

Pd-Catalyzed Homologation of Arylboronic Acids as a Platform for the Diversity-Oriented Synthesis of Benzylic C–X Bonds

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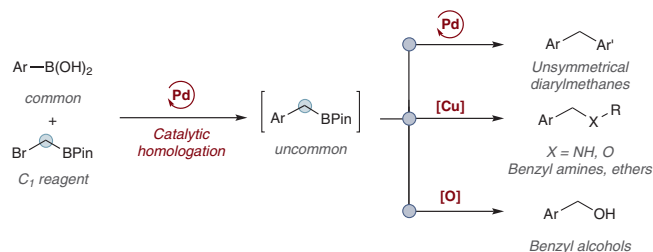
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Dedicated to Prof. Donald S. Matteson on the 60th anniversary of the reaction that bears his name.

Published as part of the Cluster

Modern Boron Chemistry: 60 Years of the Matteson Reaction



• Diversity-orientated synthesis • Simple catalytic homologation • No conventional organometallics
• Access to a range of C–X bonds • Limitations disclosed

Received: 02.06.2023

Accepted after revision: 22.06.2023

Published online: 26.06.2023 (Accepted Manuscript),

15.08.2023 (Version of Record)

DOI: 10.1055/a-2117-9878; Art ID: ST-2023-06-0252-C

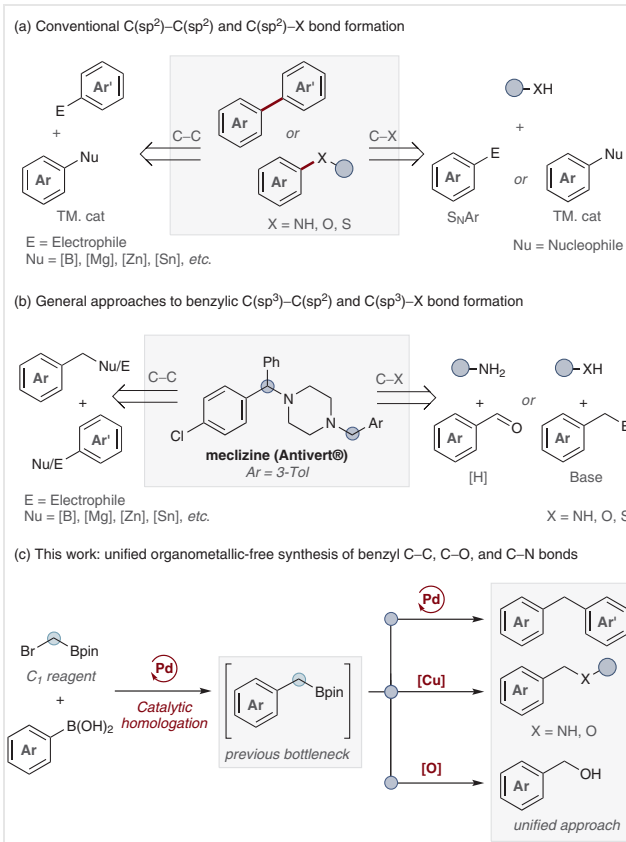
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Abstract We report a synthetic platform for the formation of benzylic C–X bonds. Benzylboronic acid pinacol (Bpin) esters are useful synthetic intermediates but are commercially uncommon, leading to preparations that typically rely upon stoichiometric metalation. Pd-catalyzed formal homologation of arylboronic acids provides access to these compounds that, in turn, allow the formation of C–C, C–O, and C–N bonds from Pd- and Cu-mediated cross-coupling or oxidative processes. This affords a wide variety of benzylic alcohols, diarylmethanes, benzyl amines, and benzyl ethers. Limitations are disclosed, and the utility is further demonstrated by the generation of analogues of meclizine.

Key words boron, catalysis, chemoselectivity, homologation, diversity-oriented synthesis

Diarylmethanes, benzyl ethers, and benzyl amines are common motifs found in bioactive molecules. Typical organometallic approaches towards the synthesis of diarylmethanes involve nucleophilic displacement of benzylic halides or the reduction of acetophenones/benzhydrols;¹ however, reactions are often limited to the availability of the organometallic reagent or the preparation of symmetric diarylmethane products. Catalytic approaches – including Suzuki–Miyaura couplings² – are known using either benzylic halides and arylboron reagents^{3,4} or aryl (pseudo)halides and typically benzylic BF₃·Ks,^{5,6} although other organoborons have been used.⁷ Among other Pd-catalyzed methods,^{8–13} Shibata has reported the synthesis of unsymmetrical diarylmethanes using diborylmethane and



Scheme 1 (a) General catalytic strategies towards C(sp²)–C(sp²) and C(sp²)–X bond formation. (b) General strategies towards benzylic C–C, C–N, and C–O bond formations. (c) This work: a diversity-oriented approach towards benzylic C–C, C–N, and C–O bonds via a catalytic arylboronic acid homologation using a halomethyl Bpin reagent.

10 mol% Pd(P-*t*Bu₃)₂.¹⁴ These methods are supplemented by similar Ir- or Ni-catalyzed processes.^{15,16} Classical alkylation or reductive amination reactions to prepare benzylic ethers

or amines often require harsh conditions and limit functional group compatibility (Scheme 1b).¹⁷ Catalytic approaches towards C–X bond formation, including Buchwald–Hartwig,¹⁸ Ullmann–Goldberg,¹⁸ and Chan–Lam couplings,¹⁹ have traditionally focused on C(sp²)–X bond formation (Scheme 1a). C(sp³)–X bond formations using Buchwald–Hartwig and Chan–Lam approaches are becoming more common but can require the use of bespoke ligands or long reaction times.^{18,19}

While historically utilized in C(sp²)–C(sp²) cross-coupling reactions, contemporary work has employed C(sp³)–B organoboron reagents as a method to prepare more C(sp³)–rich scaffolds for improved biological characteristics in medicinal chemistry.²⁰ As such, both the preparation and utilization of C(sp³)–B bonds remains a strategic focal point within academic and industrial research settings. Several benzyl boronic acids are known; however, very few are commercially available likely due to their propensity to degrade (protodeboronation).²¹ Approaches to prepare the respective benzylic boronic esters typically require the use of stoichiometric organometallic reagents from halides,^{1,22} hydroboration,^{1,23} C–H activation,²⁴ or photoredox²⁵ methods. As a conceptual alternative to the classical Matteson homologation,²⁶ which inserts a metalated carbenoid into an organoboron reagent,²⁷ we have recently disclosed an approach using Pd catalysis, arylboronic acids, and a halomethylboronic acid pinacol ester.²⁸

Based on this, we sought to deliver a unified approach towards the synthesis of unsymmetrical diarylmethanes, benzyl amines, and benzyl ethers using benzylic Bpins as common synthetic precursors via a series of Suzuki–Miyaura and Chan–Lam couplings. Oxidation of the Bpin would also provide a convenient method for the synthesis of benzyl alcohols (Scheme 1c). This divergent strategy would lead to an array of C(sp³)–X products from a commercially abundant pool of arylboronic acids, without the requirement for stoichiometric metalation.

We established benchmark systems for the development of a Suzuki–Miyaura benzylation, Chan–Lam etherification, and Chan–Lam amination using benzyl Bpins prepared via Pd-catalyzed formal homologations of arylboronic acids (Table 1). Suzuki–Miyaura cross-coupling of **3-Me** and bromobenzene was contingent on controlling the hydrolysis of the Bpin ester to generate limiting quantities of the unstable benzyl boronic acid. Yields were improved using a K₃PO₄/stoichiometric H₂O system,²⁹ rather than Ag₂O,⁷ and low loadings of Pd catalyst (1 mol%) were operative (entries 1 and 2). The switch from Pd(PPh₃)₄ to Pd(dppf)Cl₂ was essential (entry 3). A Chan–Lam etherification of benzyl Bpin with seven phenols has been reported by Kuninobu;³⁰ however, in our hands these conditions were ineffective (entry 4) and required stoichiometric quantities of Cu(OAc)₂ for an efficient reaction (entry 5, see the Supporting Information for full details). These conditions provided a more diverse range of phenols (*vide infra*) but did not

translate to the analogous amination reaction (entry 6); however, conditions reported by Partridge were effective (entry 7),³¹ with further optimization delivering no further improvement (see the Supporting Information for details). Oxidation of the homologated intermediate under Brown conditions provided the desired benzyl alcohol in quantitative yield (entry 8).

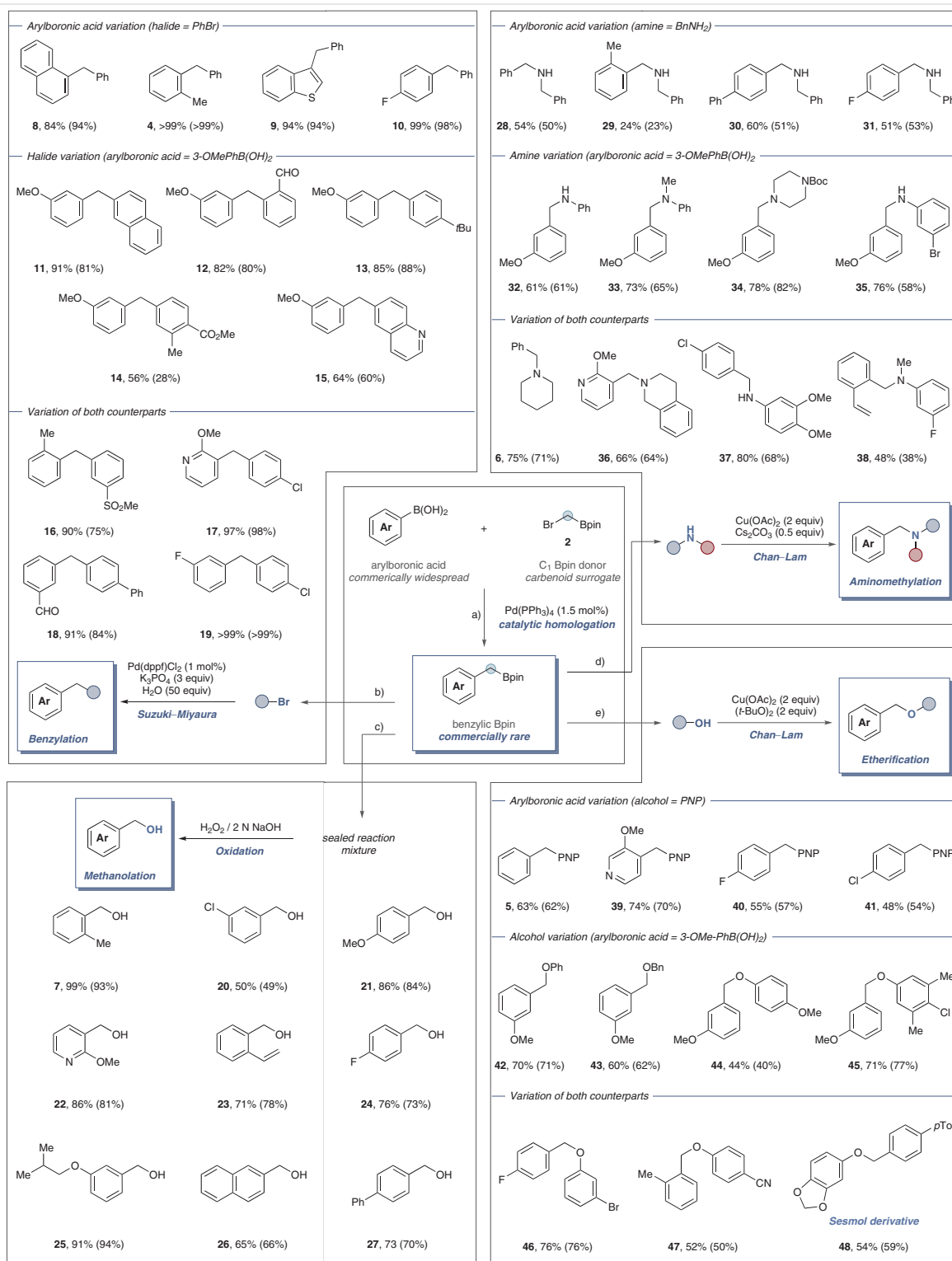
With conditions for the homologation/C–X bond formation platform in place, the generality of the four diversifications was assessed using a variety of boronic acids, bromides, amines, and alcohols (Scheme 2). For the Suzuki–Miyaura benzylation (top left), a variety of electronic and steric substitution was tolerated at very good to excellent yields. Of note was the tolerance towards heterocycles from either the Bpin (e.g., **9**, **17**) or bromide (**15**) counterparts,

Table 1 Summary of Reaction Development

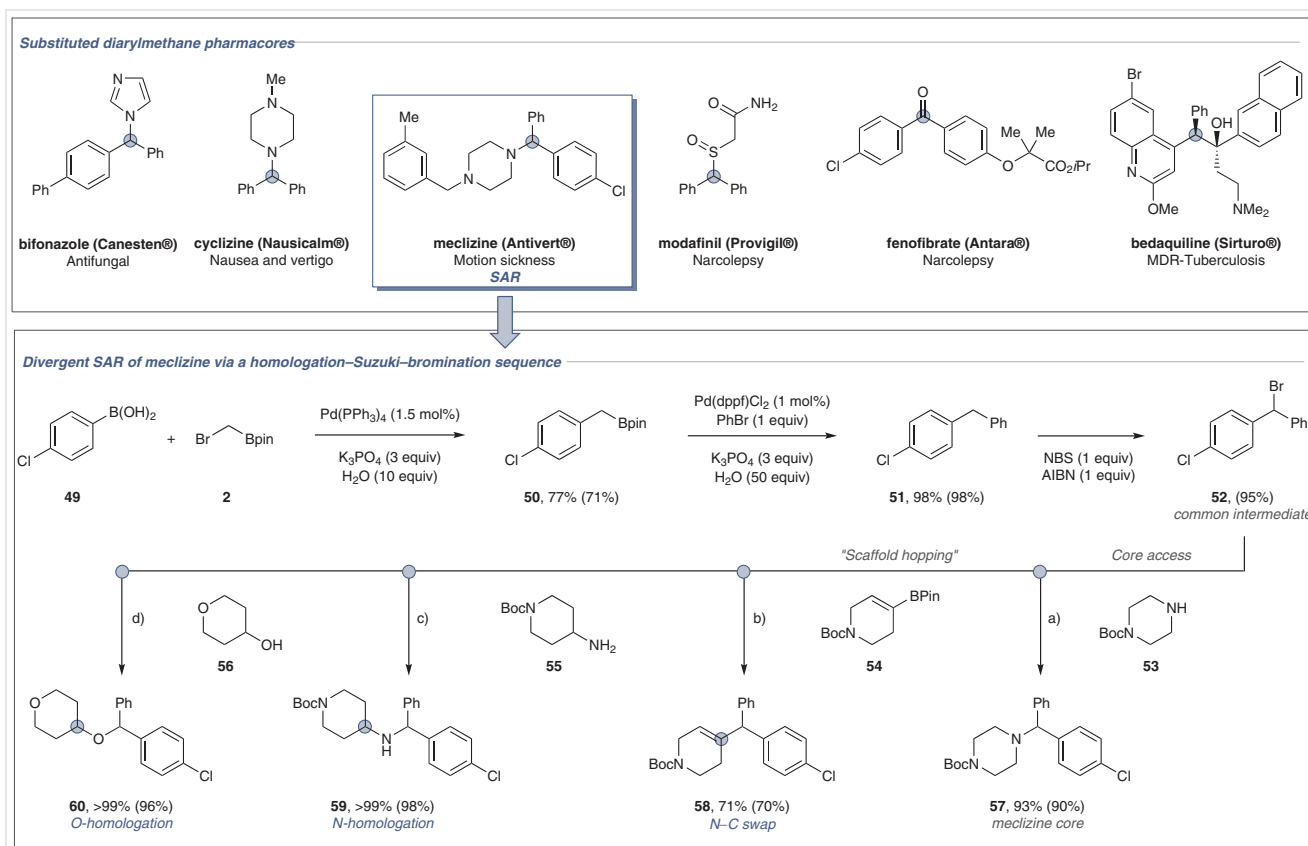
Entry	Product	Conditions	Yield (%) ^a
<i>Suzuki–Miyaura Benzylation</i>			
1	4	Pd(dba) ₂ (8 mol%), PPh ₃ (96 mol%), Ag ₂ O (2 equiv), THF, 70 °C	19
2	4	Pd(dppf)Cl ₂ (1 mol%), K ₃ PO ₄ (3 equiv), H ₂ O (50 equiv), PhMe, 90 °C	99 (99) ^b
3	4	entry 2, Pd(PPh ₃) ₄ instead of Pd(dppf)Cl ₂	30
<i>Chan–Lam Etherification</i>			
4	5	Cu(OAc) ₂ (5 mol%), (tBuO) ₂ (2 equiv), PhMe, 100 °C	22
5	5	entry 4, 2 equiv Cu(OAc) ₂	63 (62) ^b
<i>Chan–Lam Amination</i>			
6	6	see entry 5	4
7	6	Cu(OAc) ₂ (2 equiv), Cs ₂ CO ₃ (0.5 equiv), MeOH/pyridine (4:1), 50 °C	75 (71) ^b
<i>Methanolation</i>			
8	7	H ₂ O ₂ /NaOH, THF, rt	99 (93) ^b

^a Determined by ¹H NMR analysis using an internal standard (see the Supporting Information for details).

^b Isolated yield. dppf, 1,1'-bis(diphenylphosphino)ferrocene; rt, room temperature.



Scheme 2 Example scopes. Yields determined by ¹H NMR spectroscopy using an internal standard, isolated yields in brackets. a) ArB(OH)₂ (1 equiv), BrCH₂BPin (1.5 equiv), Pd(PPh₃)₄ (1.5 mol%), K₃PO₄ (3 equiv), H₂O (10 equiv), DCE, Ar, 60 °C, 24 h. b) Arylbromide (1 equiv), BnBpin (3 equiv), Pd(dppe)Cl₂ (1 mol%), K₃PO₄ (3 equiv), H₂O (50 equiv), PhMe, Ar, 90 °C, 24 h. c) Aq. H₂O₂/2 N aq. NaOH/THF (3:2:1), air, 0 °C to rt, 15 min. d) BnBpin (1 equiv), alcohol (5 equiv), Cu(OAc)₂ (2 equiv), (t-BuO)₂ (2 equiv), PhMe, Ar, 100 °C, 16 h. e) BnBpin (1 equiv), amine (4 equiv), Cu(OAc)₂ (2 equiv), Cs₂CO₃ (0.5 equiv), MeOH/pyridine (4:1), Ar, 50 °C, 16 h.



Scheme 3 Top: selected examples of substituted diarylmethanes in medicinal chemistry. Bottom: derivatization of meclizine. Yields determined by ^1H NMR spectroscopy using an internal standard, isolated yields in brackets. a) **53** (5 equiv), K_2CO_3 (3 equiv), MeCN, 80 °C, 12 h. b) **54** (3 equiv), Pd(dppf)Cl_2 (1 mol%), K_3PO_4 (3 equiv), H_2O (50 equiv), PhMe, Ar, 90 °C, 24 h. c) **55** (5 equiv), K_2CO_3 (3 equiv), MeCN, 80 °C, 12 h. d) **56** (5 equiv), K_2CO_3 (3 equiv), MeCN, 80 °C, 12 h. NBS, *N*-bromosuccinimide; AIBN, azobisisobutyronitrile. For full experimental details, see the Supporting Information.

and the tolerance towards functional groups such as aldehyde (e.g., **12**, **18**), ester (**14**), and sulfonate (**16**). Electrophile chemoselectivity was observed, leading to chloroarene products, useful for onward cross-coupling (e.g., **17**, **19**). Substitution at the *ortho* position was well tolerated (e.g., **4**, **12**, **16**, **17**), although *o*-vinyl was a notable exception (see the Supporting Information for other limitations). All oxidation reactions proceeded smoothly (bottom left), and the yields generally reflected the homologation reaction, with more sensitive functional groups (e.g., **23**) unaffected. Upon examining the Chan–Lam amination (top right), primary (**32**, **35**, **37**) and secondary anilines (**33**, **38**) and secondary aliphatic amines (**6**, **34**, **36**) were accommodated. From the Bpin ester component, *ortho* substitution was generally poor throughout (e.g., **29** and **38**, for other examples see the Supporting Information) although the substituted pyridine **36** was an exception. Assessing the corresponding Chan–Lam etherification (bottom right), the reaction was effective with electron-withdrawing (e.g., **5**, **39–41**) or neutral (e.g., **42**) phenols; however, electron-rich substrates (e.g., **44**) tended to give lower yields along with a series of unidentified side products. While benzyl alcohol

was tolerated to deliver product **43**, this was generally an exception and other alkyl alcohols were recalcitrant at either stoichiometric loading or when used as the solvent (see the Supporting Information for full limitations).

The developed homologation–benzylation Suzuki–Miyaura process uses low loadings of widely available and simple Pd catalysts, which we envisioned would serve as a straightforward route to nonsymmetrical diarylmethane pharmacophores. These chemotypes are found extensively throughout medicinal chemistry,¹ such as bifonazole, meclizine, fenofibrate, and bedaquiline (Scheme 3, top). To highlight the utility of this process, we undertook an SAR-style derivatization of meclizine (Scheme 3, bottom).

The homologation–benzylation process provided intermediate **51**, which was brominated to yield **52**.³¹ This could be used without purification for alkylation reactions to afford the meclizine core (**57**) or ‘scaffold hopping’³² alternatives appropriate for further SAR investigation in generally excellent yields (**57–60**).

In summary, a diversity-oriented approach towards the platform synthesis of unsymmetrical diarylmethanes and benzylic ethers, alcohols, and amines has been developed

via a catalytic formal homologation of arylboronic acids. These processes give straightforward access to a range of C(sp³)-C(sp²) and C(sp³)-X scaffolds from a previous synthetic bottleneck of benzyl Bpin esters and where stoichiometric metalation is avoided. All Pd-catalyzed manipulations take place at very low catalyst loadings, and complex ligand systems were avoided. The synthetic potential was further evaluated via an SAR-style derivatization of melizine.³³

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

K.A.C.B thanks the Engineering and Physical Sciences Research Council (EPSRC, Grant Number EP/W007517) and the University of St Andrews for a PhD studentship. A.J.B.W. thanks the Leverhulme Trust for a Research Fellowship and the EPSRC Programme Grant 'Boron: Beyond the Reagent' for support.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/a-2117-9878>.

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- (33) The research data supporting this publication can be accessed at <https://doi.org/10.17630/df058940-8cac-4ee2-abf4-da914cbcc446>