RESEARCH ARTICLE

Regio- and Diastereoselective Synthesis of Trisubstituted Alkenes Through Hydroalkylation of Alkynyl Boronamides

Langxuan Yang,[a] and Gojko Lalic*[a]

[a] Yang, L.; Prof. Lalic, G.
Department of Chemistry, University of Washington
109 Bagley Hall, Seattle, WA 98195 (USA)
E-mail: lalic@chem.washington.edu

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

Abstract: Hydroalkylation of alkynes is a powerful method for alkene synthesis. However, regioselectivity has been difficult to achieve in transformations of internal alkynes hindering applications in the synthesis of trisubstituted alkenes. To overcome these limitations, we explored using boryl groups as versatile directing groups that can control the regioselectivity of the hydroalkylation and subsequently be replaced in a cross-coupling reaction. The result of our exploration is a nickel-catalyzed hydroalkylation of alkynyl boronamides that provides access to a wide range of trisubstituted alkenes with high regio- and diastereoselectivity. The reaction can be accomplished with a variety of coupling partners, including primary and secondary alkyl iodides, α-bromo esters, α-chloro phthalimides, and α-chloro boronic esters. Preliminary studies of the reaction mechanism provide evidence for the hydrometalation mechanism and the formation of alkyl radical intermediates.

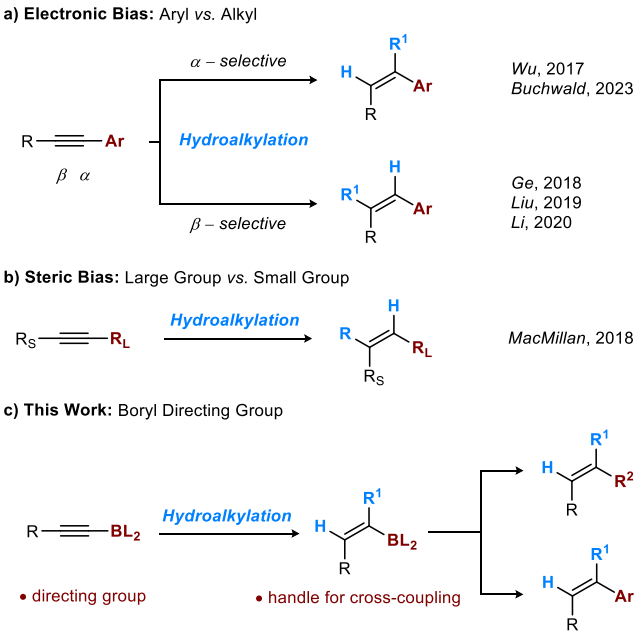
Introduction

Substituted alkenes are versatile synthetic intermediates[1] and common structural elements found in biologically active molecules and natural products.[2] As a result, improving access to this important class of compounds remains an important goal of synthetic organic chemistry. In recent years, hydroalkylation of alkynes has emerged as a powerful new approach to alkene synthesis. The most significant impact of hydroalkylation has been in the synthesis of disubstituted alkenes. Various hydroalkylation reactions now allow transformation of terminal alkynes into all three isomers of disubstituted alkenes with excellent regio- and diastereoselectivity.[3]

Hydroalkylation has had more limited applications in the synthesis of tri-substituted alkenes. The main challenge that prevents broader application of this approach has been the control of regioselectivity in the hydroalkylation of nonsymmetrical internal alkynes. So far, two main strategies have been used to address this challenge. Good regioselectivity has been achieved with activated aryl alkynes, where electronic bias introduced by an aryl group controls the regioselectivity (Scheme 1a).[4] Alternatively, sterically demanding alkyl substituents that introduce steric bias have also been used to impart good selectivity (Scheme 1b).[3b] While successful, these strategies provide access to an inherently limited scope of trisubstituted alkenes.

To develop a more general hydroalkylation method for the synthesis of trisubstituted alkenes, we envisioned the use of functionalized alkynes containing a directing group. Ideally, the directing group would control the regioselectivity of the reaction and then, after the reaction, could be removed from the molecule in a productive way. With these considerations in mind, we chose to focus on boryl directing groups (Scheme 1c), which have been used to control transition metal-catalyzed[5] and radical[6] addition reactions to unsaturated compounds. Derivatives of boronic acids such as boronic esters, *N*-coordinated boronic esters, and boronamides can be easily incorporated through borylation[7] of terminal alkynes and would allow us to explore directing groups with a wide range of steric and electronic properties. At the same time, these groups[8] could all be removed in a subsequent cross-coupling reaction that would provide access to a range of trisubstituted alkenes.

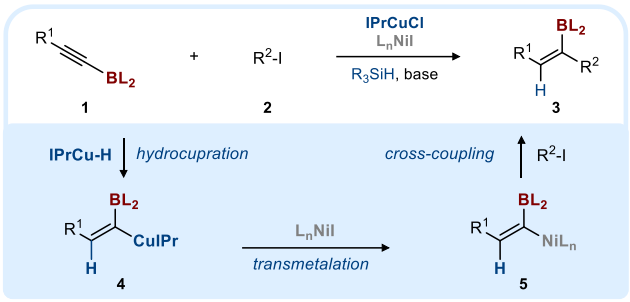
In this article, we report nickel-catalyzed hydroalkylation of alkynyl boronamides using alkyl halides as coupling partners. Introducing the boryl directing group into terminal alkynes allows the control of regioselectivity in the hydroalkylation and provides access to trisubstituted *E*-alkenyl boronamides[9] with high selectivity. We also show that the resulting alkenyl boronamides can be used to access trisubstituted alkenes, including those with all alkyl substituents.



Scheme 1. Regiocontrol in hydroalkylation of disubstituted alkynes. (a) Alkynes with electronic bias. (b) Alkynes with steric bias. (c) Focus of this work.

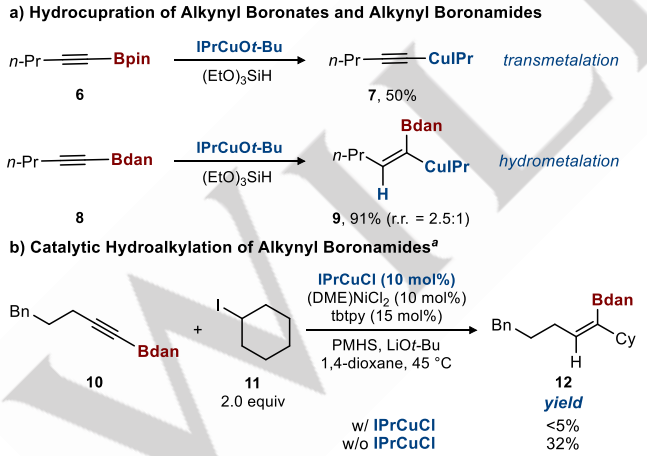
Results and Discussion

Our initial approach to the synthesis of trisubstituted alkenes is based on the method for hydroalkylation of terminal alkynes our group reported in 2019 (Scheme 2).[3e] We envisioned that the hydroalkylation of boryl alkyne **1** would proceed through copper hydride formation, followed by hydrocupration, and the nickel-catalyzed cross coupling of the alkenyl copper intermediate (**4**) with an alkyl halide. The main question we tried to answer is if boryl groups are compatible with alkenyl copper formation and if they could control the regioselectivity of the process.



Scheme 2. Reaction design.

A stoichiometric reaction between alkynyl Bpin **6** (pin = pinacolato) and IPrCuH (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) formed by premixing IPrCuO*t*-Bu[10] and $(EtO)_3SiH$[11] resulted in exclusive formation of copper acetylide **7** and no formation of the alkenyl copper complex (Scheme 3a). The formation of the copper hydride intermediate was indicated by the formation of $(EtO)_3SiO$*t*-Bu byproduct, suggesting that hydrocupration of the alkynyl Bpin had failed.

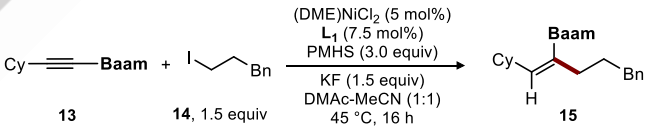


Scheme 3. Preliminary results. (a) Hydrocupration of boryl alkynes. (b) Catalytic hydroalkylation. [a] tbtpy = 4,4′,4″-tri-tert-butyl-2,2′:6′,6″-terpyridyl.

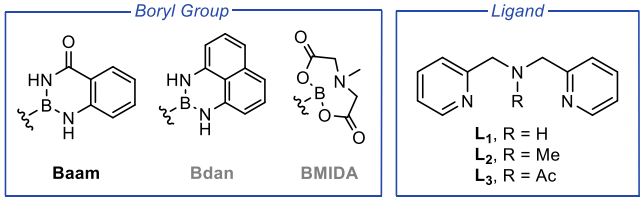
To prevent the copper acetylide formation, we turned to bromamides specifically designed by Suginome[12] to suppress transmetalation by lowering Lewis acidity of the boron.[13] With alkynyl Bdan **8** (dan = naphthalene-1,8-diaminato) in place of alkynyl Bpin, the desired alkenyl copper complex **9** is formed in 91% yield and 2.5:1 regioselectivity, with no apparent formation of the copper acetylide (Scheme 3a). Encouraged by this result, we explored the catalytic hydroalkylation of alkynyl Bdan with cyclohexyl iodide as a coupling partner and a silane as a hydride source (Scheme 3b). In a reaction promoted by the nickel-copper catalyst system previously used in hydroalkylation of terminal alkynes, we did not observe the formation of the desired trisubstituted alkene **12**. However, a control experiment performed without the copper co-catalyst produced 32% of the desired alkene product.

With the results described in Scheme 3b as the starting point, we were able to develop an efficient nickel-catalyzed reductive coupling of alkynyl boronamides and alkyl iodides (Table 1). The best results were obtained using catalyst prepared in situ from $(DME)NiCl_2$ and di-(2-picolyl)amine ligand (**L_1**), with anhydrous KF as the turnover reagent. The results in Table 1 show how the changes of different reaction parameters affect the yield of the desired product. The highest yields were obtained with derivatives of boronic acids that have relatively low Lewis acidity, such as Baam[12c] (aam = anthranilamidato) and Bdan.[12a, 12b] Both BMIDA[14] (MIDA = *N*-methyliminodiacetoxy) and Bpin, which are widely used in synthetic chemistry, gave lower yields of the desired product (entries 3 and 4). The identity of the ligand was critical to the success of the reaction, with ligand **L_1** providing the best results. Surprisingly, no previous uses of this ligand in nickel catalysis have been reported. Ligands **L_2** and **L_3** have been used in nickel catalyzed transformations,[15] together with other derivatives of **L_1**. However, both **L_2** and **L_3** were less effective in this reaction. The result obtained with **L_2** suggests that deprotonation of the central nitrogen is not essential for catalysis. Among several classes of ligands commonly used in nickel hydride chemistry, only bipyridine ligands afforded the desired product in significant yields, with dtbbpy (4,4′-di-tert-butyl-2,2′-dipyridyl) providing 56% yield (entry 7).

Table 1. Reaction parameters.[a]

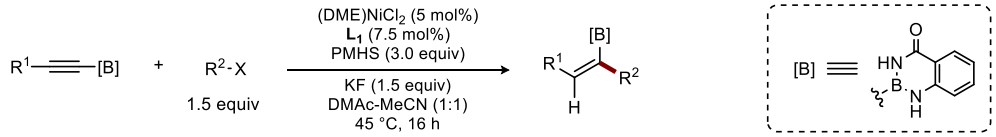


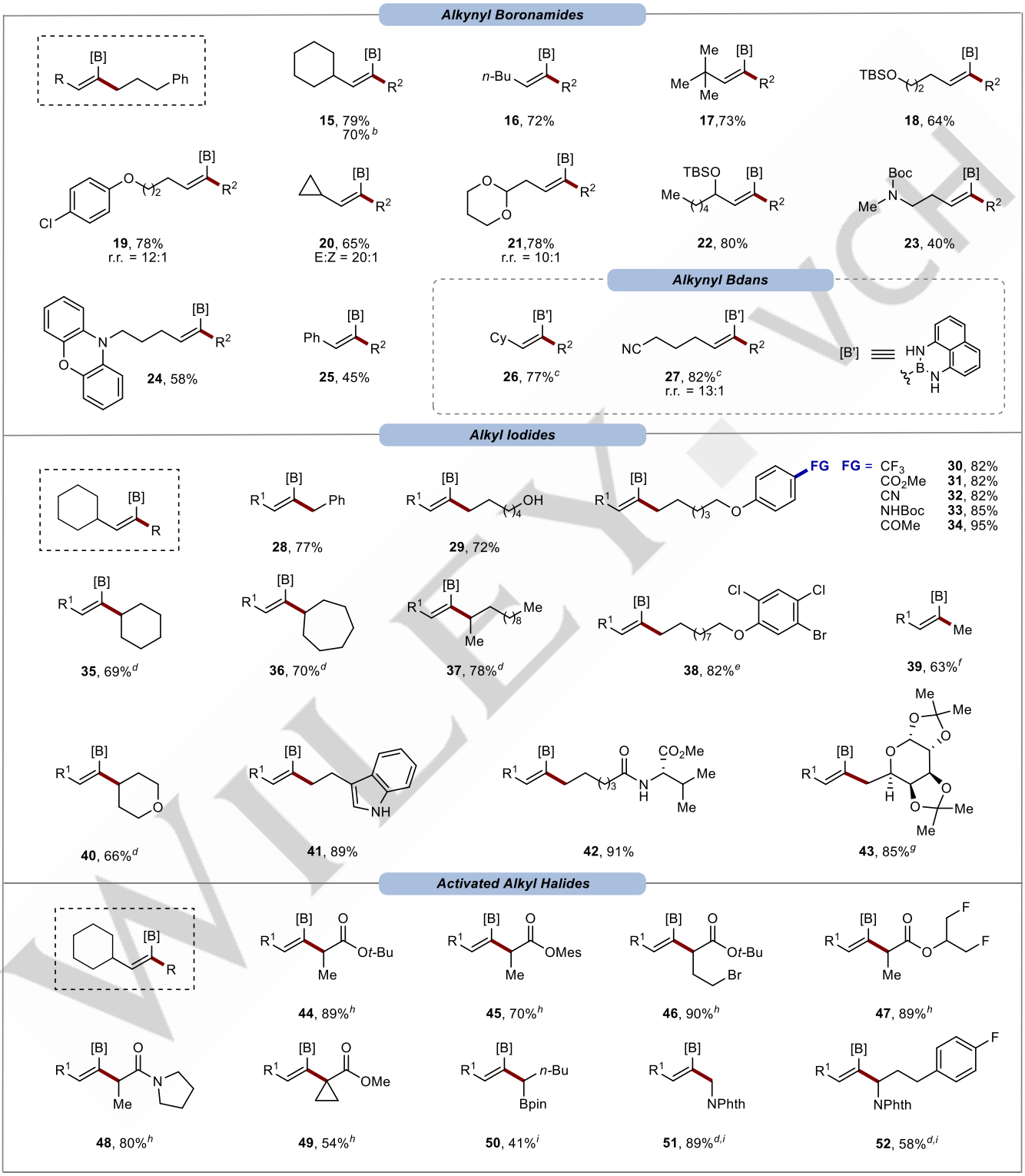
Entry	Change from Standard Conditions	Yield
1	none	85% (79%)
2	**Bdan** instead of **Baam**	82%
3	**BMIDA** instead of **Baam**	52%
4	**Bpin** instead of **Baam**	<5%
5	**L_2** instead of **L_1**	72%
6	**L_3** instead of **L_1**	35%
7	**dtbbpy** instead of **L_1**	56%
8	**tpy** instead of **L_1**	<5%
9	DMAc as solvent	82%
10	MeCN as solvent	48%
11	DMES instead of PMHS	64%
12	TMDSO instead of PMHS	46%



[a] Yields determined by ^1H NMR spectroscopy using internal standard. Isolated yields in parenthesis.

Table 2. Substrate scope.





[a] Yields of isolated products are reported. Reactions performed on 0.50 mmol scale. Regioselectivities and diastereoselectivities of isolated products > 20:1 unless specifically noted. [b] 1.5 equiv alkyl bromide with 50 mol% KI was used instead of alkyl iodide. [c] Alkynyl Bdan was used instead of Baam. [d] DMAc:MeCN = 7:3. [e] Reactions performed on 0.25 mmol scale. [f] 1.5 equiv MeOTs with 50 mol% Bu_4NI was used instead of alkyl iodide. [g] Reaction time = 72 h. [h] Alkyl bromide was used instead of alkyl iodide. [i] Alkyl chloride was used instead of alkyl iodide at 60 °C. Mes = 2,4,6-trimethylphenyl. Phth = phthaloyl.

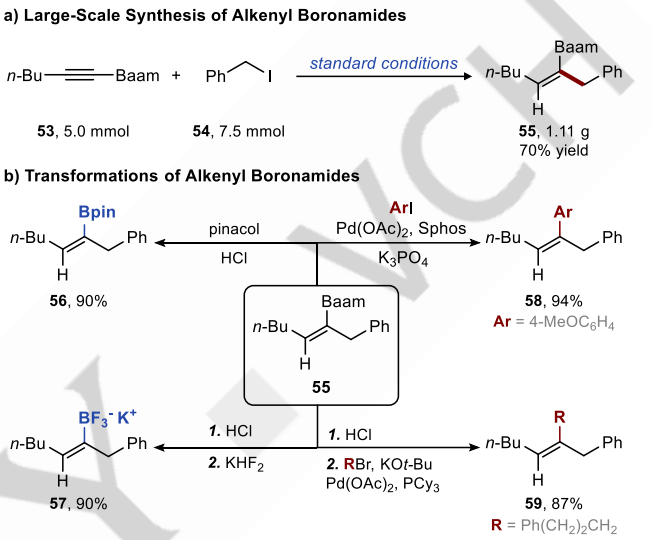
The catalyst prepared in situ using terpyridine (tpy) ligand provided virtually no product (entry 8) and that is representative of the performances of catalysts supported by other classes of ligands (see the SI). The highest yield of the desired product was obtained using a DMAc-MeCN solvent mixture. DMAc alone performed well in the initial test reaction (entry 9), but worse with other alkynyl boronamide substrates (see Supporting Information). MeCN alone provided a lower yield of the desired product (entry 10). While polymeric PMHS showed good reactivity, structurally related silanes like monomeric DEMS (DEMS = diethoxy(methyl)silane) and dimeric TMDSO (TMDSO = 1,1,3,3-tetramethyldisiloxane) gave diminished yields (entries 11 and 12). Finally, control experiments indicated that the reaction did not proceed in the absence of the ligand, the nickel precatalyst, or the silane (see the SI).

We explored the scope of the reaction using standard reaction conditions described in Table 1 (entry 1). A wide range of trisubstituted alkenyl boronamides were isolated with excellent *E*-selectivity and in most cases good regioselectivity (Table 2). Alkynyl boronamides containing protected alcohols (**18**), acetals (**21**), aryl chlorides (**19**), propargylic leaving groups (**22**), protected amines (**23**), and nitrogen-containing heteroarenes (**24**) are well tolerated. Sterically demanding alkynyl boronamides, such as **15**, **17**, and **20** performed well under the reaction conditions, while aryl alkynyl boronamides gave a diminished yield (**25**). Related alkynyl Bdans can also be used in the reaction without significant drop in yield of the desired alkene products (**26** and **27**). The resulting alkenyl Bdan products are more resistant to hydrolysis and less prone to decomposition during silica gel purification than the Baam analogues.[12c]

We also investigated the reactivity of various alkyl iodides and found that both structural and functional group diversity are well tolerated. The reaction can be accomplished in the presence of free alcohols (**29**), ketones (**34**), esters (**31**), nitriles (**32**), aryl halides (**38**), and protected amines (**33**). Alkyl iodides derived from tryptophol (**41**), valine (**42**), and galactose (**43**) were also successfully used in the reaction. Secondary alkyl iodides (**35**, **36**, **37**, and **40**) generally performed well under slightly modified conditions. Hydromethylation can be achieved using MeOTs as the electrophile with a catalytic amount of TBAI (tetra-*n*-butylammonium iodide) (**39**). Alkyl bromides can also be used as coupling partners in the presence of catalytic amount of KI as an additive (**15**).

To further expand access to trisubstituted alkenes, we explored the reactivity of several classes of activated alkyl halides. A variety of secondary α-bromo carbonyl compounds,[3f] including esters (**44**-**47**) and amides (**48**) provided the desired trisubstituted alkenes. Examination of several tertiary α-bromo esters revealed that cyclic tertiary esters yielded moderate results (**49**), while acyclic counterparts proved unreactive (see the SI). When α,γ-dibromo ester was used as the substrate, the cross-coupling reaction occurred selectively α to the carbonyl, while the γ bromide was preserved (**46**). α-chloro boronic esters[16],[17] and α-chloro phthalimides,[18] which can serve as functional equivalents of carbonyl and imino electrophiles, also participate in the reaction. Allylic boronic esters (**50**) and allylic amines (**51** and **52**) were prepared in moderate to good yields.

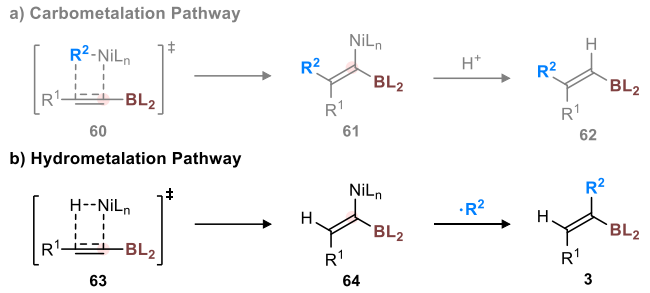
To illustrate the practical utility of the hydroalkylation reaction, trisubstituted alkenyl boronamide **55** was synthesized on gram scale in 70% yield and used in further transformations. Alkenyl boronamide **55** could be used to prepare trisubstituted pinacol boronic ester **56** and trifluoroborate salt **57**. Direct arylation of **55** can be performed with retention of the double bond geometry to afford trisubstituted alkene **58** in 94% yield.[19] Finally, trisubstituted alkene **59** was synthesized in 87% yield by deprotection and subsequent Pd-catalyzed alkylation without alkene isomerization.[20]



Scheme 4. Applications. (a) Large scale reaction. (b) Further transformations of the trisubstituted alkene product.

Closely related nickel-catalyzed reactions for hydroalkylation of alkynes have been proposed to involve either hydrometalation or carbometalation as the key step of the reaction mechanism.[4c-e] Initially, we evaluated these two categories of reaction mechanisms in the context of the regioselectivity observed in hydroalkylation of alkynyl boronamides.

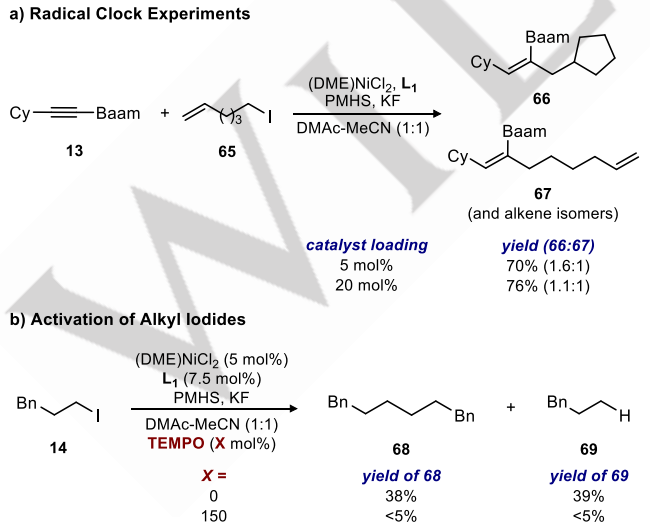
The boryl directing groups direct the insertion of boryl-substituted alkynes into transition metal complexes with the boryl group proximal to the metal center. The same selectivity has been observed across different metal catalysts and different types of insertion reactions.[5] The proximal selectivity has been attributed to electronic effects of boryl groups[5d, 5f] or to their direct interactions with the metal center.[5c] In our case, if the carbometalation step were a part of the reaction mechanism (Scheme 5a), it would be regio-determining and would be expected to provide the other regioisomer of the alkene product (**62**). On the other hand, the mechanism involving hydrometalation (Scheme 5b) is consistent with the observed regioselectivity. If the hydrometalation were product determining, the expected proximal regioselectivity in this step would lead to the observed selectivity of the hydroalkylation. The reversible hydrometalation, while not product determining, is also compatible with the observed selectivity.[21] The performance of Baam, Bdan, and BMIDA groups suggests electronic effects as a significant contributor to the observed regioselectivity. However, we cannot exclude additional contribution from a direct interaction between the metal and Baam directing group.



Scheme 5. Regioselectivity in carbometalation (a) and hydrometalation (b) pathways.

The hydrometalation mechanism has not been extensively explored in nickel-catalyzed hydroalkylation of alkynes. As a result, we based our further mechanistic analysis on more detailed investigations of closely related hydroalkylations of alkenes.[22] Four related, but distinct, mechanisms that involve nickel (I/III) catalytic cycle have been proposed in these reactions.[23] The main difference between the four alternatives is in the timing of the alkyl halide activation relative to the nickel hydride formation and the hydrometalation steps.

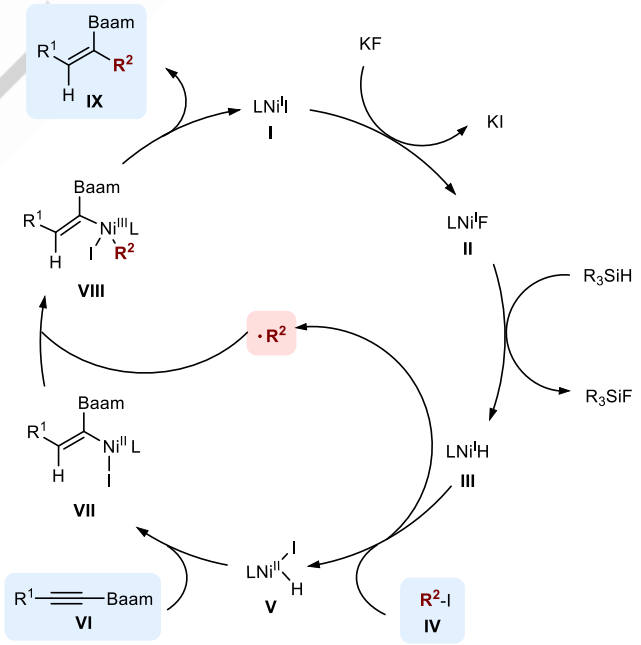
To further test hydrometalation as the key step of the reaction and probe which variant of hydrometalation mechanism is most likely in our case, we did a set of preliminary experiments. Alkynyl boronamide **13** and 6-iodo-1-hexene (**65**) were subjected to standard conditions and delivered the cyclized product **66** in 43% yield and a mixture of uncyclized alkene isomers **67** in 27% yield (Scheme 6a). The ratio of the cyclized and the linear product (**66**:**67**) depends on the catalyst concentration, indicating that the alkyl radical lifetime changes with nickel catalyst concentration. This is a strong indication for the formation of a free alkyl radical intermediate that is being trapped by a nickel catalyst,[24] one of the hallmarks of hydroalkylation mechanisms that involve a hydrometalation step.



Scheme 6. Studies of the reaction mechanism. (a) Radical clock experiments. (b) Radical trap experiments with alkyl iodide.

We also explored conditions for the formation of the alkyl radical. We found that under the reaction conditions in the absence of the alkyne (Scheme 6b), homodimerization of the alkyl halide was observed (**68**) together with the formation of the dehalogenation product **69**. Furthermore, the formation of the two products was fully suppressed in the presence of 1.5 equiv of TEMPO, with 80% of the alkyl halide retained, and TEMPOH adduct as the major new product. The results of these experiments are consistent with the formation of the alkyl radical intermediate in a reaction of an alkyl halide with a nickel hydride complex formed in the presence of a silane. When present, TEMPO reacts with the nickel hydride and prevents the reaction with the alkyl halide.[25] Similar experiments performed in the absence of the silane with high loading of nickel(I) complexes indicated an inefficient formation of alkyl radicals (see Supporting Information).

Considering the results of our experiments and the available information about related hydroalkylation of alkenes,[23] we propose a mechanism presented in Scheme 7. The hydroalkylation reaction is initiated by ligated Ni^{I} precursor **I**, which then generates nickel hydride species **III** in the presence of potassium fluoride and the silane. Subsequently, **III** reacts with alkyl iodide to form an alkyl radical and $Ni^{II}H$ species **V**, followed by regioselective hydrometalation of the alkynyl boronamide to give alkenyl nickel (II) species **VII**.[26] The capture of the alkyl radical to form Ni^{III} intermediate **VIII** is followed by a reductive elimination to release the desired trisubstituted product and regenerate **I**. Based on the available data, the product determining step can be either the hydrometalation or the reductive elimination. Further studies are required to differentiate between the available mechanistic hypothesis and determine the step(s) responsible for the observed regioselectivity.



Scheme 7. Proposed reaction mechanism.

There are indications that an alternative mechanism is operational with activated alkyl bromides. In their investigation of the mechanism for reductive coupling of α-bromo carbonyls, Fu et al have proposed bromine atom transfer by nickel (I) catalyst prior to the formation of the nickel hydride complex.[22e, 27] We

suspect that a similar alternative mechanism may be operational in our case with activated alkyl halides.

Conclusion

We have developed a nickel-catalyzed hydroalkylation of alkynyl boronamides. The reaction allows reductive cross coupling of alkynyl boronamides with several classes of coupling partners, including primary and secondary alkyl iodides, α-bromo esters, α-chloro phthalimides, and α-chloro boronic esters. The reaction can be successfully performed in the presence of alcohols, Boc-protected primary and secondary amines, ketones, esters, aryl halides, and nitriles. After purification, the alkenyl boronamide products are obtained with generally high regio- and diastereoselectivity. We have demonstrated that boryl functional group that controlled the regiochemistry of the hydroalkylation reaction can be efficiently removed in a subsequent cross-coupling reaction. Palladium catalyzed alkylation and arylation reactions of alkenyl boronamides provide access to a variety of trisubstituted alkenes. Preliminary exploration of the reaction mechanism indicates hydrometalation of the alkynyl boronamide as the key step in activation of the alkyne. The nickel hydride intermediate is implicated in the activation of the alkyl halide and results in the formation of the free alkyl radical intermediate that is trapped by a nickel complex.

Acknowledgements

This work was supported by the NSF (award #2102231). NIH provided funding for instrument support (S10 OD030224-01A1).

Keywords: Nickel • Hydroalkylation • Alkenes • Homogeneous Catalysis

[1] P. Knochel, G. A. Molander, in *Comprehensive Organic Synthesis, Vol. 5*, Elsevier, Amsterdam, **2014**.

[2] P. Ertl, T. Schuhmann, *J. Nat. Prod.* **2019**, *82*, 1258-1263.

[3] a) X.-Y. Lu, J.-H. Liu, X. Lu, Z.-Q. Zhang, T.-J. Gong, B. Xiao, Y. Fu, *Chem. Commun.* **2016**, *52*, 5324-5327; b) N. A. Till, R. T. Smith, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2018**, *140*, 5701-5705; c) C. W. Cheung, F. E. Zhurkin, X. Hu, *J. Am. Chem. Soc.* **2015**, *137*, 4932-4935; d) M. R. Uehling, A. M. Suess, G. Lalic, *J. Am. Chem. Soc.* **2015**, *137*, 1424-1427; e) A. Hazra, J. Chen, G. Lalic, *J. Am. Chem. Soc.* **2019**, *141*, 12464-12469; f) A. Hazra, J. A. Kephart, A. Velian, G. Lalic, *J. Am. Chem. Soc.* **2021**, *143*, 7903-7908; g) K. Nakamura, T. Nishikata, *ACS Catal.* **2017**, *7*, 1049-1052; h) M. T. Lee, M. B. Goodstein, G. Lalic, *J. Am. Chem. Soc.* **2019**, *141*, 17086-17091; i) Y. Li, D. Liu, L. Wan, J.-Y. Zhang, X. Lu, Y. Fu, *J. Am. Chem. Soc.* **2022**, *144*, 13961-13972; j) L. Yu, L. Lv, Z. Qiu, Z. Chen, Z. Tan, Y.-F. Liang, C.-J. Li, *Angew. Chem., Int. Ed.* **2020**, *59*, 14009-14013.

[4] a) H.-P. Deng, X.-Z. Fan, Z.-H. Chen, Q.-H. Xu, J. Wu, *J. Am. Chem. Soc.* **2017**, *139*, 13579-13584; b) D. A. Kutateladze, B. K. Mai, Y. Dong, Y. Zhang, P. Liu, S. L. Buchwald, *J. Am. Chem. Soc.* **2023**, *145*, 17557-17563; c) X.-Y. Lu, M.-L. Hong, H.-P. Zhou, Y. Wang, J.-Y. Wang, X.-T. Ge, *Chem. Commun.* **2018**, *54*, 4417-4420; d) Z.-F. Zhu, J.-L. Tu, F. Liu, *Chem. Commun.* **2019**, *55*, 11478-11481; e) X.-Y. Lu, C.-C. Liu, R.-C. Jiang, L.-Y. Yan, Q.-L. Liu, Q.-Q. Wang, J.-M. Li, *Chem. Commun.* **2020**, *56*, 14191-14194.

[5] a) R. N. Khanizeman, E. Barde, R. W. Bates, A. Guérinot, J. Cossy, *Org. Lett.* **2017**, *19*, 5046-5049; b) Y. Gao, Z.-Q. Wu, K. M. Engle, *Org. Lett.* **2020**, *22*, 5235-5239; c) R. Melot, T. J. Saiegh, A. Fürstner, *Chem. Eur. J.* **2021**, *27*, 17002-17011; d) E. E. Lin, J.-Q. Wu, F. Schäfers, X.-X. Su, K.-F. Wang, J.-L. Li, Y. Chen, X. Zhao, H. Ti, Q. Li, T.-M. Ou, F. Glorius, H. Wang, *Commun. Chem.* **2019**, *2*, 34; e) Y. Zheng, J. Jiang, Y. Li, Y. Wei, J. Zhang, J. Hu, Z. Ke, X. Xu, L. Zhang, *Angew. Chem., Int. Ed.* **2023**, *62*, e202218175; f) V. B. Corless, A. Holownia, H. Foy, R. Mendoza-Sanchez, S. Adachi, T. Dudding, A. K. Yudin, *Org. Lett.* **2018**, *20*, 5300-5303.

[6] G. J. Lovinger, J. P. Morken, *Eur. J. Org. Chem.* **2020**, *2020*, 2362-2368.

[7] S. Nandy, S. Paul, K. K. Das, P. Kumar, D. Ghorai, S. Panda, *Org. Biomol. Chem.* **2021**, *19*, 7276-7297.

[8] A. J. J. Lennox, G. C. Lloyd-Jones, *Chem. Soc. Rev.* **2014**, *43*, 412-443.

[9] a) C. Huang, D. Wu, Y. Li, G. Yin, *J. Am. Chem. Soc.* **2023**, *145*, 18722-18730; b) W. Su, T.-J. Gong, Q. Zhang, Q. Zhang, B. Xiao, Y. Fu, *ACS Catal.* **2016**, *6*, 6417-6421; c) R. Alfaro, A. Parra, J. Alemán, J. L. García Ruano, M. Tortosa, *J. Am. Chem. Soc.* **2012**, *134*, 15165-15168; d) T. Itoh, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc.* **2016**, *138*, 7528-7531.

[10] N. P. Mankad, D. S. Laitar, J. P. Sadighi, *Organometallics* **2004**, *23*, 3369-3371.

[11] A. S. Wells, *OPR&D* **2010**, *14*, 484-484.

[12] a) H. Noguchi, K. Hojo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 758-759; b) H. Noguchi, T. Shioda, C.-M. Chou, M. Suginome, *Org. Lett.* **2008**, *10*, 377-380; c) H. Ihara, M. Koyanagi, M. Suginome, *Org. Lett.* **2011**, *13*, 2662-2665.

[13] S. Kamio, H. Yoshida, *Adv. Synth. Catal.* **2021**, *363*, 2310-2324.

[14] a) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716-6717; b) J. Li, A. S. Grillo, M. D. Burke, *Acc. Chem. Res.* **2015**, *48*, 2297-2307.

[15] A. J. Rago, A. Vasilopoulos, A. W. Dombrowski, Y. Wang, *Org. Lett.* **2022**, *24*, 8487-8492.

[16] D. S. Matteson, *Tetrahedron* **1998**, *54*, 10555-10607.

[17] a) D. S. Matteson, D. Majumdar, *J. Am. Chem. Soc.* **1980**, *102*, 7588-7590; b) H. A. Sharma, J. Z. Essman, E. N. Jacobsen, *Science* **2021**, *374*, 752-757; c) D. Wang, J. Zhou, Z. Hu, T. Xu, *J. Am. Chem. Soc.* **2022**, *144*, 22870-22876.

[18] Z.-P. Yang, D. J. Freas, G. C. Fu, *J. Am. Chem. Soc.* **2021**, *143*, 2930-2937.

[19] S. Kamio, I. Kageyuki, I. Osaka, H. Yoshida, *Chem. Commun.* **2019**, *55*, 2624-2627.

[20] J. H. Kirchhoff, M. R. Netherton, I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 13662-13663.

[21] In this scenario, the reductive elimination would be regiodetermining step and either isomer of the product would be accessible regardless of the regioselectivity of the hydrometalation step.

[22] a) X. Lu, B. Xiao, Z. Zhang, T. Gong, W. Su, J. Yi, Y. Fu, L. Liu, *Nat. Commun.* **2016**, *7*, 11129; b) S. Bera, X. Hu, *Angew. Chem., Int. Ed.* **2019**, *58*, 13854-13859; c) F. Zhou, J. Zhu, Y. Zhang, S. Zhu, *Angew. Chem., Int. Ed.* **2018**, *57*, 4058-4062; d) S.-Z. Sun, C. Romano, R. Martin, *J. Am. Chem. Soc.* **2019**, *141*, 16197-16201; e) Z. Wang, H. Yin, G. C. Fu, *Nature* **2018**, *563*, 379-383; f) S.-J. He, J.-W. Wang, Y. Li, Z.-Y. Xu, X.-X. Wang, X. Lu, Y. Fu, *J. Am. Chem. Soc.* **2020**, *142*, 214-221; g) S. Bera, R. Mao, X. Hu, *Nat. Chem.* **2021**, *13*, 270-277; h) D. Qian, S. Bera, X. Hu, *J. Am. Chem. Soc.* **2021**, *143*, 1959-1967; i) S. Wang, J.-X. Zhang, T.-Y. Zhang, H. Meng, B.-H. Chen, W. Shu, *Nat. Commun.* **2021**, *12*, 2771.

[23] Z. Zhang, S. Bera, C. Fan, X. Hu, *J. Am. Chem. Soc.* **2022**, *144*, 7015-7029.

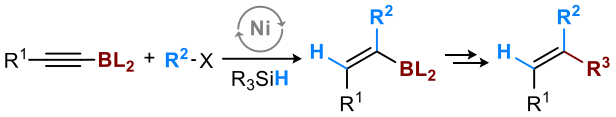
[24] a) S. Biswas, D. J. Weix, *J. Am. Chem. Soc.* **2013**, *135*, 16192-16197; b) J. Choi, P. Martín-Gago, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 12161-12165; c) C. E. Ash, P. W. Hurd, M. Y. Darensbourg, M. Newcomb, *J. Am. Chem. Soc.* **1987**, *109*, 3313-3317; d) R. J. Kinney, W. D. Jones, R. G. Bergman, *J. Am. Chem. Soc.* **1978**, *100*, 7902-7915.

[25] A. C. Albéniz, P. Espinet, R. López-Fernández, A. Sen, *J. Am. Chem. Soc.* **2002**, *124*, 11278-11279.

[26] We cannot exclude an alternative mechanism in which hydrometalation happens prior to the activation of the alkyl iodide. In this alternative mechanism, the alkenyl nickel intermediate would react with the alkyl iodide to form the free alkyl radical.

[27] N. D. Schley, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 16588-16593.

Entry for the Table of Contents



E-stereoselective | regioselective | broad substrate scope

We explored the use of a boryl group as a traceless directing group in the nickel-catalyzed hydroalkylation of alkynes. The approach allows highly selective synthesis of trisubstituted alkenes.