Drug Discovery

Deutsche Ausgabe: DOI: 10.1002/ange.201604652
Internationale Ausgabe: DOI: 10.1002/anie.201604652

Synthesis of Complex Druglike Molecules by the Use of Highly Functionalized Bench-Stable Organozinc Reagents

Thomas J. Greshock, Keith P. Moore, Ray T. McClain, Ana Bellomo, Cheol K. Chung, Spencer D. Dreher, Peter S. Kutchukian, Zhengwei Peng, Ian W. Davies, Petr Vachal, Mario Ellwart, Sophia M. Manolikakes, Paul Knochel,* and Philippe G. Nantermet*

Dedicated to Professor K. C. Nicolaou on the occasion of his 70th birthday

Abstract: *The reactivity of a representative set of 17 organozinc pivalates with 18 polyfunctional druglike electrophiles (informers) in Negishi cross-coupling reactions was evaluated by high-throughput experimentation protocols. The high-fidelity scaleup of successful reactions in parallel enabled the isolation of sufficient material for biological testing, thus demonstrating the high value of these new solid zinc reagents in a drug-discovery setting and potentially for many other applications in chemistry. Principal component analysis (PCA) clearly defined the independent roles of the zincates and the informers toward druggable-space coverage.*

The late-stage functionalization of highly complex, heteroatom-containing molecules is an important step in the optimization of pharmaceutically active molecules.[1] C–C bond-forming reactions are a critical component of the toolbox of any medicinal chemist[2] and enable the introduction of functionalized aryl, heteroaryl, benzylic, and alkyl substituents into a complex druglike molecule containing multiple functionalities. Having access to building blocks with functional-group tolerance and general reactivity towards complex, physicochemically desirable, heteroatom-containing molecules allows for greater flexibility in optimizing various druglike properties.

For many years, boron and zinc organometallics have been the workhorses for sp^2–sp^2 and sp^2–sp^3 bond-forming reactions.[3] Boronates,[4] boronic acids,[5] and BF_3K[6] salts have proven to be robust and bench-stable, with excellent behavior in sp^2–sp^2 coupling reactions. Their ease of synthesis, stability, and wide availability have made boronic derivatives a favorite of medicinal chemists. However, they have several shortcomings, including the less-than-desirable reactivity and inherent instability of some boron species.[7] In contrast, organozinc reagents display exquisite reactivity in most coupling reactions. They also possess the distinct advantage of reacting well in allylation,[8] benzylation, acylation, and conjugate-addition reactions,[9] and in addition reactions with aldehyde electrophiles.[10] Standard organozinc reagents (RZnX), however, are air- and moisture-sensitive species, thus limiting their synthetic application. Knochel recently demonstrated that organozinc pivalates (RZnOPiv) afford, after solvent evaporation, solid organozinc compounds with much improved air and moisture stability and with reactivity comparable to that of RZnX.[11,12] These reagents can be weighed out on the benchtop and have the potential for extended shelf life. Herein, we report that these functionalized organozinc pivalates (ArZnOPiv, BnZnOPiv, and HetZnOPiv) are highly efficient reagents for the functionalization of various complex molecules, and hence represent valuable building blocks for both synthetic and medicinal chemists.

A set of polyfunctional benzylic, aryl, and heteroaryl zinc pivalates **1**–**17** were prepared and stored in sealed/inerted ampules containing approximately 0.125 mmol of each reagent (Figure 1).[13] These zinc pivalates were first evaluated on the microscale in high-throughput mode by using 3-bromo-5-phenylpyridine as a test substrate and surveying a variety of

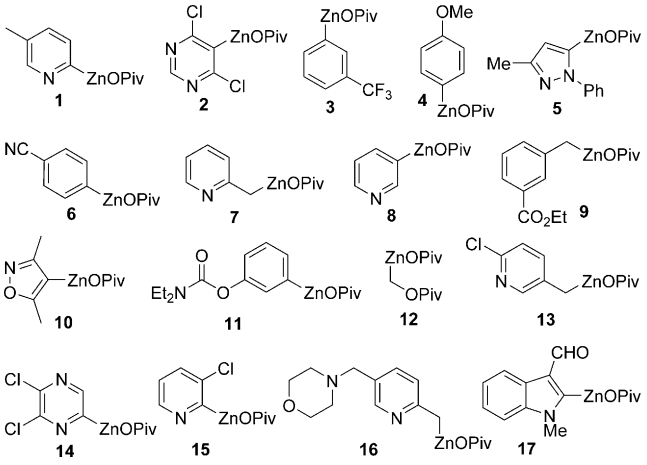
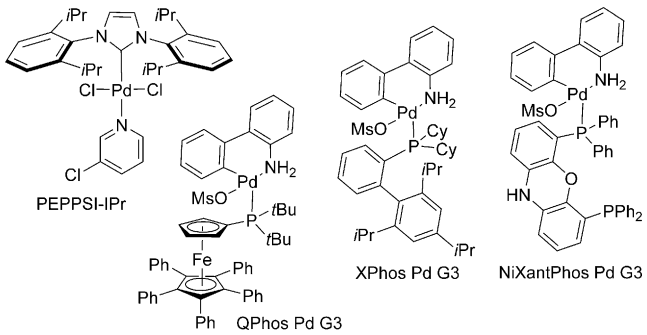


Figure 1. Set of polyfunctional aryl, benzyl, and heteroaryl zinc pivalates.

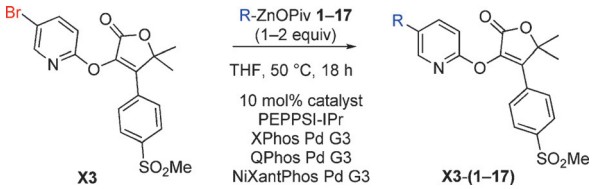
[*] T. J. Greshock, K. P. Moore, R. T. McClain, A. Bellomo, C. K. Chung, S. D. Dreher, P. S. Kutchukian, Z. Peng, I. W. Davies, P. Vachal, P. G. Nantermet
Discovery Chemistry, Process Chemistry, and Structural Chemistry
Merck Research Laboratories, Merck & Co., Inc.
West Point, PA 19486 (USA)
E-mail: thomas_greshock@merck.com
M. Ellwart, S. M. Manolikakes, Prof. Dr. P. Knochel
Ludwig-Maximilians-Universität München, Department Chemie
Butenandtstrasse 5–13, Haus F, 81377 München (Germany)
E-mail: paul.knochel@cup.uni-muenchen.de

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201604652.

ligands and reaction conditions. This initial screening led to the identification of four high-performing catalyst systems: PEPPSI-IPr,[14] XPhos Pd G3,[15] QPhos Pd G3,[16] and NiXantPhos Pd G3.[17]



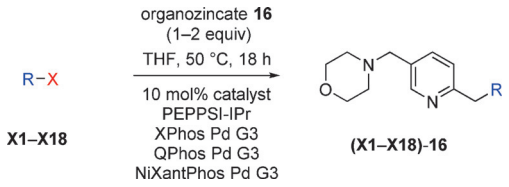
The densely functionalized bromopyridine **X3** (Scheme 1) was then treated with organozinc pivalates **1**–**17** and the four high-performing catalysts from the first screen in THF at 50 °C



Scheme 1. Screening of the 17 organozinc pivalates against aryl bromide **X3** and four precatalysts.

for 18 h to yield products **X3-(1–17)**.[18] Good to excellent reactivities were observed for all four catalysts, and XPhos Pd G3 and NiXantPhos Pd G3 showed the strongest performance across all zincates. For this evaluation, the total product area percentage in the ultra-performance liquid chromatography (UPLC) trace was used as a crude measure of reaction efficiency to provide information on conditions suitable for scaleup in parallel mode (data not shown).[19] More accurate screening yields (Figure 2B) were later determined by using product standards from larger-scale reactions (see below). These initial microscale experiments provided a solid platform for scaleup in parallel and confidence in the reactivity of organozinc pivalates with complex aryl halide substrates.

To complement the screening of multiple zinc pivalates against a single aryl halide, we next turned our attention to reactions of a single zincate with a chemistry informer library[20] of 18 complex aryl halides (Figure 2A, Scheme 2). The informer library is a set of complex molecules that was designed to best capture the broad array of chemical functionality encompassed in "druglike" space, and to help evaluate the performance of chemistry across aryl halides; it has previously been bench-marked against the Pd, Cu, and Ni C–N coupling-reaction literature.[20] RZnOPiv **16**, which was shown to have excellent reactivity in prescreening, was evaluated against the informer library in reactions carried



Scheme 2. C(sp^3)–C(sp^2) coupling reactions of the organozinc pivalate **16** with the R–X informer plate.

out with the four preferred catalysts in THF at 50 °C for 18 h (Scheme 2). This evaluation, based on total product area (data not shown), revealed conclusively that XPhos Pd G3 was superior to the other three catalyst systems for high-complexity substrates.

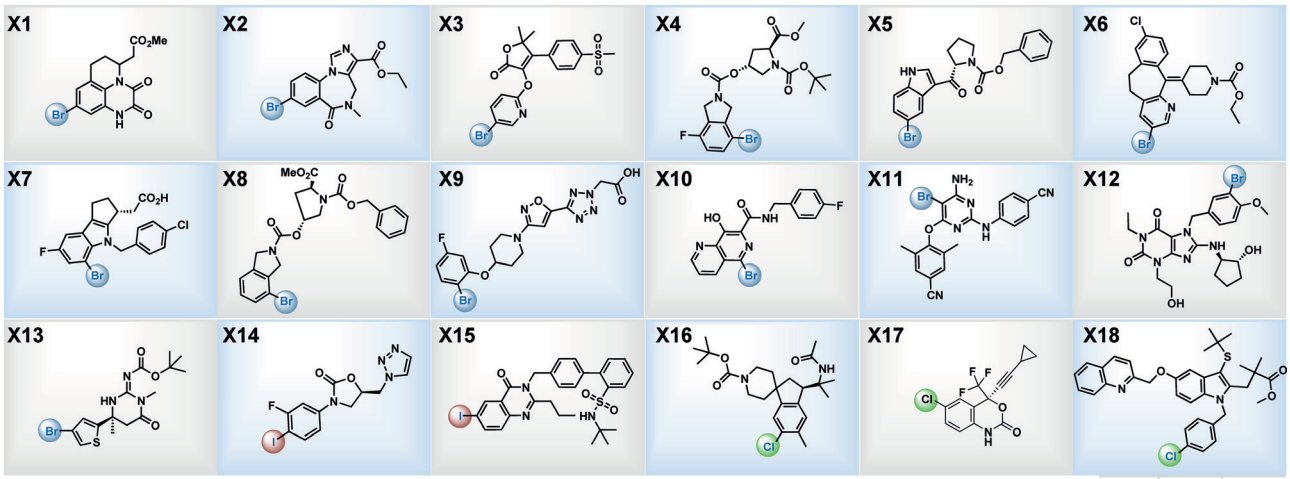
We next turned to the parallel scaleup and MS-directed high-throughput purification (HTP) of compounds **X3-(1–17)** and **(X1-X18)-16**. For the sake of experimental simplicity, parallel chemistry is preferably performed with a single set of reaction conditions if possible, but a more customized approach with specific catalyst systems for each substrate on the basis of screening data can be used.[21] In this case, we chose the former approach, and subjected bromopyridine **X3** to the best overall set of conditions identified in our screening experiments; thus, we treated **X3** with 3 equivalents of each organozinc pivalate and XPhos Pd G3 (10 mol%) in THF at 50 °C for 18 h (Table 1). Overall, there was good correlation between the early screening results and the yields observed for the isolated products. The success rate, as defined by the isolation of 1–2 mg of pure product, which typically supports Tier 1 assays[22] for many drug-discovery programs, was also

Table 1: Library scaleup and high-throughput purification of organozincates **1**–**17** with informer **X3** and organozincate **16** with informers **X1**–**X18**.

Product	Isolated mass [mg]/ yield [%][a]	Product	Isolated mass [mg]/ yield [%][a]
X3-1	18/ 6	**X1-16**	0/0
X3-2	0/0	**X2-16**	12/18
X3-3	5/9	**X3-16**	21/33
X3-4	16/30	**X4-16**	24/39
X3-5	42/71	**X5-16**	2/2
X3-6	9/17	**X6-16**	7/12
X3-7	22/43	**X7-16**	0/0
X3-8	20/40	**X8-16**	29/48
X3-9	22/37	**X9-16**	2/3
X3-10	7/13	**X10-16**	0/0
X3-11	39/62[b]	**X11-16**	0/0
X3-12	2/4	**X12-16**	1/2
X3-13	13/23	**X13-16**	0/0
X3-14	7/12[c]	**X14-16**	21/36
X3-15	15/27[c]	**X15-16**	8/14
X3-16	21/33	**X16-16**	29/43
X3-17	40/67	**X17-16**	16/22
		X18-16	39/63

[a] Reaction conditions: XPhos Pd G3 (10 mol%), THF, 50 °C, 18 h. [b] Reaction conditions: PEPPSI-IPr (10 mol%), THF, 50 °C, 18 h. No product was isolated when the standard conditions with XPhos Pd G3 were used. [c] Reaction conditions: Qphos Pd G3 (10 mol%), THF, 50 °C, 18 h. No product was isolated when the standard conditions with XPhos Pd G3 were used.

A



B

informer X3		Zincate																			
Entry	Conditions (Scheme 1)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Avg. Yield	# Yields >20%	# Yields >10%
1	PEPPSI - iPr, THF 50 °C, 18 h	81	0	49	67	100	76	39	70	29	33	83	0	10	0	7	6	1.4	38	10	10
2	XPhos Pd G3, THF 50 °C, 18 h	66	0	26	75	92	24	46	41	32	16	4.7	0	4	0	29	40	92	34	11	12
3	QPhos Pd G3, THF 50 °C, 18 h	49	0	47	80	97	46	18	57	32	21	33	0	17	43	49	18	52	39	13	15
4	NiXantPhos Pd G3, THF 50 °C, 18 h	45	0	59	84	100	54	14	40	27	11	62	0	13	12	0	12	95	37	9	14

C

Zincate 16		ArBr													ArI		ArCl				
Entry	Conditions (Scheme 2)	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11	X12	X13	X14	X15	X16	X17	X18	Avg. Yield	# Yields >20%	# Yields >10%
1	PEPPSI - iPr, THF 50 °C, 18 h	0	0	6	15	0	8	0	0	3	0	0	0	0	6	0	0	0	23	3	1	2
2	XPhos Pd G3, THF 50 °C, 18 h	0	46	40	59	13	60	0	0	42	0	0	13	0	47	36	100	14	100	32	9	12
3	QPhos Pd G3, THF 50 °C, 18 h	0	19	18	25	3	23	0	0	23	0	0	9	0	5	9	3	1	17	9	3	6
4	NiXantPhos Pd G3, THF 50 °C, 18 h	0	19	12	11	0	31	0	0	0	0	0	0	0	10	3	1	0	12	5	1	5

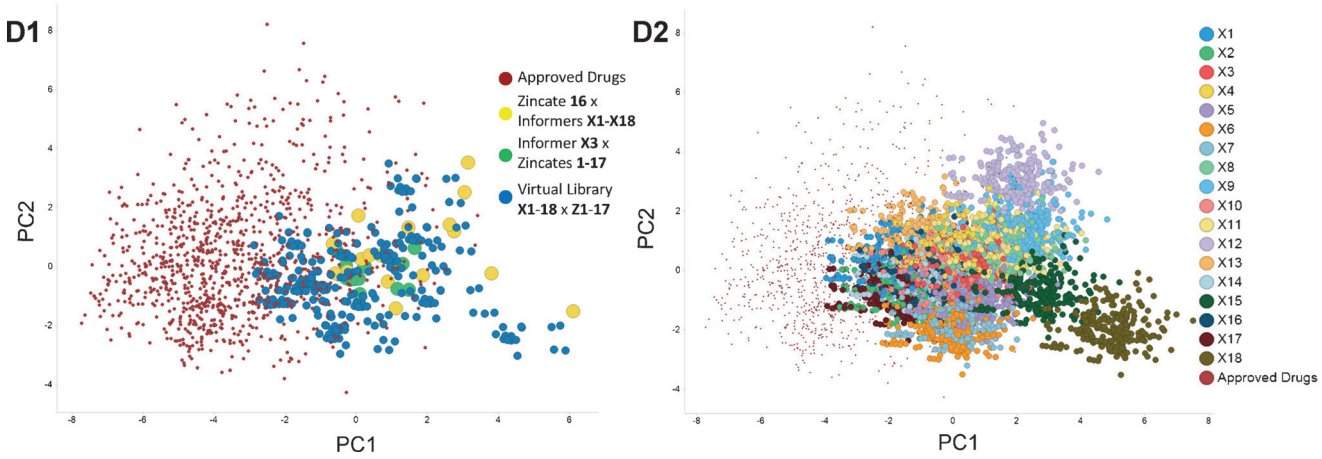


Figure 2. A) Informer plate of 18 polyfunctional "druglike" electrophiles. B) Microscreening results for informer **X3** with 17 zincates (**1**–**17**) across four precatalysts. For experimental details, see the Supporting Information. C) Microscreening results for zincate **16** with 18 informers (**X1**–**X18**) across four precatalysts. For experimental details, see the Supporting Information. D1) Products formed from Negishi coupling reactions of zincate **16** with informers **X1**–**X18** (yellow), informer **X3** with zincates **1**–**17** (green), and a virtual library of the remaining combinations in the grid **X1**–**X18** by **1**–**17** (blue) mapped onto the principal component analysis of marketed drugs (red). D2) Products formed from Negishi coupling reactions of 405 virtual zincates with informers **X1**–**X18** mapped onto the principal component analysis of marketed drugs.

impressive (94%, 16/17). Organozinc pivalates **5** and **17**, which showed high conversion in screening (data not shown), were isolated in 71 and 67% yield, respectively, after high-throughput purification. As predicted by screening, zincate **11** demonstrated low conversion to the product during scaleup when subjected to these conditions with XPhos Pd G3. Since higher conversion was observed with PEPPSI-IPr in the screening mode, zincate **11** was tested on scale under the alternative conditions with PEPPSI-IPr, and the desired product was isolated in 62% yield. Similarly, QPhos Pd G3 was used to give pure samples in reactions of **X3** with zincates **14** and **15**. These results show the accuracy of the screening

data and also point to the value of applying a customized set of conditions for each building block that did not react successfully under the general set of conditions to improve overall success in a library.[21]

We next moved to the library scaleup and high-throughput purification of a single zinc reagent with the complex-molecule informer library (Figure 2A). Zinc reagent **16** (3 equiv) was treated with each aryl halide and XPhos Pd G3 (10 mol%) in THF at 50°C for 18 h. The screening data (not shown) once again correlated well with the yields observed in the library synthesis (Table 1). The yields for many reactions are not particularly high, but lower yields are not unusual or critical for parallel chemistry and HTP workflows, since yield has limited impact in early drug-discovery space. Within these limitations, the overall success rate was again very satisfying (72%, 13/18).

The isolation of pure products during the parallel scaleup efforts enabled the calculation of assay yields from the original microscreen conversion data (Figure 2B,C). In our second screen (Scheme 2), we found that 9/18 informer substrates exhibited good reactivity (>20% assay yield) in the presence of the XPhos Pd G3 catalyst system, with another three compounds giving useful conversion into desired product (>10% yield). This result compares favorably with the best Pd C–N reactions from our initial benchmarking study with this same informer compound set,[20] and is similar to those observed under the best copper-catalysis conditions we identified in that study, thus giving us confidence that the coupling of zincates with the XPhos Pd G3 protocol is a valid synthetic approach. When the less complex substrate 3-bromo-5-phenylpyridine (initial screen) was used, or only aryl halide **X3** (Scheme 1), there appeared to be no discernable difference among catalysts (Figure 2B). This study very clearly underlines the problem of using simple model substrates to demonstrate the utility of a chemical transformation and highlights the value of the chemistry informer library approach (Scheme 2, Figure 2A), in which only the use of application-relevant complexity can reveal the true value of a synthetic method.

A fully developed chemistry informer library approach to synthetic-reaction appraisal, along with cheminformatic methods, also enables a holistic understanding of chemical-space coverage. To demonstrate how the compounds we prepared fit within druglike chemical space, we performed principal component analysis (PCA)[20a] on various sets of products derived from zincates and members of the highly complex informer library (Figure 2D). This analysis enables powerful visualization of the important aggregate physicochemical properties, such as AlogP and the number of H-bond donors/acceptors of informer–zincate-derived products, relative to actual drug structures. As expected, the yellow dots cover a wider space (driven by the high structural diversity of the larger informers), whereas the green dots offer a higher level of granularity within a defined subspace (defined by the informer **X3**), thus demonstrating that zincates **1**–**17**, although smaller, do provide chemical-space-coverage enrichment. This discrepancy reflects a drug-discovery setting, in which different cores (informers) allow for diverse chemical-subspace access, and final optimization is performed with multiple reagents of the same type (zincates). The evaluation of all remaining virtual products **[1–17]*[X1–X18]** (blue) from the current set clearly illustrates the combined value of informers and zincates, thus providing yet further chemical-space-coverage enhancement. To expand our analysis, we carefully selected a virtual library of 405 organozincates that could be derived from commercially available halides.[23] Figure 2D2 illustrates the products of such zincates with informers **X1**–**X18**, along with the added level of granularity obtained by expanding the zincate set from 17 to 405 members.

In conclusion, we have shown that functionalized solid aryl, heteroaryl, and benzylzinc pivalates are excellent reagents for Negishi coupling reactions relevant to highly complex molecules typically found in drug discovery. Our results serve to extend the scope of the use of organozinc pivalates beyond traditional methodology studies by providing insight into the performance (positive or negative) of these reagents in previously unprecedented, challenging cross-coupling reactions. Good correlation of screening conversion with scaleup yield was observed, thus resulting in a high success rate for isolation of the 1–2 mg quantity of product typically required for analyzing on- and off-target activity in vitro (94%, 16/17 and 72%, 13/18; Table 1). Principal component analysis demonstrated that the molecules synthesized are highly relevant to the desirable druglike physicochemical property space. This powerful performance should provide medicinal chemists with a high degree of confidence to apply these new, solid organozinc pivalates in their drug-discovery campaigns. Efforts to employ cheminformatic and screening methodologies to drive the design, preparation, and deployment of additional novel organozinc pivalate reagents are ongoing.

Keywords: druglike molecules · high-throughput screening · late-stage functionalization · medicinal chemistry · organozinc reagents

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 13714–13718
Angew. Chem. **2016**, *128*, 13918–13922

[1] a) H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7222; b) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369; c) D. A. DiRocco, K. Dykstra, S. Krska, P. Vachal, D. V. Conway, M. Tudge, *Angew. Chem. Int. Ed.* **2014**, *53*, 4802; *Angew. Chem.* **2014**, *126*, 4902; d) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546.

[2] a) P. A. Wender, M. K. Hilinski, A. V. W. Mayweg, *Org. Lett.* **2005**, *7*, 79; b) M. G. Campbell, T. Ritter, *Org. Process Res. Dev.* **2014**, *18*, 474.

[3] *Metal-Catalyzed Cross-Coupling Reactions*, *Vol. 2* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.

[4] a) S. J. Lee, K. C. Gray, J. S. Paek, M. D. Burke, *J. Am. Chem. Soc.* **2008**, *130*, 466; b) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961; c) H. Noguchi, K. Hojo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 758.

[5] a) N. Miyaura, K. Yamada, H. Suginome, A. Suzuki, *J. Am. Chem. Soc.* **1985**, *107*, 972; b) A. Suzuki, *Pure Appl. Chem.* **1985**, *57*, 1749; c) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

[6] a) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302; b) G. A. Molander, B. Canturk, *Angew. Chem. Int. Ed.* **2009**, *48*, 9240; *Angew. Chem.* **2009**, *121*, 9404.

[7] a) N. Kudo, M. Perseghini, G. C. Fu, *Angew. Chem. Int. Ed.* **2006**, *45*, 1282; *Angew. Chem.* **2006**, *118*, 1304; b) A. J. J. Lennox, G. C. Lloyd-Jones, *Isr. J. Chem.* **2010**, *50*, 664.

[8] a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117; b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) E. Erdik, *Tetrahedron* **1992**, *48*, 9577; d) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker in *Organic Reactions*, Wiley, New York, **2001**, p. 417.

[9] a) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; b) C. K. Reddy, A. Devasagayaraj, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 4495; c) S. Berger, F. Langer, C. Lutz, P. Knochel, T. A. Mobley, C. K. Reddy, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1496; *Angew. Chem.* **1997**, *109*, 1603; d) A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221; e) C. Kofink, P. Knochel, *Org. Lett.* **2006**, *8*, 4121.

[10] A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665; *Angew. Chem.* **2010**, *122*, 4769.

[11] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205; *Angew. Chem.* **2011**, *123*, 9372; b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9428; *Angew. Chem.* **2012**, *124*, 9563; c) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754; d) C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302; e) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289.

[12] Although abbreviated as RZnOPiv for clarity, these zinc reagents contain Mg and Li salts (responsible for their enhanced stability). NMR and crystallographic experiments showed that a more accurate description of these zinc reagents is RZnX·Mg(OPiv)$_2$·LiCl: A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg, *Angew. Chem. Int. Ed.* **2014**, *53*, 2706; *Angew. Chem.* **2014**, *126*, 2744.

[13] See the Supporting Information.

[14] C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743.

[15] N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* **2013**, *4*, 916.

[16] N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553.

[17] J. Zhang, A. Bellomo, N. Trongsiriwat, T. Jia, P. J. Carroll, S. D. Dreher, M. T. Tudge, H. Yin, J. R. Robinson, E. J. Schelter, P. J. Walsh, *J. Am. Chem. Soc.* **2014**, *136*, 6276.

[18] For ease of setup in the screening mode, the organozinc reagent was added in portions of 4 mass equivalents relative to the substrate. In most cases, this amount translates to just 1–2 equivalents of the zinc compound.

[19] Although percentage product area is not a true depiction of yield, it is a good approximation of reaction efficiency and a consistent way of comparing screening data across various substrates and conditions.

[20] a) P. S. Kutchukian, J. F. Dropinski, K. D. Dykstra, B. Li, D. A. DiRocco, E. C. Streckfuss, L.-C. Campeau, T. Cernak, P. Vachal, I. W. Davies, S. W. Krsksa, S. D. Dreher, *Chem. Sci.* **2016**, *7*, 2604; b) E. B. Corcoran, M. T. Pirnot, S. Lin, S. D. Dreher, D. A. DiRocco, I. W. Davies, S. L. Buchwald, D. W. C. MacMillan, *Science* **2016**, *353*, 279.

[21] A. Buitrago Santanilla, E. L. Regalado, T. Pereira, M. Shevlin, K. Bateman, L.-C. Campeau, J. Schneeweis, S. Berritt, Z.-C. Shi, P. G. Nantermet, Y. Liu, R. Helmy, C. J. Welch, P. Vachal, I. W. Davies, T. Cernak, S. D. Dreher, *Science* **2015**, *347*, 49.

[22] Tier 1 assays usually include some or all of the following in vitro assays: target engagement/functional assay (enzymatic, receptor-binding, channel-gating, etc.), microsome/hepatocyte stability, permeability, solubility, transporter susceptibility, plasma protein binding, CYP inhibition, and relevant off-target counter-screening. A quantity of 200–400 μL of a 10 mM solution of 1–2 mg of the pure product in dimethyl sulfoxide typically enables all Tier 1 assays, which generally require less than 10 μL of solution each.

[23] A total of 405 structurally diverse virtual zincates were chosen from 10000 commercially available aryl and heteroaryl bromides. Clustering by structural and physicochemical properties by the use of Pipeline Pilot v2017 of Biovia (http://accelrys.com/products/collaborative-science/biovia-pipeline-pilot/), followed by crowdsourcing selection with the opensource informatics tool *DataWarrior* (DOI: 10.1021/ci500588j), allowed for maximal diversity selection of drug-discovery-relevant building blocks.

Received: May 12, 2016
Revised: August 15, 2016
Published online: September 30, 2016

