Organic Letters

pubs.acs.org/OrgLett

Letter

Electro-alkynylation: Intramolecular Rearrangement of Trialkynylorganoborates for Chemoselective C(sp^2)−C(sp) Bond Formation

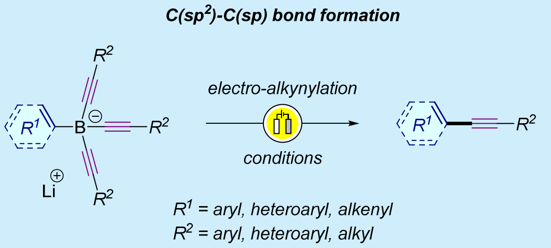
Arif Music,[†] Constantin M. Nuber,[†] Yannick Lemke, Philipp Spieß, and Dorian Didier*

Cite This: *Org. Lett.* 2021, 23, 4179−4184

Read Online

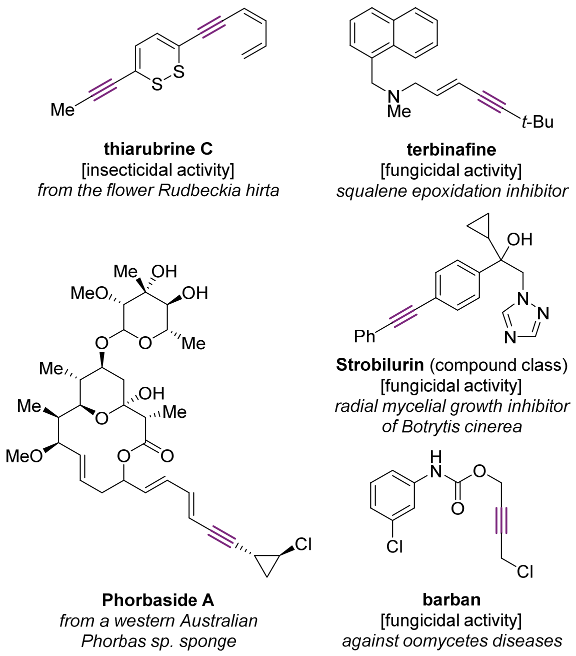
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: An alternative and complementary transformation for the synthesis of aryl- and heteroaryl-substituted alkynes is presented that relies on a chemoselective electrocoupling process. Tetraorganoborate substrates were logically designed and simply accessed by transmetalations using readily or commercially available organotrifluoroborate salts.



Alkynes are important functional groups in organic chemistry that can be found in many natural compounds and bioactive molecules.[1] Scheme 1 depicts a selection of a few of these structures. While the rather simple bisalkyne thiarubrine C was isolated from the flower Bubdeckia hirta and possesses insecticidal activity,[2] much more complex architectures have been reported—such as phorbaside A—to occur naturally in phorbas species sponges.[3] Synthetic derivatives include terbinafine,[4] the compound class of strobilurins,[5] and barban,[6] showing different inhibition patterns with antifungal activities (Scheme 1).

Scheme 1. Alkyne-Containing Natural and Bioactive Compounds



Alkynes are also often used as versatile intermediates in synthesis, constituting reactive moieties in stereoselective hydrogenations,[7] halogenations,[8] (3 + 2)-Huisgen cycloadditions,[9] hydro-[10] and carbometalations,[11] gold-catalyzed rearrangements,[12] and cyclopropenations.[13]

Classical methods for their construction comprise well-established Corey−Fuchs reactions of aldehydes,[14] Seyferth−Gilbert homologations of ketones,[15] Fritsch−Buttenberg−Wiechell rearrangements,[16] Pd-catalyzed Sonogashira couplings of terminal alkynes,[17] or simple 1,2-eliminations.[18]

A thorough literature survey has revealed that stable arylborate salts undergo intramolecular aryl−aryl coupling under oxidative conditions using chemical oxidants such as vanadium oxides[19] or zinc[20] and iridium complexes (Scheme 2).[21] Such rearrangement was most recently exemplified by Studer and co-workers, illustrating the access to unsymmetrical biaryl systems using Bobbitt's salt.[22] Pioneered by the groups of Geske and Waldvogel on symmetrical biaryls,[23] the electro-[24] and photocouplings[25] of nonsymmetrical tetraorganoborates were achieved by our group in 2020, establishing a reliable and functional group tolerant way toward heterobiaryl

Received: April 1, 2021
Published: May 18, 2021

https://doi.org/10.1021/acs.orglett.1c01126

Scheme 2. Literature on Organoborate Rearrangements

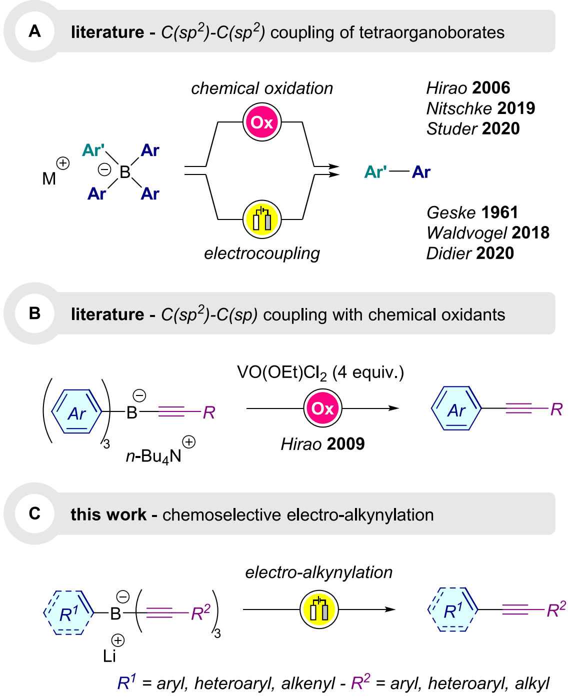
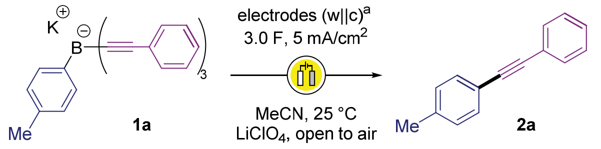


Table 1. Optimizations of the Electro-alkynylation



entry	w||c	deviation from conditions	conv.[b]
1	C||C	none	49%
2	C||C	$NaBF_4$ instead of $LiClO_4$	19%
3	C||C	$LiBF_4$ instead of $LiClO_4$	10%
4	C||C	$LiPF_6$ instead of $LiClO_4$	44%
5	C||C	+ 5% H_2O	53%
6	C||C	+ 5% HFIP	45%
7	C||C	+ 5% MeOH	58%
8	C||C	+ 5% EtOH	59%
9	Pt||Pt	+ 5% MeOH	59%
10	RVC||RVC	+ 5% EtOH	72%
11	RVC||RVC	+ 7% EtOH	77%
12	RVC||RVC	+ 7% EtOH, no $LiClO_4$	67%

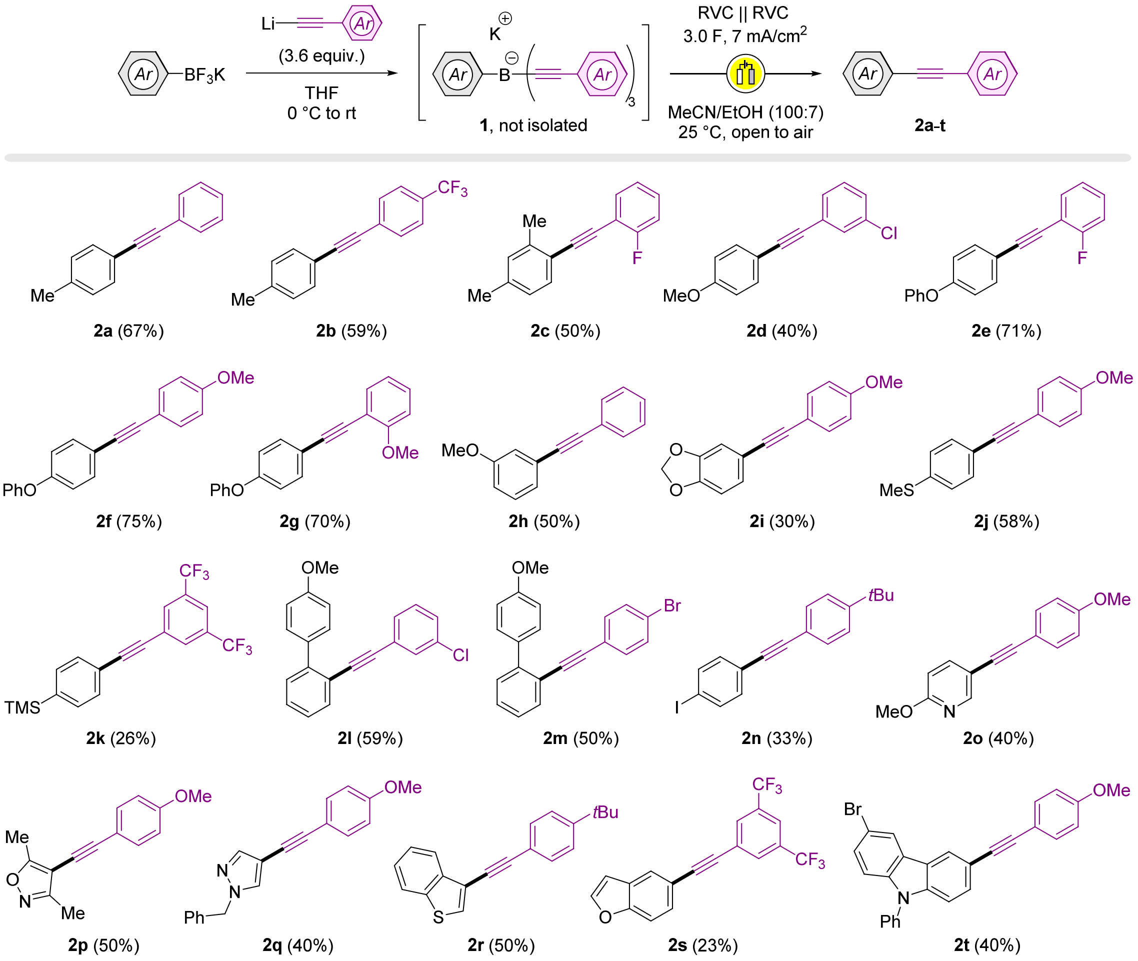
[a] w||c = working vs counter electrode. [b] Conversions measured by gas chromatography using *n*-undecane as an internal standard.

products (Scheme 2A). The only example of alkynylborate rearrangement was described by Hirao and co-workers, who employed stoichiometric amounts of chemical oxidants ($VO(OEt)Cl_2$) toward arylated alkynes (Scheme 2B).[26] Building on our previous studies on electrochemical C−C bond formation, we present herein an unprecedented electro-alkynylation reaction for the chemoselective generation of $C(sp^2)-C(sp)$ bonds (Scheme 2C), as it offers a nonprecious and nontoxic transition metal alternative.

Our optimizations began with the synthesis of model substrate **1a**, possessing one *p*-tolyl moiety and three alkynyl residues. The careful choice of such distribution was dictated by mechanistic considerations (vide infra) in order to prevent homocoupling reactions. As a matter of fact, aryl moieties should be easier to oxidize than alkynyl groups, as supported by cyclic voltammetry experiments.[27] Preliminary results indicated that alternating the current increased the conversion of products. It was therefore more convenient to use a symmetrical electrode system (working and counter electrodes of identical composition). A first set of conditions employing graphite electrodes (C||C) in the presence of $LiClO_4$ as an electrolyte furnished 49% of internal alkyne **2a** (entry 1, Table 1). While changing the nature of the electrolyte did not improve the conversion (entries 2−4), the introduction of a protic solvent positively influenced the course of the transformation (entries 5−8), hitting 59% yield with ethanol (entry 8), therefore avoiding the use of toxic methanol (entry 7). If switching to platinum electrodes (entry 9) gave similar conversions, reticulated vitreous carbon electrodes (RVC||RVC) proved to be the most efficient with 72% conversion (entry 10). Maximum conversion was reached with 7% of ethanol in solution (entry 11). It was however observed that the RVC electrodes tend to degrade over time in the presence of $LiClO_4$, presumably due to lithium intercalation. Reactions performed without electrolyte gave 67% of product **2a** (entry 12), without decomposition of the electrodes, and sufficient conductivity in solution provided by salt **1a** (approximately 0.04 M). These conditions—although leading to slightly lower yields—were chosen to explore the scope of the transformation. It is important to note that increasing the number of electrons engaged in the reaction, changing the intensity of the current, or applying an inert atmosphere only led to decreasing yield.[27] We also chose to let the reaction open to air for more convenience, as it was shown that a slight decrease in yield was observed under inert conditions. Interestingly, chemical oxidants employed for comparison (DDQ, I_2, $K_2S_2O_8$) did not furnish any desired product **2a** (see Supporting Information). Ex situ generated $VO(OEt)Cl_2$ (4 equiv) was also used as a chemical oxidant for comparison, resulting in a lower yield of **2a** (42%),[27] which we attributed to the high oxidation potential of the starting borate salt.

Compound **2a** was isolated in 67% yield, and the process was further exemplified using diversely substituted trialkynylarylborates **1**. These salts were simply accessed from the corresponding commercially or readily available aryl trifluoroborates through triple transmetalation using alkynyllithium reagents. They were engaged in the electro-coupling reaction under the optimized conditions described above without purification. Yields for arylated products **2** are therefore given as a result of a two-step process (Scheme 3). Halogenated aryl alkynes were first introduced, furnishing the corresponding disubstituted acetylenes **2b−e** in reasonable yields. Electron-donating groups at para- and ortho-positions on the alkyne moiety gave compounds **2f** and **2g** in good yields up to 75%. Diversely functionalized starting aryl-BF_3K proved to be tolerated in the transformation (**2h−k**), although acetal **2j** was only isolated in 30% yield, and the presence of TMS groups generally lowered the efficiency of the reaction (**2k**). Interestingly, *o*-substituted arylborates underwent intramolecular coupling to give **2l** and **2m** in 50 to 59% yields. Our previous studies showed that such a substitution pattern could hinder the C−C bond formation.[24] Iodinated structure **2n** was also formed in 33% yield, opening possibilities for further functionalization.

Scheme 3. Scope of the Transformation toward Bisarylated Alkynes



Heteroarylborates were examined next. Electron-deficient pyridyl compound **2o** was isolated in 40% yield, and electron-rich aromatics such as isoxazoles **2p**, pyrazoles **2q**, benzothiophenes **2r**, and benzofurans **2s** were formed with various efficiencies with yields ranging from 23 to 50%. A brominated carbazole moiety was successfully introduced, giving product **2t** in 40% yield.

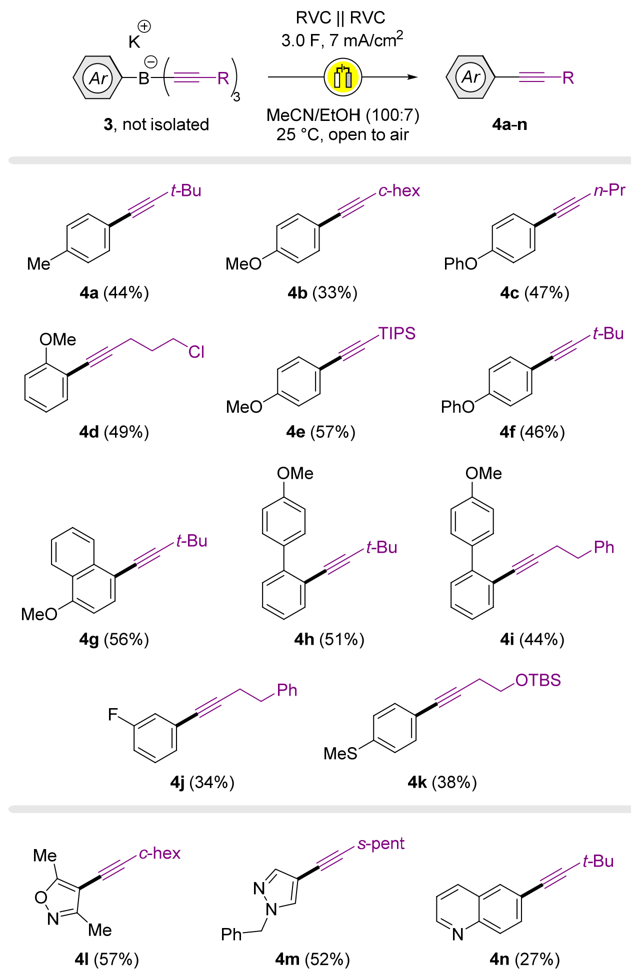
The scope of the transformation with alkylated acetylenes was evaluated next. Addition of the desired alkynyllithium was conducted as previously toward the formation of trialkynylarylborates **3**, which were engaged in the electro-coupling reaction without prior purification. Although a large variety of compounds **4** emerged from this new procedure (Scheme 4), yields of alkyl-aryl acetylene were generally lower than the ones observed in the previous case on bisarylated structures **2** (Scheme 3). Primary, secondary (cyclohexyl), and tertiary (*tert*-butyl) alkyl groups were introduced to give alkyne products **4a**−**k** in 27−57% two-step overall yield. The electrochemical transformation demonstrated fair tolerance toward halogenated alkyl residues (**4c** and **4d**, up to 49% yield), and an o-substituted biaryl moiety did not pose steric problems (**4h** and **4i**, up to 51% yield).

Given our previous observations on organoborate rearrangements, cyclovoltammetric measurements, and new theoretical insights performed at the quantum-chemical level,[27] we propose the following mechanism for the electro-alkynylation (Scheme 5).

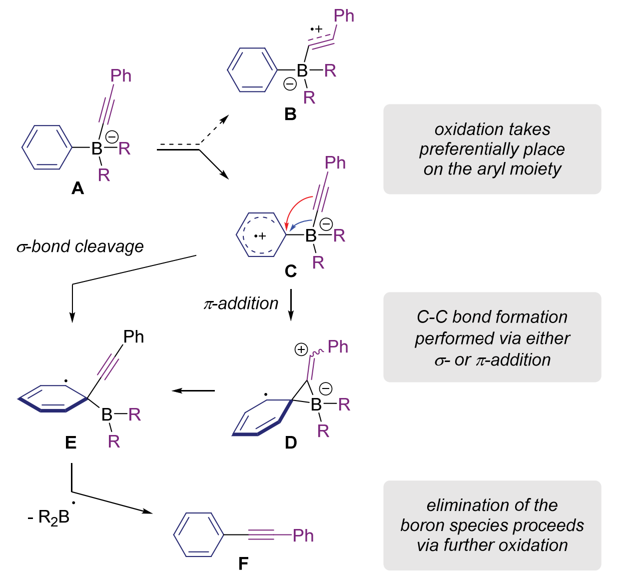
Oxidation of the trialkynylarylborate **A** occurs chemoselectively on the aryl moiety (**C**) rather than on the alkynyl group, which would lead to an unfavorable vinyl radical cation **B**. The C−C bond can then form either through σ-bond cleavage or π-bond addition, giving intermediates **E** and **D**, respectively. Further oxidation is assumed to enable the elimination of the boron moiety to regenerate the aromaticity in the formation of **F**. The observation of such chemoselectivity supports a one-electron-triggered rearrangement under electrochemical oxidation, in contrast with Hirao's chemical oxidation involving triaryl-(monoalkynyl) borate substrates (two-electron process).

Encouraged by these promising results, we challenged the access to functionalized enyne motifs, widely spread in natural compounds and useful intermediates in synthesis.[28] For chemoselectivity reasons similar to those above, the choice was made to use tetravalent borate salts with a 1:3 alkenyl/alkynyl ratio, the alkenyl moiety getting preferentially oxidized over the alkynyl groups (Scheme 6). Ex situ generated alkenyl-trialkynylborates **5** of various nature were therefore submitted to electrocoupling conditions. The scope of the reaction was explored with diversely substituted *β*-styryls and arylated alkynes possessing either electron-donating or -withdrawing groups (MeO or F), furnishing enyne products **6a**−**e** in 36−51% yields.

Scheme 4. Scope of the Transformation Towards Alkyl-Arylated Alkynes

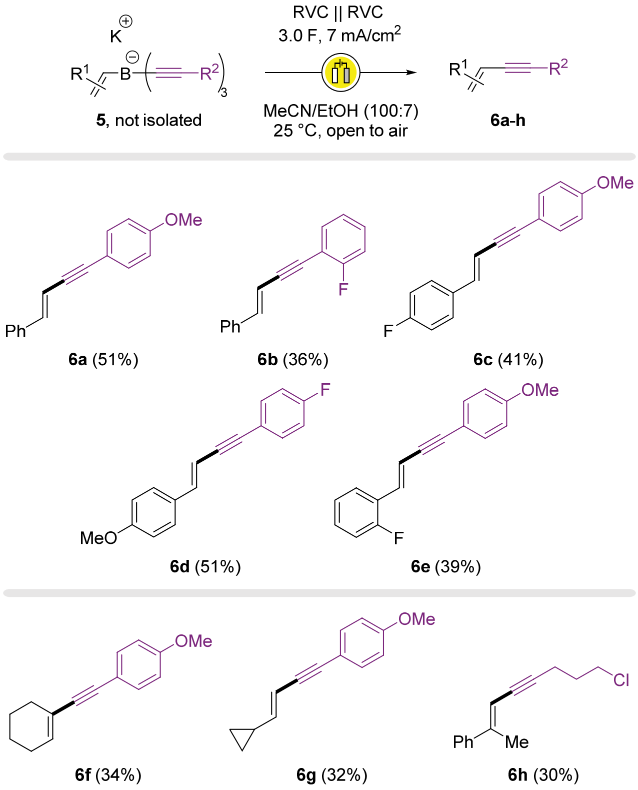


Scheme 5. Proposed Mechanism



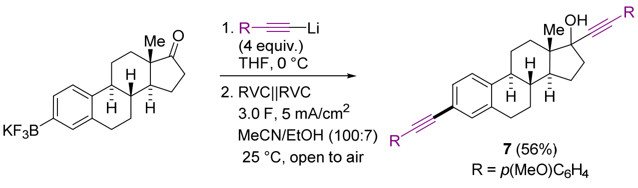
Efforts were then made to introduce alkyl groups on the alkene and the alkyne parts, but only moderate yields (up to 34%) were obtained in all cases (**6f–h**).

Scheme 6. Scope of the Transformation toward Enynes



We finally sought to functionalize the estrone scaffold via electro-alkynylation (Scheme 7). In such cases, 4 equiv of the alkynyllithium reagent had to be used in order to fully transform the trifluoroborate reagent due to the additional nucleophilic addition onto the carbonyl group. The bis-alkynylated compound was therefore isolated in 56% yield.

Scheme 7. Functionalization of the Estrone Scaffold



In summary, we have developed a new transition-metal-free strategy for the functionalization of alkynes. Once again, electrochemistry proved useful to trigger the rearrangement of tetraorganoborates for the unprecedented creation of C(sp^2)–C(sp) bonds. Although its efficiency does not yet compete with classical methods, such a protocol provides an elegant alternative for cross-coupling reaction of acetylene derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01126.

Contains all experimental procedures and characterization (IR, LRMS, and HRMS and ^{1}H, ^{13}C, ^{19}F, and ^{11}B NMR data) for all new compounds (PDF)

Accession Codes

CCDC 2074207 contains 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

Dorian Didier − *Department of Chemistry and Pharmacy, Ludwig-Maximilians-Universität München, 81377 Munich, Germany*; orcid.org/0000-0002-6358-1485; Email: dorian.didier@cup.uni-muenchen.de

Authors

Arif Music − *Department of Chemistry and Pharmacy, Ludwig-Maximilians-Universität München, 81377 Munich, Germany*; orcid.org/0000-0002-4786-1268

Constantin M. Nuber − *Department of Chemistry and Pharmacy, Ludwig-Maximilians-Universität München, 81377 Munich, Germany*

Yannick Lemke − *Department of Chemistry and Pharmacy, Ludwig-Maximilians-Universität München, 81377 Munich, Germany*

Philipp Spieß − *Department of Chemistry and Pharmacy, Ludwig-Maximilians-Universität München, 81377 Munich, Germany*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.orglett.1c01126

Author Contributions

[†]A.F. and C.M.N. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

D.D. and A.M. are grateful to the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft (DFG grant: DI 2227/2-1 and Heisenberg fellowship: DI 2227/4-1), and the Ludwig-Maximilians University (LMU Excellence) for PhD funding and financial support.

■ REFERENCES

(1) (a) Wang, D.; Gao, S. Alkyne chemistry in crop protection. *Org. Chem. Front.* **2014**, *1*, 556−566. (b) Lamberth, C. *Bioorg. Med. Chem.* **2009**, *17*, 4047−4063.

(2) Guillet, G.; Philogene, B. J. R.; O'Meara, J.; Durst, T.; Arnason, J. T. Multiple modes of insecticidal action of three classes of polyacetylene derivatives from Rudbeckia hirta. *Phytochemistry* **1997**, *46*, 495.

(3) Leroux, P.; Chapeland, F.; Giraud, T.; Brygoo, Y.; Gredt, M. Inheritance and Mechanisms of Resistance to Anilinopyrimidine Fungicides in Botrytis Cinerea (Botryotinia Fuckeliana). In *Modern Fungicides and Antifungal Compounds II*; Lyr, H., Russell, P. E., Dehne, H. W., Sisler, H. D., Eds.; Intercept: Andover, 1999; pp 297−303.

(4) Paterson, I.; Davies, R. D. M.; Marquez, R. Total Synthesis of the Callipeltoside Aglycon. *Angew. Chem., Int. Ed.* **2001**, *40*, 603−607.

(5) Stehmann, C.; de Waard, M. A. Sensitivity of populations ofBotrytis cinerea to triazoles, benomyl and vinclozolin. *Pestic. Sci.* **1995**, *44*, 183.

(6) Juenge, E. C.; Spangler, P. J. Study of 4-Amino-2-butyn-1-ol and Preparation of the Reverse Carbamate of the Selective Herbicide. *J. Org. Chem.* **1964**, *29*, 226.

(7) Munslow, I. J. Modern Reduction Methods. In *Modern Reduction Methods*; Andersson, P. G., Munslow, I. J., Eds.; Wiley VCH, 2008; Chapter 15.

(8) Larock, R. C.; Zhang, L. Halogenation of alkynes. In *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; John Wiley & Sons, 2018.

(9) (a) Huisgen, R. 1,3-Dipolar Cycloadditions. Past and Future. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565−598. (b) Wang, L.-J.; Tang, Y. Intermolecular 1,3-Dipolar Cycloadditions of Alkenes, Alkynes, and Allenes. In *Comprehensive Organic Synthesis II*; Elsevier, 2014; pp 1342−1383.

(10) Chen, J.; Guo, J.; Lu, Z. Recent Advances in Hydrometallation of Alkenes and Alkynes via the First Row Transition Metal Catalysis. *Chin. J. Chem.* **2018**, *36*, 1075−1109.

(11) Murakami, K.; Yorimitsu, H. Recent advances in transition-metal-catalyzed intermolecular carbomagnesiation and carbozincation. *Beilstein J. Org. Chem.* **2013**, *9*, 278−302.

(12) Campeau, D.; León Rayo, D. F.; Mansour, A.; Muratov, K.; Gagosz, F. Gold-Catalyzed Reactions of Specially Activated Alkynes, Allenes, and Alkenes. *Chem. Rev.* **2020**, DOI: 10.1021/acs.chemrev.0c00788.

(13) (a) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. A New Chiral Rh(II) Catalyst for Enantioselective [2 + 1]-Cycloaddition. Mechanistic Implications and Applications. *J. Am. Chem. Soc.* **2004**, *126*, 8916−8918. (b) Rullière, P.; Cyr, P.; Charette, A. B. Difluorocarbene Addition to Alkenes and Alkynes in Continuous Flow. *Org. Lett.* **2016**, *18*, 1988−1991.

(14) Corey, E. J.; Fuchs, P. L. A synthetic method for formyl→ethynyl conversion. *Tetrahedron Lett.* **1972**, *13*, 3769−3772.

(15) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. Reactions of dimethylphosphono-substituted diazoalkanes. $(MeO)_2P(O)CR$ transfer to olefins and 1,3-dipolar additions of $(MeO)_2P(O)C(N_2)R$. *J. Org. Chem.* **1971**, *36*, 1379−1386. (b) Gilbert, J. C.; Weerasooriya, U. Diazoethenes: their attempted synthesis from aldehydes and aromatic ketones by way of the Horner-Emmons modification of the Wittig reaction. A facile synthesis of alkynes. *J. Org. Chem.* **1982**, *47*, 1837−1845.

(16) Jahnke, E.; Tykwinski, R. R. The Fritsch−Buttenberg−Wiechell rearrangement: modern applications for an old reaction. *Chem. Commun.* **2010**, *46*, 3235−3249.

(17) Chinchilla, R.; Nájera, C. The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry. *Chem. Rev.* **2007**, *107*, 874−922.

(18) Shaw, R.; Elagamy, A.; Althagafi, I.; Pratap, R. Synthesis of alkynes from non-alkyne sources. *Org. Biomol. Chem.* **2020**, *18*, 3797−3817.

(19) Mizuno, H.; Sakurai, H.; Amaya, T.; Hirao, T. Oxovanadium(V)-catalyzed oxidative biaryl synthesis from organoborate under O_2. *Chem. Commun.* **2006**, 5042−5044.

(20) Lu, Z.; Lavendomme, R.; Burghaus, O.; Nitschke, J. R. A Zn_4L_6 Capsule with Enhanced Catalytic C−C Bond Formation Activity upon C_{60} Binding. *Angew. Chem., Int. Ed.* **2019**, *58*, 9073−9077.

(21) Abley, P.; Halpern, J. Oxidation of tetraphenylborate by hexachloroiridate(IV). *J. Chem. Soc. D* **1971**, 1238−1239.

(22) Gerleve, C.; Studer, A. Transition-Metal-Free Oxidative Cross-Coupling of Tetraarylborates to Biaryls Using Organic Oxidants. *Angew. Chem., Int. Ed.* **2020**, *59*, 15468−15473.

(23) (a) Geske, D. H. The Electrooxidation of the Tetraphenylborate Ion; An Example of a Secondary Chemical Reaction Following the Primary Electrode Process. *J. Phys. Chem.* **1959**, *63*, 1062. (b) Geske, D. H. Evidence for the Formation of Biphenyl by Intramolecular Dimerization in the Electrooxidation of Tetraphenylborate Ion. *J. Phys. Chem.* **1962**, *66*, 1743−1744. (c) Beil, S. B.; Möhle, S.; Enders, P.; Waldvogel, S. R. Electrochemical instability of highly fluorinated tetraphenyl borates and syntheses of their respective biphenyls. *Chem. Commun.* **2018**, *54*, 6128−6131.

(24) (a) Music, A.; Baumann, A. N.; Spieß, P.; Plantefol, A.; Jagau, T. C.; Didier, D. Electrochemical Synthesis of Biaryls via Oxidative Intramolecular Coupling of Tetra(hetero)arylborates. *J. Am. Chem. Soc.* **2020**, *142*, 4341−4348. (b) Baumann, A. N.; Music, A.; Dechent, J.; Müller, N.; Jagau, T. C.; Didier, D. Electro-Olefination—A Catalyst Free Stereoconvergent Strategy for the Functionalization of Alkenes. *Chem. - Eur. J.* **2020**, *26*, 8382−8387.

(25) Music, A.; Baumann, A. N.; Boser, F.; Müller, N.; Matz, F.; Jagau, T. C.; Didier, D. Photocatalyzed Transition-Metal-Free Oxidative Cross-Coupling Reactions of Tetraorganoborates. *Chem. - Eur. J.* **2021**, *27*, 4322−4326.

(26) Amaya, T.; Tsukamura, Y.; Hirao, T. Selective Oxidative Ligand Coupling of Organoborates Bearing an Alkynyl Group. *Adv. Synth. Catal.* **2009**, *351*, 1025−1028.

(27) See Supporting Information.

(28) (a) El-Jaber, N.; Estevez-Braun, A.; Ravelo, A. G.; Muñoz-Muñoz, O.; Rodriguez-Afonso, A.; Murguia, J. R. Acetylenic Acids from the Aerial Parts of Nanodea muscosa. *J. Nat. Prod.* **2003**, *66*, 722. (b) Fontana, A.; d'Ippolito, G.; D'Souza, L.; Mollo, E.; Parameswaram, P. S.; Cimino, G. New Acetogenin Peroxides from the Indian Sponge Acarnus bicladotylota. *J. Nat. Prod.* **2001**, *64*, 131. (c) Rudi, A.; Schleyer, M.; Kashman, Y. Clathculins A and B, Two Novel Nitrogen-Containing Metabolites from the Sponge Clathrina aff. reticulum. *J. Nat. Prod.* **2000**, *63*, 1434. (d) Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukumoto, S.; Imamura, K.; Tokuyama, T.; Torres, J. A.; Snelling, R. R.; Jones, T. H. Occurrence and Significance of Decahydroquinolines from Dendrobatid Poison Frogs and a Myrmicine Ant: Use of ^{1}H and ^{13}C NMR in Their Conformational Analysis. *J. Nat. Prod.* **1999**, *62*, 5. (e) Saito, S.; Yamamoto, Y. Recent Advances in the Transition-Metal-Catalyzed Regioselective Approaches to Polysubstituted Benzene Derivatives. *Chem. Rev.* **2000**, *100*, 2901. (f) Bergman, R. G. Reactive 1,4-dehydroaromatics. *Acc. Chem. Res.* **1973**, *6*, 25. (g) Zweifel, G.; Polston, N. L. Selective hydroboration of conjugated diynes with dialkylboranes. A convenient route to conjugated cis-enynes, .alpha.,.beta.-acetylenic ketones, and cis,cis-dienes. *J. Am. Chem. Soc.* **1970**, *92*, 4068.