Heterocycle Synthesis

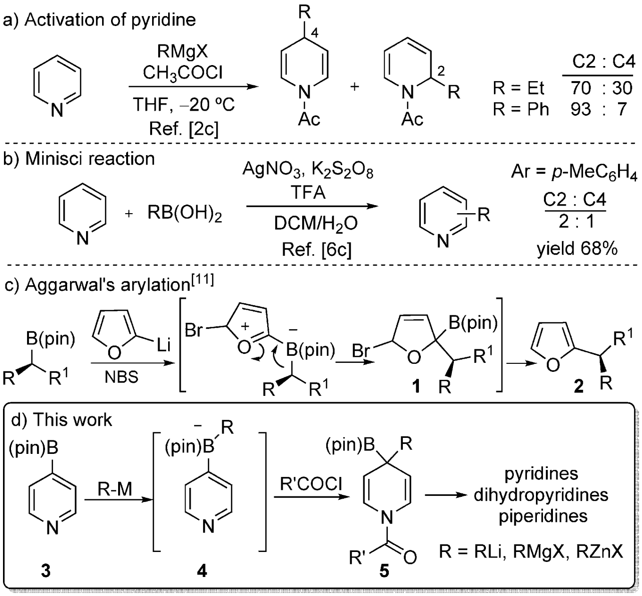
International Edition: DOI: 10.1002/anie.201510027
German Edition: DOI: 10.1002/ange.201510027

Synthesis and Utility of Dihydropyridine Boronic Esters

*Santanu Panda, Aaron Coffin, Q. Nhu Nguyen, Dean J. Tantillo, and Joseph M. Ready**

Abstract: *When activated by an acylating agent, pyridine boronic esters react with organometallic reagents to form a dihydropyridine boronic ester. This intermediate allows access to a number of valuable substituted pyridine, dihydropyridine, and piperidine products.*

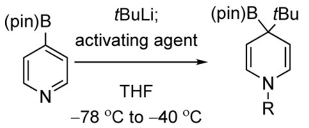
Pyridines and their derivatives are common motifs found in drugs and natural products. Current FDA-approved drugs include 62 pyridines, 10 dihydropyridines, and 72 piperidines.[1] For this reason, methods for their preparation are valuable for drug discovery and natural products synthesis. Traditional Chichibabin reactions involve the addition of nucleophiles to activated pyridines, although they generally show poor regioselectivity (Scheme 1 a).[2–4] Enhanced regioselectivity has been observed by Knochel and co-workers by using substrates with electron-withdrawing groups at C3.[5] Alternatively, Minisci reactions feature addition of alkyl or aryl radicals to a heteroarene. Poor regioselectivity is usually observed, and the 2-substituted products generally predominate (Scheme 1 b).[6] Transition metal catalyzed coupling reactions can also generate substituted pyridines, but they do not provide dearomatized products.[7] Recently, C–H functionalization strategies have emerged as attractive routes to the pyridine scaffold.[8]



Scheme 1. Selected functionalization of pyridines. NBS = *N*-bromosuccinimide, THF = tetrahydrofuran.

We became interested in exploring the utility of boronic esters in the synthesis of nitrogen heterocycles.[9] By way of background, Matteson demonstrated the ability of α-chloro boronic esters to undergo homologation upon treatment with lithiated reagents.[10] In these reactions, an alkyl group migrates from boron to an adjacent electrophile. Building on this mechanistic platform, the group of Aggarwal developed an ingenious coupling of aryl lithium reagents with boronic esters (Scheme 1 c). Thus, addition of an aryl lithium to the boronic ester with subsequent halogenation-induced 1,2-alkyl migration forms the new C–C bond (**1**). Loss of (pin)BBr formed the aromatic product **2**.[11] We recognized that a similar mechanism could be accessible with pyridines, but that the dearomatized intermediates might be isolable. Thus, acylation of boronate **4** could prompt a 1,2-migration to form a new C–C bond (Scheme 1 d). Importantly, this sequence would retain the boron moiety (**5**) and allow subsequent functionalization. Unlike prior work, the transformation would allow access to both the aromatic and dearomatized products. As we were preparing this manuscript, the group of Aggarwal described a synthesis of substituted heteroarenes from boronic esters and heteroaryl lithium reagents using a related strategy.[12] Prompted by their disclosure, herein we describe a method for the preparation of pyridines, dihydropyridines, and piperidines. It shows wide scope with regard to the organometallic nucleophile and leads to complex dearomatized products.

We began our studies with the addition of *tert*-BuLi to 4-pyridineboronic acid pinacol ester (Scheme 2). Upon activation of the pyridine, the desired dihydropyridines **6**–**12** were formed in good yield. The reaction worked well to yield amides, carbamates, and sulfonamides. Likewise, both anhydrides and acid chlorides generated amides with equal facility.



Product	Activating agent	Yield [%]
6	BzCl	82
7	CbzCl	82
8	CCl_3COCl	88
9	TFAA	84
10	Boc_2O	83
11	2-I-C_6H_4COCl	84
12	TsCl	69

Scheme 2. Generation of dihydropyridines. Yield is that of isolated product. Boc = *tert*-butoxycarbonyl, Bz = benzoyl, Cbz = carboxybenzyl, TFAA = trifluoroacetic anhydride, Ts = 4-toluenesulfonyl.

---

[*] S. Panda, A. Coffin, Prof. J. M. Ready
Department of Biochemistry, Division of Chemistry
UT Southwestern Medical Center
5323 Harry Hines Blvd., Dallas, TX 75390-0938 (USA)
E-mail: joseph.ready@utsouthwestern.edu

Q. N. Nguyen, Dr. D. J. Tantillo
Department of Chemistry, UC Davis
One Shields Ave, Davis, CA 95616 (USA)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201510027.

As shown, the ability to incorporate diverse N-activating groups allows subsequent derivatization of the dihydropyridine. The structure of the amide **11** was confirmed by X-ray analysis.

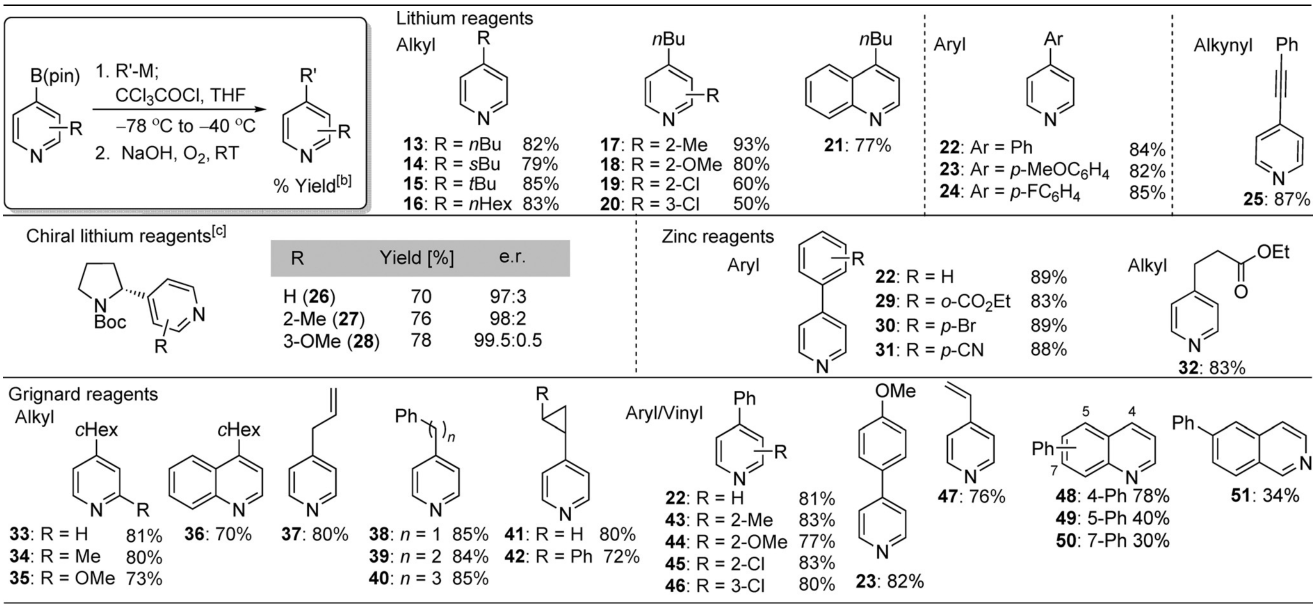
Upon treatment of the dihydropyridine with oxygen and base, rapid formation of the substituted pyridine was observed.[13] A broad range of substituted pyridines and quinolones were synthesized as highlighted in Table 1. Primary, secondary, and tertiary alkyl lithium reagents were successfully used, as were aryl and alkynyl lithium species. Optically active lithiated Boc-pyrrolidine was an excellent substrate, thus leading to the pyridines **26–28** in high yields and high enatiomeric ratios.[14] To introduce functionalized nucleophiles, we explored the use of aryl and alkyl zinc reagents. Ester, bromo, and cyano groups were all accommodated (**29–31**). Although the reaction worked well with aryl zinc halides, the analogous reaction using alkyl zinc reagents proved more difficult. Accordingly, we used a mixed zinc reagent derived from the zinc chloride and *tert*-butyl magnesium chloride and achieved good yields of the ester **32**.[5] Additionally, alkyl, aryl, and vinyl Grignard reagents provided the pyridines in high yields. Two cyclopropyl Grignard reagents were incorporated without any evidence of ring opening (**41**, **42**). Overall, the reaction is notable for its ability to 1) incorporate sp^3-, sp^2-, and sp-hybridized carbon nucleophiles, 2) accommodate organolithium, organozinc, and organomagnesium reagents, and 3) introduce electrophilic functional groups including nitriles and esters.

This coupling not influenced by the substitution on the pyridine ring itself. Electron-donating and electron-withdrawing groups were tolerated at the 2- and 3-positions (**17–20**, **27–28**, **34–35**, **43–46**). The observation that the 2-chloropyridine was a suitable substrate is particularly noteworthy since these reagents readily participate in cross-coupling reactions. Thus their successful application highlights the mildness of the method while retaining the 2-chloro group for subsequent chemistry. This reaction was also applied to quinoline 4-boronic esters, giving good yields for these substrates (**21**, **36**, **48**). Expansion of this methodology to 5- and 7-borono-quinolines and 6-borono-isoquinoline was only modestly successful (**49–51**). Additionally, the 2-pyridyl boronic esters were too unstable for the current reaction conditions,[7b] thus providing large amounts of protodeborylated pyridines.

Typical oxidations of boronic esters require peroxides, so the facile oxidation shown in Table 1 was surprising.[12] The rate of this oxidation is insensitive to the nature of activating group (both steric and electronic), but qualitatively dependent on the substituent at the 4-position (Ph > primary alkyl > tertiary alkyl). These observations suggest a radical mechanism. Indeed, trialkyl boranes are known to react with oxygen to generate alkyl radicals.[15] However, we observed no ring opening of the cyclopropyl ring in **42**, which indicates that the lifetime of any radical must be short.

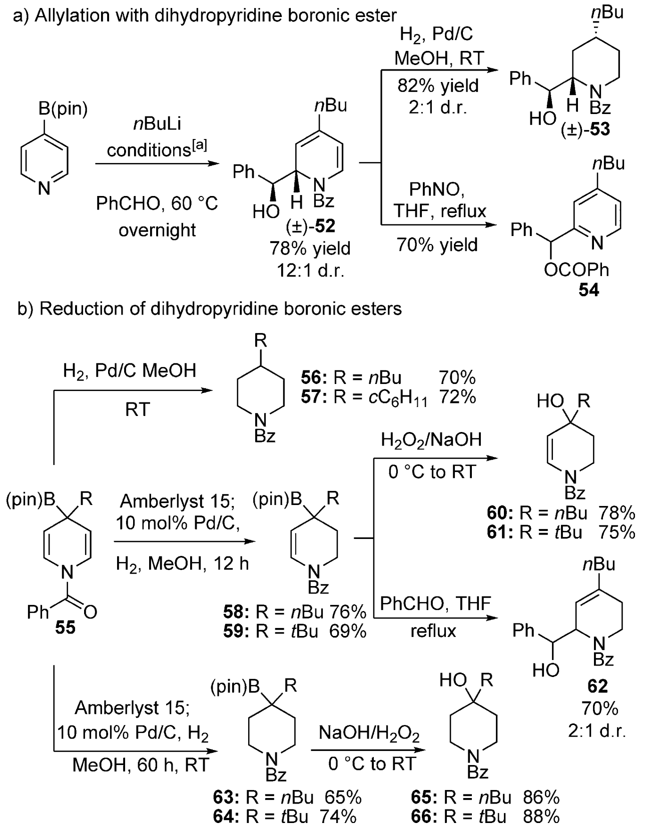
Hall and co-workers previously prepared tetrahydropyridines featuring an allylic boronic ester, and they showed that such compounds participated in allylation reactions.[16] By contrast, the 4-boryl-4-dihydropyridine products described here are unknown reagents. Therefore we next explored their synthetic utility. For example, addition of the allyl boronate to benzaldehyde generated the desired homoallylic alcohol (±)-**52** with good yield and diastereoselectivity (Scheme 3 a).[17] Hydrogenation of (±)-**52** gave the trisubstituted piperidine (±)-**53** while oxidation provided the disubstituted pyridine **54**,

Table 1: Substrate scope for preparation of substituted pyridines.[a]

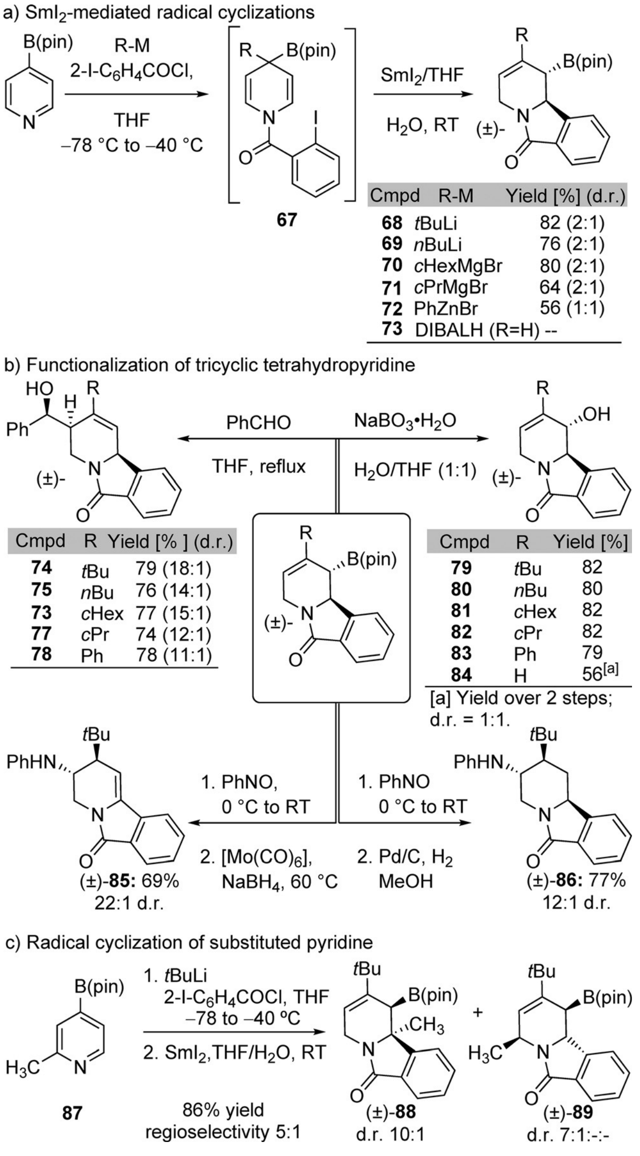


R	Yield [%]	e.r.
H (**26**)	70	97:3
2-Me (**27**)	76	98:2
3-OMe (**28**)	78	99.5:0.5

[a] Typical conditions: het-B(pin) (1 equiv, 0.3 mmol), R-M (1.1 equiv), −78 °C, CCl$_3$COCl (2 equiv), −78 to −40 °C; 10% NaOH (aq.), RT, O$_2$ balloon. [b] Yield of isolated product. [c] Typical conditions: (−)sparteine (1.3 equiv, 0.39 mmol), sBuLi (1.3 equiv, 0.39 mmol), *N*-Boc pyrrolidine (1.3 equiv, 0.39 mmol); het-B(pin) (1 equiv, 0.3 mmol), −78 °C, CCl$_3$COCl (3.5 equiv), −78 °C; saturated aq. Na$_2$CO$_3$ RT, O$_2$ balloon. het-B(pin) = heteroaryl pinacol boronic ester.



Scheme 3. Functionalization of dihydropyridine intermediates. [a] *n*BuLi (1 equiv), BzCl (1.1 equiv); then PhCHO (4 equiv).



Cmpd	R-M	Yield [%] (d.r.)
68	*t*BuLi	82 (2:1)
69	*n*BuLi	76 (2:1)
70	*c*HexMgBr	80 (2:1)
71	*c*PrMgBr	64 (2:1)
72	PhZnBr	56 (1:1)
73	DIBALH (R=H)	--

Cmpd	R	Yield [%] (d.r.)
74	*t*Bu	79 (18:1)
75	*n*Bu	76 (14:1)
73	*c*Hex	77 (15:1)
77	*c*Pr	74 (12:1)
78	Ph	78 (11:1)

Cmpd	R	Yield [%]
79	*t*Bu	82
80	*n*Bu	80
81	*c*Hex	82
82	*c*Pr	82
83	Ph	79
84	H	56[a]

[a] Yield over 2 steps; d.r. = 1:1.

Scheme 4. Cyclization of dihydropyridines with SmI_2. DIBAL = iBu_2AlH.

in which the benzoyl group migrated from N to O. In this way the (pin)B moiety was used to functionalize both C2 and C4 of the pyridine ring, a distinguishing characteristic of the current method relative to Suzuki couplings and related reactions.[7,12]

In addition to trapping the allyl boronic ester, we also investigated reduction of the crude dihydropyridine (Scheme 3b). Surprisingly, upon treatment with Pd/C in methanol under a hydrogen atmosphere, the deborylated 4-substituted piperidines were the predominant products (**56**, **57**). However, when the unpurified dihydropyridine was treated with an acidic resin prior to hydrogenation, we obtained the tetrahydropyridines **58** and **59**. Longer reaction times yielded the piperidine boronic esters **63** and **64**. We hypothesized that a base that is present in the reaction medium, could be promoting protodeborylation, and that Amberlyst 15 could be quenching this base.[18] Indeed, addition of LiOH in the reduction of the tetrahydropyridine **58** generated the deborylated product **56**.[13] Finally, both the tetrahydropyridines and the piperidines could be oxidized with peroxide to form tertiary alcohols (**60**, **61** and **65**, **66**). Alternatively, **58** added to benzaldehyde to furnish the alcohol **62**.

Our initial studies demonstrated that a variety of activating groups could be used in the dearomatization (Scheme 2). Building on this observation, we considered whether the acylating group could incorporate functionality to initiate a radical cyclization (Scheme 4a). In this context, we found that SmI_2 affected the desired ring-closing reaction of the aryl iodide **67**.[19] Unexpectedly, C−C bond formation was accompanied by a 1,2-boron shift and olefin transposition to give the allyl boronic esters (±)-**68**–**73**. Various additives were screened to improve the yield the reaction including HMPA, water, methanol, and trimethylamine. The addition of water (2–3 equiv relative to Sm) proved essential to obtain good yields.[20] This reaction incorporated aryl, tertiary, secondary, and primary alkyl groups derived from organolithium, organomagnesium, and organozinc reagents. Additionally DIBALH transferred hydride to provide (±)-**73**, which was unstable but could be isolated after oxidation [(±)-**84**]. While only modest diastereoselectivity was observed for the cyclization, the diastereomers could readily be separated by silica gel chromatography in high yield.

The tricyclic allyl boronic esters (±)-**68**–**73** emerged as versatile synthetic intermediates (Scheme 4b). Thus, addition to benzaldehyde afforded the desired homoallylic alcohols (±)-**74**–**78** stereoselectively. Alternatively, oxidation of the boronic esters with sodium perborate gave the corresponding secondary alcohols (±)-**79**–**84** in high yield and complete stereospecificity. Amination of the allyl boronic ester (±)-**69** with nitrosobenzene followed by reduction with [$Mo(CO)_6$]/$NaBH_4$ generated the enamide (±)-**85** with very high diastereoselectivity.[21] X-ray crystallography confirmed the surprising observation that [$Mo(CO)_6$]/$NaBH_4$ isomerized the olefin to form the conjugated (±)-**85**.[22] Alternatively, hydrogenation with Pd/C gave the tetrasubstituted piperidine (±)-**86** with a d.r. value of 12:1. Interestingly, addition of allylboronates to nitrosobenzenes are generally O-selective.[19b] By contrast, we observed complete N-selectivity to afford the indicated amine products instead of alcohols.

The dearomatization/SmI_2-mediated cyclization of 2-substituted pyridine **87** led to two noteworthy observations. First, cyclization favored the more hindered product possessing a quaternary stereocenter (**88**/**89** 5:1). Second, unlike the 2-unsubstitued pyridines, this substrate cyclized with high diastereoselectivity (10:1). The relative stereochemistry was initially assigned by comparison of experimental ^1H and ^{13}C chemical shifts with those computed for possible diastereomers using quantum chemical methods [mPW1PW91/6-311 + G(2d,p)//M06-2X/6-31 + G(d,p), scaled].[23] The structure was later confirmed by X-ray crystallography, thus indicating that DFT methods can be used for other products for which crystallography is not feasible.

The SmI_2-mediated cyclization of the **67** presumably involves reductive generation of an aryl radical. Next, 5-*exo*-trig cyclization might be accompanied by migration of the B(pin) moiety. We are unaware of previous examples of radical migrations of boronic esters. Current efforts aim to characterize this process more completely and determine its generality. Of note, performing the cyclization in the presence of D_2O formed (±)-[D]**68** with deuterium incorporation at C6. Finally, we remain uncertain why the 2-substituted pyridine **87** cyclized with high regio- and diastereoselectivity. The ground-state conformation of this substrate orients the large aryl ring towards the unsubstituted C6. Clearly, cyclization occurs from an alternative conformation. Understanding these provocative observations, and expanding the synthetic applications of the dihydropyridine boronic esters are the subjects of ongoing studies.

Acknowledgments

Financial support provided by the NIH (R01GM102403) and the Welch Foundation (I-1612). X-ray crystallography performed by Dr. M. F. Yousufuddin (UT Arlington) and Dr. V. Lynch (UT Austin). NSF CHE030089 supported computational resources.

Keywords: allylic compounds · boron · heterocycles · samarium iodide · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 2205–2209
Angew. Chem. **2016**, *128*, 2245–2249

---

[1] a) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274; b) C. T. Walsh, *Tetrahedron Lett.* **2015**, *56*, 3075–3081; c) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 166–187.
[2] Reviews on addition to activated pyridines: a) J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642–2713; b) H. Andersson, R. Olsson, F. Almqvist, *Org. Biomol. Chem.* **2011**, *9*, 337–346; c) D. L. Comins, S. O'Connor in *Advances in Heterocyclic Chemistry*, *Vol. 44* (Ed.: R. K. Alan), Academic Press, New York, **1988**, pp. 199–267; d) D. M. Stout, A. I. Meyers, *Chem. Rev.* **1982**, *82*, 223–243.
[3] For examples of Lewis-acid-mediated addition to pyridines, see: a) Q. Chen, T. León, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 8746–8750; *Angew. Chem.* **2014**, *126*, 8891–8895; b) J. L. Jeffrey, R. Sarpong, *Org. Lett.* **2012**, *14*, 5400–5403.
[4] For current examples of addition to activated pyridines, see: a) P. Zhang, A. M. Cook, Y. Liu, C. J. Wolf, *J. Org. Chem.* **2014**, *79*, 4167–4173; b) S. V. Tsukanov, D. L. Comins, *Angew. Chem. Int. Ed.* **2011**, *50*, 8626–8628; *Angew. Chem.* **2011**, *123*, 8785–8787.
[5] Q. Chen, X. M. du Jourdin, P. Knochel, *J. Am. Chem. Soc.* **2013**, *135*, 4958–4961.
[6] For reviews and current examples of the Minisci reaction, see: a) F. Minisci, E. Vismara, F. Fontana, *Heterocycles* **1989**, *28*, 489–519; b) D. C. Harrowven, B. J. Sutton, *Prog. Heterocycl. Chem.* **2004**, *16*, 27–53; c) I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196; d) M. A. J. Duncton, *Med. Chem. Commun.* **2011**, *2*, 1135–1161; e) F. O'Hara, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2013**, *135*, 12122–12134.
[7] For recent examples of Suzuki–Miyaura couplings, see: a) G. A. Molander, B. Canturk, L. E. Kennedy, *J. Org. Chem.* **2009**, *74*, 973–980; b) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963; c) K. Billingsley, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366; d) K. L. Billingsley, K. W. Anderson, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 3484–3488; *Angew. Chem.* **2006**, *118*, 3564–3568; e) N. Kudo, M. Perseghini, G. C. Fu, *Angew. Chem. Int. Ed.* **2006**, *45*, 1282–1284; *Angew. Chem.* **2006**, *118*, 1304–1306.
[8] a) F. Romanov-Michailidis, K. F. Sedillo, J. M. Neely, T. Rovis, *J. Am. Chem. Soc.* **2015**, *137*, 8892–8895; b) S. Duttwyler, S. Chen, M. K. Takase, K. B. Wiberg, R. G. Bergman, J. A. Ellman, *Science* **2013**, *339*, 678–682; c) P. Guo, J. M. Joo, S. Rakshit, D. Sames, *J. Am. Chem. Soc.* **2011**, *133*, 16338–16341; d) M. Wasa, B. T. Worrell, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2010**, *49*, 1275–1277; *Angew. Chem.* **2010**, *122*, 1297–1299; e) Y. Nakao, Y. Yamada, N. Kashihara, T. Hiyama, *J. Am. Chem. Soc.* **2010**, *132*, 13666–13668; f) A. Larivée, J. J. Mousseau, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 52–54; g) L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021.
[9] a) M. Burns, S. Essafi, J. R. Bame, S. P. Bull, M. P. Webster, S. Balieu, L. W. Dale, C. P. Butts, J. N. Harvey, V. K. Aggarwal, *Nature* **2014**, *513*, 183–188; b) A. Suzuki, S. Nozawa, N. Miyaura, M. Itoh, H. C. Brown, *Tetrahedron Lett.* **1969**, *10*, 2955–2958; c) H. C. Brown, G. Zweifel, *J. Am. Chem. Soc.* **1961**, *83*, 486–487.
[10] D. S. Matteson, *J. Org. Chem.* **2013**, *78*, 10009–10023.
[11] a) A. Bonet, M. Odachowski, D. Leonori, S. Essafi, V. K. Aggarwal, *Nat. Chem.* **2014**, *6*, 584–589; b) J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778–782.
[12] J. Llaveria, D. Leonori, V. K. Aggarwal, *J. Am. Chem. Soc.* **2015**, *137*, 10958–10961.
[13] See the Supporting Information for details.
[14] G. Barker, J. L. McGrath, A. Klapars, D. Stead, G. Zhou, K. R. Campos, P. O'Brien, *J. Org. Chem.* **2011**, *76*, 5936–5953.

[15] a) H. C. Brown, M. M. Midland, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 692 – 700; *Angew. Chem.* **1972**, *84*, 702 – 710; b) H. C. Brown, M. M. Midland, *J. Am. Chem. Soc.* **1971**, *93*, 3291 – 3293.

[16] S. Lessard, F. Peng, D. G. Hall, *J. Am. Chem. Soc.* **2009**, *131*, 9612 – 9613.

[17] M. J. Hesse, S. Essafi, C. G. Watson, J. N. Harvey, D. Hirst, C. L. Willis, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2014**, *53*, 6145 – 6149; *Angew. Chem.* **2014**, *126*, 6259 – 6263.

[18] M. J. Hesse, C. P. Butts, C. L. Willis, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2012**, *51*, 12444 – 12448; *Angew. Chem.* **2012**, *124*, 12612 – 12616.

[19] a) M. Szostak, N. J. Fazakerley, D. Parmar, D. J. Procter, *Chem. Rev.* **2014**, *114*, 5959 – 6039; b) D. J. Edmonds, D. Johnston, D. J. Procter, *Chem. Rev.* **2004**, *104*, 3371 – 3404; c) D. P. Curran, M. J. Totleben, *J. Am. Chem. Soc.* **1992**, *114*, 6050 – 6058; d) D. P. Curran, T. L. Fevig, C. P. Jasperse, M. J. Totleben, *Synlett* **1992**, 943 – 961.

[20] a) D. Parmar, K. Price, M. Spain, H. Matsubara, P. A. Bradley, D. J. Procter, *J. Am. Chem. Soc.* **2011**, *133*, 2418 – 2420; b) M. Szostak, M. Spain, D. J. Procter, *Nat. Protoc.* **2012**, *7*, 970 – 977; c) E. Prasad, R. A. Flowers, *J. Am. Chem. Soc.* **2005**, *127*, 18093 – 18099.

[21] a) Y. Li, S. Chakrabarty, A. Studer, *Angew. Chem. Int. Ed.* **2015**, *54*, 3587 – 3591; *Angew. Chem.* **2015**, *127*, 3657 – 3661; b) R. E. Kyne, M. C. Ryan, L. T. Kliman, J. P. Morken, *Org. Lett.* **2010**, *12*, 3796 – 3799.

[22] H. Frauenrath, T. Philipps, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 274; *Angew. Chem.* **1986**, *98*, 261.

[23] a) M. W. Lodewyk, M. R. Siebert, D. J. Tantillo, *Chem. Rev.* **2012**, *112*, 1839 – 1862; b) Q. N. N. Nguyen, D. J. Tantillo, *Chem. Asian J.* **2014**, *9*, 674 – 680.

Received: October 27, 2015