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Reductive Decarboxylative Alkynylation of *N*-Hydroxyphthalimide Esters with Bromoalkynes

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Abstract

A new method for the synthesis of terminal and internal alkynes from the nickel-catalyzed decarboxylative coupling of *N*-hydroxyphthalimide esters (NHP esters) and bromoalkynes is presented. This reductive cross-electrophile coupling is the first to use a C(sp)-X electrophile, and appears to proceed via an alkynylnickel intermediate. The internal alkyne products are obtained in 41–95% yield without the need for a photocatalyst, light, or strong oxidant. The reaction displays a broad scope of carboxylic acid and alkyne coupling partners and can tolerate an array of functional groups including a carbamate N-H, halogen, nitrile, olefin, ketone, and ester. Mechanistic studies suggest that this process does not involve an alkynylmanganese reagent and involves nickel-mediated bond formation.

Graphical Abstract

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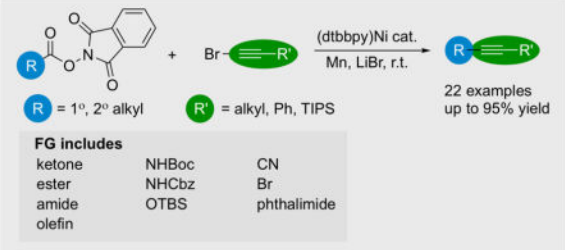

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Supporting information for this article is given via a link at the end of the document.

Keywords

Cross-electrophile coupling; Homogeneous catalysis; Alkynes; Alkylation; Cross-coupling

Cross-electrophile coupling[1] has recently been shown to be a general approach to the formation of C-C bonds and the number and type of electrophiles that can be cross-coupled has grown rapidly in the past decade. The formation of $C(sp^3)$-$C(sp^2)$ bonds has been the most studied,[2],[3] but the selective formation of $C(sp^2)$-$C(sp^2)$[4] and $C(sp^3)$-$C(sp^3)$[5] bonds has also been demonstrated (Scheme 1). In particular, the coupling of aryl[2] and vinyl halides[3] with alkyl halides has proven to be a useful alternative to other cross-coupling approaches.[6] In contrast, cross-electrophile coupling to form C(sp)-$C(sp^x)$ bonds has not been demonstrated (Scheme 1), even though bromoalkynes are easily generated from terminal alkynes.[7] [8]

This absence in the literature could be related to a number of potential problems. First, the high reactivity of bromoalkynes could pose a selectivity problem.[9] Second, the low steric bulk of the alkyne could lead to rapid transmetalation and homocoupling to form diynes. Finally, alkynes can act as radical acceptors and strong ligands, potentially leading to catalyst inhibition and side reactions.

We were motivated to explore the reactivity of alkynyl electrophiles in order to develop a new synthesis of alkylated alkynes from carboxylic acids. The most often used solution for this transformation is through the Corey-Fuchs reaction[10] or the Seyferth-Gilbert homologation[11] of aldehydes to terminal alkynes. While this approach has proven useful, it often requires the synthesis of the aldehyde from the more abundant carboxylic acid, strong base to effect the rearrangement, and additional steps if an internal alkyne is desired.

We envisioned a more convergent approach, the decarboxylative coupling of an *N*-hydroxyphthalimide (NHP) ester with an alkynyl bromide (Scheme 2).[12],[13] Strategically, this approach differs from the above strategy because it avoids the aldehyde intermediate. Additionally, the alkyne component can be substituted, allowing for direct synthesis of functionalized internal alkynes. While this exact transformation is unknown, related strategies have been investigated recently. For example, the oxidative decarboxylation of aliphatic acids to form alkyl radicals with subsequent capture by alkynyl electrophiles.[14] Concurrent with these studies, Fu reported on the coupling of terminal alkynes with α-amino NHP esters[15] and Baran reported on the coupling of *N*-hydroxytetrachlorophthalimide (TCNHPI) esters with alkynylzinc or magnesium reagents.[16] Our proposed approach would avoid the need for organometallic reagents and the more expensive TCNHPI[17] without being limited to α-amino acid derivatives.[15] Although this approach would use alkyne electrophiles, bromoalkynes[7] are more easily prepared than ethynylbenziodoxolones[18] or alkynyl sulfones.[14a–c]

Initial results using conditions we reported for the coupling of iodoarenes to NHP esters[13a] resulted in a low yield of the cross-product (Table 1, entry 1, **3a**) and a large amount of the homodimer (**diyne**). Two changes solved this selectivity problem (entries 1–3): changing the reductant from Zn to Mn (from 11 to 43% yield) and adding in LiBr as an additive (43% to

78% yield).[4c, 19] Examination of several other salts showed that both LiCl and LiBr improve the yield of cross-product at the expense of diyne formation. Stoichiometric amounts of LiBr were required to observe a beneficial effect (entries 8 and 9). Small improvements in yield were obtained when using an excess of either coupling partner (entries 10 and 11).

Control experiments showed that both nickel and ligand were essential for this transformation (entries 12 and 13). A redox active ester appears to be required because **1b** was not consumed under these reaction conditions (entry 14). Other redox-active esters (HOBt or HOAt esters **1c** and **1d**) were also not consumed under these conditions (entry 14).

Under the optimized conditions, various alkyl NHP esters and bromoalkynes were cross-coupled successfully in 41–95% yield (Table 2). Functional group compatibility is promising, and the reaction tolerates ketones (**3b** and **3c**), esters (**3d**) and the N-H of secondary carbamates (**3e**). The high reactivity of the NHP esters compared to other alkyl electrophiles was demonstrated in product **3f**, where an alkyl bromide was tolerated, albeit in moderate yield. Another advantage of the NHP esters is that readily available amino acids can be easily converted into useful alkynyl amino acids (**3g**) and alkynyl amines (**3k** and **3m**). Propargylglycine, obtainable from **3g** by routine deprotection, has been made on large scale to support pharmaceutical synthesis.[20] Our route, from aspartic acid, is an attractive alternative to the chiral auxiliary approach that was recently reported.[21] Linoleic acid was coupled to form **3i** in high yield without isomerization of the *Z*-olefins. Although these reactions were set up in a glovebox for convenience, the chemistry could be run on preparative scale (5 mmol NHP ester) on the benchtop without the need for strict exclusion of moisture and air. Subsequent removal of the TIPS protecting group with nBu$_4$NF (1 M in THF) gave the terminal alkyne in 84% yield over the two steps.

α-Branched redox-active esters were suitable substrates for the alkynylation reaction (**3j**-**n**), but reactions with dibranched substrates did not form product. The value of using an aliphatic acid as a source for the alkyl moiety was demonstrated with these compounds, as the corresponding alkyl halides are not commercially available or fail to couple.[22] For example, 3-halotetrahydrofurans, 2-halopyrrolidines, and 2-amido alkyl halides are not easily accessible starting materials, whereas the corresponding aliphatic acids are relatively affordable and can be successfully transformed into the alkynylation products in moderate to good yields (**3j**, **3k** and **3m**).

Next, the scope of the bromoalkynes was tested in our reductive coupling method. Both the alkyl substituted and the phenyl substituted bromoalkynes were coupled with 3,3-dimethylbutanoic acid NHP ester in good yields (**3o** and **3p**). Several functional groups can be appended onto the alkyl chain of the bromoalkynes including malonate (**3q**), OTBS (**3r**), cyanide (**3s**), phthalimide (**3t**), and alkene (**3u**), without preventing product formation.

Not all substrates tested coupled in high yield under these conditions. An NHP ester with a free carboxylic acid and a bromoalkyne with a free hydroxyl group resulted in low yields. Finally, NHP esters that would generate an allylic or benzylic radical failed to give alkynylation products.

Three potential mechanisms were proposed: 1) in-situ formation of an alkynyl manganese reagent and subsequent nickel-catalyzed cross-coupling,[16] 2) nickel-catalyzed radical generation[13b, 23],[13a] and outer-sphere addition of the free radical to the bromoalkyne; [14a–c] 3) sequential reaction of two electrophiles with the nickel catalyst and bond-formation at nickel.[24] At this time, we can rule out the first two mechanistic possibilities (*vide infra*).

Given the high reactivity of alkynyl bromides and the positive effect of LiBr on the reaction outcome, an additive known to increase the rate of insertion of Mn or Zn,[25] we suspected an alkynylmanganese reagent might be an intermediate. However, when silylated bromoalkyne **2a** was subjected to standard conditions without adding nickel or ligand (Scheme 3a), the bromoalkyne was not consumed and only a trace of hydrodebrominated alkyne was observed. This shows that direct insertion of Mn into the C-Br bond is slow and suggests that Mn serves to reduce a nickel intermediate. Although we are unsure of the role of LiBr in minimizing formation of diyne, our own work and that of Osakada and Yamamoto[26] suggests that diyne arises from dialkynylnickel(II) intermediates. Added LiBr could slow ligand exchange between alkynylnickel(II) intermediates, inhibiting diyne formation.

Two experiments suggested the presence of a free alkyl radical in the reaction. The NHP ester of cyclopropylacetic acid (**1v**) reacted to form the rearranged product exclusively (Scheme 3b).[24], [27–28] In addition, a standard reaction run in the presence of TEMPO formed both the expected cross product and alkylated TEMPO (Scheme 3c).[27a] This product required nickel, confirming that nickel is required for radical generation.

While these results are consistent with mechanism two, the coupling of a free-radical with the bromoalkyne to form product is unlikely for three reasons. First, it has been reported that this process is not high yielding.[14a, 14c, 18] Second, our studies have shown that the ligand on nickel is essential to bond formation but not consumption of the NHP ester (Table 1, entry 12).[13a] Third, the major challenge during reaction optimization was too-rapid consumption of the bromoalkyne and subsequent diyne formation, a process that requires an alkynylnickel intermediate (Table 1 and Scheme 3d).

Finally, we briefly studied the reactivity of two possible nickel intermediates to shed light on the mechanism (Scheme 3d). The nickel(0) complex (dtbbpy)Ni^0(cod) reacted rapidly with both electrophiles at rt, in each case forming an as-yet unidentified organonickel intermediate (**5** and **6**).[29] Both of these intermediates, either after isolation and washing to remove excess electrophile or without isolation, react with the complementary electrophile to form cross-product.[22e],[30] While these studies demonstrate that an inner-sphere, nickel-mediated mechanism is possible, further studies will be required before a complete catalytic cycle can be proposed.[24]

In conclusion, the reductive alkynylation to form a C(sp)-C(sp^3) bond has been achieved, opening a new class of reactions to cross-electrophile coupling and demonstrating that even highly reactive electrophiles can be coupled selectively. The resulting method provides a convenient and direct synthesis of a wide variety of internal alkynes from convenient precursors and useful alternative to methods that proceed via olefination or use alkyl halides.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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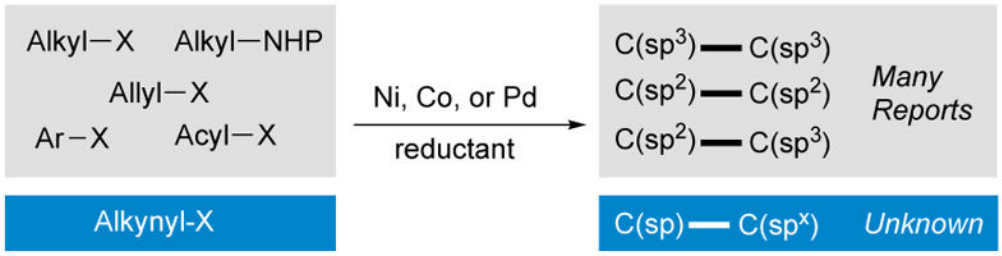
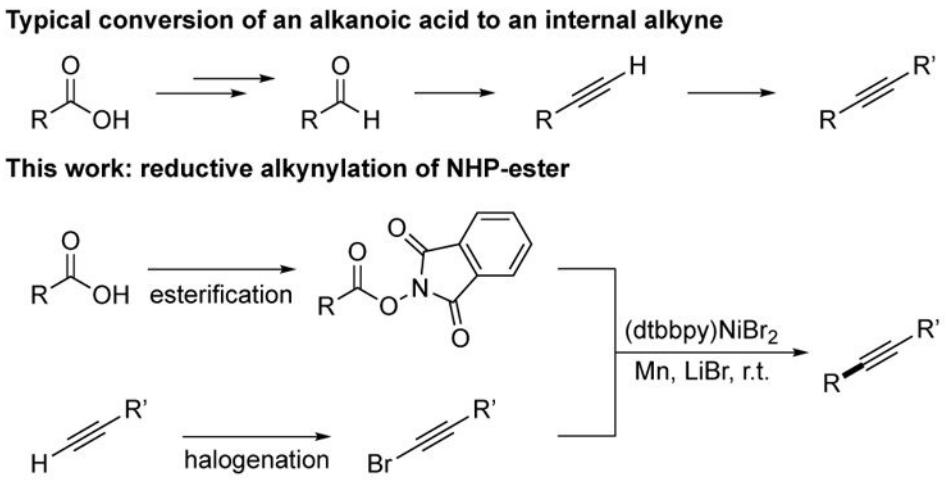
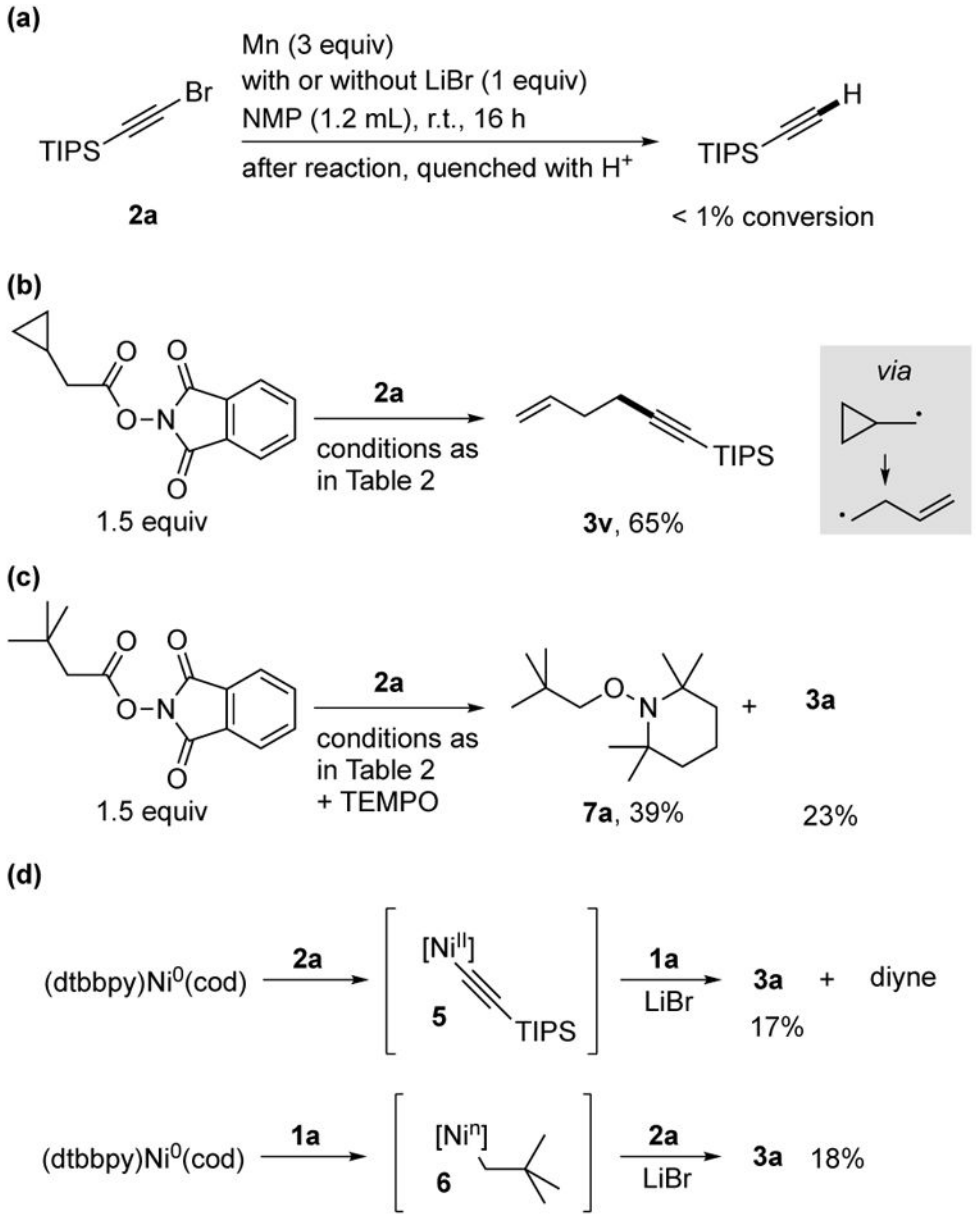
29. For further details on these experiments and preliminary characterization of the intermediates, see the Supporting Information. Although the organonickel intermediates are paramagnetic, EPR data suggests a integer-spin complex, such as tetrahedral or octahedral nickel(II), and not a ½-integer spin complex.
30. Similar to this situation, both alkylnickel(II) and arylnickel(II) intermediates are known to react with the complementary electrophile to form alkylated arenes. See ref. 24 and references cited therein.



Scheme 1.
Types of bonds formed by reductive cross-electrophile coupling.



Scheme 2.
Comparison of alkynylation strategies.

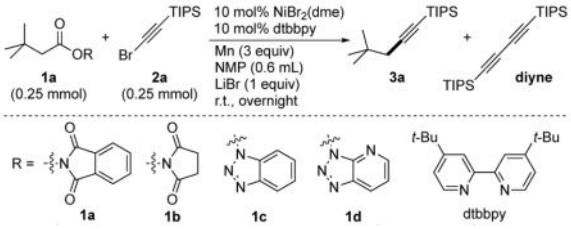


Scheme 3.

Mechanistic studies: (a) reaction of bromoalkyne with Mn, (b) cyclopropylmethyl radical rearrangement, (c) TEMPO radical trap, and (d) reactivity of nickel towards the two electrophiles.

Table 1

Optimization of the decarboxylative alkynylation.

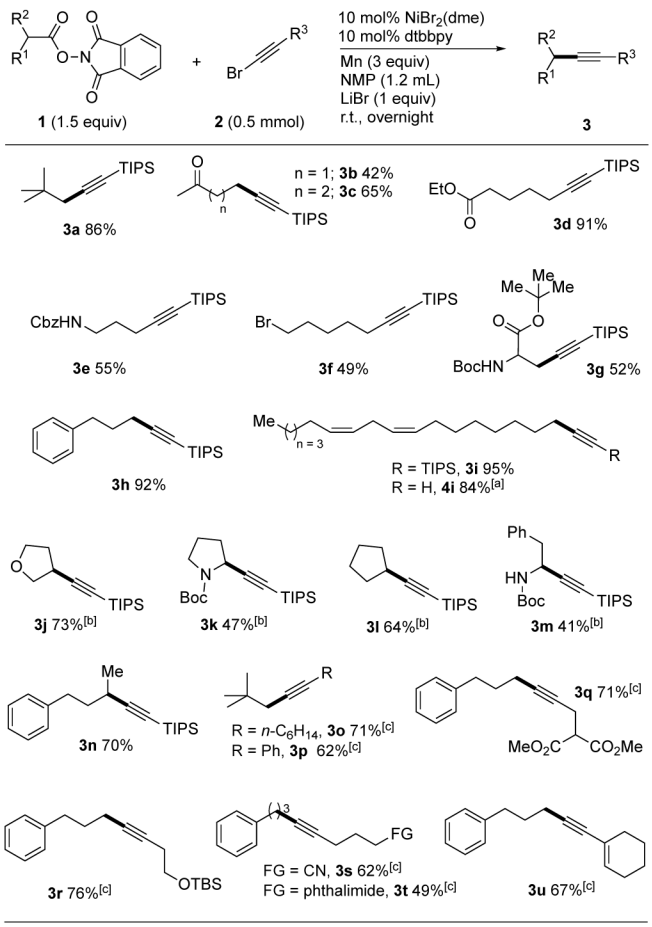


Entry	Change from Conditions in Scheme	Yield of 3a[a]	Yield of diyne[a]
1	Zn instead of Mn, omit LiBr	11	40
2	omit LiBr	43	23
3	none	78	11
4	LiCl instead of LiBr	67	9
5	KF instead of LiBr	42	21
6	KBr instead of LiBr	43	16
7	NaI instead of LiBr	46	19
8	LiBr (2 equiv)	78	14
9	LiBr (0.5 equiv)	53	13
10	1.5 equiv of **1a**	89 (**86**)	8
11	1.5 equiv **2a**	84	18
12	omit dtbbpy	n.d.	6
13	omit $NiBr_2$(dme)	n.d.	n.d
14	**1b–d** instead of **1a**	n.d.	>40

[a]Corrected GC yield using *n*-dodecane as the internal standard; isolated yield in parentheses.

Table 2

Substrate scope of NHP-ester and bromoalkyne.



[a]This reaction was run on 3.3 mmol scale and the crude product was deprotected with TBAF before isolation. Yield is over two steps.

[b]Reaction run at 50 °C.

[c]Reaction run at lower concentration (1.8 mL of NMP).