

Cite this: *Chem. Sci.*, 2018, **9**, 5191Received 1st April 2018  
Accepted 12th May 2018DOI: 10.1039/c8sc01486h  
[rsc.li/chemical-science](http://rsc.li/chemical-science)

## Introduction

$\alpha$ -Aminoboronic acids are currently of great interest for modern pharmaceutical development and several such

compounds including bortezomib and ixazomib have recently been approved as new small molecule drugs. These structures are prized for their ability to inhibit the proteasome and various serine proteases, making them particularly attractive as potential anticancer, antibacterial or antiviral drugs.<sup>1</sup> Known synthetic approaches include addition of nitrogen substituted carbon to electrophilic boron,<sup>2</sup> addition of nucleophilic boron to activated imines,<sup>3</sup>  $S_N2$  like displacements of amines to halomethyl boronic acid derivatives,<sup>4</sup> decarboxylative deborylations<sup>5</sup> or hydroaminations of

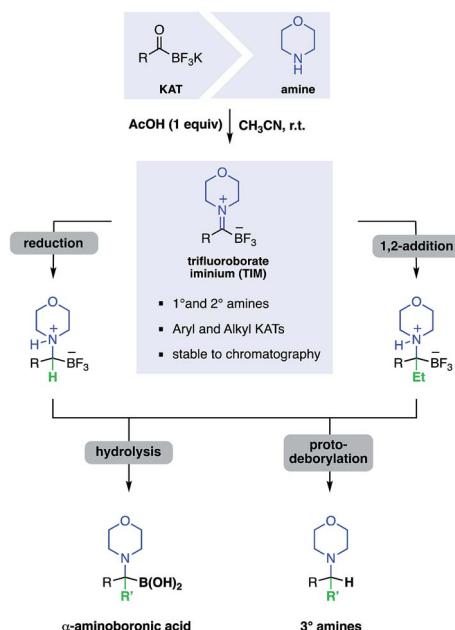


Fig. 1 Overview of the chemistry of TIMs including formation from KATs and transformation to  $\alpha$ -aminotri fluoroborates and  $\alpha$ -aminoboronic acids.

Table 1 Conditions for the formation of TIMs

Entry	Amine	Acid	Conditions	Conversion
1	2.0 M in THF	None	$CH_3CN$ (0.2 M), 8 h	<5% <sup>a</sup>
2	HCl salt	None	$CH_3CN$ (0.2 M), 1 h	94% <sup>b</sup>
3	2.0 M in THF	AcOH	$CH_3CN$ (0.2 M), 15 min	93% <sup>b</sup>
4	2.0 M in THF	$CF_3CO_2H$	$CH_3CN$ (0.2 M), 15 min	90% <sup>b</sup>
5	2.0 M in THF	AcOH	DMF (0.2 M), 1 h	100% <sup>a</sup>
6	2.0 M in THF	AcOH	$CH_3CN$ (0.02 M), 5 h	98% <sup>a</sup>
7	2.0 M in THF	AcOH	$CH_3CN$ (0.002 M), 8 h	97% <sup>a</sup>

<sup>a</sup> Product detected by LC-MS and TLC and conversion determined by LC-MS. <sup>b</sup> Isolated yields.

*Laboratorium für Organische Chemie, Department of Chemistry and Applied Biosciences, ETH Zurich, Zürich, Switzerland 8093. E-mail: bode@org.chem.ethz.ch; Web: <http://www.bode.ethz.ch>*

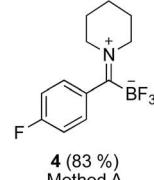
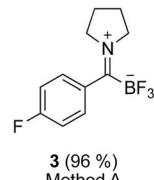
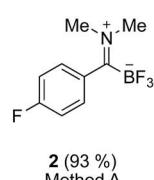
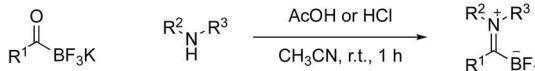
† Electronic supplementary information (ESI) available: Procedures, characterisation data, and spectra. CCDC 1833580–1833584. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8sc01486h

‡ T. S. and A. S. contributed equally to this work.

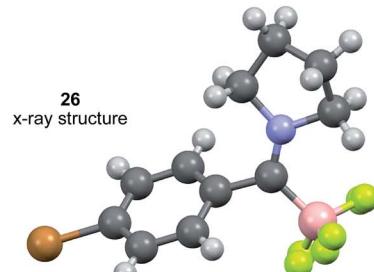
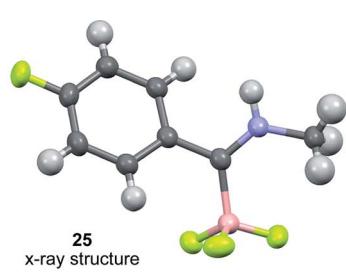
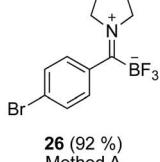
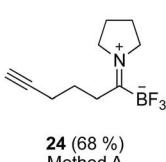
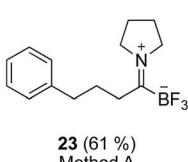
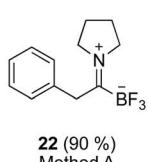
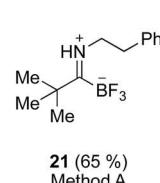
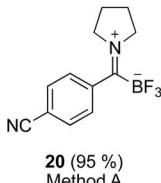
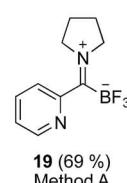
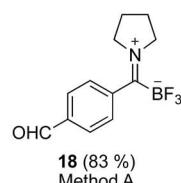
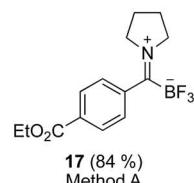
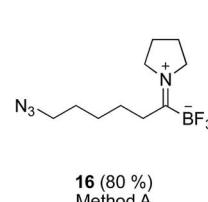
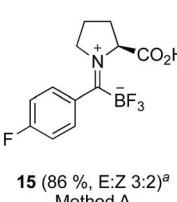
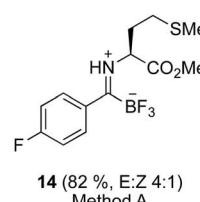
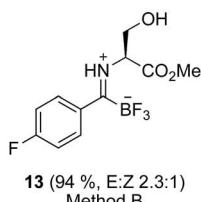
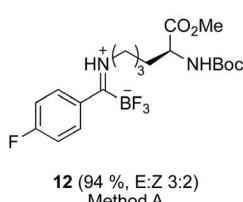
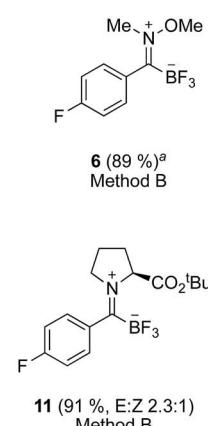
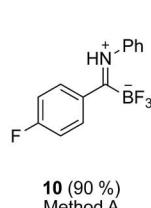
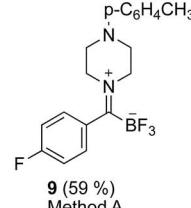
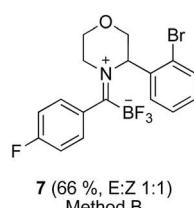
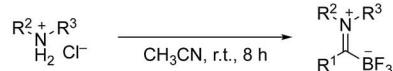
vinylboronic acid derivatives<sup>6</sup> but to date there are few methods suitable for the preparation of molecules derived from tertiary amines and bearing a fully substituted boron containing carbon.

In this report, we document the facile formation of stable trifluoroborate-iminiums (TIMs) from KATs and primary or secondary amines and their use for the synthesis of secondary and tertiary  $\alpha$ -aminoboronic acids. A few structures similar to

## Method A:



## Method B:



Scheme 1 Substrate scope for the formation of TIMs from KATs and amines. <sup>a</sup>DMF used instead of CH<sub>3</sub>CN.



TIMs have been reported previously, but little is known about their chemistry and properties.<sup>7</sup> Yudin and co-workers observed the formation of imines from MIDA acyl boronates and amines, however they were only able to isolate the reduction products, not the iminium ions.<sup>8</sup> In contrast, we have found that TIMs are air, moisture, and chromatographically stable and are easily formed under simple conditions in high yield. They serve as convenient intermediates for the synthesis of  $\alpha$ -amino-trifluoroborates – which can be readily hydrolyzed to the boronic acids – by reduction or nucleophilic addition. This route offers a simple, broadly applicable route to  $\alpha$ -amino-boronic acids, particularly those that would be difficult to access by established approaches (Fig. 1).

## Results and discussion

Experience from our group on amide-forming reactions of KATs with hydroxylamines or N-Cl amines established that KATs show little or no intrinsic reactivity with simple amines under aqueous conditions. For instance, our recent report on protein PEGylation using PEG-KAT reagents was conducted in glycine buffer and we have recently disclosed that amide formation from KATs and amines in the presence of a chlorinating agent does not proceed *via* an iminium intermediate.<sup>9</sup> We reasoned, however, that iminium formation could occur under non-aqueous conditions (Table 1). Although KATs are generally insoluble in most organic solvents, sparing solubility is observed in acetone, DMF, acetonitrile, DMSO and other polar, aprotic solvents. Simply mixing KATs and amines did not lead to substantial iminium formation, however the addition of acid – presumably to form a salt with the liberated potassium ion – led to clean formation of the highly soluble TIMs and the corresponding inorganic salt (entry 2). Based on these observations, we found that zwitterion formation occurs cleanly under a variety of conditions and with numerous acidic additives, including HCl, AcOH, and CF<sub>3</sub>CO<sub>2</sub>H. Conveniently, the amine hydrochloride salts can also be employed directly in the reaction.

The TIMs can be formed from both secondary and primary amines, in which case they are isolated as a chromatographically stable, protonated imine zwitterion (Scheme 1). TIMs are typically white solids stable to air, moisture and standard aqueous workup. They are readily formed chemoselectively in the presence of nearly all common functional groups, including carboxylic acids, esters, nitriles, and aldehydes.

Unlike iminium ions derived from aldehydes or ketones, TIMs show no tendency to form enamines and are kinetically inert under aqueous conditions. Studies on exchange reactions with exogenous amines are currently in progress, but in preliminary studies this does not appear to be a major pathway. Intrigued by their unexpectedly high chemical inertness, we performed numerous tests on their stability, as summarized in Table 2. At no point did we observe protodeborylation products. The only products identified from their decomposition were the starting amine and KAT. Under more basic conditions (pH 8.0–9.0), the TIMs eventually broke down to the constituent KATs and amines.

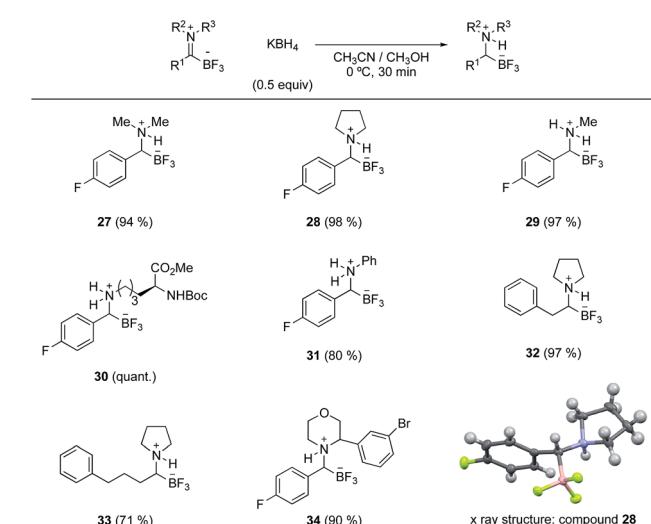
Table 2 Stability tests for TIMs toward different reagents and in buffers at different pHs

Entry	Conditions	Conversion <sup>a</sup>		
		2 h	16 h	24 h
1	Et <sub>3</sub> N (5.00 equiv.)			0%
2	Piperidine (20.0 equiv.)			0%
3	CF <sub>3</sub> CO <sub>2</sub> H (0.1 mL) <sup>b</sup>			0%
4	aq. HCl (0.1 M, pH 1.2)			0%
5	aq. citric acid (0.1 M, pH 2.0)			0%
6	aq. citric acid/K <sub>2</sub> HPO <sub>4</sub> buffer (0.1 M, pH 3.0)	0%	2%	
7	aq. citric acid/K <sub>2</sub> HPO <sub>4</sub> buffer (0.1 M, pH 5.0)	2%	5%	
8	aq. KH <sub>2</sub> PO <sub>4</sub> /K <sub>2</sub> HPO <sub>4</sub> buffer (0.1 M, pH 7.0)	4%	14%	19%

<sup>a</sup> Conversion determined using LC-MS. <sup>b</sup> CH<sub>2</sub>Cl<sub>2</sub> used as solvent instead of CH<sub>3</sub>CN. Solvolysis of the BF<sub>3</sub> group was never observed under aqueous conditions.

Based on the known chemistry of iminiums as excellent electrophiles in polar addition reactions, we anticipated that TIMs would undergo nucleophilic addition. The formation of stable zwitterionic iminiums offers an opportunity to conduct bond forming reactions on species that would otherwise be difficult to form or prone to enamine formation. We were pleased to find that TIMs, including those derived from secondary amines, underwent clean reduction to give mono-substituted  $\alpha$ -amino-trifluoroborates in the presence of KBH<sub>4</sub> (Scheme 2).

A great challenge is nucleophilic addition of carbon nucleophiles to iminiums. A few examples of the addition of organometallic compounds to iminiums are known, but these appear to be limited to aldehyde derived or non-enolizable iminiums.<sup>10</sup>



Scheme 2 Substrate scope for the reduction of TIMs yielding monosubstituted  $\alpha$ -amino-trifluoroborates.

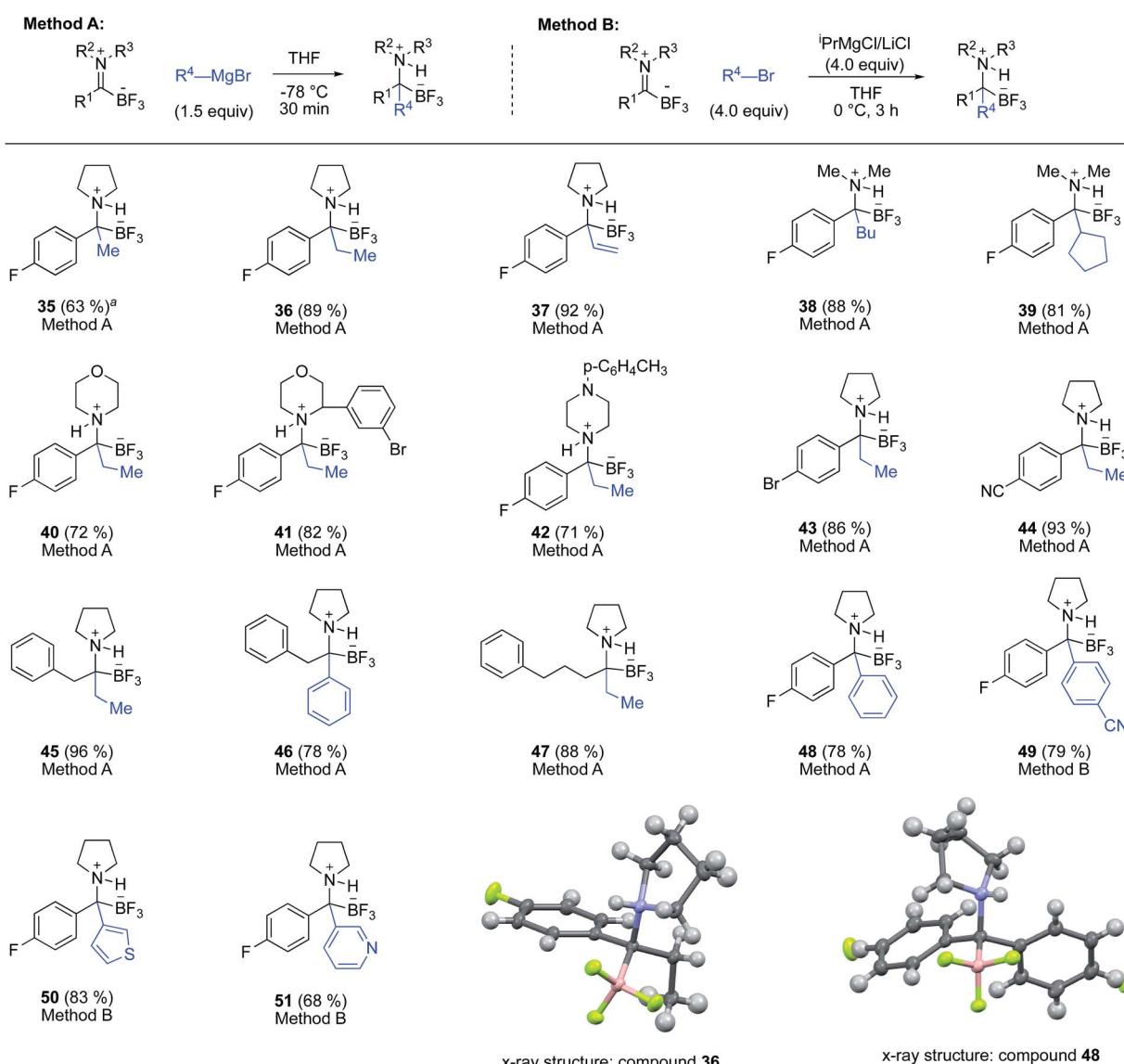


We sought to employ the remarkable stability of the TIMs to access the fully substituted  $\alpha$ -aminotri fluoroborates, including those containing cyclic tertiary amines. Therefore, we established conditions for the addition of Grignard reagents to TIMs derived from secondary amines. These couplings proceeded well for a broad scope of TIMs and Grignard reagents and the resulting fully substituted  $\alpha$ -aminotri fluoroborates were isolated in high yields. Linear alkyl, vinyl and even sterically more demanding branched alkyl and aryl Grignards added smoothly to both aromatic and aliphatic TIMs. At no point did we observe diminished yields due to enamine formation. For the addition of substituted aromatic and heteroaromatic Grignard reagents, Knochel's Turbo-Grignard chemistry<sup>11</sup> was successfully employed (Scheme 3).

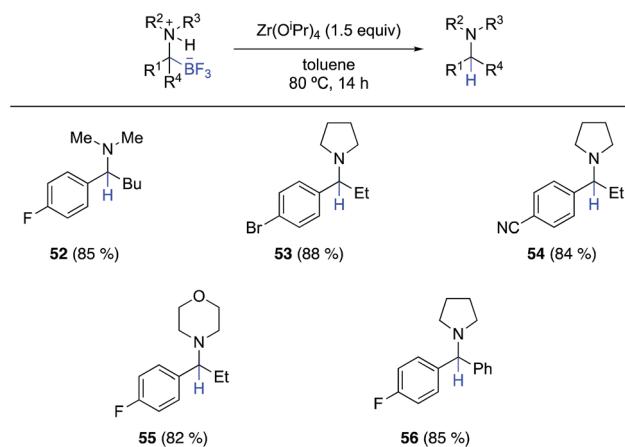
The  $\alpha$ -aminotri fluoroborates are themselves interesting compounds, isolated as internal salts. A few simpler variants have been prepared and shown to undergo cross-coupling reactions under palladium or photoredox catalysis. Molander

demonstrated that aminomethyltrifluoroborates can be coupled to various aryl- and hetaryl halides or mesylates under Suzuki–Miyaura conditions.<sup>12</sup> Different amino acid derived Boc-aminomethyltrifluoroborates were coupled to aryl bromides under photoredox conditions by the same group.<sup>13</sup> Suginome was able to cross-couple chiral  $\alpha$ -(acylamino)benzylboronic esters to aryl bromides with inversion of configuration.<sup>14</sup> Unfortunately, all attempts to subject these more substituted substrates to cross coupling conditions were unsuccessful, possibly due to the increased steric demands of the substrates in comparison to the successful examples studied by Molander and Suginome.

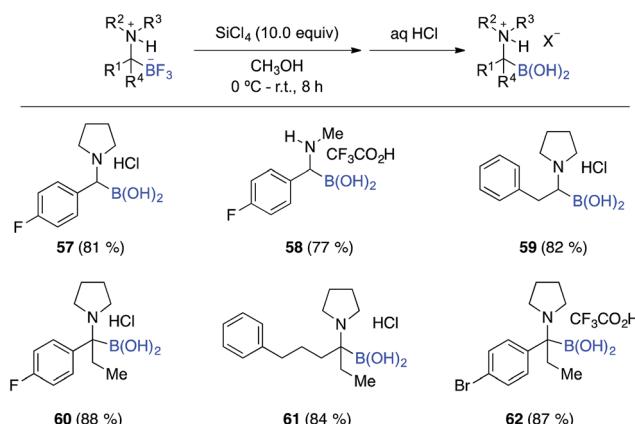
In the course of these cross coupling studies, we identified conditions for clean protodeborylation of some substrates. The best results were obtained with  $Zr(O^iPr)_4$  in toluene (Scheme 4). Unfortunately, these conditions were not successful with all substrates, particularly those lacking an  $\alpha$ -aryl substituent on the  $\alpha$ -aminotri fluoroborate. Further investigations on the



Scheme 3 Substrate scope for the addition of Grignard reagents to TIMs yielding fully substituted  $\alpha$ -aminotri fluoroborates.



Scheme 4 Substrate scope for the protodeborylation of fully substituted  $\alpha$ -aminotri fluoroborates using  $Zr(O'Pr)_4$ .



Scheme 5 Substrate scope for the formation of  $\alpha$ -aminoboronic acids from  $\alpha$ -aminotri fluoroborates using  $SiCl_4$ . Compound 58 and 62 were isolated as TFA salts after purification by preparative HPLC.

mechanism of this unexpected reaction and the origin of the limitations are in progress, as are continued efforts to effect cross coupling of the  $\alpha$ -aminotri fluoroborates.

The ultimate goal of this research was the formation of  $\alpha$ -aminoboronic acids, as these compounds have emerged as important structures in drug design and lack good, convergent approaches for their synthesis. Several conditions for the formation of boronic acids are known in literature, however these conditions did not yield the desired boronic acids for our substrates.<sup>15</sup>  $SiCl_4$  is known for defluorination of organotri fluoroborates,<sup>16</sup> and we identified  $SiCl_4$  in  $CH_3OH$  as the optimal conditions for the conversion of the  $\alpha$ -aminotri fluoroborates to the boronic acids. The boronic acid products are isolated as their HCl salts after treatment with aqueous HCl (Scheme 5).

## Conclusions

In summary, we established the facile synthesis of TIMs from amines and KATs, which were found to be stable zwitterionic

compounds with properties and stabilities suitable for further development. TIMs can be easily reduced with hydride reagents or participate in C–C bond forming reactions with Grignard reagents to give  $\alpha$ -aminotri fluoroborates. The  $\alpha$ -aminotri fluoroborates can be hydrolyzed to  $\alpha$ -aminoboronic acids. Along with the increasing synthetic and commercial availability of KATs, this chemistry enables the synthesis of fully substituted  $\alpha$ -aminoboronic acids, that are difficult to access with methods known to date.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support was provided by the European Research Council (ERC Starting Grant 306793 – CASAA). Support for T. S. was generously provided by Sumitomo Dainippon. We thank the LOC Mass Spectrometry Service, the LOC NMR Service, and the SmOCC crystallography service for analyses. We want to thank Sizhou M. Liu (ETH Zürich) for preparation of some aliphatic KAT starting materials, Adelaïde Savoy (ETH Zürich) for help with the “Turbo-Grignard” reaction, Alberto Osuna Gálvez (ETH Zürich), and Dino Wu (ETH Zürich) for helpful discussions.

## Notes and references

- (a) P. C. Trippier and C. McGuigan, *Med. Chem. Commun.*, 2010, **1**, 183; (b) R. Smoum, A. Rubinstein, V. M. Dembitsky and M. Srebnik, *Chem. Rev.*, 2012, **112**, 4156; (c) J. Hiratake and J. Oda, *Biosci., Biotechnol., Biochem.*, 1997, **61**, 211; (d) C. Kettner, L. Mersinger and R. Knabb, *J. Biol. Chem.*, 1990, **265**, 18289; (e) N. C. J. Strynadka, R. Martin, S. E. Jensen, M. Gold and J. B. Jones, *Nat. Struct. Biol.*, 1996, **3**, 688; (f) R. M. Dunsdon, J. R. Greening, P. S. Jones, S. Jordan and F. X. Wilson, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1577; (g) B. A. Teicher, G. Ara, R. Herbst, V. J. Palombella and J. Adams, *Clin. Cancer Res.*, 1999, **5**, 2638.
- E. S. Priestley and C. P. Decicco, *Org. Lett.*, 2000, **2**, 3095.
- (a) M. A. Beenen, C. An and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 6910; (b) A. W. Buesking, V. Bacauanu, I. Cai and J. A. Ellman, *J. Org. Chem.*, 2014, **79**, 3671; (c) C. Solé, H. Gulyás and E. Fernández, *Chem. Commun.*, 2012, **48**, 3769; (d) K. Hong and J. P. Morken, *J. Am. Chem. Soc.*, 2013, **135**, 9252; (e) D. Wang, P. Cao, B. Wang, T. Jia, Y. Lou, M. Wang and J. Liao, *Org. Lett.*, 2015, **17**, 2420.
- (a) D. S. Matteson and T. C. Cheng, *J. Org. Chem.*, 1968, **33**, 3055; (b) D. S. Matteson, K. M. Sadhu and G. E. Lienhard, *J. Am. Chem. Soc.*, 1981, **103**, 5241; (c) D. S. Matteson and K. M. Sadhu, *Organometallics*, 1984, **3**, 614; (d) V. Martichonok and J. B. Jones, *J. Am. Chem. Soc.*, 1996, **118**, 950; (e) M. B. Kostova, D. M. Rosen, Y. Chen, R. C. Mease and S. R. Denmeade, *J. Med. Chem.*, 2013, **56**, 4224; (f) G. A. Molander and J. Ham, *Org. Lett.*, 2006, **8**,



2031; (g) S. Adachi, A. B. Cognetta III, M. J. Niphakis, Z. He, A. Zajdlik, J. D. St. Denis, C. C. G. Scully, B. F. Cravatt and A. K. Yudin, *Chem. Commun.*, 2015, **51**, 3608.

5 (a) C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan and P. S. Baran, *Science*, 2017, **356**, 1045; (b) D. Hu, L. Wang and P. Li, *Org. Lett.*, 2017, **19**, 2770; (c) A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers and V. K. Aggarwal, *Science*, 2017, **357**, 283.

6 D. Nishikawa, K. Hirano and M. Miura, *J. Am. Chem. Soc.*, 2015, **137**, 15620.

7 (a) A. M. Dumas and J. W. Bode, *Org. Lett.*, 2012, **14**, 2138; (b) T. Wang, L. Liu, S. Grimme, C. G. Daniliuc, G. Kehr and G. Erker, *Chem.-Asian J.*, 2016, **11**, 1394; (c) D. J. Brauer, H. Bürger, S. Buchheim-Spiegel and G. Pawelke, *Eur. J. Inorg. Chem.*, 1999, 255.

8 D. B. Diaz, C. C. G. Scully, S. K. Liew, S. Adachi, P. Trinchera, J. D. St. Denis and A. K. Yudin, *Angew. Chem., Int. Ed.*, 2016, **55**, 12659.

9 (a) A. M. Dumas, G. A. Molander and J. W. Bode, *Angew. Chem., Int. Ed.*, 2012, **51**, 5683; (b) H. Noda, G. Erős and J. W. Bode, *J. Am. Chem. Soc.*, 2014, **136**, 5611; (c) D. Mazunin, N. Broguiere, M. Zenobi-Wong and J. W. Bode, *ACS Biomater. Sci. Eng.*, 2015, **1**, 456; (d) A. O. Gálvez, C. P. Schaack, H. Noda and J. W. Bode, *J. Am. Chem. Soc.*, 2017, **139**, 1826; (e) C. J. White and J. W. Bode, *ACS Cent. Sci.*, 2018, **4**, 197.

10 (a) H. Böhme and P. Plappert, *Chem. Ber.*, 1975, **108**, 2827; (b) H. Böhme and P. Plappert, *Chem. Ber.*, 1975, **108**, 3574; (c) N. Millot, C. Piazza, S. Aviolio and P. Knochel, *Synthesis*, 2000, **7**, 941; (d) T. Murai, Y. Mutoh, Y. Ohta and M. Murakami, *J. Am. Chem. Soc.*, 2004, **126**, 5968; (e) C. Fischer and E. M. Carreira, *Org. Lett.*, 2004, **6**, 1497; (f) M. Suginome, L. Uehlin and M. Murakami, *J. Am. Chem. Soc.*, 2004, **126**, 13196; (g) M. Shimizu, H. Itou and M. Miura, *J. Am. Chem. Soc.*, 2005, **127**, 3296.

11 A. Krasovskiy and P. Knochel, *Angew. Chem., Int. Ed.*, 2004, **43**, 3333.

12 (a) G. A. Molander and F. Beaumard, *Org. Lett.*, 2011, **13**, 1242; (b) J. Raushel, D. L. Sandrock, K. V. Josyula, D. Pakyz and G. A. Molander, *J. Org. Chem.*, 2011, **76**, 2762.

13 M. El Khatib, R. A. M. Serafim and G. A. Molander, *Angew. Chem., Int. Ed.*, 2016, **55**, 254.

14 (a) T. Ohmura, T. Awano and M. Suginome, *Chem. Lett.*, 2009, **38**, 664; (b) T. Ohmura, T. Awano and M. Suginome, *J. Am. Chem. Soc.*, 2010, **132**, 13191; (c) T. Awano, T. Ohmura and M. Suginome, *J. Am. Chem. Soc.*, 2011, **133**, 20738.

15 (a) G. A. Molander, L. N. Cavalcanti, B. Canturk, P. S. Pan and L. E. Kennedy, *J. Org. Chem.*, 2009, **74**, 7364; (b) S. R. Inglis, E. C. Y. Woon, A. L. Thompson and C. J. Schofield, *J. Org. Chem.*, 2010, **75**, 468; (c) D. W. Blevins, M. L. Yao, L. Yong and G. W. Kabalka, *Tetrahedron Lett.*, 2011, **52**, 6534; (d) G. W. Kabalka and V. Coltuclu, *Tetrahedron Lett.*, 2009, **50**, 6271; (e) A. K. L. Yuen and C. A. Hutton, *Tetrahedron Lett.*, 2005, **46**, 7899.

16 (a) D. S. Matteson and G. Y. Kim, *Org. Lett.*, 2002, **4**, 2153; (b) B. J. Kim and D. S. Matteson, *Angew. Chem., Int. Ed.*, 2004, **43**, 3056.

