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Alkyne Ligation Handles: Propargylation of Hydroxyl, Sulfhydryl, Amino, and Carboxyl Groups via the Nicholas Reaction

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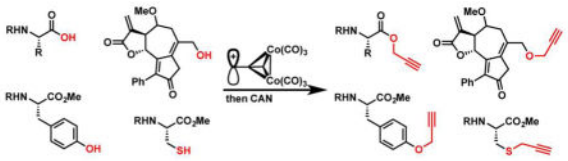
Abstract

The Nicholas reaction has been applied to the installation of alkyne ligation handles. Acid-promoted propargylation of hydroxyl, sulfhydryl, amino, and carboxyl groups using dicobalt hexacarbonyl-stabilized propargylium ions is reported within. This method is especially useful for the introduction of propargyl groups into base-sensitive molecules, thereby expanding the toolbox of methods for the incorporation of alkynes for bioorthogonal reactions. High-value molecules are used as the limiting reagent and various propargylium ion precursors are compared.

Graphical Abstract



Widespread use of the Huisgen 1,3-dipolar cycloaddition between azides and alkynes to form 1,2,3-triazoles, a click reaction,[1] has led to increased interest in transformations used to synthesize and/or install alkynyl groups.[2] Typically, when readying substrates for a click reaction, late-stage propargylation or 5-hexynoylation reactions of hydroxyl or amino groups are used to attach the desired alkynes.[2] Propargylation of a hydroxyl group is usually achieved by a Williamson ether synthesis under basic conditions where the corresponding alkoxide is reacted with propargyl bromide (Figure 1, eq 1). Src-directed probe **1**, was prepared using this approach, but required protection of the 3′- and 5′-hydroxyl groups and 6-amino group to avoid over-propargylation.[3] Propargylation has also been accomplished by converting a hydroxyl group into a leaving group (i.e. a mesylate) and replacing it with propargyl amine.[4]

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Supporting Information

The SI is available free of charge on the ACS Publications website at DOI: Full experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

Another commonly used protocol for installing an alkynyl group is a carbodiimide-mediated coupling reaction between 5-hexynoic acid and a hydroxyl or amino group (Figure 1, eq 2).[2b,5] The Duocarmycin probe **2** exemplifies a product obtained from an EDC[6]-mediated coupling reaction between a cyclic, secondary amino group and 5-hexynoic acid.[7] While carbodiimide couplings offer non-basic, neutral conditions, they require expensive reagents and/or the tedious removal of urea-related byproducts.

Many other methods are available for the functionalization of a compound with an alkynyl group;[2,8] however, despite these options, challenges still arise when alkynylating functionally dense natural products and chemical probes for applications such as activity-based protein profiling[9] for target identification.[10] For example, during investigations to label two different sesquiterpene analogs with alkynyl groups (*vide infra*), these analogs were unstable to the basic conditions required for propargylation. Although the hexynoylation reaction could serve as an alternative for appendage of an alkyne ligation handle via an allylic ester linkage, concerns about the metabolic stability of ester-containing probes in cell culture lowered enthusiasm for this approach.[11] Consequently, a method for propargylation of these sesquiterpene analogs and other biomechanistic probes under non-basic conditions was needed.

Herein, we report our studies to establish the Nicholas reaction as an alternative protocol for the propargylation of high-value small molecules. The Nicholas reaction involves the addition of a nucleophile to the cobalt-stabilized propargylic carbocation **3**, generated by treating the corresponding dicobalt hexacarbonyl complexed ($Co_2(CO)_6$-) propargyl alcohol with acid. Alkyne **4** is formed after oxidative decomplexation (Figure 1, eq 3).[12] While it is well known that the Nicholas reaction can be used to effect propargylation reactions of hetero-nucleophiles, classical conditions require excess nucleophile relative to the cobalt-carbonyl complex, even as the solvent in some cases, limiting its utility in the preparation of alkyne ligation handles.[13] Conditions where the nucleophile is the limiting reagent would expand the utility of this approach.

With the goal of increasing the efficiency of the Nicholas reaction, we began our reaction condition investigations using molecularly complex alcohol **5** as the limiting reagent. Initially, a reaction was carried out with a 1:1.1:1.4 ratio of the nucleophile **5**, **6a**, and BF_3OEt_2 respectively. However, these conditions led to a moderate yield of 40% so we focused on using higher equivalents of **6a** and BF_3OEt_2. We varied the molar equivalencies of complex **6a** and the Lewis-acid (BF_3OEt_2) while keeping the order of addition constant. To reduce the likelihood of the alcohol and ester groups of **5** tying up the BF_3OEt_2, $Co_2(CO)_6$-propargyl alcohol **6a** was added to BF_3OEt_2 to form the propargyl cation, followed by the addition of alcohol **5**. Using this addition order and a 1:2:2.5 molar ratio of alcohol **5**, complex **6a**, and BF_3OEt_2, $Co_2(CO)_6$-propargyl ether **7** was obtained in 47% yield (entry 1) after stirring for 4.5 h at 0 °C. Increasing the equivalents of BF_3OEt_2 and complex **6a** afforded **7** in 36% yield (entry 2). Adding alcohol **5** more slowly lowered the yield of **7** to 28%, (entry 3).

In view of these unfruitful results, the order of addition was examined. Adding alcohol **5** to BF_3OEt_2 prior to addition of complex **6a** did not affect the yield of **7**, obtained in 44% yield

(entry 4). Next, alcohol **5** (1 equiv) and BF_3OEt_2 (2.5 equiv) were added sequentially to $Co_2(CO)_6$-propargyl alcohol **6a** (2 equiv), which increased the yield of **7** to 55% (entry 5). With this same order of addition, increasing the amount of complex **6a** and BF_3OEt_2 lowered the yield of **7** to 22% (entry 6). For all of these examples, **6a** was prepared, isolated, and purified, by column chromatography, before the reaction. While it is recognized that this complex is stable to air and moisture, it was reasoned that forming **6a** *in situ* may be advantageous.[13c] To this end, complex **6a** was formed *in situ* from propargyl alcohol and dicobalt octacarbonyl, followed by the sequential addition of alcohol **5** and BF_3OEt_2 to afford the highest yield of **7** (60%, entry 7). A final attempt to improve the reaction conditions by lowering the reaction temperature only resulted in decreased yields of **7**.[14] Decomplexation of cobalt complex **7** was achieved using ceric ammonium nitrate (CAN) in acetone to readily afford alkyne **8** in 97% yield without the need for purification (Scheme 1). Use of *N*-methylmorpholine-*N*-oxide (NMO) as an oxidant in this transformation resulted in decomposition of **7**.[15]

Next, the generality of these optimized reaction conditions was tested on hydroxyl, sulfhydryl, amino, and carboxyl containing amino acids; a class of compounds selected for their richness of functionality and the utility of propargylated peptides for biochemical applications.[1d,2a,16] Unfortunately, when subjecting *N*-Boc-L-serine methyl ester (**9a**) to the optimized reaction conditions, **10a** was obtained in 20% yield while 76% of the starting material **9a** was recovered (Table 2, entry 1). Similarly, when *N*-Fmoc-L-serine methyl ester (**9b**) was subjected to the same conditions, **10b** was isolated in 29% yield with 63% recovered **9b** (entry 3). In both of these examples, $Co_2(CO)_6$-propargyl alcohol **6a** was fully consumed and the dimerized $Co_2(CO)_6$-propargyl alcohol was obtained, resulting from the propargylium cation reacting more readily with the hydroxyl group of **6a**. To overcome this competing homodimerization reaction, $Co_2(CO)_6$-methyl propargyl ether **6b** was examined.[12c] Reaction of *N*-Boc-L-serine methyl ester (**9a**) with **6b** afforded **10a** in 97% yield (entry 2). The yield of **10b** also increased significantly to 54% when using complex **6b (**entry 4). Use of propargyl acetate for the synthesis of **10a** and **10b** gave yields comparable to complex **6a** (See Supporting Information (SI)).

Next, we tested this method for the propargylation of cysteine thiols, a transformation typically accomplished using basic alkylation conditions.[2a,17] Thiols react efficiently in the Nicholas reaction; however, application has been limited to the synthesis of sulfur containing macrocycles.[12c,18] *N*-acetyl- and *N*-Fmoc-L-cysteine ethyl ester (**9c** and **9d**) were reacted with complex **6a** giving the corresponding $Co_2(CO)_6$-alkynes **10c** and **10d** in high yields of 86% and 71% (Entries 5, 6). *N*-Fmoc cysteine **9d** was also reacted with methyl propargyl ether complex **6b**, which gave a comparable yield of 67% for **10d (**entry 7).

To evaluate the phenolic side chain of tyrosine in the Nicholas reaction, *N*-Boc-L-tyrosine methyl ester (**9e**) was reacted with complex **6a**.[13a] Two major products were observed; the desired product, **10e**, was isolated in 45% yield (57% based on recovered **9e**) (entry 8), while an unstable byproduct was obtained in trace amounts. ^{1}H NMR analysis of this byproduct revealed aromatic signals integrating for three protons, resulting from electrophilic aromatic substitution (see SI, S5).[12c] Because **9e** was recovered along with

complete consumption of **6a**, complex **6b** was tested. This reaction required a longer reaction time and did not improve the yield of **10e** (23% yield, entry 9) due to Boc instability.[19] When the *N*-Fmoc tyrosine ester **9f** was reacted with complex **6a**, **10f** was formed in 6% yield (56% based on recovered starting material) (entry 10). Employing complex **6b** resulted in a significantly improved yield to 73% (entry 11). A byproduct, presumably formed by electrophilic aromatic substitution, was also observed by TLC for these reactions.

Amino groups were tested by subjecting L-proline methyl ester (**9g**) to the Nicholas reaction with **6a**. Consumption of **9g** was observed by TLC within 15 min with no evidence of **10g (**entry 12). We presume the BF_3OEt_2 coordinates with the nitrogen of proline. To circumvent this issue, the cationic propargylium ion was prepared as tetrafluoroborate salt **6c** by reacting complex **6a** with tetrafluoroboric acid in diethyl ether at 0 °C.[12b,20] Reaction of **6c** with proline ester **9g** in DCM at 0°C afforded $Co_2(CO)_6$-alkyne **10g** in 46% yield (entry 13). The primary amine of L-phenylalanine methyl ester (**9h**) also proved to be an effective nucleophile; when reacted with **6c**, dialkylation afforded amine **10h** in 59% yield (entry 14).

Carboxyl groups were also subjected to the Nicholas reaction conditions. Only a few examples of carboxyl groups serving as a nucleophile in the Nicholas reaction have been reported. [21] Reaction of *N*-Bz-D-phenylalanine (**9i**) with complex **6a** and BF_3OEt_2 afforded $Co_2(CO)_6$-propargyl ester **10i** in 60% yield (entry 15). Reaction of **9i** with complex **6c** afforded a lower yield for **10i** (18%, entry 16); thus, the utility of preformed propargylium salt is not necessarily general.

$Co_2(CO)_6$-alkyne modified amino acids **10a-j** underwent oxidative decomplexation with CAN. The propargyl derivatives of serine, cysteine, tyrosine, and phenylalanine **11a-f, i** were afforded in high yields (75–94%). A moderate yield of 56% was observed for the formation of dipropargylamine **11h (**entry 14). Proline alkyne derivative **11g** appeared to be unstable, permitting isolation and NMR characterization only once prior to decomposition (entry 12).

To effect mono-alkynylation of primary amines, an alternative tetrafluoroborate salt **12** was prepared from $Co_2(CO)_6$-2-methyl-3-butyn-2-ol (Scheme 2). Reaction of **12** with phenylalanine ester **9h** afforded the mono-alkynylated propargyl amine **13** after oxidative decomplexation.

Finally, to show the synthetic utility of these conditions for base-sensitive, functionally dense molecules we applied the Nicholas reaction conditions to two sesquiterpene analogs. Base-sensitive guaianolide analog **14**, previously synthesized in our group, was reacted with $Co_2(CO)_6$-propargyl alcohol **6a**, formed *in situ*, and BF_3OEt_2, to give the $Co_2(CO)_6$-alkyne derivative in 46% yield.[22] Reaction with CAN generated alkyne probe **15** in quantitative yield.

Melampomagnolide B (MelB) (**16**) has been used as a parthenolide mimic for conjugation to biotin via an ester-linkage.[23, 24] However, these biotinylated compounds may have metabolic stability issues for *in vivo* biochemical experiments. Formation of the alternative ether linkage using the allylic alcohol handle has proven to be difficult; MelB is base sensitive and

the allylic hydroxyl group was unreactive in our hands towards oxidation or bromination.[25] Reaction of MelB (**16**) with $Co_2(CO)_6$-propargyl alcohol complex **6a** and BF_3OEt_2 afforded the corresponding $Co_2(CO)_6$-alkyne product after 1 h in 19% yield. A shortened reaction time of 10 min gave a 41% yield (45% yield based on recovered **16**), suggesting the $Co_2(CO)_6$-alkyne product was unstable to the reaction conditions. Reacting MelB (**16**) with $Co_2(CO)_6$-methyl propargyl ether **6b** gave a 39% yield of the coupled product. Cobalt decomplexation afforded the MelB alkyne probe **17** in 94% yield (Scheme 3).

In conclusion, the Nicholas reaction conditions described provide an acid-mediated alternative for propargylation of molecularly complex compounds. Reaction conditions were optimized for use of high-value nucleophiles as limiting reagents, a practice atypical for the Nicholas reaction. A number of functional groups acted as the nucleophilic species, including hydroxyl, sulfhydryl, carboxyl, and amino groups. For substrates that react slower than the competing dimerization of $Co_2(CO)_6$-propargyl alcohol **6a**, use of methyl propargyl ether complex **6b** improved yields. Propargylation of amino groups required the preparation of propargylium tetrafluoroborate salts. Mono- and di-alkynylation of a primary amino group was achieved selectively depending on the steric nature of the propargylium ion. Bz, Cbz, Ac, and Fmoc amine protecting groups were all tolerated. Finally, these conditions provided an alternative propargylation strategy for base-sensitive sesquiterpene analogs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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23. (a) Macias FA, Galindo JCG, Massanet GM. Phytochemistry. 1992; 31:1969–1977.(b) Nasim S, Pei S, Hagen FK, Jordan CT, Crooks PA. Bioorg Med Chem. 2011; 19:1515–1519. [PubMed: 21273084]
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25. Attempts to manipulate the allylic alcohol of 17 included use of: PCC, PDC, Dess-Martin periodinane, and PBr_3.

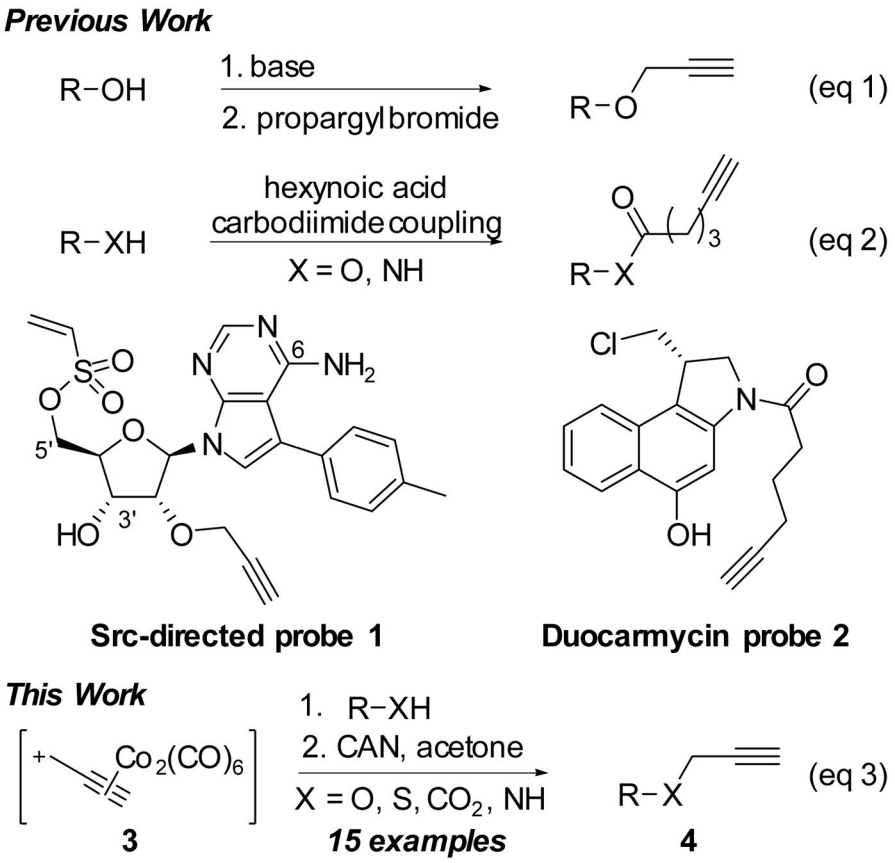
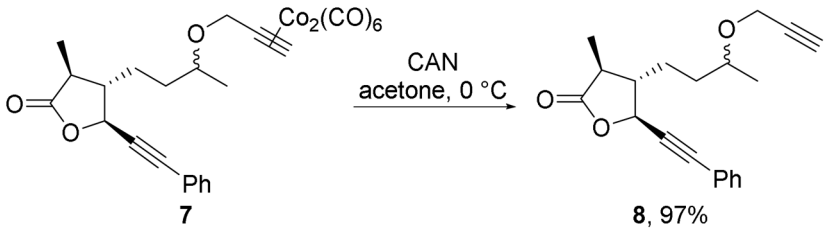
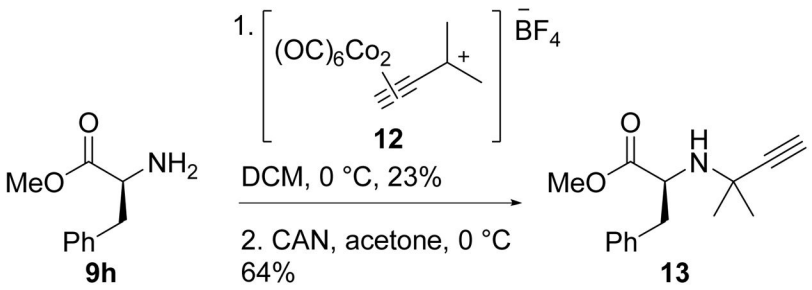


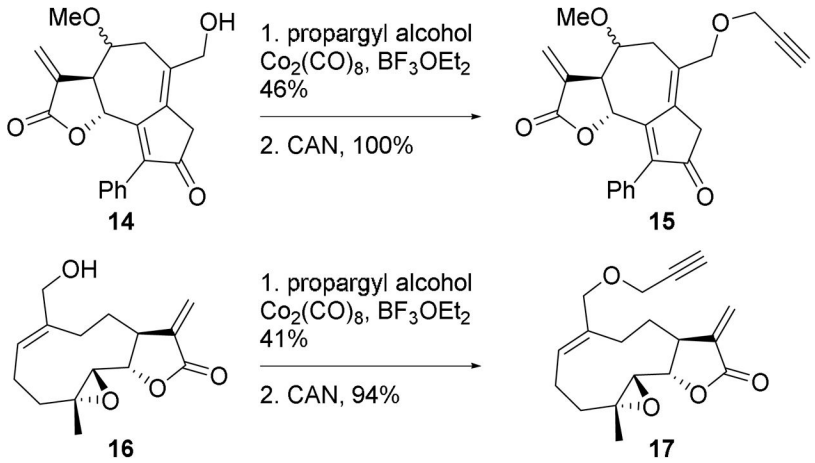
Figure 1.
Synthetic methods for alkyne incorporation.



Scheme 1.
Decomplexation of $Co_2(CO)_6$-alkyne 7.



Scheme 2.
Reaction of primary amine 9h with BF_4^- salt 12.



Scheme 3.
Synthesis of alkyne probes 15 and 17.

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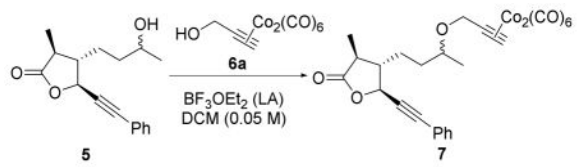
Table 1

Optimization of Nicholas Reaction with alcohol 5.



entry	equiv (5:6a:LA)	order of addition	temp (°C)	time (h)	yield (%)
1[a]	1:2:2.5	LA, **6a**, **5**	0	4.5	47
2	1:3:5	LA, **6a**, **5**	0	4	36
3	1:2:2.5	LA, **6a**, **5**[c]	0	4	28
4[a]	1:2:2.5	LA, **5**, **6a**	0	4.5	44
5[b]	1:2:2.5	**6a**, **5**, LA	0	4	55
6	1:3:5	**6a**, **5**, LA	0	5	22
7[b]	1:2:2.5	**6a**, **5**, LA[d]	0	3.5	60

[a]Dimerized product of **6a** was isolated in 33–34% yield.

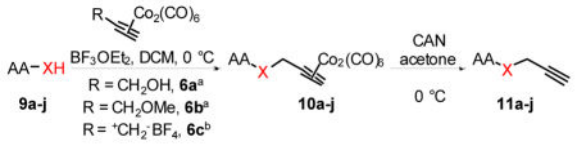
[b]Dimerized product of **6a** was isolated in 25–28% yield.

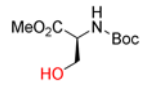
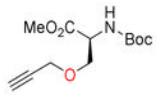
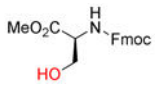
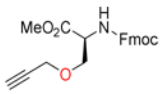
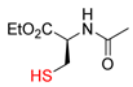
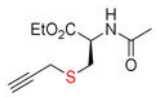
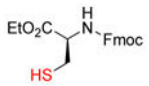
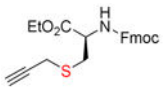
[c]Alcohol **5** was added dropwise over 5 min.

[d]Complex **6a** was generated *in situ* from propargyl alcohol and $Co_2(CO)_8$

Table 2

Synthesis of alkyne modified amino acids (AA).



entry	AA-XH, 9	6	time (h)	10, yield (%)	11, yield (%)
1	 **9a**	**6a**	1	**10a**, 20	 **11a**, 90
2	**9a**	**6b**	1	**10a**, 97	
3	 **9b**	**6a**	1	**10b**, 29	 **11b**, 90
4	**9b**	**6b**	1	**10b**, 54	
5	 **9c**	**6a**	2	**10c**, 86	 **11c**, 83
6	 **9d**	**6a**	0.75	**10d**, 71	 **11d**, 92
7	**9d**	**6b**[c]	2	**10d**, 67	

entry	AA-XH, 9	6	time (h)	10, yield (%)	11, yield (%)
8		**6a**	1	**10e**, 45	
	9e				**11e**, 75
9	**9e**	**6b**	3	**10e**, 23	
10		**6a**	1	**10f**, 6	
	9f				**11f**, 81
11	**9f**	**6b**	1	**10f**, 73	
12		**6a**	0.25	**10g**, 0	
	9g				**11g**[d]
13	**9g**	**6c**	1.5	**10g**, 46	
14		**6c**	1.5	**10h**, 59	
	9h				**11h**, 56
15		**6a**	2	**10i**, 60	
	9i				**11i**, 90

entry	AA-XH, 9	6	time (h)	10, yield (%)	11, yield (%)
16	**9i**	**6c**	**10i**, 18		

Nucleophilic group (-XH) of amino acid (AA) highlighted in red.

[a] Complexes **6a** and **6b** were formed *in situ*.

[b] BF_3OEt_2 is not used when using **6c**.

[c] Use of isolated **6b** gave highest yield.

[d] **11g** is unstable. For additional examples, see SI.