Regioselective trans-Carboboration of Propargyl Alcohols
Hongming Jin and Alois Fürstner* Max-Planck-Institut für Kohlenforschung, 45470 Mülheim/Ruhr, Germany

Supporting Information

ABSTRACT: Proper choice of the base allowed trans-diboration of propargyl alcohols with B$_2$(pin)$_2$ to evolve into an exquisitely regioselective procedure for net trans-carboboration. The method is modular as to the newly introduced carbon substituent (aryl, methyl, allyl, benzyl, alkynyl), which is invariably placed distal to the −OH group.

As a substructure of polyketide origin, allylic alcohols of type B are prominently featured in innumerable natural products. Our group has recently devised a new entry into this important motif based on a sequence commencing with a stereochemically unorthodox trans-hydrometalation of a propargyl alcohol followed by C-methylation of the resulting product A by formal cross-coupling (Scheme 1). This methodology is very functional group tolerant and has already stood the test of total synthesis. For its exquisite regioselectivity, however, the procedure does not broker formation of the isomeric motif D (R = Me), which is equally prominent in the polyketide estate.

Inspired by a literature report, we saw an opportunity to attain compounds of type D via formal trans-carboboration, although broadly applicable manifestations of this type of reactivity are exceedingly rare. Specifically, it is known that propargyl alcohols such as 1a, on deprotonation with nBuLi, followed by reaction with B$_2$(pin)$_2$ in THF at increased temperature, undergo trans-selective diboration to give 4-borylated 1,2-oxaborolol derivatives 3a after hydrolytic workup (Scheme 2). The reaction likely passes through the mixed ate-complex 2a; in one case, this putative intermediate has been subjected to subsequent Suzuki coupling with 4-tolyl iodide in the presence of catalytic palladium and aqeous KOH as a promoter. In the present context, it is important to note that both boron sites of 2a reacted under these conditions to give the tetrasubstituted alkene 4a in 64% yield. Because ate-complexes per se are competent intermediates for cross-coupling, we surmised that addition of excess base might actually be unnecessary. Rather, advantage could be taken of the distinct chemical character to the two boron centers in a compound of type: cross-coupling should occur selectively at the endocyclic borate site, whereas the tricoordinate boron moiety is expected to persist in the absence of external base: if so, many opportunities for downstream functionalization can be envisaged. As the borate site does not survive workup (see the formation of product 3a), any such selective derivatization is contingent on the ability to generate and manipulate an ate-complex of type in “one pot”.

However, our initial efforts to intercept the putative intermediate 2 derived from the model substrate 1b by simply

Received: April 8, 2019
Published: April 17, 2019
complementing the original recipe for trans-diboration \(^3\) with an appropriate electrophilic partner (PhI, PhOTf, \([\text{Ph}_2\text{I}]\text{OTf}\), MeI, allyl bromide), a catalytic amount of a palladium source (Pd(OAc)\(_2\), Pd\(_2\)(dba)\(_3\), Pd(PPh\(_3\))\(_4\)), and an adequate phosphine ligand (PPh\(_3\), PCy\(_3\), P(o-tol), P(2-furyl), X-Phos, dppf, Xantphos, etc.) basically met with failure (Table 1, entries 1—4).

Table 1. Optimization of the trans-Arylboration \(^a\)

| entry | base | PhX | [Pd] | ligand | 5b (%) |
|-------|------|-----|------|--------|-------|
| 1     | LiHMDS | PhOTf | Pd(OAc)\(_2\) | dppf | 0\(^c\) |
| 2     | LiHMDS | PhOTf | Pd(OAc)\(_2\) | dppf | <10\(^c\) |
| 3     | NaHMDS | PhI | Pd(PPh\(_3\))\(_4\) | 0 |
| 4     | NaHMDS | PhOTf | Pd\(_2\)(dba)\(_3\) | P(o-tol)\(_3\) | 31 |
| 5     | NaHMDS | PhOTf | Pd\(_2\)(dba)\(_3\) | P(o-tol)\(_3\) | 62\(^d\) |
| 6     | NaHMDS | PhOTf | Pd\(_2\)(dba)\(_3\) | P(2-furyl) | 81\(^d\) |
| 7     | NaHMDS | PhOTf | Pd\(_2\)(dba)\(_3\) | P(2-furyl) | 82\(^d\) |

\(^a\)Unless stated otherwise, the reactions were performed in THF at 70 °C (bath temperature). 77.3% of 3b was obtained after workup: 62% of 3b and 9% of 4b were formed. \(^d\)In 1,4-dioxane. \(^e\)In 1,2-dichloroethane + THF (10 equiv).

In most cases, the boracyle 3b was formed as the major product; it was accompanied by varying amounts of the proto-deborylated compound 4b but only traces—if any—of the desired product 5b.

In an attempt to rationalize this reticence, we wondered whether the borate subunit in 2 actually subsists under the chosen conditions. Earlier work from this laboratory on the “9-MeO-9-BBN variant” of the Suzuki reaction showed that the stability of ate-complexes of type 7 derived from the highly Lewis acidic 6 and polar organometallic reagents R−M is strongly cation-dependent (Scheme 3).\(^{13,14}\) The ease of scrambling complex 7 as the competent nucleophile for cross-coupling into unproductive 8 and 9 roughly follows the order: Na\(^+\) ≈ R\(^+\) < Li\(^+\) ≪ MgX\(_3\), ZnX\(_2\). The analogous equilibration of the borate unit in 2 is arguably more facile because it derives from an inherently much less Lewis acidic RB(OR)\(_2\) entity.\(^{15}\)

Under this premise, a lithium counterion is unlikely to be the ideal escort as the neutral boron species 2’ might be favored, which will not engage in cross-coupling in the absence of an external base. Therefore, we rescreened different counterions with the hope of stabilizing the critical borate intermediate 2, even though the original report on trans-diboration had identified nBuLi as the optimal promoter.\(^4\)

In accord with the empirical order observed in our previous study,\(^{13,14}\) replacement of nBuLi by NaHMDS\(^16\) opened the doorway to the desired net trans-carbaboronation chemistry (Table 1; for further details, see the Supporting Information). In a first foray, trans-diboration was merged with classical Suzuki-type sp\(^2\)−sp\(^2\) coupling: to this end, the use of diaryliodonium salts in combination with Pd\(_2\)(dba)\(_3\)/P(2-furyl)\(_3\) proved optimal. Although the reaction proceeded well in 1,4-dioxane in many cases, the use of 1,2-dichloroethane/THF (10 equiv) was found to be more general (Figure 1). The crude products are usually very clean, but partial loss of material upon flash chromatography on silica diminishes the isolated yields. In the case of tert-propargyl alcohols as the substrates, the basic conditions can entail retro-alkynylation, leading to the formation of the corresponding ketones as minor impurities.
formation occurred exclusively distal to the alcohol substituent. Extensive NMR investigations and crystallographic data confirmed connectivity and double bond geometry of the products (for the structures of compounds 3b, 5b, n, and 10i in the solid state, see the Supporting Information). Once again, the observed regio- and stereoselectivities were excellent as were the functional group tolerance; moreover, the method scales well. It is important to note that O-methylation of the propargylic alcohol substrate did not interfere with productive trans-methylboration to any noticeable extent, which indicates a perfect orchestration of events along the reaction coordinate.

For this very reason, other reactive electrophiles are equally competent partners (Figure 3). Specifically, allyl and benzyl bromide could be used without O-alkylation intervening. Likewise, the incorporation of an alkynyl substituent was successful; the resulting enynes 13 are regioisomeric to the products formed by the transition-metal-free trans-alkynylboration using RC≡C≡B(pin) as the reagent recently described in the literature. Overall, these data show that the concept underlying this new trans-carboboration manifold is pleasingly general, although its different incarnations require some catalyst optimization. Further extensions are subject to ongoing investigations in our laboratory.

The alkynyl boronate products thus formed lend themselves to numerous downstream transformations; only a few possibilities are shown in Scheme 4: (i) Although protodeborylation of 10 “wastes” the valuable C−B bond, it leads to the important polyketide motif D cited in the introduction; as shown for product 14, the reaction can be readily achieved using catalytic AgNO3 (ii) Addition of aq NaOH “arms” the remaining boron atom in 10 for cross-coupling with a second electrophilic partner. In this manner, two different hydrocarbyl residues can be stitched trans to each other across the triple bond, the resulting tetrasubstituted alkenes such as 15 are difficult to make in rigorously stereodefined format by other means. This aspect is highlighted by the concise approach to compound 22, which is a key metabolite of the nonsteroidal estrogen receptor modulator idoxifen (Scheme 5); this example further substantiates the compatibility of the method with alkyl as well as aryl halides. (iii) Oxidation of the C−B bond23 in 10 unmasks the corresponding acyloin whereas directed epoxidation affords the building block 17 with high diastereoselectivity. (iv) Addition of catalytic amounts of Sc(OTf)3 as an oxophilic Lewis acid activates the allylic −OH group of 5c without damaging the C−B bond as evident from the intramolecular Friedel–Crafts alkylation, furnishing the borylated indene. (v) Finally, we note that the triple bond of compounds 13 constitutes yet another valuable handle for functionalization; the formation of the tetrasubstituted bory-
luted furan 19 with the aid of AuCl₃ as a carbophilic catalyst illustrates this aspect. ⁶⁻²⁷

In summary, a robust yet modular procedure for net carboboration of propargyl alcohols is reported. The transformation is distinguished by the unorthodox trans-addition mode and benefits from exquisite regio- and chemoselectivity. For these virtues and for the multifaceted character of the resulting products, we expect that the new method qualifies for many applications. Studies along these lines are currently ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01225.

Experimental section including characterization data, NMR spectra of new compounds, and supporting crystallographic data (PDF)

Accession Codes

CCDC 1895345–1895348 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author
*E-mail: fuerstner@kofo.mpg.de.

ORCID

Alois Fürstner: 0000-0003-0098-3417

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Generous financial support by the MPG is gratefully acknowledged. We thank Prof. C. W. Lehmann and Mr. J. Rust, at this institute, for solving the X-ray structures in the Supporting Information.

REFERENCES

(1) Fürstner, A. trans-Hydrogenation, gem-Hydrogenation and trans-Hydrometallation of Alkynes. An Interim Report on an Unorthodox Reactivity Paradigm. J. Am. Chem. Soc. 2019, 141, 11–24.

(2) Huwyler, N.; Radkowski, K.; Rummelt, S. M.; Fürstner, A. Two Enabling Strategies for the Stereoselective Conversion of Internal Alkynes into Trisubstituted Alkenes. Chem. - Eur. J. 2017, 23, 12412–12419.

(3) (a) Rummelt, S. M.; Preindl, J.; Sommer, H.; Fürstner, A. Selective Formation of a Trisubstituted Alkene Motif by trans-Hydrosilylation/Still Stille Coupling: Application to the Total Synthesis and Late-Stage Modification of 5,6-Dihydrocineromycins B. Angew. Chem., Int. Ed. 2015, 54, 6241–6245. (b) Meng, Z.; Souliart, L.; Monks, B.; Huwyler, N.; Herrmann, J.; Müller, R.; Fürstner, A., “Motif-Oriented” Total Synthesis of Nannocystin Ax. Preparation and Biological Assessment of N.; Herrmann, J.; Murakami, M. Palladium- and Nickel-Catalyzed IntraMolecular Cyanoboration of Alkynes. J. Am. Chem. Soc. 2003, 125, 6358–6359.

(4) Daini, M.; Yamamoto, A.; Suginome, M. Palladium-Catalyzed trans- and cis-Carboboration of Alkynes Tethered to Chloroborane with Organorhenium Reagents: Ligand Dependent Complementary Stereoselectivity. J. Am. Chem. Soc. 2008, 130, 2918–2919. (c) Daini, M.; Yamamoto, A.; Suginome, M. Nickel-Catalyzed Cyclizative trans-Carboboration of Alkynes through Activation of Boron-Chlorine Bonds by Using Organometallic Reagents as Donors or Organic Groups. Asian J. Org. Chem. 2013, 2, 968–976. (d) Suginome, M. Catalytic Carboborations. Chem. Rev. 2010, 10, 348–358.

(5) For related trans-alkynylboration, in which the boron reagent delivers the alkynyl substituent, see: Nagami, M.; Hirano, K.; Kanai, M.; Wang, C.; Saito, T.; Miyamoto, K.; Murakana, A.; Uchiyama, M. Transition Metal-Free trans-Selective Alknylation of Alkynes. J. Am. Chem. Soc. 2017, 139, 12358–12361.

(6) For pioneering studies on trans-carboboration, see the following and references cited therein: (a) Suginome, M.; Yamamoto, A.; Murakami, M. Palladium- and Nickel-Catalyzed Intramolecular Cyanoboration of Alkynes. J. Am. Chem. Soc. 2003, 125, 6358–6359. (b) Daini, M.; Yamamoto, A.; Suginome, M. Palladium-Catalyzed trans- and cis-Carboboration of Alkynes Tethered to Chloroborane with Organorhenium Reagents: Ligand Dependent Complementary Stereoselectivity. J. Am. Chem. Soc. 2008, 130, 2918–2919. (c) Daini, M.; Yamamoto, A.; Suginome, M. Nickel-Catalyzed Cyclizative trans-Carboboration of Alkynes through Activation of Boron-Chlorine Bonds by Using Organometallic Reagents as Donors or Organic Groups. Asian J. Org. Chem. 2013, 2, 968–976. (d) Suginome, M. Catalytic Carboborations. Chem. Rev. 2010, 10, 348–358.

(7) For other trans-carbometalations of internal alkynes, see the following and literature cited therein: (a) Asao, N.; Matsukawa, Y.; Yamamoto, Y. trans-Allylstannation of Certain Acetylenes Catalyzed by ZrCl₄. Chem. Commun. 1996, 1513–1514. (b) Miura, K.; Toh, D.; Honda, T.; Saito, H.; Ito, H.; Hosomi, A. Allylstannylation of Alkenes via a Radical Process: Stereoselective Synthesis of Di- and Trisubstituted Vinylstannanes. Tetrahedron Lett. 1996, 37, 8539–8542.

(8) For other trans-carbometalations of internal alkynes, see the following and literature cited therein: (a) Asao, N.; Matsukawa, Y.; Yamamoto, Y. trans-Allylstannation of Certain Acetylenes Catalyzed by ZrCl₄. Chem. Commun. 1996, 1513–1514. (b) Iwamoto, T.; Nishikori, T.; Nakagawa, N.; Takaya, H.; Nakamura, E. Iron-Catalyzed anti-Stereoselective Carbosilylation of Internal Alkynes. Angew. Chem., Int. Ed. 2017, 56, 13298–13301. (e) Wang, S.; Zhang, J.; Kong, L.; Tan, Z.; Bai, Y.; Zhu, G. Palladium-Catalyzed anti-Selective Fluoroalkylboration of Internal and Terminal Alkynes. Org. Lett. 2018, 20, 5631–5634.

(9) For cyclization reactions thought to involve a trans-carbometalation step, see the following for leading references and literature cited therein: (a) Xie, X.; Liu, Y.; Yang, Y. Nickel-Catalyzed Cyclization of Alkynes through the Generation of Allyl/Alkenyl-Metal Complexes. Angew. Chem., Int. Ed. 2018, 139, 5815–5820. (b) Clarke, C.; Incerti-Pradillos, C. A.; Lam, H. W. Enantioselective Nickel-Catalyzed anti-Carbometalative Cyclizations of Alkynyl Electrophiles Enabled by Reversible Alkenylnickel E/Z Isomerization. J. Am. Chem. Soc. 2016, 138, 8068–8071. (e) Reisinger, A.; Jones, P. G.; Weitz, D. B. trans-Carbocarbonation of Internal Alkynes through a Formal anti-Carbopalladation/C-H Activation Cascade. Angew. Chem., Int. Ed. 2018, 57, 10610–10614.

(10) For trans-hydroboration of internal alkynes, see: Sundararaju, B.; Fürstner, A. A trans-Selective Hydroboration of Internal Alkynes. Angew. Chem., Int. Ed. 2013, 52, 14050–14054.

(11) For related trans-diboration (silaboration) of strongly polarized alkynes, see: (a) Nagao, K.; Ohmiya, H.; Sawamura, M. Anti-Selective Vicinal Silyboration and Diboration of Alkynes through Phosphine Organocatalysis. Org. Lett. 2015, 17, 1304–1307. (b) Verma, A.; Sned, R. F.; Dai, Y.; Slebdnick, C.; Yang, Y.; Yu, H.; Yao, F.; Santos, W. L. Substrate-Assisted, Transition-Metal-Free Diboration of Alkynamides with Mixed Diboron: Regio- and Stereoselective Access to trans-1,2-
Vinyldiboronates. *Angew. Chem., Int. Ed.* 2017, 56, S111–S115.
(c) Fritzemeier, R.; Santos, W. L. Bronsted Base-Mediated Regio- and Stereoselective *trans*-SilaBoration of Propargylamines: Access to 1,2-Vinylborasilanes. *Chem. - Eur. J.* 2017, 23, 15534–15537.
(12) (a) Suzuki, A. Cross-Coupling Reactions of Organoboranes: An Easy Way to Construct C-C Bonds. *Angew. Chem., Int. Ed.* 2011, 50, 6722–6737. (b) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* 1995, 95, 2447–2483.
(13) (a) Fürstner, A.; Seidel, G. Palladium-Catalyzed Arylation of Polar Organometallics Mediated by 9-Methoxy-9-Borabicyclo[3.3.1]-nonane: Suzuki Reactions of Extended Scope. *Tetrahedron* 1995, 51, 11165–11176. (b) Fürstner, A.; Nikolakis, K. Ethynylation of Aryl Halides by a Modified Suzuki Reaction: Application to the Syntheses of Combretastatin A-4, A-5 and Lunularic Acid. *Liebigs Ann.* 1996, 1996, 2107–2113.
(14) Seidel, G.; Fürstner, A. Suzuki Reactions of Extended Scope: The ‘9-MeO-9-BBN Variant’ as a Complementary Format for Cross Coupling. *Chem. Commun.* 2012, 48, 2055–2070.
(15) For a review concerning such issues and how they impact cross-coupling, see: Lennox, A. J. J.; Lloyd-Jones, G. C. Transmetalation in the Suzuki-Miyaura Coupling: The Fork in the Trail. *Angew. Chem., Int. Ed.* 2013, 52, 7362–7370.
(16) KHMDs can also be used; in most cases, the yields are comparable or marginally lower. NaH instead of NaHMDS, however, proved much less adequate, which suggests that the released hexamethyldisilazane also plays a role in the reaction; see the Supporting Information.
(17) 11B NMR confirms the presence of a tricoordinate (δB ∼ 31 ppm, br) and a tetracoordinate boron center (δB = 11 ppm) in the putative intermediate 2b formed from 1b on treatment with NaHMDS and B2(pin); for details, see the Supporting Information.
(18) (a) Carreras, J.; Caballero, A.; Pérez, P. J. Alkenyl Boronates: Synthesis and Applications. *Chem. - Asian J.* 2019, 14, 329–343. (b) Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011.
(19) Ping, Y.; Chang, T.; Wang, K.; Huo, J.; Wang, J. Palladium-catalyzed Borylation of Conjugated Enynes through Carbene Migratory Insertion: Synthesis of Furfuryl-substituted Alkenylboronates. *Chem. Commun.* 2019, 55, 59–62.
(20) For a special case of *trans*-addition of two carbon residues to terminal alkenes, see the following and literature therein: Li, Z.; Garcia-Dominguez, A.; Nevada, C. Pd-Catalyzed Stereoselective Carboperoxidation of Alkynes. *J. Am. Chem. Soc.* 2015, 137, 11610–11613.
(21) For an alternative, consisting of a cascade comprising a Suzuki reaction, see: Gomes, F.; Echeverria, P.-G; Fürstner, A. Iron- or Palladium-Catalyzed Reaction Cascades Merging Cycloisomerization and Cross-Coupling Chemistry. *Chem. - Eur. J.* 2018, 24, 16814–16822.
(22) Hardcastle, I. R.; Horton, M. N.; Osborne, M. R.; Hewer, A.; Jarman, M.; Phillips, D. H. Synthesis and DNA Reactivity of α-Hydroxylated Metabolites of Nonsteroidal Antiestrogens. *Chem. Res. Toxicol.* 1998, 11, 369–374.
(23) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. Sodium Perborate: A Mild and Convenient Reagent for Efficiently Oxidizing Organoboranes. *J. Org. Chem.* 1989, 54, 5930–5933.
(24) Hussain, M. M.; Hernandez Toribio, J.; Carroll, P. J.; Walsh, P. J. Synthesis of 2-Keto-anti-1,3-diols by Chemoselective Tandem Oxidation of 3-(B(pin))-Substituted Allylic Alcohols. *Angew. Chem., Int. Ed.* 2011, 50, 6337–6340.
(25) Guo, S.; Liu, Y. A Facile Zr-mediated Multicomponent Approach to Arylated Allylic Alcohols and its Application to the Synthesis of Highly Substituted Indenes and Spiroindenes. *Org. Biomol. Chem.* 2008, 6, 2064–2070.
(26) Fürstner, A.; Davies, P. W. Catalytic Carbophilic Activation: Catalysis by Platinum and Gold π-Acids. *Angew. Chem., Int. Ed.* 2007, 46, 3410–3449.

(27) Du, X.; Song, F.; Lu, Y.; Chen, H.; Liu, Y. A General and Efficient Synthesis of Substituted Furans and Dihydrofurans via Gold-catalyzed Cyclization of (Z)-2-en-4-yn-1-ols. *Tetrahedron* 2009, 65, 1839–1845.