Alkynes

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Nickel-Catalyzed Stereoselective Dicarbofunctionalization of Alkynes

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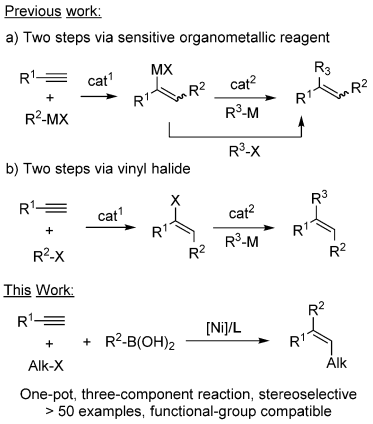
Abstract: *A nickel-catalyzed three-component reaction involving terminal alkynes, boronic acids, and alkyl halides is presented herein. Trisubstituted alkenes can be obtained in a highly regio- and stereocontrolled manner by the simultaneous addition of both aryl and alkyl groups across the triple bond in a radical-mediated process. The reaction, devoid of air- and moisture-sensitive organometallic reagents and catalysts, is operationally simple and offers a broad scope and functional-group tolerance.*

Alkynes represent one of the most flexible building blocks used in modern organic and organometallic chemistry. As a result, catalytic transformations of these π-systems are at the forefront of research activities in both academia and industry.[1] In this context, the one-pot difunctionalization of alkynes by the generation of two new C–C bonds is particularly appealing, as efficient dicarbofunctionalizations allow the straightforward assembly of molecular complexity.[2] Furthermore, these methods produce tetra- and trisubstituted alkenes, whose construction in a stereoselective manner is in high demand.[3] Two main strategies have been devised towards this latter goal by taking advantage of transition metal catalyzed cross-coupling reactions with organometallic reagents. The first one involves the generation of nucleophilic vinyl metal species which are subsequently engaged in reactions with suitable electrophiles.[4] Alternatively, vinyl halide intermediates are isolated and then subsequently used in well-established cross-coupling reactions.[5] Most of the above-mentioned processes either require the preparation or use of air- or water-sensitive reagents, which imposes limitations in their synthetic applicability (Scheme 1, top). Thus, the one-pot functionalization of alkynes by transition metal catalyzed multicomponent reactions to generate alkenes in a stereocontrolled fashion would be advantageous.[6] In this regard, Cook et al. have reported a highly efficient palladium-catalyzed intramolecular alkyne insertion/Suzuki multicomponent reaction of unactivated alkyl iodides.[7] Interestingly, nickel catalysts[8] have proved efficient for catalyzing the coupling of alkyl halides and organometallic reagents across alkynes, although the scope and functional-group compatibility of the reaction is limited to the use of a few sensitive magnesium and zinc reagents.[9] Notably, none of these methods is suitable for the incorporation of α-functionalized alkyl halides. Based on our ongoing interest in the efficient



Scheme 1. Comparison of methods to stereoselectively produce trisubstituted alkenes from alkynes.

functionalization of alkynes,[6b,c] we present herein a nickel-catalyzed stereoselective synthesis of trisubstituted alkenes through a radical-mediated, multicomponent addition of alkyl halides and organoboron reagents across terminal alkynes. The reaction, devoid of air- and moisture-sensitive organometallic reagents and catalysts, presents a broad functional-group compatibility, thus enabling the rapid construction of molecular complexity in a streamlined form under mild reaction conditions (Scheme 1, bottom).

We set out to explore whether both activated and unactivated alkyl halides could be efficiently incorporated across triple bonds. The reaction between phenylacetylene, 4-(*tert*-butyl)phenylboronic acid and ethyl 2-bromopropanoate[10] was first evaluated (Table 1). After a preliminary optimization,[11] nickel catalysts in combination with different ligands were explored with benzene as the solvent at 80 °C in the presence of two equivalents of K_3PO_4. $NiCl_2$·DME together with **L1** and **L2** failed to produce the desired product (entry 1). In contrast, the use of the Tolterpy ligand **L3** produced **1a** in 12 % yield (entry 2). Other nickel sources including $Ni(NO_3)_2·6H_2O$, $[Ni(acac)_2]$, and $[NiCl_2(Ph_3P)_2]$ were screened (entries 3–5) with the latter complex providing the desired alkene in 55 % yield. After temperature and solvent optimization (entries 6 and 7), and switching to $[NiCl_2(Py)_4]$, an air- and moisture-stable precatalyst,[12] **1a** was obtained in an improved 79 % yield (entry 8).

With the optimized reaction conditions in hand, we set out to explore the scope of this transformation. First, different arylboronic acids were investigated in combination with phenylacetylene (Table 2, top). Electron-donating as well as electron-withdrawing groups were well tolerated as demonstrated by the reactions to produce **1b–g** and **1h–l**, respectively, which proceeded with complete regio- and stereocon-

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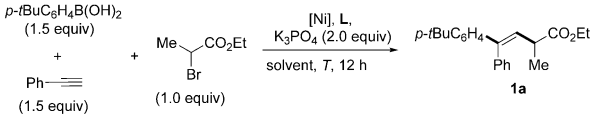
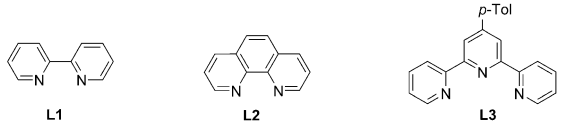
Table 1: Optimization of the reaction conditions.

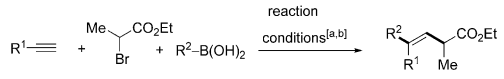


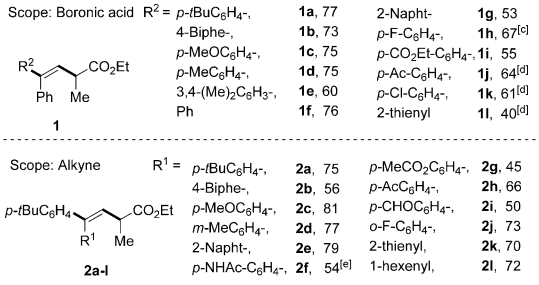


Entry	Catalyst (10 mol%)	Solvent (0.1 M)	Ligand (10 mol%)	T [°C]	Yield [%][a]
1	$NiCl_2$·DME	C_6H_6	**L1** or **L2**	80	0
2	$NiCl_2$·DME	C_6H_6	**L3**	80	12
3	$Ni(NO_3)_2$·6 H_2O	C_6H_6	**L3**	80	18
4	$[Ni(acac)_2]$	C_6H_6	**L3**	80	0
5	$[NiCl_2(PPh_3)_2]$	C_6H_6	**L3**	80	55
6	$[NiCl_2(PPh_3)_2]$	C_6H_6	**L3**	100	58
7	$[NiCl_2(PPh_3)_2]$	1,4-dioxane	**L3**	100	77
8	$[NiCl_2(Py)_4]$	1,4-dioxane	**L3**	100	79 (77)

[a] Yield determined by ^{1}H NMR spectroscopy with *p*-nitroacetophenone as an internal standard. Yield of product isolated after column chromatography is given within parentheses. acac = acetylacetonate, DME = dimethoxyethane, Py = pyridine.

Table 2: Reaction scope with respect to boronic acids and alkynes.

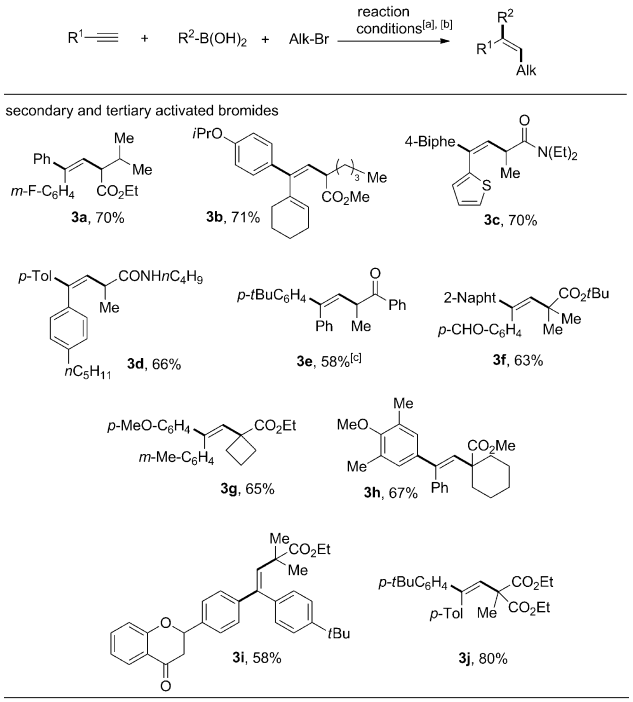




[a] Optimized reaction conditions: Table 1, entry 8. [b] All compounds were obtained as single isomers. Yield is that of product isolated after column chromatography. [c] 120 °C. [d] $[NiCl_2(PPh_3)_2]$ (20 mol%), **L3** (20 mol%). [e] Alkyne (1.0 equiv), 4-(*tert*-butyl)phenylboronic acid (1.5 equiv), ethyl 2-bromopropanoate (1.5 equiv). 4-Biphe = 4-biphenyl.

trol in all cases. The reaction with 2-napthtylboronic acid was scaled-up (2 mmol), thus furnishing the desired alkene **1g** in 53% yield. X-ray diffraction analysis of the acid derived from **1g** confirmed the structural assignment of the reaction products.[11] The substitution pattern on the alkyne was evaluated next (Table 2, bottom). Using 4-(*tert*-butyl)phenylboronic acid as partner, aryl alkynes bearing different groups were submitted to the standard reaction conditions and furnished the corresponding trisubstituted alkenes in high yields with perfect stereocontrol in favor of the *anti*-addition product (**2a–l**). The functional-group tolerance is truly remarkable, as demonstrated by the efficient conversion of substrates bearing amides, esters, ketones, aldehydes, or conjugated alkenes into the desired products. In contrast, non-conjugated alkynes and alkyl boronic acids could not be successfully engaged in these transformations.

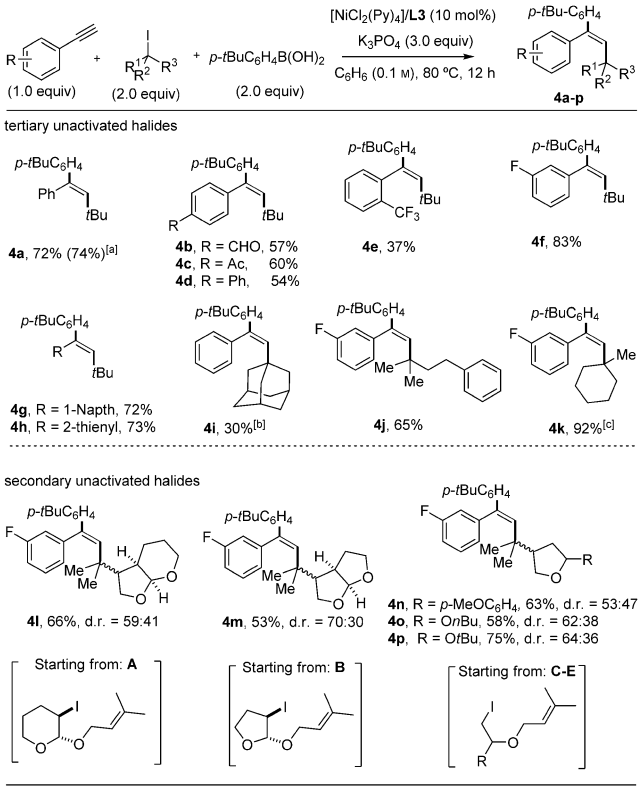
The nature of the alkyl radical precursor was investigated next (Scheme 2). The reactions of ethyl 2-bromo-3-methylbutanoate and ethyl 2-bromohexanoate furnished products **3a** (70%) and **3b** (71%), respectively. Amides, as well as ketones could also be used at α-position to the C–Br bond,



Scheme 2. Reaction scope for activated alkyl bromides. [a] Reaction conditions: Table 1, entry 8. [b] All compounds were obtained as single isomers (> 99:1). Yields are those of products isolated after column chromatography. [c] $[NiCl_2(PPh_3)_2]$ (20 mol%), **L3** (20 mol%) as a 5:1 *E*/*Z* mixture in C_6H_6.

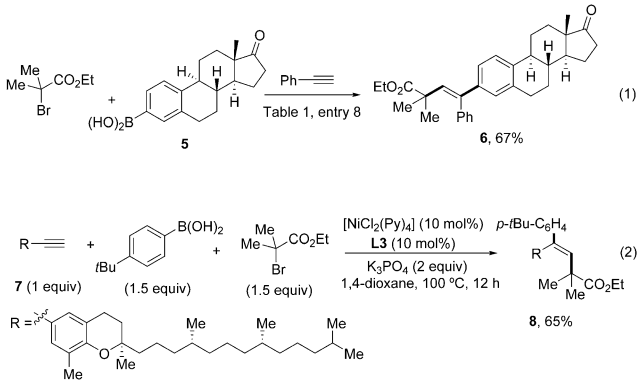
thus highlighting the functional-group tolerance of the reaction (**3c–e**). Interestingly, tertiary bromides displayed also a good reactivity as demonstrated by the reactions to produce alkenes **3f–j**. Unactivated alkyl halides were also evaluated (Scheme 3). First, the reaction of 4-(*tert*-butyl)phenylboronic acid with *tert*-butyl iodide in the presence of an array of alkynes was explored. The corresponding products **4a–h** could be isolated in up to 83% yield. 1-Iodoadamantane, (3-iodo-3-methylbutyl)benzene, and 1-iodo-1-methylcyclohexane could be efficiently incorporated as demonstrated by the reactions to produce the compounds **4i–k**.

X-ray diffraction analysis of **4i** confirmed the assigned configuration of the products.[11] The reactions of 3-fluorophenylacetylene with 4-(*tert*-butyl)phenyl-boronic acid in the presence of primary and secondary unactivated alkyl iodides (**A–E**) delivered the corresponding cyclization/addition/coupling products **4l–p** with perfect stereocontrol in the olefin configuration but low diastereoselectivity in the tetrahydrofuran ring.[13]

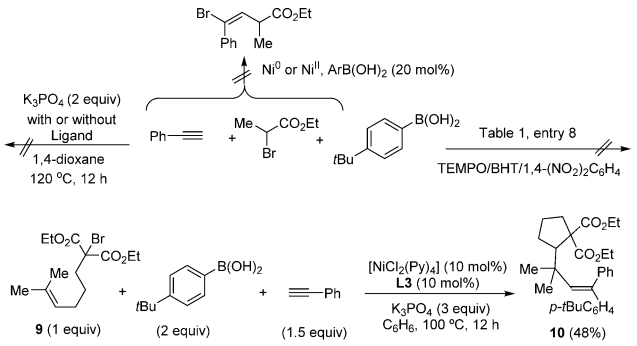


Scheme 3. Reaction scope for unactivated alkyl iodides. Yields are those of products isolated after column chromatography. All compounds were obtained as single isomers (>99:1). [a] Reaction with *t*BuBr at 100 °C. [b] 100 °C. [c] *Z*/*E* ratio: 98:2.

The transformations shown in Equations (1) and (2), using natural-product-derived starting materials, provide additional evidence for the flexibility of this methodology.



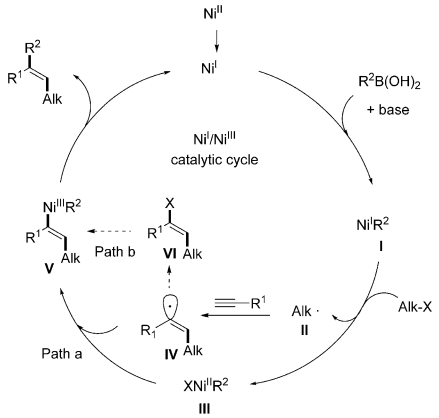
Control experiments were also carried out. Radical inhibitors added to the reaction mixture substantially reduced the product formation (Scheme 4, top right).[11] In the absence of nickel, even at higher temperature, the reaction did not proceed at all, thus showing that the metal is key for a successful outcome (Scheme 4, top left).[14] Experiments carried out with nickel(0) or nickel(II) in the absence of boronic acid or combining nickel(II) with a substoichiometric



Scheme 4. Control experiments. BHT = 2,6-di-*tert*-butyl-4-methylphenol, TEMPO = 2,2,6,6,-tetramethylpiperidine-N-oxyl.

amount of the boron partner showed no vinyl halide formation, thus indicating that a simple [Ni]/L system is not responsible for the C–X activation (Scheme 4, top middle). The reaction of **9**, as well as the reactions reported for the unactivated alkyl iodides **A**–**E**, support a radical-mediated process, given the preferred addition to the more reactive alkene moiety (Scheme 4, bottom).

We hypothesize that the nickel(I) species produced in situ in the reaction media are able to react with the boronic acid reagent in a transmetallation step producing the R^2Ni^I intermediate **I** (Scheme 5). This complex reacts with the



Scheme 5. Proposed reaction mechanism.

alkyl halide to produce the alkyl radical **II** together with $R^2Ni^{II}X$ (**III**). Intermediate **II** undergoes intermolecular addition to the C≡C bond, thus affording the vinyl radical **IV**. The subsequent recombination between **III** and **IV** would give the key nickel(III) species **V**, which undergoes reductive elimination to produce the corresponding trisubstituted alkene while regenerating nickel(I) (path a).[15] Formation of the corresponding vinyl halide **VI** as a potential reaction intermediate in these transformations (path b) seems to be ruled out based on all control experiments. Furthermore, the Suzuki-coupling on preformed vinyl bromides under the reaction conditions did not occur with complete stereofidelity, thus signaling that a potential halogen-atom transfer is not

competing with trapping of the radical by the nickel complex (see the Supporting Information).[16] The high stereoselectivity of the reaction is rationalized on the basis of a fast-interconverting *E*/*Z* vinyl radical **IV**,[17] which incorporates an external radical opposite to the alkyl group.

In summary, a simple, functional-group tolerant, nickel-catalyzed three-component reaction of terminal alkynes with boronic acids and activated and unactivated secondary and tertiary alkyl halides is presented here. The method, involving the simultaneous addition of both aryl and alkyl groups across the alkyne, streamlines the access to trisubstituted alkenes in a highly regio- and stereocontrolled manner. This radical-mediated process, devoid of sensitive organometallic reagents, presents a high functional-group compatibility and synthetic applicability even for highly complex settings.

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Keywords: alkyl halides · alkynes · boron · nickel · radicals

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