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Ni-Catalyzed Intermolecular Carboacylation of Internal Alkynes via Amide C–N Bond Activation

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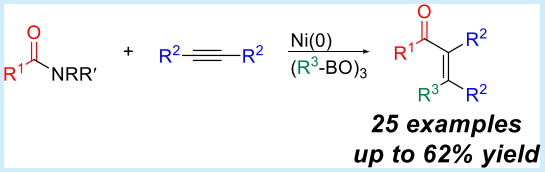
ABSTRACT: The Ni-catalyzed carboacylation of alkynes with amide electrophiles and triarylboroxines is presented. The reaction generates all-carbon tetrasubstituted alkene products in up to 62% yield. $NiCl_2$·glyme is used as an inexpensive precatalyst in the absence of any external reductant or exogenous ligand. Design of Experiment (DoE) was used to achieve the best combination of yield and stereoselectivity in this acylative carbodifunctionalization of alkynes to generate highly substituted enones.



Tetrasubstituted alkenes containing four carbon substituents form a synthetically challenging yet versatile class of molecules prevalent in several pharmaceuticals and biologically active compounds.[1] With the advent of transition-metal-catalyzed cross-coupling reactions, alkynes have emerged as coupling partners for a variety of carbodifunctionalization reactions to generate tetrasubstituted alkenes.[2] Among these alkyne carbodifunctionalization reactions, acylative approaches to generate fully substituted enones are underdeveloped. Nomura and co-workers reported rhodium-catalyzed coupling of acid chlorides and alkynes in the presence of a disilane reductant to generate fully substituted enones (Scheme 1a).[3] Recently, Wu and co-workers developed palladium-catalyzed carbonylative arylacylations of alkynes with aryl iodides and arylboronic acids in the presence of carbon monoxide as the carbonyl source (Scheme 1b).[4] While each of these approaches provides access to highly substituted enones from simple starting materials with high diastereoselectivity, they involve precious metal catalysts and require either a stoichiometric reductant and high reaction temperatures to drive decarbonylation or carbon monoxide gas and stoichiometric copper(II) trifluoroacetate.

We sought to identify an earth-abundant catalyst for coupling of alkynes with a carboxylic acid derivative and an arylboron nucleophile to generate fully substituted enones. Our group has developed a series of nickel-catalyzed acylative alkene difunctionalization reactions triggered by activation of a carboxylic acid derivative.[5] However, related acylative difunctionalizations of alkynes utilizing carboxylic acid derivatives as acyl electrophiles are underdeveloped. Herein, we disclose the Ni-catalyzed intermolecular carboacylation of internal alkynes with amides and triarylboroxines (Scheme 1c).

Building on our prior studies in nickel-catalyzed alkene carboacylation, we chose to study the reaction of *N*-benzoyl-*N*-phenylbenzamide **1a**, 4-octyne **2a**, and a variety of boron nucleophiles with $Ni(cod)_2$ as the precatalyst. The reaction with sodium tetraphenylborate **3a** produced the carboacylation

Scheme 1. Current Methods for Tetrasubstituted Enone Synthesis

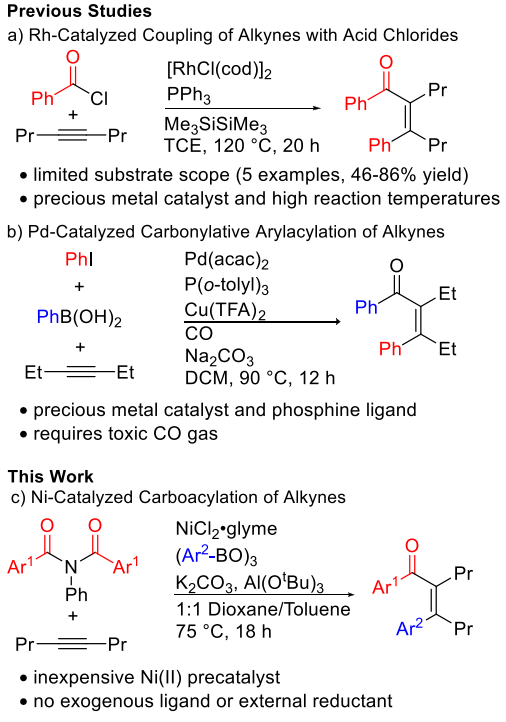


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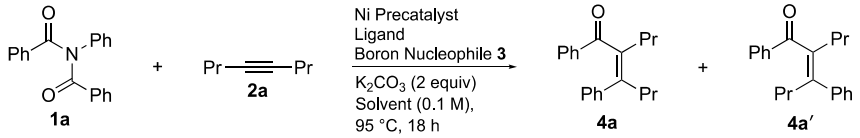
Table 1. Identification of Reaction Conditions[a]



entry	precatalyst (mol %)	ligand (mol %)	nucleophile (equiv)	additive (mol %)	temp (°C)	solvent	yield[b] (%)	dr (*Z*/*E*)[b]
1	$Ni(cod)_2$ (10)	none	$NaBPh_4$ (2)	H_3BO_3 (200)	95	benzene	23	1.3:1
2	$Ni(cod)_2$ (10)	none	BPh_3 (2)		95	benzene	50	0.8:1
3	$Ni(cod)_2$ (10)	BrettPhos (10)	BPh_3 (2)		95	benzene	62	0.7:1
4	$Ni(cod)_2$ (10)	BrettPhos (10)	PhBpin (2)		95	benzene	<5	nd[c]
5	$Ni(cod)_2$ (10)	BrettPhos (10)	$PhB(OH)_2$ (2)		95	benzene	31	2.1:1
6	$Ni(cod)_2$ (10)	BrettPhos (10)	$PhB(OH)_2$ (2)		95	dioxane	41	1.9:1
7	$Ni(cod)_2$ (10)	BrettPhos (5)	$PhB(OH)_2$ (2)		95	dioxane	36	1.8:1
8	$Ni(cod)_2$ (10)	none	$PhB(OH)_2$ (2)		95	dioxane	32	1.7:1
9	$NiCl_2$·glyme (10)	none	$PhB(OH)_2$ (2)		95	dioxane	35	1.7:1
10	$NiCl_2$·glyme (20)	none	$PhB(OH)_2$ (2)		95	dioxane	46	1.5:1
11	$NiCl_2$·glyme (20)	none	$PhB(OH)_2$ (5)		95	dioxane	66	0.7:1
12	$NiCl_2$·glyme (20)	none	$PhB(OH)_2$ (5)	$Al(O^tBu)_3$ (20)	95	dioxane	90	0.7:1
13	$NiCl_2$·glyme (20)	none	$PhB(OH)_2$ (5)	$Al(O^tBu)_3$ (20)	80	dioxane	78	1.6:1
14	$NiCl_2$·glyme (20)	none	$PhB(OH)_2$ (3)	$Al(O^tBu)_3$ (20)	80	dioxane	65	2.5:1
15	$NiCl_2$·glyme (20)	none	$PhB(OH)_2$ (1.5)	$Al(O^tBu)_3$ (20)	80	dioxane	22	4.5:1
16[d]	$NiCl_2$·glyme (20)	none	$PhB(OH)_2$ (1)	$Al(O^tBu)_3$ (20)	80	dioxane	27	8.7:1
17[d]	$NiCl_2$·glyme (20)	none	$(PhBO)_3$ (1)	$Al(O^tBu)_3$ (20)	80	dioxane	66	4.9:1
18[d]	$NiCl_2$·glyme (20)	none	$(PhBO)_3$ (1)	$Al(O^tBu)_3$ (20)	80	1:1 dioxane/toluene	69	4.2:1
19[d,e]	$NiCl_2$·glyme (20)	none	$(PhBO)_3$ (1)	$Al(O^tBu)_3$ (10)	75	1:1 dioxane/toluene	62	5.3:1
20[d,f]	$NiCl_2$·glyme (20)	none	$(PhBO)_3$ (1)	$Al(O^tBu)_3$ (10)	75	1:1 dioxane/toluene	23	6.0:1

[a]Reaction conditions: **1a** (0.100 mmol), **2a** (0.500 mmol), boron nucleophile 3 (0.200 mmol), K_2CO_3 (0.200 mmol), Ni precatalyst (0.010 mmol), solvent (1 mL, 0.1 M), 18 h. [b]Determined by GC with tridecane as an internal standard. [c]dr: not determined. [d]Reaction run at 0.500 M concentration. [e]Optimized conditions: **1a** (0.100 mmol), **2a** (0.500 mmol), triphenylboroxine **3e** (0.100 mmol), $NiCl_2$·glyme (0.020 mmol), K_2CO_3 (0.225 mmol), $Al(O^tBu)_3$ (0.010 mmol), 1:1 dioxane/toluene (0.200 mL, 0.500 M), 75 °C, 18 h. [f]Reaction run at 1.00 mmol scale.

products **4a** and **4a′** in 23% yield as a 1.3:1 ratio of *Z* and *E* stereoisomers (Table 1, entry 1). We have previously established that the addition of boric acid to sodium tetraphenylborate generates triphenylborane in situ and that triphenylborane can be an active nucleophile in alkene carboacylation reactions.[5a] Adding triphenylborane **3b** as the nucleophile increased the yield to 50% with a 0.8:1 dr (Table 1, entry 2). After evaluating a variety of exogenous ligands, we found that a nickel complex of BrettPhos catalyzes the alkyne carboacylation in the presence of triphenylborane **3b** as the nucleophile and forms the enone products in 62% yield as a 0.7:1 diastereomeric mixture (Table 1, entry 3). The limited commercial availability of sodium tetraarylborates and triarylboranes led us to study the development of alkyne carboacylation reactions with arylboronic acid nucleophiles and their boronate ester derivatives. The reaction of imide **1a**, 4-octyne **2a**, and PhBpin does not form enone **4a** in measurable yield with a nickel complex of BrettPhos as the catalyst (entry 4). However, the analogous reaction with phenylboronic acid as the arylboron nucleophile leads to the formation of enone **4a** in 31% yield with 2.1:1 diastereoselectivity (entry 5). During our initial attempts to improve the yield of the model reaction with phenylboronic acid, we found that using 1,4-dioxane as the solvent led to slightly higher yields of the enone products (entry 6). Due to the large number of potentially significant variables in this reaction, we turned to Design of Experiment to more efficiently explore the chemical space relevant to this reaction.[6] An initial screen of variables showed us that ligand loading did not have a significant effect on the yield of the reaction (Table 1, entries 6–8, and Table S3). The model reaction generated enone **4a** in 32% yield in the absence of the BrettPhos ligand (entry 8). The reaction conducted in the presence of a cheap, readily accessible nickel(II) precatalyst, $NiCl_2$·glyme, formed the enone product in similar yield when compared to the reaction run with $Ni(cod)_2$ as the precatalyst (entry 9). The addition of an exogenous ligand to the reaction of 4-octyne with imide **1a** and phenylboronic acid proved detrimental with $NiCl_2$·glyme as the precatalyst (Table S4). Increasing the catalyst loading to 20 mol % led to the formation of the carboacylation product in 46% yield with 1.5:1 dr (Table 1, entry 10, and Table S5). The yield of the model reaction could be further improved to 66% by increasing the loading of phenylboronic acid to 5 equiv (entry 11). In our attempts to further increase the yield of the enone product, we observed a plateau in the yield between 60 and 65% with our initial set of reaction variables. In many cases, conversion of imide **1a** was incomplete, which led us to hypothesize that inhibition of the nickel catalyst by the enone product may be limiting the efficiency of the alkyne carboacylation reaction. Addition of 30 mol % of enone **4a** to the reaction led to a decrease in the yield to 13% (Table S6). To minimize coordination of the enone product to the nickel catalyst, we studied our model reaction in the presence of Lewis acid additives (Table S7). The alkyne carboacylation reaction formed enone **4a** in 90% yield with a 0.7:1 dr when 20 mol % of aluminum *tert*-butoxide was added to the reaction mixture (Table 1, entry 12, and Table S8). While the yield of the alkyne carboacylation is excellent, the dr is not synthetically useful.

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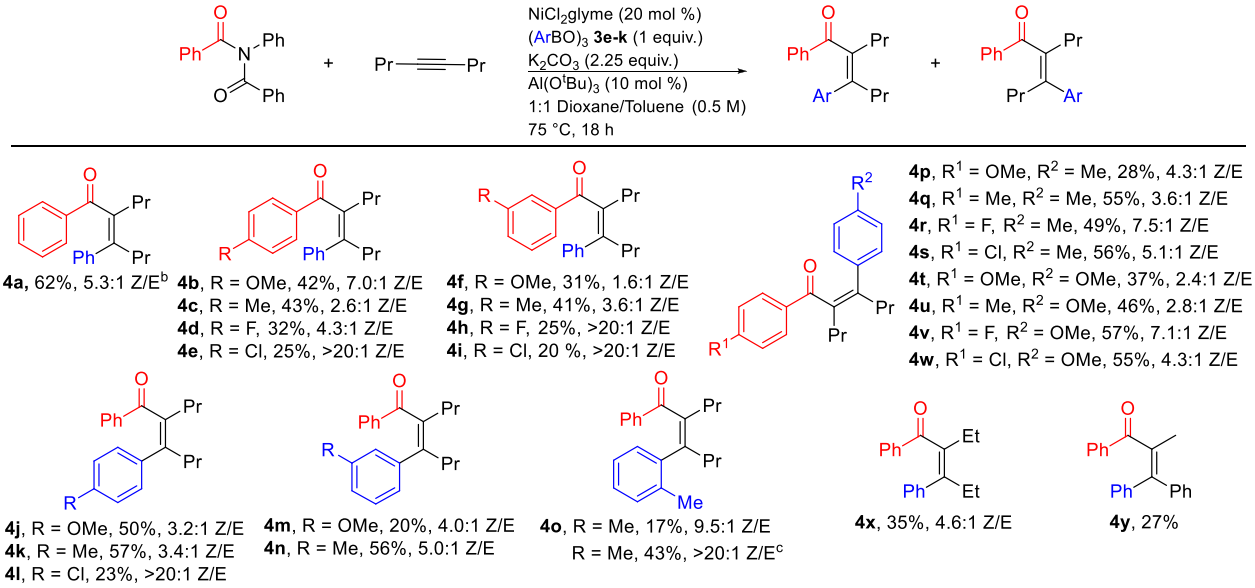
Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.100 mmol), **2a** (0.500 mmol), **3** (0.100 mmol), $NiCl_2$·glyme (0.020 mmol), K_2CO_3 (0.225 mmol), $Al(O^tBu)_3$ (0.010 mmol), 1:1 dioxane/toluene (0.200 mL, 0.500 M), 75 °C, 18 h. [b]*Z*/*E* ratios determined by ^1H NMR. [c]Reaction run with 5 equiv of 2-MePhB$(OH)_2$.

At this point, we attempted to identify reaction conditions that led to the best balance between yield and diastereoselectivity. We observed that decreasing the temperature of the reaction to 80 °C and reducing the number of equivalents of phenylboronic acid led to a decrease in yield of the carboacylation product but an increase in the diastereoselectivity (entries 13−15). These results suggest that phenylboronic acid may play a key role in isomerization of the initially formed *Z*-diastereomer to the *E*-diastereomer, presumably through the formation of a nickel hydride by oxidative addition into the O−H bond of phenylboronic acid.[7] Increasing the concentration of the reaction to 0.5 M led to a slight increase in the yield of enone **4a** and significantly improved the diastereoselectivity (entry 16). If the formation of a nickel hydride intermediate plays a key role in the isomerization of the enone product, removal of the O−H bonds by changing the nucleophile to triphenylboroxine may minimize the formation of nickel hydride intermediates. Indeed, the reaction of 4-octyne **2a** with imide **1a** and triphenylboroxine generated enone **4a** in 66% yield with an increased diastereoselectivity of 4.9:1 (entry 17). Finally, we performed two additional Design of Experiments to identify a mixed solvent system (Table 1, entry 18, and Table S9) and to arrive at our optimized reaction conditions (Table S10). Reactions run under our optimized conditions produce the enone product **4a** in 62% yield with a 5.3:1 dr (entry 19). Lowering the loading of 4-octyne **2a** led to a decrease in the yield of enone product **4a**.

Having identified reaction conditions that generate the enone product of alkyne carboacylation with a balance of product yield and diastereomeric ratio, we next evaluated the scope of our alkyne carboacylation reaction with various *N*-benzoyl-*N*-phenybenzamides (Scheme 2). The reaction of imides containing electron-donating groups substituted at the *para*- or *meta*-position led to the formation of enone products **4b**−**4c** and **4g** in 41−43% yield and 2.6−7.0:1 dr. Deactivating groups, such as halogens, at the *para*- or *meta*-position of the imide substrates led to lower yields of enone products **4d**−**4f** and **4h**−**4i** (20−32%). Notably, halogenated imides reacted to generate enones **4e**, **4h**, and **4i** with >20:1 diastereoselectivity. The reaction of *N*-phenyl-4-(trifluoromethyl)-*N*-(4-(trifluoromethyl)benzoyl)benzamide did not produce the enone product in >5% yield, nor did the reaction of an asymmetric imide, *N*-benzoyl-*N*-phenyl-4-(trifluoromethyl)-benzamide.

We then studied the scope of the alkyne carboacylation reaction with respect to triarylboroxine nucleophiles. Reactions of triarylboroxines containing electron-donating groups produced the enone products **4j**,**4k** and **4m**,**4n** in 20−57% yield with 3.2−5.0:1 dr. Triarylboroxines with electron-withdrawing substitutents were generally unreactive, but the reaction of tris(4-chlorophenyl)boroxine produced enone **4l** in 23% yield and >20:1 dr. The reaction of tris(2-methylphenyl)boroxine formed enone **4o** in 17% yield with 9.5:1 dr. The low yield and relatively slow rate of isomerization of enone **4o** led us to run the alkyne carboacylation reaction with 5 equiv of 2-methylphenylboronic acid. This reaction generated enone **4o** in 43% yield and >20:1 dr. The reactions of imides containing electron-withdrawing groups led to generally lower yields of the enone products; however, the yield of the alkyne carboacylation reactions could be improved by reacting *N*-benzoyl-*N*-phenylbenzamides containing deactivating substituents with triarylboroxines containing activating substituents. Reactions of these combinations of imide electrophiles and arylboron nucleophiles formed enones **4p**−**4w** in 28−57% yield and 2.4−7.5:1 dr.

To evaluate the scope of the reaction with respect to the alkyne coupling partner, we studied reactions of 3-hexyne, 1-phenyl-1-propyne, and diphenylacetylene. The carboacylation of 3-hexyne formed enone **4x** in 35% yield and 4.6:1 dr. The reaction of 1-phenyl-1-propyne with imide **1a** and triphenylboroxine generated enone **4y** in 27% yield as a single regioisomeric product. In addition, the reaction of 1-phenyl-1-propyne with imide **1a** and tris(4-methylphenyl)boroxine

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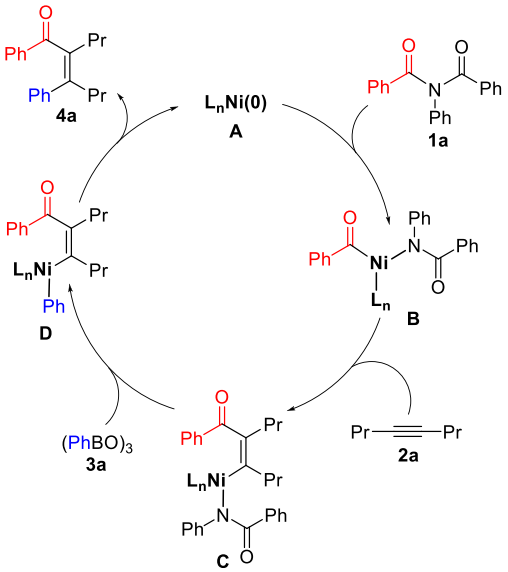
occurred with complete regioselectivity but generated the enone product in 30% yield as a 1:1 mixture of inseparable diastereomers. Carboacylations of 1,2-diarylacetylenes did not occur to form enone products in >5% yield.

Based on our previous studies of nickel-catalyzed alkene carboacylation reactions, we propose the following catalytic cycle for nickel-catalyzed alkyne carboacylation (Scheme 3).

Scheme 3. Proposed Mechanism

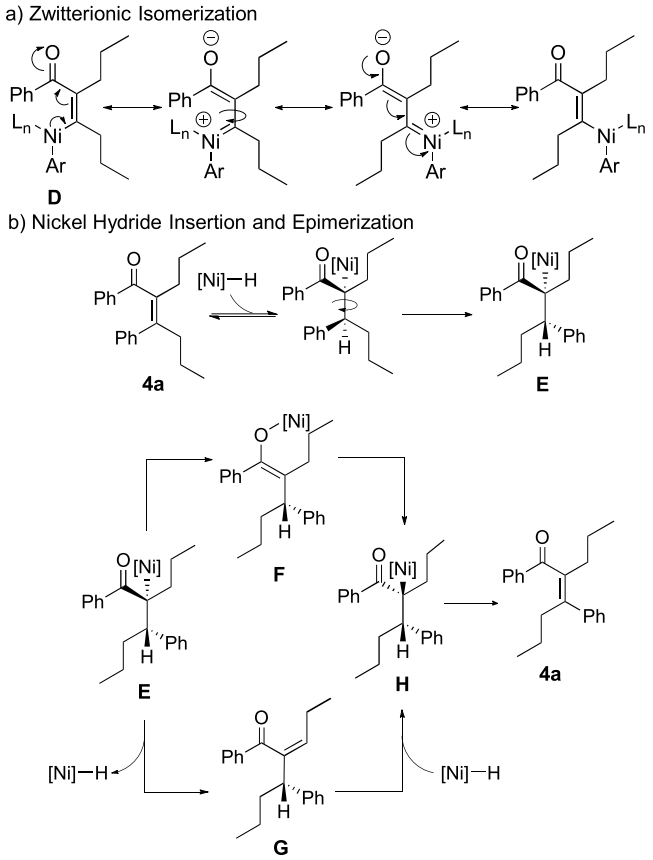


Oxidative addition of the Ni(0) catalyst **A** into the C−N bond of the imide electrophile **1a** generates an acyl-Ni(II)-amido intermediate **B**. Migratory insertion of the alkyne **2a** into the Ni(II)-acyl bond affords a vinyl-Ni(II)-amido complex **C**. Transmetalation with triphenylboroxine **3a** forms vinyl-Ni(II)-aryl intermediate **D**. Subsequent reductive elimination yields the desired carboacylation product **4a** and regenerates the Ni(0) catalyst. We propose that migratory insertion precedes transmetalation based on the observation of little to no benzophenone in our reactions.

This mechanism accounts for the initial formation of the *Z*-isomer of **4a** due to *syn*-addition of the alkyne into the Ni−C(acyl) bond of intermediate **B**. In order to understand the formation of the *E*-isomer, we considered several potential mechanistic pathways. Isomerization of vinyl transition-metal intermediates is known to occur through a pathway involving zwitterionic intermediates, stabilized by electron-donating ligands (Scheme 4a).[8] In our substrate scope of the alkyne carboacylation reaction, we observed that reactions of arylboroxines containing electron-donating groups led to lower diastereomeric ratios when compared with reactions of arylboroxines containing electron-withdrawing groups. These results are consistent with isomerization through the pathway shown in Scheme 4a, as an electron-rich aryl ligand could stabilize the zwitterionic nickel intermediate and facilitate isomerization to the *E*-isomer. While this isomerization pathway in Scheme 4a may be operative, it does not account for the observation that the diastereoselectivity of the alkyne carboacylation decreases when the loading of phenylboronic acid increases (Table 1, entries 13−15).

We theorized that a second isomerization pathway may be operative and involve migratory insertion of the enone product into a nickel hydride species (Scheme 4b).[9] The nickel hydride

Scheme 4. Proposed Mechanisms for Isomerization to *E*-Isomer



could potentially be formed in the reaction via oxidative addition of the nickel catalyst into the O−H bond of phenylboronic acid. When a sample of the *Z*-isomer of enone **4a** (>20:1 dr) was exposed to $NiCl_2$·glyme, potassium carbonate, and 5 equiv of phenylboronic acid for 4 h, a 2.5:1 mixture of *Z*- and *E*-isomers was observed. Replacing phenylboronic acid with triphenylsilane and $Ni(cod)_2$ as a source of nickel hydride led to the formation of diastereomeric enone products with 2.7:1 dr within 2 h. These results suggest that isomerization via nickel hydride species can also occur. If enone **4a** undergoes migratory insertion into a nickel hydride, the newly formed single bond can freely rotate to place the nickel *anti* to the *β*-hydrogen as in intermediate **E**. However, the nickel cannot undergo *β*-hydride elimination from this intermediate; therefore, epimerization at the *α*-center would be required for *β*-hydride elimination to occur. We considered two possible epimerization pathways involving either a nickel enolate (Scheme 4b, intermediate **F**) or *β*-hydride elimination from the alkyl chain and subsequent reinsertion (Scheme 4b, intermediate **G**). If trisubstituted alkene **G** is formed via *β*-hydride elimination from the propyl group, deuterium incorporation into the propyl group should be observed in the presence of a nickel deuteride. However, attempts to generate a nickel deuteride using deuterated phenylboronic acid, deuterated methanol, or deuterated phenylsilane did not result in deuterium incorporation into the enone product. This observation suggests that epimerization does not occur through a *β*-hydride elimination and is more likely to occur through nickel enolate **F**. Upon epimerization of the nickel

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enolate to intermediate **H**, *syn* β-hydride elimination may occur to form the *E*-isomer of **4a**.

In summary, we have developed a Ni-catalyzed intermolecular carboacylation of alkynes utilizing amides as acyl electrophiles and readily accessible triarylboroxines as nucleophiles. This reaction enables the generation of all-carbon tetrasubstituted enone products in up to 62% yield. Design of Experiment studies were utilized to identify reaction conditions that lead to a balance between yield and diastereoselectivity. Efforts to develop additional alkene and alkyne carbodifunctionalization reactions are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01607.

Experimental procedures, Design of Experiment data, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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