A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
GDCh
International Edition
www.angewandte.org

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201712428
Angew. Chem. 10.1002/ange.201712428

Link to VoR: http://dx.doi.org/10.1002/anie.201712428
http://dx.doi.org/10.1002/ange.201712428

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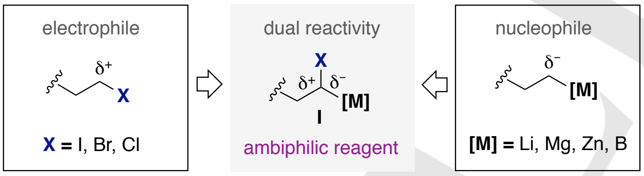
Ni-catalyzed Umpolung Arylation of Ambiphilic α-Bromo Boronic Esters

Shang-Zheng Sun and Ruben Martin*

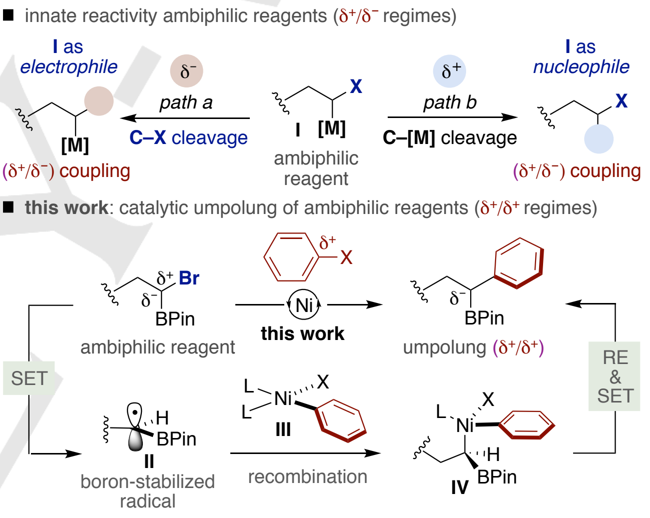
Abstract: A Ni-catalyzed reductive arylation of ambiphilic α-bromo boronic esters with aryl halides is described. This platform provides an unrecognized opportunity to promote catalytic umpolung reactivity of ambiphilic reagents with aryl halides, thus unlocking a new cross-coupling strategy that complements existing technologies for the preparation of densely functionalized alkyl organometallic reagents from simple and accessible precursors.

The dual role of ambiphilic reagents as nucleophiles and electrophiles has attracted considerable attention, holding promise to provide new knowledge in synthetic design (Scheme 1).[1] Despite the synthetic potential of ambiphilic α-halogenated organometallics (**I**),[2],[3] their use remains confined to their innate reactivity profile; while nucleophiles react at the electrophilic C–X site (Scheme 2, *path a*), functionalization at the nucleophilic C–M terminus occurs with electrophilic species (Scheme 2, *path b*). These observations contribute to the perception that **I** cannot be used in cross-electrophile coupling reactions,[4] one of the most rapidly growing disciplines of catalysis research with improved practicality and versatility when compared to conventional nucleophilic/electrophilic regimes. Such a void terrain, however, might provide an unrecognized opportunity to alter the innate reactivity of ambiphilic reagents **I** in the presence of easy-to-handle electrophiles via catalytic reversal of polarity.[5] If successful, such a platform might offer a counterintuitive new approach for preparing densely functionalized organometallic reagents,[6] key carbon synthons of paramount synthetic importance for building up molecular complexity.



Scheme 1. Ambiphilic Reagents

As part of our interest in Ni-catalyzed reductive coupling reactions,[7] we questioned whether a generic umpolung strategy could be designed for the direct arylation of readily-accessible α-bromo alkylboronic esters with aryl halides (Scheme 2, *bottom*).[8],[9] Our design principle is based on the intermediacy of transient radical intermediates **II** that might be stabilized by the adjacent α-boron atom,[10],[11] setting the basis for a recombination with **III** prior to C–C reductive elimination (RE), and a final single-electron transfer (SET). We anticipated that such umpolung route would result in a pathway that might be complementary to existing protocols for the preparation of alkyl boronic esters,[12],[13] including the use of **I** with well-defined alkyl organozinc reagents via nucleophilic/electrophilic regimes (Scheme 2, *path a*).[14] Herein, we describe the successful realization of this goal. This protocol is characterized by its mild conditions and excellent chemoselectivity profile while obviating the need for carbogenic nucleophilic organometallic species without compromising its application profile.



Scheme 2. Catalytic Umpolung Reactivity with Ambiphilic Reagents.

Our study began by evaluating the reductive arylation of easily-accessible **1a** with **2a** (Scheme 3). After careful optimization of all reaction parameters,[15] a cocktail consisting of Ni(COD)$_2$ (5 mol%) and 4,4'-dimethoxy-2,2'-bipyridine (**L3**, 5 mol%) in THF/DMPU at 30 ºC with Zn as reducing agent afforded **3a** in 80% isolated yield. As shown in entries 2 and 3, the use of nickel(II) precatalysts resulted in a significant lower yield.[16] Likewise, the use of structurally-related 1,10-phenanthroline (**L5**) or 2,2'-bipyridines other than **L3** resulted in markedly lower yields of **3a** (entries 4-7). A significant erosion in yield was observed in THF or DMPU, tacitly indicating that the combination of THF/DMPU was critical for obtaining good yields of **3a** (entries 8-9). Notably, modest results were observed with Mn or even TDAE as reducing agent (entries 10-11). The latter finding is particularly noteworthy,[17] leaving a reasonable doubt that an in situ generated organozinc species comes into play.[18] As anticipated, rigorous control experiments revealed that all of the reaction parameters were critical for the catalytic umpolung arylation to occur (entry 12).[15],[19]

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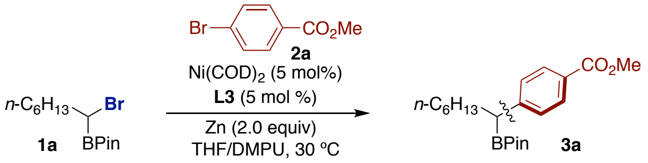
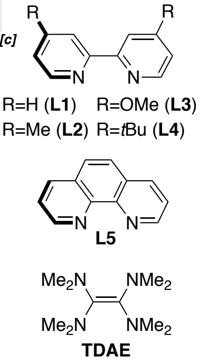
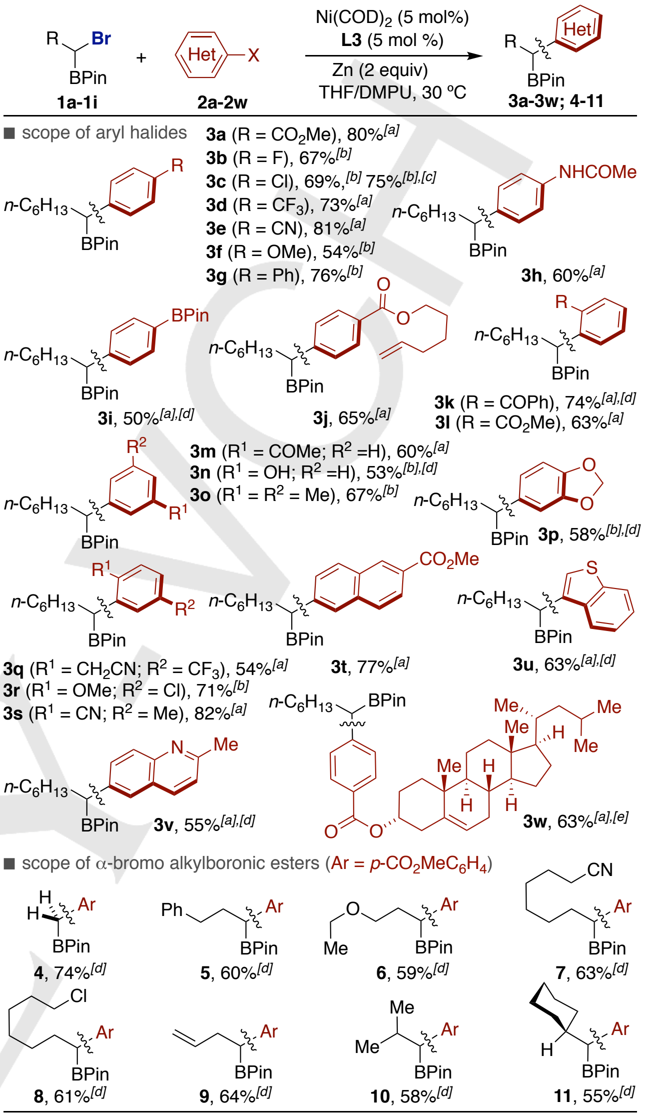


Entry	Deviation from standard conditions	3a (%)[a]
1	***None***	***84 (80)[b], 54[c]***
2	Using $NiBr_2$ (5 mol%)	3
3	Using $Ni(acac)_2$ (5 mol%)	0
4	**L1** instead of **L3**	58
5	**L2** instead of **L3**	80
6	**L4** instead of **L3**	73
7	**L5** instead of **L3**	59
8	THF as the solvent	20
9	DMPU as the solvent	28[d]
10	Mn instead of Zn	54
11	TDAE instead of Zn	51
12	No $NiBr_2$·diglyme, no **L5** or no Zn	0



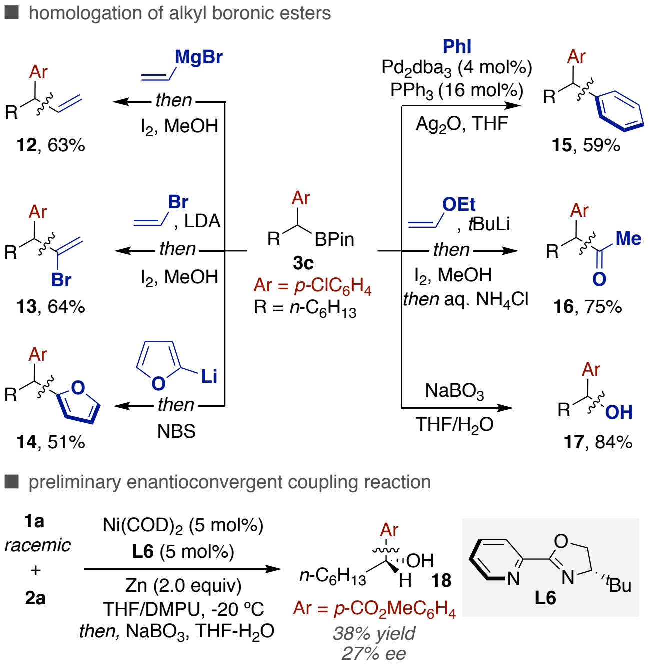
Scheme 3. Optimization of the reaction conditions. **1a** (0.20 mmol), **2a** (0.22 mmol), $Ni(COD)_2$ (5 mol%), **L3** (5 mol%), Zn (0.40 mmol), THF/DMPU (20:1, 0.20 M) at 30 ºC. [a] Yields determined by NMR spectroscopy using CH_2Br_2 as internal standard. [b] Isolated yields. [c] $Ni(COD)_2$ (1 mol%), 12 h. [d] $Ni(COD)_2$ (10 mol%). DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone.

As shown in Scheme 4, a host of electron-rich and electron-poor aryl halides reacted with good to excellent yields with the Ni/**L3** couple, independent of whether they were sterically biased or not.[19] Heteroaryl halides could also be employed as substrates, albeit giving slightly lower yields (**3u, 3v**). Particularly noteworthy is the chemoselectivity profile of this method, as esters (**3a, 3j, 3l, 3t, 3w**), nitriles (**3e, 3q, 3s**), alkenes (**3j, 3w**) amides (**3h**), free hydroxyl groups (**3n**), ketones (**3k, 3m**) and acetals (**3p**) were all well-accommodated, thus constituting a useful supplement to existing catalytic methods for preparing alkyl organometallic reagents.[6] Equally interesting was the ability to tolerate aryl boron reagents (**3i**) and a diverse set of aryl halides (**3b, 3c, 3r**), leaving ample room for subsequent manipulation. Notably, this reaction could be executed on a gram scale, affording **3c** in 75% yield. Encouraged by these initial findings, we turned our attention to exploring the substitution pattern on the α-bromo alkylboronic ester backbone. As shown, a variety of differently-substituted side-chains, including those containing ethers (**6**), nitriles (**7**), alkyl halides (**8**) or alkenes (**9**), could be well-tolerated. Likewise, the reaction could be applied for unsubstituted side-chains (**4**) or for β-substituted branched products (**10, 11**). Unfortunately, however, α-bromo alkylated boronic esters bearing a quaternary carbon could not participate in the targeted arylation event. with substantial amounts of the starting material being recovered unaltered. Taken together, these results serve as a testament to the prospective impact of our method, representing an alternative catalytic platform for preparing functionalized alkyl organometallic reagents.[6],[12-14]

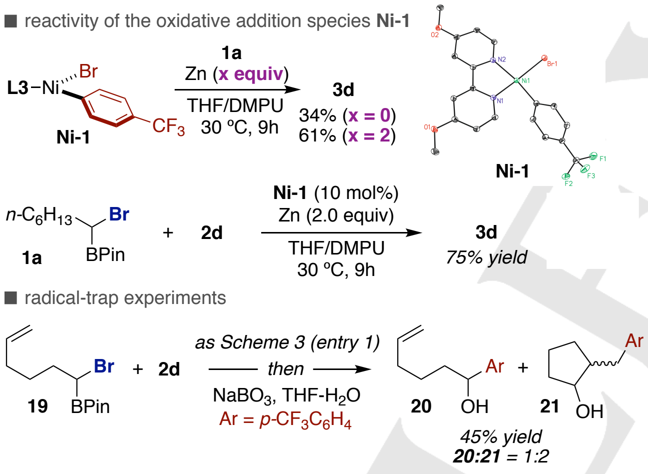


Scheme 4. Generality of the nickel-catalyzed cross-electrophile coupling of ambiphilic α-bromo boronic esters: As scheme 3 (entry 1); yields of isolated product, average of at least two independent runs. [a] X = Br. [b] X = I. [c] 4 mmol **1a** were utilized. [d] $Ni(COD)_2$ (10 mol%), 12 h. [e] dr = 1:1.

The utility of this method is further illustrated in Scheme 5. As expected, **3c** could participate in conventional oxidations with $NaBO_3$ (**17**)[20] or carbon homologations for incorporating alkene functions at the C–B terminus with Grignard reagents (**12**)[21] or bromoethylene (**13**).[22] The introduction of (hetero)aryl or carbonyl motifs was within reach by treatment with organolithium reagents (**14, 16**)[23] or Suzuki-Miyaura protocols (**15**).[24] If boron-stabilized radical intermediates **II** intervene (Scheme 2), we anticipated that enantioconvergent reductive arylations could be developed when using racemic precursors and appropriate chiral ligands.[25] As shown in Scheme 5 (bottom), **18** could be preliminary obtained with modest enantioselectivities under a Ni/**L6** regime. However, it is worth noting that the current catalytic enantioconvergent cross-electrophile portfolio remain predominantly confined to the use of benzyl electrophiles.[26],[27]



Scheme 5. Synthetic Application Profile.



Scheme 6. Preliminary Mechanistic Experiments

Next, we decided to gather indirect evidence about the mechanism by studying the reactivity of the oxidative addition species (Scheme 6). Although we were unable to identify the oxidative addition of **1a** to Ni/**L3**, exposure of **2d** to Ni(COD)$_2$ and **L3** cleanly delivered **Ni-1** as a crystalline solid, the structure of which was characterized by X-ray crystallography.[15],[28] **Ni-1** was shown to be catalytically competent, as **3d** was obtained in 75% yield. More importantly, **Ni-1** was found to react in a stoichiometric fashion with **1a** regardless of whether Zn was present or not. The non-negligible yield of **3d** in the absence of Zn is particularly noteworthy, suggesting an initiation consisting of SET from **Ni-1** to **1a**, leading to a boron-stabilized radical intermediate **II** (Scheme 2, *bottom*).[29] The intermediacy of **II** was further corroborated in radical-trap experiments with **19** as substrate, resulting in a 1:2 mixture of direct arylation product **20** to ring-closed 5-*exo-trig* cyclization **21** (Scheme 6, *bottom*).[30] Taken together, these results can be tentatively be ascribed to a mechanism consisting of an oxidative addition of **2** to Ni(0)/**L3** followed by recombination with **II**. Reductive elimination from **IV** delivers the product and Ni(I)/**L3** that triggers a SET to **1a**, leading to Ni(II)/**L3** that ultimately recovers the propagating Ni(0)/**L3** with Zn.[31],[32]

In summary, we have designed a Ni-catalyzed protocol that unlocks an opportunity to promote a reversal of polarity in ambiphilic α-bromo boronic esters within the cross-electrophile coupling arena. The mild conditions, excellent chemoselectivity profile and ready availability of its easy-to-handle precursors constitute a straightforward alternative to existing technologies en route to densely functionalized alkyl organometallics. Further investigations into related processes, and the identification of the mechanistic intricacies, are currently ongoing in our laboratories.

Acknowledgements

We thank ICIQ, MINECO (CTQ2015-65496-R & Severo Ochoa Accreditation SEV-2013-0319) and the Cellex Foundation for support. We also thank E. Escudero/E. Martin for X-ray crystallographic data. S. –Z. Sun thanks MINECO and Severo Ochoa for a FPI fellowship.

Keywords: cross-coupling • nickel • umpolung • C–C formation

[1] For selected examples on the importance of ambiphilic reagents: (a) Z. He, A. Zajdlik, A. K. Yudin, *Acc. Chem. Res.* **2014**, *47*, 1029; (b) A. S. Dudnik, N. Chernyak, C. Huang, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2010**, *49*, 8729; *Angew. Chem.* **2010**, *122*, 8911; (c) T. B. Samarakoon, M. Y. Hur, R. D. Kurtz, P. R. Hanson, *Org. Lett.* **2010**, *12*, 2182; (d) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716.

[2] (a) C. Cárdenas, N. Rabi, P. W. Ayers, C. Morell, P. Jaramillo, P. Fuentealba, *J. Phys. Chem. A*, **2009**, *113*, 8660; (b) *Metal-Catalyzed Cross-Coupling Reactions;* A. de Meijere, S. Bräse, M. Oestreich, Eds.; Wiley-VCH: Weinheim, Germany, 2004; (c) G. Köbrich, *Angew. Chem. Int. Ed.* **1972**, *11*, 473; *Angew. Chem.* **1972**, *84,* 557.

[3] Selected references: (a) E. La Cascia, A. B. Cuenca, E. Fernandez, *Chem. Eur. J.* **2016**, *22*, 18737; (b) L. –P. B. Neaulieu, J. F. Schneider, A. B. Charette, *J. Am. Chem. Soc.* **2013**, *135*, 7819; (c) S. P. Thomas, R. M. French, V. Jheengut, V. K. Aggarwal, *The Chemical Record,* **2009**, *9*, 24; (d) G. A. Molander, Ham, J. *Org. Lett.* **2006**, *8*, 2031; (e) R. W. Hoffmann, M. Bronstrup, M. Muller, *Org. Lett.*, **2003**, *5*, 313; (f) V. Schulze, P. G. Nell, A. Burton, R. W. Hoffmann, *J. Org. Chem.* **2003**, *68*, 4546; (g) D. S. Matteson, R. Ray, *J. Am. Chem. Soc.* **1980**, *102*, 7590, and citations therein.

[4] (a) J. Gu, X. Wang, W. Xue, H. Gong, *Org. Chem. Front.* **2015**, *2*, 1411; (b) J. D. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767; (c) T. Moragas, A. Correa, R. Martin, *Chem. Eur. J.* **2014**, *20*, 8242; (d) C. E. I. Knappke, S. Grupe, D. Gaїtner, M. Corpet, C. Gosmini, A. Jacobi von Wangelin, *Chem. Eur. J.* **2014**, *20*, 6828.

[5] D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239; *Angew. Chem.* **1979**, *91*, 259.

[6] Selected reviews: (a) J. Choi, G. C. Fu, *Science* **2017**, *356*, 7230; (b) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417.

[7] Selected references: (a) F. Juliá-Hernández, T. Moragas, J. Cornella, R. Martin, *Nature* **2017**, *545,* 84; (b) M. Van Gemmeren, M. Borjesson, A.

Tortajada, S.−Z. Sun, K. Okura, R. Martin, *Angew. Chem., Int. Ed.* **2017**, *56*, 6558; *Angew. Chem.* **2017**, *129*, 6658; (c) M. Borjesson, T. Moragas, R. Martin, *J. Am. Chem. Soc.* **2016**, *138*, 7504; (d) E. Serrano, R. Martin, *Angew. Chem., Int. Ed.* **2016**, *55*, 11207; *Angew. Chem.* **2016**, *128*, 11373; (e) T. Moragas, M. Gaydou, R. Martin, *Angew. Chem., Int. Ed.* **2016**, *55*, 5053; *Angew. Chem.* **2016**, *128*, 5137.

[8] Preparation of α-bromo alkylborons: D. S. Matteson, R. Soundararajan, O. C. Ho, W. Gatzweiler, *Organometallics* **1996**, *15*, 152.

[9] For selected references dealing with the synthetic utility of α-halogenated alkylboron reagents: (a) A. Hercouet, C. Baudet, B. Carboni, *Tetrahedron Lett.* **2004**, *45*, 8749; (b) K. Takai, N. Shinomiya, M. Ohta, *Synlett* **1998**, *3*, 253; (c) P. K. Jadhav, H.-W. Man, *J. Org. Chem.* **1996**, *61*, 7951; (d) R. J. Mears, A. Whiting, *Tetrahedron* **1993**, *49*, 177; (e) D. S. Matteson, *Chem. Rev.* **1989**, *89*, 1535.

[10] Selected references: (a) J. C. Walton, A. J. McCarroll, Q. Chen, B. Carboni, R. Nziengui, *J. Am. Chem. Soc.* **2000**, *122*, 5455; (b) B. Quiclet-Sire, S. Z. Zard, *J. Am. Chem. Soc.* **2015**, *137*, 6762; (c) J. Grotewold, E. A. Lissi, J. C. Scaiano, *J. Organomet. Chem.* **1969**, *19*, 431; (d) D. S. Matteson, *J. Am. Chem. Soc.* **1960**, *82*, 4228.

[11] Such stabilization is probably due to the effective delocalization of the radical through the vacant p orbital of the neighboring boron atom, suggesting substantial stabilization by C–B π-bonding.

[12] (a) *Boronic acids: preparation and applications in organic synthesis and medicine (*Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**; (b) C. M. Crudden, D. Edwards, *Eur. J. Org. Chem.* **2003**, 4695. (c) N. Miyaura *in Catalytic Heterofunctionalization* (Eds.: A. Togni, H. Grüzmacher), Wiley-VCH, Weinheim, 2001, pp 1-46. (d) S. A. W. Christopher, M. Vogels, *Curr. Org. Chem.* **2005**, *9*, 687.

[13] Selected metal-catalyzed borylation of secondary alkyl halides: (a) T. C. Atack, S. P. Cook, *J. Am. Chem. Soc.,* **2016**, *138*, 6139; (b) S. K. Bose, S. Brand, H. O. Omoregie, M. Haehnel, J. Maier, G. Bringmann, T. B. Marder, *ACS Catal*. **2016,** *6,* 8332; (c) S. K. Bose, K. Fucke, L. Liu, P. G. Steel, T. B. Marder, *Angew. Chem., Int. Ed.* **2014**, *53*, 1799; *Angew. Chem.* **2014**, *126*, 1829; (d) T. C. Atack, R. M. Lecker, S. P. Cook, *J. Am. Chem. Soc.* **2014**,*136*, 9521; (e) J. Yi, J.-H. Liu, J. Liang, J.-J. Dai, C.-T. Yang, Y. Fu, L. Liu, *Adv. Synth. Catal.* **2012**, *354*, 1685; (f) A. S. Dudnik, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 10693; (g) H. Ito, K. Kubota, *Org. Lett.* **2012**,*14,* 890.

[14] J. Schmidt, J. Choi, A. T. Liu, M. Slusarczyk, G. C. Fu, *Science* **2016**, *354*, 1265.

[15] For details, see Supporting Information

[16] The addition of COD to entries 2-3 did not lead to improved yields. For the use of COD as non-innocent ligand, see: (a) A. J. Nett, W. Zhao, P. M. Zimmerman, J. Montgomery, *J. Am. Chem. Soc.* **2015**, *137*, 7636; **(**b) J. Cornella, E. Gómez-Bengoa, R. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 1997; (c) A. Fürstner, K. Majima, R. Martin, H. Krause, E. Kattnig, R. Goddard, W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992.

[17] TDAE (-0.62V vs SCE) possesses an otherwise similar redox potential to that shown for Zn (-0.76V vs SCE). For selected recent Ni-catalyzed cross-electrophile couplings conducted with TDAE in lieu of Mn or Zn, see: (a) L. L. Anka-Lufford, K. M. M. Huihui, N. J. Gower, L. K. G. Ackerman, D. J. Weix, *Chem. –Eur. J.* **2016**, *22*, 11564; (b) A. García-Domínguez, Z. Li, C. Nevado, *J. Am. Chem. Soc.* **2017**, *139*, 6835.

[18] Exposure of **1a** to Zn in THF/DMPU followed by I_2 quench did not result in **1a-I**, but rather recovered **1a** unaltered. These results argue against the intervention of organozinc derivatives as reaction intermediates.

[19] The mass balance of the reactions accounts for unreacted starting material and homocoupling of aryl halide.

[20] J. Cossy, *In Comprehensive Organic Functional Group Transformations II;* A. Katritzky, R. J. K. Taylor, Eds.; Elsevier: Oxford, 2004.

[21] R. P. Sonawane, V. Jheengut, C. Rabalakos, R. Larouche-Gauthier, H. K. Scott, V. K. Aggarwal, *Angew. Chem., Int. Ed.*, **2011**, *50*, 3760; *Angew. Chem.* **2011**, *123,* 3844.

[22] Y. Wang, A. Noble, E. L. Myers, V. K. Aggarwal, *Angew. Chem., Int. Ed.*, **2016**, *55*, 4270; *Angew. Chem*. **2016**, *128* ,4342.

[23] a) A. Bonet, M. Odachowski, D. Leonori, S. Essafi, V. K. Aggarwal, *Nat. Chem.*, **2014**, *6*, 584; b) See ref. 21.

[24] D. Imao, B. W. Glasspole, V. S. Laberge, C. M. Crudden, *J. Am. Chem. Soc.*, **2009**, *131*, 5024.

[25] For excellent reviews on enantiodivergent cross-coupling reactions: (a) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *Chem. Rev.* **2015**, *115*, 9587; (b) ref. 6a.

[26] For a selection of enantioconvergent cross-electrophile reactions of racemic benzyl (pseudo)halides: (a) K. E. Poremba, N. T. Kadunce, N. Suzuki, A. H. Cherney, S. E. Reisman, *J. Am. Chem. Soc.* **2017**, *139*, 5684; (b) Suzuki, N.; Hofstra, J. L.; Poremba, K. E.; Reisman, S. E. *Org. Lett.* **2017**, *19*, 2150; (c) L. K. G. Ackerman, A. –L. Lukiana; M, Naodovic, D. J. Weix, *Chem. Sci.* **2015**, *6*, 1115.

[27] For an exception using α-chloro nitrile derivatives, see: N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc.* **2015**, *137*, 10480.

[28] CCDC 1588879 (**Ni-1**) contain the supplementary crystallographic data for this paper and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[29 For mechanistic intricacies of cross-electrophile couplings via SET: (a) S. Biswas, D. J. Weix, *J. Am. Chem. Soc*. **2013**, *135,* 16192; (b) ref. 4b.

[30] A linear relationship of **20:21** was observed at different Ni/**L3** ratios, suggesting that a radical-escape rebound-type mechanism might intervene in this reaction. See ref. 15.

[31] For a similar mechanistic scenario, see refs. 17b and 29.

[32] For a mechanistic hypothesis, see ref. 15.

10.1002/anie.201712428

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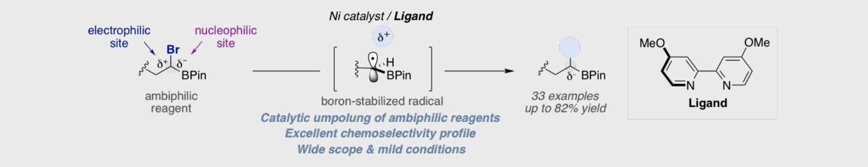

Catalytic umpolung of ambiphilic reagents
Excellent chemoselectivity profile
Wide scope & mild conditions

A nickel-catalyzed reductive arylation of ambiphilic α-bromo boronic esters with aryl halides has been developed. This mild and exceedingly tolerant methodology unlocks an opportunity to promote a catalytic cross-electrophile coupling of ambiphilic reagents with aryl halides via formal reversal of polarity, representing a straightforward alternative for preparing densely functionalized organometallics.

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Page No. – Page No.

Ni-catalyzed umpolung arylation of ambiphilic α–bromo boronic esters