Alkene Functionalization

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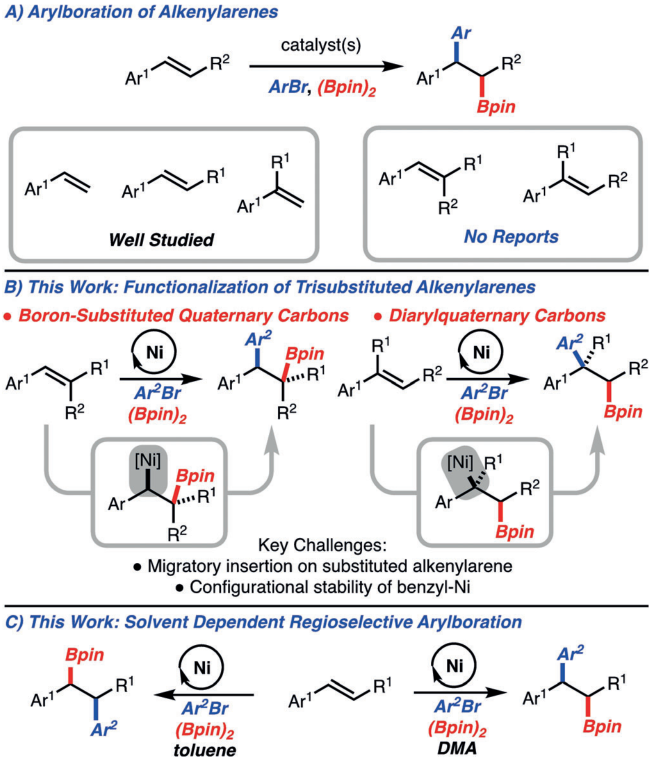
Nickel-Catalyzed Arylboration of Alkenylarenes: Synthesis of Boron-Substituted Quaternary Carbons and Regiodivergent Reactions

*Liang-An Chen, Alan R. Lear, Pin Gao, and M. Kevin Brown**

Abstract: *A method for the construction of boron-substituted quaternary carbons or diarylquaternary carbons by arylboration of highly substituted alkenylarenes is presented. A wide range of alkenes and arylbromides can participate in this reaction thus allowing for a diverse assortment of products to be prepared. In addition, a solvent dependent regiodivergent arylboration of 1,2-disubstituted alkenylarenes is presented, thus greatly increasing the scope of products that can be accessed.*

Alkene difunctionalization is a significant synthetic strategy as molecular complexity can be rapidly generated.[1] Within this broad area, alkene carboboration has emerged as an effective strategy that allows for a diverse range of groups to be installed across the alkene by taking advantage of the synthetic versatility of the C−B bond.[2,3] Over the last five years, alkene arylboration methods have emerged with contributions from our lab[4] and others.[5] The arylboration of alkenylarenes is well developed with mono-, 1,2-di-, and 1,1-disubstituted alkenes (Scheme 1 A).[4,5] Notably, functionalization of trisubstituted alkenylarenes remains a challenge. We sought to develop an arylboration of these classes of substrates because the products would contain boron-substituted quaternary carbons or diarylquaternary carbons, motifs that are currently difficult to access (Scheme 1 B). In particular, synthesis of boron-substituted quaternary carbons from widely available alkenes was seen as a key motivation for this study. Notable advances in the synthesis of boron substituted quaternary carbons from alkenes include conjugate addition/allylic substitution,[6] hydroboration/diboration,[7] conjunctive cross coupling,[8] and aminoboration[9,10] The majority of the known approaches utilize alkenes with strong activating groups (e.g. substituted acrylates) or directing groups. The approach outlined herein is appealing as simple alkenylarenes are the starting materials and two bonds and two stereogenic centers are generated.



Scheme 1. Arylboration of alkenylarenes.

Early attempts from our group to develop arylboration reactions of trisubstituted alkenylarenes with Cu/Pd-catalysis were unsuccessful.[4a–e] However, our recent discovery of a Ni-catalyzed arylboration of unactivated alkenes,[4g,h] prompted us to explore Ni-catalysis in the context of highly substituted alkenylarenes. Herein, we disclose a method for the arylboration of a wide range of trisubstituted alkenylarenes that leads to the formation of challenging boron-substituted quaternary carbons or diarylquaternary carbons (Scheme 1 B). In addition, we have uncovered a solvent dependent regiodivergent arylboration of 1,2-disubstiuted alkenylarenes that further increases the utility of this method (Scheme 1 C).

Arylboration of trisubstituted alkenylarenes under previously reported Ni-catalysis conditions resulted in low to moderate yield of the desired products due to incomplete conversion.[4g,h] Evaluation of reaction conditions ultimately led to the finding that use of DMA as solvent led to high yield of product (compare Table 1, entries 1 and 2). Unexpectedly, it was also found that premixing KOEt and (Bpin)$_2$ prior to the addition of substrates and catalyst led to higher yields (compare Table 1, entries 1 and 3). Presumably premixing of KOEt and (Bpin)$_2$ serves to sequester KOEt. It has been reported that alkoxide bases and Ni^{II} salts can result in the formation of nanoparticles, which may deactivate the Ni-catalyst in this case.[11] While 5 mol% $NiCl_2$(DME) and

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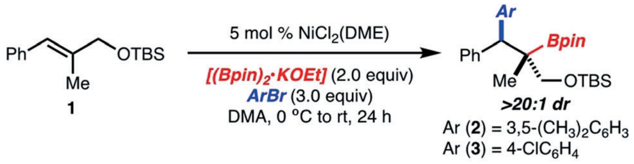
[*] Dr. L.-A. Chen, A. R. Lear, Prof. M. K. Brown
Department of Chemistry, Indiana University
800 E. Kirkwood Ave., Bloomington, IN 47405 (USA)
E-mail: brownmkb@indiana.edu

Dr. P. Gao
Department of Chemistry, School of Science, Xi'an Key Laboratory of Sustainable Energy Material Chemistry, MOE Key Laboratory for Nonequilibrium Synthesis and Modulation of Condensed Matter
Xi'an Jiaotong University, Xi'an, Shaanxi, 710049 (China)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/anie.201904861.

Table 1: Change from standard conditions.



Entry	Change from standard conditions	Product	Yield [%][a]
1	no change	**2**	98
2	THF instead of DMA	**2**	21
3	no premixing of $(Bpin)_2$ and KOEt	**2**	79
4	1.5 equiv ArBr instead of 3.0 equiv ArBr	**2**	65
5	2 mol% $NiCl_2(DME)$ instead of 5 mol% $NiCl_2(DME)$	**2**	75
6	glovebox free reaction setup	**2**	94
7	no change	**3**	65
8	THF instead of DMA	**3**	20
9	no premixing of $(Bpin)_2$ and KOEt	**3**	29

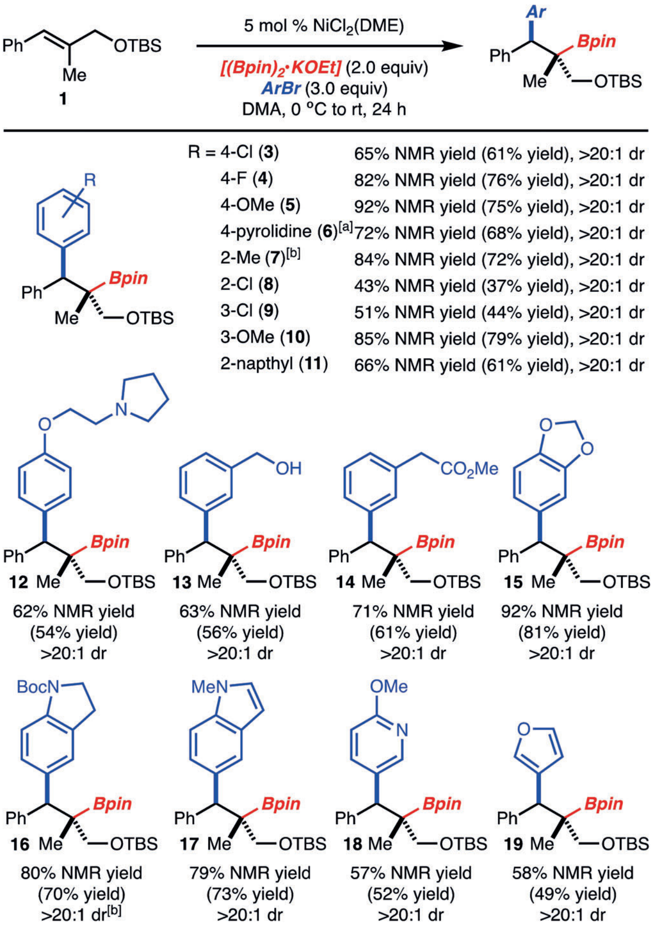
Reactions performed on 0.2 mmol scale. [a] Yield determined by ^{1}H NMR analysis of the unpurified reaction mixture with an internal standard.

3.0 equiv aryl bromide were found to be optimal, lower catalyst loading or fewer equivalents of aryl bromide still resulted in useful yields (Table 1, entries 4 and 5). In addition, the reaction could be setup without the aid of glovebox techniques with little change in efficiency (Table 1, entries 6). Finally, it should be noted that the optimal conditions were particularly crucial for arylbromides bearing electron-withdrawing groups (compare Table 1, entries 7–9).

Under the optimized conditions arylbromides bearing electron donating, electron withdrawing and sterically demanding substituents were well tolerated (Scheme 2). Various functional groups such as amines, alcohols, esters, and amides did not greatly impede the reaction. Finally, heterocycles could also be employed, albeit with slightly reduced yields. The primary limitation with respect to arylbromide scope is that strongly electron-withdrawing substituents such as CF_3 resulted in low yields of product and formation of significant quantities of ArBpin.

Regarding the scope of alkenes that can be used, several points are noteworthy (Scheme 3): 1) For the synthesis of boron-substituted quaternary carbons, the substitution pattern of the aryl group could be altered with various electron withdrawing, electron donating, sterically demanding substituents. 2) Both cyclic and acyclic substrates are suitable for this process. 3) The formation of **30** and **37** occurred with high levels of diastereoselectivity. In these cases, while the identity of the major diastereomer could not be confirmed, the arylboration likely occurred from the least hindered face of the alkene. 4) For substrates with acyclic substituents, yield decreased with more sterically demanding substituents (compare **2** and **33**). 5) The synthesis of diarylquaternary carbons can be achieved with both acyclic and cyclic substrates (products **38**–**44**).

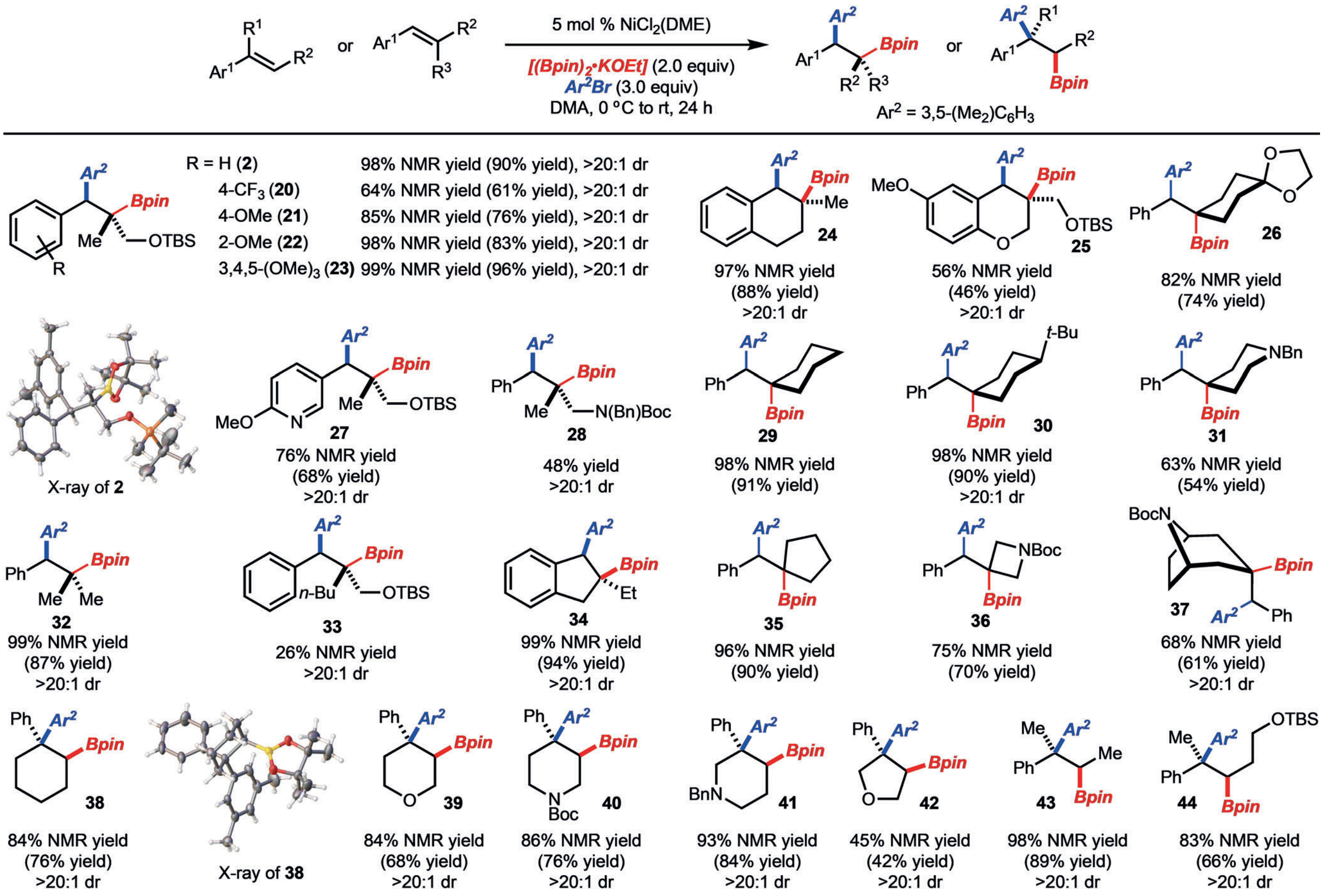
The arylboration could also be performed on gram scale (Scheme 4). Furthermore, the C−B bond could be elaborated through oxidation (product **47**) and Matteson homologation/oxidation (product **48**). Alcohol **48** could be advanced to



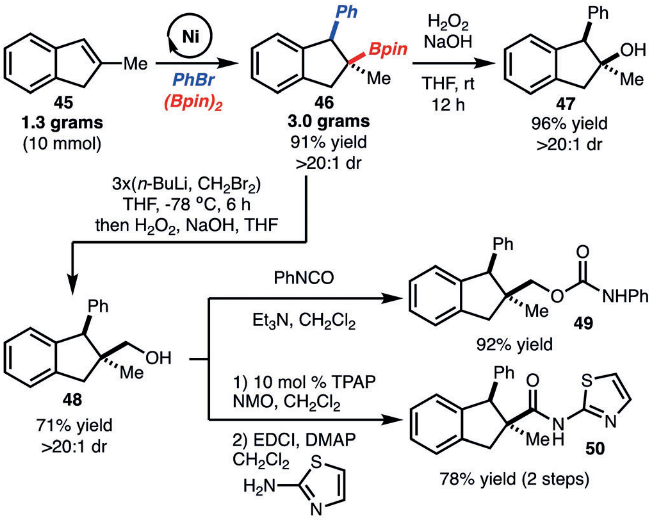
Scheme 2. Reaction with various arylbromides. Yield of product after isolation. NMR yield determined by ^{1}H NMR analysis of the unpurified reaction mixture with an internal standard. [a] Reaction with the 4-OMeAr analog of **1** used. [b] Products **7** and **16** were oxidized to the alcohol before isolation. Reactions performed on 0.4 mmol scale.

Glucocorticoid receptor modulators through standard sequences.[12] Previously, these molecules were prepared by a non-stereoselective 6-step sequence. The route illustrated here required 3–4 operations, is stereoselective, and represents an orthogonal approach to the construction of biologically active molecules from alkenes.

In the course of these investigations, 1,2-disubstituted alkenylarenes were also probed. Under the standard conditions, **51** was generated in excellent selectivity (Table 2, entry 1). Interestingly, the observation was made that if toluene was used as a co-solvent, the formation of regioisomer **52** (> 20:1 dr) was observed (Table 2, entry 2). Increasing the amount of toluene revealed that regioisomer **52** could be generated as the major product, albeit in low yield (Table 2, entry 7). Continued optimization led to the finding that higher reaction temperatures (60 °C vs. rt), use of KOMe (vs. KOEt), and excess alkene (relative to arylbromide) resulted in exclusive formation of **52** (Table 2, entry 12). Thus, through a simple change in solvent and minor modification to reaction conditions, the arylboration could be tuned to favor either regioisomer **51** or **52**. Prior studies have demonstrated that product **51** can be prepared by a Cu/Pd-catalyzed arylboration.[4,5] The Ni-catalyzed reaction reported herein offers an



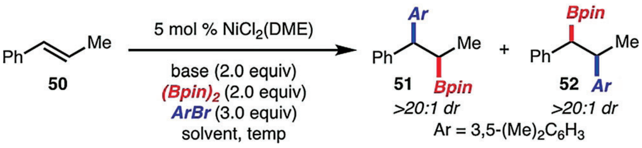
Scheme 3. Arylboration of trisubstituted alkenes. See Scheme 2 for details.



Scheme 4. Gram scale reaction and further transformations.

alternative that utilizes a simple catalyst. Methods for the synthesis of the regioisomeric product **52** do not exist. However, a recent report from Song, has demonstrated that styrene derivatives, but not 1,2-disubstituted alkenylarenes, can undergo Pd-catalyzed arylboration with aryldiazonium salts and $(Bpin)_2$.[5c]

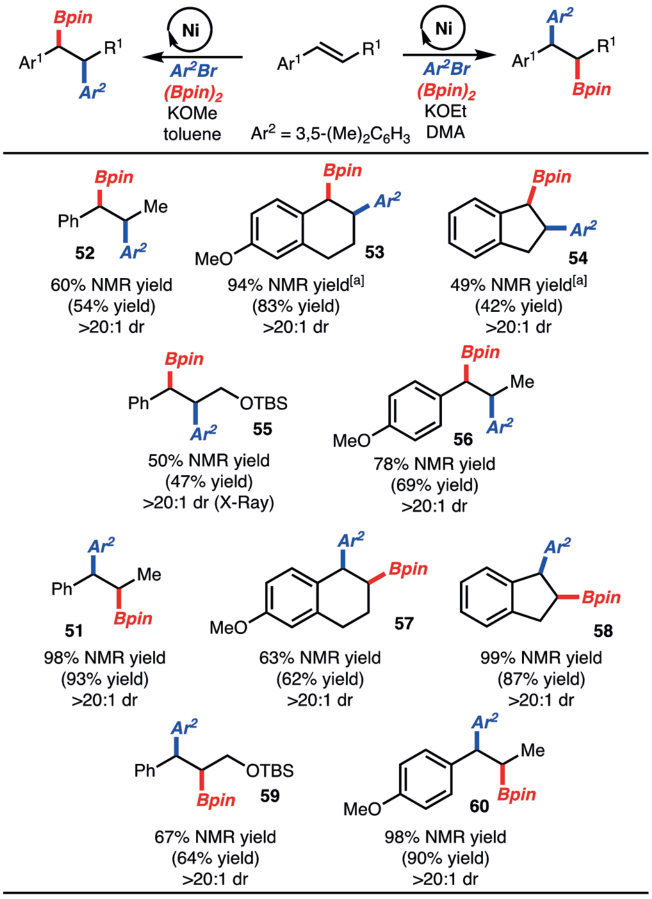
Table 2: Regiodivergent arylboration of 1,2-disubstituted alkenylarenes.



Entry	Solvent	Temp [°C]	Base	Yield [%][a]	**51:52**
1	DMA	rt	KOEt	98	$>$99:1
2	toluene:DMA (1:1)	rt	KOEt	98	93:1
3	toluene:DMA (5:1)	rt	KOEt	42	34:1
4	toluene:DMA (10:1)	rt	KOEt	28	14:1
5	toluene:DMA (50:1)	rt	KOEt	15	4.6:1
6	toluene:DMA (160:1)	rt	KOEt	17	2.3:1
7	toluene	rt	KOEt	15	1:9
8	toluene	60	KOEt	55	1:2.2
9	toluene	60	KOMe	42	1:5
10[b]	toluene	60	KOMe	42	1:36
11[b,c]	toluene	60	KOMe	45	1:39
12[c,d]	toluene	60	KOMe	58	1:$>$99

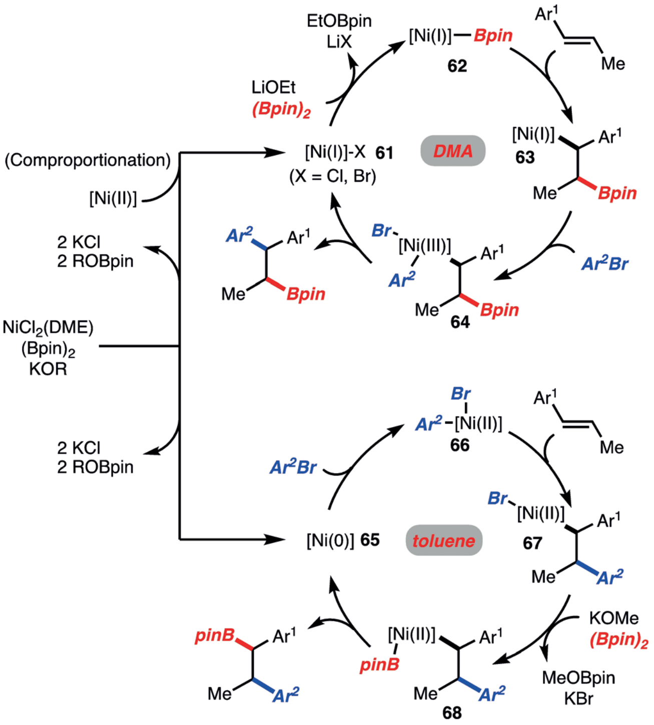
Reactions performed on 0.2 mmol scale. [a] Combined yield of **51** and **52** determined by GC using a calibrated internal standard. [b] ArBr (1.2 equiv). [c] $NiCl_2$(DME) (15 mol%). [d] Alkene (2.0 equiv), ArBr, (1.0 equiv).

Under conditions outlined in Table 2 entries 1 and 12 both acyclic and cyclic 1,2-disubstituted alkenylarenes participated in the reactions with excellent regioselectivity and diastereoselectivity (products **51**–**60**) (Scheme 5). While arylboration in DMA worked well with trisubstituted alkenes (Schemes 2–3), the conditions with toluene did not proceed, and starting material was recovered.



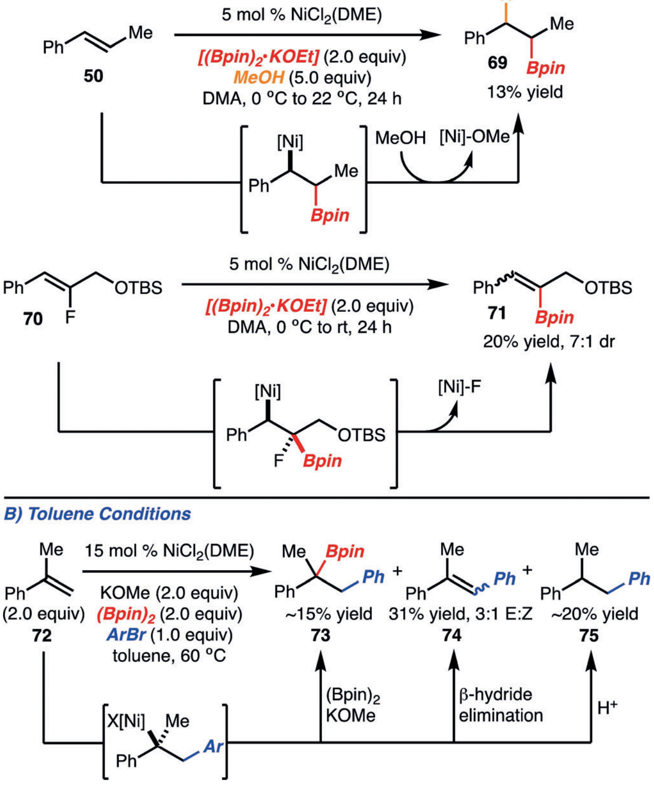
Scheme 5. Regiodivergent arylboration. See Table 2, entries 1 and 12 for conditions (0.4 mmol scale). Yield of product after isolation. NMR yield determined by ^{1}H NMR analysis of the unpurified reaction mixture with an internal standard. [a] Reaction with 1.0 equiv alkene and 1.2 equiv ArBr.

To account for the different regioselectivities observed in different solvents, two catalytic cycles are proposed (Scheme 6). In the case of reactions performed in DMA, and on the basis of prior studies, we propose that [Ni]-Bpin complex **62** is generated, which undergoes reaction with an alkene.[4g,h,13] The regioselectivity of the migratory insertion occurs to generate benzyl-[Ni]-complex **63** regardless of alkene substitution pattern. The formation of product may occur through an oxidative addition with ArBr followed by reductive elimination via **64**. In the case of reactions in toluene, it is proposed that migratory insertion occurs from Ni^{II}ArBr complex **66**.[14] The regioselectivity is determined though formation of benzyl-[Ni]-complex **67**. Transmetalation with (Bpin)$_2$ and reductive elimination then occurs to generate product.



Scheme 6. Putative catalytic cycles.

A) DMA Conditions



Scheme 7. Mechanistic experiments.

Support for the proposed catalytic cycles is illustrated in Scheme 7. It was found that addition of MeOH to the reaction mixture resulted in formation of protoboration adduct **69**, thus suggesting that Bpin is incorporated prior to the aryl group.[4g,h] In addition, reaction of vinyl fluoride **70** led to the formation of vinyl boronic ester **71**. Since direct cross coupling with vinyl fluorides is slow at ambient temperatures,[15,16] it is suggested that the product formation occurs via 1,2-elimination of the corresponding alkyl-[Ni]-complex.[17] With respect to the mechanistic proposal for the reaction in toluene, it was observed that use of α-methyl styrene (**72**) led to products resulting from a Heck-type reaction (**74**) and hydroarylation (**75**). The formation of these adducts can be rationalized with competitive reactions of the corresponding benzyl-[Ni]-complex via β-hydride elimination or protonation, respectively.[18] At this stage, the role of solvent in determining the regioselectivity is not clear and is under investigation.

In summary, the synthesis of challenging boron-substituted quaternary carbons and diarylquaternary carbons has been achieved through an arylboration reaction. Furthermore, the arylboration regioselectivity of 1,2-disubstituted alkenylarenes can be tuned by altering the solvent, revealing a practical system in which diverse and versatile products can be accessed.[19]

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenes · arylboration · boron · cross coupling · nickel

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[1] a) V. Saini, B. J. Stokes, M. S. Sigman, *Angew. Chem. Int. Ed.* **2013**, *52*, 11206 – 11220; *Angew. Chem.* **2013**, *125*, 11414 – 11429; b) J. R. Coombs, J. P. Morken, *Angew. Chem. Int. Ed.* **2016**, *55*, 2636 – 2649; *Angew. Chem.* **2016**, *128*, 2682 – 2696.

[2] For reviews regarding carboboration, see: a) Y. Shimizu, M. Kanai, *Tetrahedron Lett.* **2014**, *55*, 3727; b) K. Semba, T. Fujihara, J. Terao, Y. Tsuji, *Tetrahedron* **2015**, *71*, 2183; c) F. Lazreg, F. Nahra, C. S. J. Cazin, *Coord. Chem. Rev.* **2015**, *293–294*, 48; d) E. C. Neeve, S. J. Geier, I. A. I. Mkhalid, S. A. Westcott, T. B. Marder, *Chem. Rev.* **2016**, *116*, 9091; e) D. Hemming, R. Fritzemeier, S. A. Westcott, W. L. Santos, P. G. Steel, *Chem. Soc. Rev.* **2018**, *47*, 7477.

[3] C. Sandford, V. K. Aggarwal, *Chem. Commun.* **2017**, *53*, 5481.

[4] a) K. B. Smith, K. M. Logan, W. You, M. K. Brown, *Chem. Eur. J.* **2014**, *20*, 12032; b) K. M. Logan, K. B. Smith, M. K. Brown, *Angew. Chem. Int. Ed.* **2015**, *54*, 5228; *Angew. Chem.* **2015**, *127*, 5317; c) K. M. Logan, M. K. Brown, *Angew. Chem. Int. Ed.* **2017**, *56*, 851; *Angew. Chem.* **2017**, *129*, 869; d) K. B. Smith, M. K. Brown, *J. Am. Chem. Soc.* **2017**, *139*, 7721; e) S. R. Sardini, M. K. Brown, *J. Am. Chem. Soc.* **2017**, *139*, 9823; f) A. M. Bergmann, S. K. Dorn, K. B. Smith, K. M. Logan, *Angew. Chem. Int. Ed.* **2019**, *58*, 1719; *Angew. Chem.* **2019**, *131*, 1733; g) K. M. Logan, S. R. Sardini, S. D. White, M. K. Brown, *J. Am. Chem. Soc.* **2018**, *140*, 159; h) S. R. Sardini, A. L. Lambright, G. L. Trammel, H. H. Omer, P. Liu, M. K. Brown, *J. Am. Chem. Soc.* **2019**, *141*, 9391.

[5] a) K. Semba, Y. Nakao, *J. Am. Chem. Soc.* **2014**, *136*, 7567; b) K. Semba, Y. Ohtagaki, Y. Nakao, *Org. Lett.* **2016**, *18*, 3956; c) K. Yang, Q. Song, *Org. Lett.* **2016**, *18*, 5460; d) B. Chen, P. Cao, X. Yin, Y. Liao, L. Jiang, J. Ye, M. Wang, J. Liao, *ACS Catal.* **2017**, *7*, 2425; e) W. Wang, C. Ding, Y. Li, Y. Li, L. Peng, G. Yin, *Angew. Chem. Int. Ed.* **2019**, *58*, 4612; *Angew. Chem.* **2019**, *131*, 4660; f) Z. Liu, X. Li, T. Zeng, K. M. Engle, *ACS Catal.* **2019**, *9*, 3260; g) For a 1,1-arylboration, see: H. M. Nelson, B. D. Williams, J. Miro, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 3213.

[6] a) I. H. Chen, L. Yin, W. Itano, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 11664; b) I. H. Chen, L. Yin, M. Kanai, M. Shibasaki, *Org. Lett.* **2010**, *12*, 4098; c) J. M. O'Brien, K. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10630 – 10633; d) S. Radomkit, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2014**, *53*, 3387; *Angew. Chem.* **2014**, *126*, 3455; *Angew. Chem. Angew.-Chem.* **2014**, *126*, 3455; e) X. Feng, J. Yun, *Chem. Eur. J.* **2010**, *16*, 13609; f) A. Guzman-Martinez, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10634.

[7] a) T. P. Blaisdell, T. C. Caya, L. Zhang, A. Sanz-Marco, J. P. Morken, *J. Am. Chem. Soc.* **2014**, *136*, 9264; b) H. A. Kerchner, J. Montgomery, *Org. Lett.* **2016**, *18*, 5760; c) V. M. Shoba, N. C. Thacker, A. J. Bochat, J. M. Takacs, *Angew. Chem. Int. Ed.* **2016**, *55*, 1465; *Angew. Chem.* **2016**, *128*, 1487; d) S. Chakrabarty, J. M. Takacs, *J. Am. Chem. Soc.* **2017**, *139*, 6066.

[8] a) M. Silvi, C. Sandford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2017**, *139*, 5736; b) M. Kischkewitz, K. Okamoto, C. Muck-Lichtenfeld, A. Studer, *Science* **2017**, *355*, 936; c) J. A. Myhill, L. Zhang, G. J. Lovinger, J. P. Morken, *Angew. Chem. Int. Ed.* **2018**, *57*, 12799; *Angew. Chem.* **2018**, *130*, 12981; d) Z. Tao, K. A. Robb, J. L. Panger, S. E. Denmark, *J. Am. Chem. Soc.* **2018**, *140*, 15621.

[9] K. Kato, K. Hirano, M. Miura, *J. Org. Chem.* **2017**, *82*, 10418.

[10] For a selected example of an alternative approach, see: T. C. Atack, S. P. Cook, *J. Am. Chem. Soc.* **2016**, *138*, 6139.

[11] I. Buslov, F. Song, X. Hu, *Angew. Chem. Int. Ed.* **2016**, *55*, 12295 – 12299; *Angew. Chem.* **2016**, *128*, 12483 – 12487.

[12] J. Duan, B. Jiang, PCT Int. Appl. WO 2007073503, **2007**.

[13] Ni^{I} may form through a comproportion pathway, as illustrated in Scheme 6. For a review regarding Ni^{I}, see: C.-Y. Lin, P. P. Power, *Chem. Soc. Rev.* **2017**, *46*, 5347.

[14] P. Gao, L.-A. Chen, M. K. Brown, *J. Am. Chem. Soc.* **2018**, *140*, 10653.

[15] X.-W. Liu, J. Echavarren, C. Zarate, R. Martin, *J. Am. Chem. Soc.* **2015**, *137*, 12470.

[16] For β-fluoro elimination of an alkyl-Ni-complex, see: L. Zhou, C. Zhu, P. Bi, C. Feng, *Chem. Sci.* **2019**, *10*, 1144.

[17] For a Cu-catalyzed variant, see: H. Sakaguchi, Y. Uetake, M. Ohashi, T. Niwa, S. Ogoshi, T. Hosoya, *J. Am. Chem. Soc.* **2017**, *139*, 12855.

[18] The proton source may arise from the byproduct of β-hydride elimination.

[19] After the submission of this manuscript a Ni-catalyzed arylboration of vinylarenes was reported, see: W. Wang, C. Ding, H. Pang, G. Yin, *Org. Lett.* **2019**, *21*, 3968.

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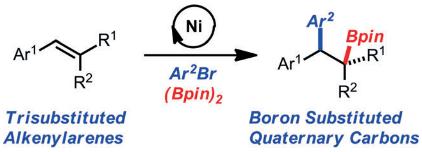
Communications

Alkene Functionalization

L.-A. Chen, A. R. Lear, P. Gao, M. K. Brown* ▮▮▮▮–▮▮▮▮

Nickel-Catalyzed Arylboration of Alkenylarenes: Synthesis of Boron-Substituted Quaternary Carbons and Regiodivergent Reactions



Boron-substituted quaternary carbon or diarylquaternary carbon centers are constructed by arylboration of highly substituted alkenylarenes. A wide range of alkenes and arylbromides can participate in this reaction. In addition, a solvent dependent regiodivergent arylboration of 1,2-disubstituted alkenylarenes is presented, thus greatly increasing the scope of products that can be accessed.