt to slow decomposition of **1b**; however, no improvement in the yield of **3b** was observed (see ESI for details). We reasoned that if the decomposition of **1b** to **5** was faster than addition across DCA (**2**), increasing the reaction temperature could favor the formation of **3b**. Indeed, increasing the reaction temperature to 80 °C, led to 69% isolated yield of **3b**, and reduction in the formation of **5** (Entry 12); however, small amounts of **3b'** were formed. Applying exogenous TMSCl as an additive to the higher temperature conditions both reduced decomposition of **1b** and prevented the formation of **3b'** (Entry 13 versus entries 11 and 12).

As a final attempt to decrease the decomposition of **1b**, we considered mixed solvent systems. While the polar solvent MeCN gave the greatest yield of protonated **4b**, the use of MeCN also led to decreased formation of **5** (Entry 9 vs entries 6–8). *Via* a detailed screening of MeCN as a co-solvent (see ESI for additional details), we found that adding 10% MeCN gave the best isolated yield of **3b** when used in conjunction with TMSCl at 80 °C (Entry 15; optimized Conditions A). Finally, using DCA (**2**) as a solution in MeCN at 80 °C led to the greatest conversion to trisubstituted olefin **4b** (Entry 16; optimized Conditions B). All screening reactions and subsequent studies on the scope of the reaction were performed on a 0.2 mmol scale, though we found that we could increase the scale to 0.5 mmol and 1 mmol, with little effect on the yield, and could decrease the catalyst loading to 5 mol% with only a small decrease in the isolated yield of **3b**. However, in consideration of the safety issue of DCA at high temperature, we did not pursue increasing the scale of the reaction further.

The addition of nucleophiles across DCA is well-known to produce *trans*-dichloroolefins.^{9c, 13d} However, to unambiguously confirm the geometry of the olefin, we treated products

3b and **4b** with 2,4-dinitrophenylhydrazine (DNP); the derivatives **3b-DNP** and **4b-DNP** were crystalline, and we confirmed the *anti*-geometry by single crystal X-ray diffraction (Fig. 1). The geometry of other adducts **3** and **4** were assigned by analogy.

With these optimized conditions in hand, we investigated the scope of this catalytic Nakamura-type reaction under both Conditions A and B (Table 2). We found that the addition of the silyl enol ethers **1** across DCA **2** generally proceeded smoothly, and the tetrasubstituted olefins **3** were isolated in moderate yields.²³ The products bearing electron-rich groups (**3c**, **3d**, **3e**) were generally isolated in higher yields than those containing electron-withdrawing groups (**3f**, **3g**, **3h**). The α -tetralone derived substrate **3i** was isolated in moderate yield, as were alkyl methyl ketone based substrates **3j** and **3k**. The application of Conditions B were somewhat less general. α -Vinylated acetophenone derivatives with electron-donating groups (**4c**, **4d**, **4e**) were isolated in good yields, as was the *p*-chloro analogue **4f**. While the *p*-bromo compound was observed *via* crude ¹H NMR spectroscopy, we were unable to isolate **4g** due to decomposition during column chromatography. Similarly, tetralone adduct **4i** appeared to have formed *via* ¹H NMR analysis of the crude material, but was unstable and decomposed upon column chromatography. We were unable to confirm formation of either *m*-trifluoromethyl acetophenone adduct **4h** or *t*-butyl methyl ketone derivative **4j**, though adamantyl derivative **4k** was isolated in good yield.

Interestingly, we observed partial C(sp²)-H silylation when some silyl enol ethers were exposed to the silver catalyst and DCA (Scheme 2). Tetrasubstituted olefins **3l** and **3l'** were isolated in 42% and 30% yields, respectively. The thiophene based silyl enol ether **1m** led to tetrasubstituted olefins **3m** and **3m'**, in 50% and 14% isolated yields. The mechanism for the formation of **3l'** and **3m'** is unclear at this point. Typical C-H silylation reactions occur from hydrosilanes,²⁴ and the regioselectivity is surprising, given that carbonyl groups typically direct silylation to occur *ortho* to themselves.²⁵ While detailed studies to elucidate the mechanism are warranted, it appears that under the standard conditions, an unknown reactive silyl source is being formed *in situ*, as exposing a ketone to the silver catalyst and chlorotrimethylsilane did not lead to C-H silylation (Scheme 2, equation A, bottom).

Finally, we varied both the substituents on the silyl enol ether and the exogenous silyl source to study their influence on the reaction outcome under Conditions A (Scheme 3). The parent trimethylsilyl enol ether gave the adduct **3b-TMS** in 75% yield. The slightly more bulky triethylsilyl **1b-TES** yielded the tetrasubstituted olefin **3b-TES** in 43% yield. The very bulky *tert*-butyldimethylsilyl enol ether **1b-TBS** was unreactive under the standard conditions, but the dimethylphenylsilyl enol ether **1b-DMPS** led to tetrasubstituted olefin **3b-DMPS** in 39% yield. Most interestingly, when we exposed trimethylsilyl enol ether **1b-TMS** to the silver catalyst, DCA, and chlorotriethylsilane, the TMS group was preferentially incorporated into the olefin over TES, giving more than twice **3b-TMS** over **3b-TES** (Scheme 3, equation B). This further supports our supposition that the silyl enol ether is a reactive silyl source under these conditions.

As a simple mechanistic picture, it seems likely that the π bond in DCA is activated by silver triflate,²⁶ followed by attack of the silyl enol ether to form a putative vinylsilver species with an *anti*-geometry.²⁷ We postulate that in a non-polar solvent, the disassociated

silyl group from the silyl enol ether remains closely associated with the organosilver species, and quenches it to yield the tetrasubstituted olefin **3**. However, in a polar solvent, the ion pair can separate, and the vinylsilver complex is quenched by adventitious water to give the trisubstituted olefins **4**. The observed reactivity is unique to that of DCA, as other alkynes, including methyl propiolate, dimethyl acetylenedicarboxylate, and phenylacetylene remain unreactive under these conditions.

In conclusion, we report here a Nakamura-type reaction between silyl enol ethers and DCA, which can generate either tri- or tetrasubstituted olefins, controlled by a simple switch of the solvent. Both sets of products contain highly functionalizable handles, and are useful building blocks to form more complex olefin compounds. Furthermore, we have discovered interesting silyl transfer processes, for which the mechanisms are a current line of investigation and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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19. Dichloroacetylene is a known explosive. The addition of diethyl ether minimizes the risk of explosion, and while we have not experienced any incidents either using it in situ, or distilling it, caution is highly recommended. See ESI for more details.
20. Isolated yields of **3** decreased after the DCA was stored for longer than one week.
21. We suspect that **3b'** is the geometrical isomer of **3b**. However, we were unsuccessful in all attempts to isolate and fully characterize it; all compounds **3** and **4** were isolated as stereoisomerically pure compounds.
22. Further increasing the amount of TMSCl to superstoichiometric amounts gave no further improvement.
23. In some cases, small amounts of the protiated olefin **4** could be detected by TLC.
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Highlights:

- Silver catalyzed activation of dichloroacetylene towards addition
- Highly trans selective addition of enol ether across dichloroacetylene
- Silyl versus proton transfer controlled via solvent
- Highly functionalized tri- and tetrasubstituted alkenes selectively obtained
- Unusual C-H silylation observed in select cases

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A. Hilt's Co^I catalyzed reactions of dienes with alkynes (refs 11,12)

B. Target arene & discovery:

C. Halides and nucleophilic alkynes and C-nucleophiles with alkyne electrophiles:

Dihalosilylalkenes (refs 15,16)

elaborate halogen sources
cryogenic conditions

Nakamura reaction (ref 14)

requires highly activated alkynes
requires monosubstituted alkynes

Scheme 1.

A. Hilt's cobalt catalyzed reaction of *O*-functionalized dienes with alkynes. **B.** Observed reactivity of Danishefsky's diene **1a** and dichloroacetylene **2**. **C.** Other reactions of electrophiles and nucleophiles with alkynes.

Scheme 2.

C(sp²)-H silylation was observed in the reaction of *p*-fluoroacetophenone (**A**) and 3-thiophene (**B**) derived silyl enol ethers with DCA.

Table 1.

Selected optimization experiments between silyl enol ether **1a** and dichloroacetylene **2**.

Entry	[M] (10 mol%)	Solvent ^b	Additive	T (°C)	3b:4b:5	3b:3b'	yield (%) ^c
1 ^d	Cu(MeCN) ₄ PF ₆	-	-	50			0
2 ^d	Cu(OTf) ₂	-	-	50			(30)
3 ^d	AgOTf	-	-	50			(28)
4	Cu(OTf) ₂	-	-	50	1:0:2.4	1:0.1	25
5	AgOTf	-	-	50	1:0:1.3	1:0.2	40
6	AgOTf	toluene	-	50	1:0:3.6	1:0.6	17
7	AgOTf	hexane	-	50	1:0:3.6	1:0.9	10
8	AgOTf	DCM	-	50	1:0.05:1.5	1:0.3	30
9	AgOTf	MeCN	-	50	1:3.1:3.5	1:0.4	15
10	AgOTf	DMF	-	50	0:0:1	-	0
11	AgOTf	-	TMSCl ^e	50	1:0:1	1:0	50
12	AgOTf	-	-	80	1:0:0.3	1:0.1	70 (69)
13	AgOTf	-	TMSCl ^e	80	1:0:0.4	1:0	71 (67)
14	AgOTf	-	TMSCl ^e MeCN ^f	80	1:0.22:0.22		70
⇒15	AgOTf	-	TMSCl ^e , MeCN ^g	80	1:0:0.25	1:0	80(75)
⇒16	AgOTf	MeCN ^h	-	80	1:3.6:0.07	1:0	62 ⁱ

^aUsing 0.2 mmol **1a** and 1 mL DCA solution in ether (1 M).^b“.” Represents using only ether as a solvent; otherwise, a 1:1 solvent:ether mixture was used.^c¹H NMR yield using CH₂Br₂ as an internal standard; isolated yield of **3b** indicated in brackets.^dReaction time was 24 h.^eUsing an additional 0.68 equiv TMSCl.^fUsing 0.5 mL MeCN.^gUsing 0.1 mL MeCN.^hDCA **2** was prepared in a solution of MeCN.ⁱIsolated yield of **4a**.

Table 2.

Substrate scope for the addition of silyl enol ethers **1c-1k** to dichloroacetylene **2** under Conditions A to give tetrasubstituted olefins **3c-3k** or trisubstituted olefins **4c-4f, 4k** under Conditions B.^{a,b}

^aUsing 0.2 mmol scale for the reaction.

^bYields of isolated, analytically pure material.

^c0.67 equiv of TMSCl was added.

^dProduct was identified by ¹H NMR analysis of the crude reaction mixture, but decomposed upon column chromatography.

^eProduct not identified by ¹H NMR analysis of the crude reaction mixture.