

Synthesis of Previously Inaccessible Borylated Heterocycle Motifs Using Novel Boron-Containing Amphoteric Molecules**

Piera Trinchera, Victoria B. Corless, and Andrei K. Yudin*

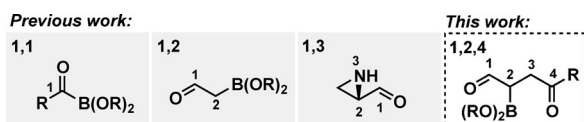
Abstract: The photoredox-organocatalyzed α -alkylation of the α -MIDA boryl aldehyde with a range of α -bromoketones resulted in the first examples of boron-containing 1,4-dicarbonyl compounds. These novel trifunctional amphoteric molecules, which bear an additional, strategically placed electrophilic site compared to the starting amphoteric α -boryl aldehyde, were subjected to double-condensation reactions in the presence of various nucleophiles. As a result, a variety of synthetically challenging 3-borylated pyrroles and furans and 4-borylated pyridazines were generated. The borylated regioisomers accessible with this condensation-based strategy are distinctly different from those arising from the well-known lithiation and C–H activation processes.

Since 2006, our laboratory has been interested in developing kinetically amphoteric molecules.^[1] These bifunctional structures contain orthogonal nucleophilic and electrophilic functional groups that are stabilized against premature inter- and intramolecular reactions. Our main strategy has been to map nucleophilic carbon and nitrogen functional groups relative to carbon–oxygen double bonds. The counting system shown in Scheme 1 allows us to refer to different amphoteric environ-

ment in further exploring kinetically amphoteric molecules, we decided to increase their topological complexity by introducing an additional electrophilic site of reactivity. We envisioned that the resulting molecules might be suitable starting materials for accessing novel boron-containing heteroarenes with unusual regiochemistry. Herein, we describe the enabling method that allows us to install carbon–boron bonds within 1,4-dicarbonyl motifs (Scheme 1). The corresponding trifunctional 1,2,4-amphoteric molecules have proven to be amenable to double-condensation reactions. The application of this previously inaccessible structural motif showcases how medicinally important boron-containing heterocycles can be efficiently synthesized. Significantly, almost all of the borylated molecules reported in this paper are new, demonstrating that our strategy augments the existing methods by providing access to synthetically challenging heterocycles with uncommon substitution patterns.

In light of the recently demonstrated reactivity of boryl enamines, which maintain their C–B bond during α -halogenation reactions,^[4] we pursued the pyrrolidine-catalyzed α -alkylation of the parent α -MIDA boryl aldehyde **1**. This approach allowed us to investigate an unexplored aspect of α -boryl aldehyde reactivity and, at the same time, to access the desired boron-containing 1,4-dicarbonyl compounds. We opted to utilize photoredox organocatalysis to test the feasibility of this approach. This strategy exploits the electron-rich nature of enamines to merge photoredox catalysis with organocatalysis to carry out the α -functionalization of aldehydes in the presence of an electrophilic radical source.^[5] We initially investigated the use of 2-bromoacetophenone (**2a**) as the radical source (Table 1). The reaction, performed on a 0.5 mmol scale in the presence of [Ru(bpy)₃]Cl₂, 2,6-lutidine, and pyrrolidine, was stirred in DMF at room temperature under irradiation with a household 23 W compact fluorescent light (CFL) bulb. After 24 hours, ¹H NMR data revealed nearly complete conversion of the starting aldehyde into the desired dicarbonyl product **3a**. Only a trace amount of the α -bromo boryl aldehyde side product, derived from the addition of the bromine radical to the boryl enamine, was detected. Aqueous work-up and purification by column chromatography furnished **3a** as a bench-stable solid in 48% yield.

This result prompted us to test the generality of the preparation of 1,4-dicarbonyl boronates (Table 1). Commercially accessible aromatic α -bromoketones were reacted with the parent boryl aldehyde under the aforementioned conditions. Most substrates smoothly participated in α -alkylation without any modifications to the standard conditions. In a few cases, an additional 20 mol % of pyrrolidine was found to be beneficial to improve conversion. The reaction worked well



Scheme 1. Examples of different classes of kinetically amphoteric molecules developed since 2006.

ments by enumerating the atoms that separate the nodes of opposing reactivity. The molecules developed thus far include 1,1-, 1,2-, and 1,3-systems.

By exploiting the unique properties of MIDA-protected boronic acid derivatives (MIDA = *N*-methyliminodiacetic acid),^[2] we have generated a variety of novel amphoteric organoboron reagents in which the nucleophilic C–B bond and the electrophilic carbonyl group coexist.^[1,3] Driven by our

[*] Dr. P. Trinchera, V. B. Corless, Prof. Dr. A. K. Yudin
Davenport Research Laboratories
Department of Chemistry, University of Toronto
80 St. George St., Toronto, ON, M5S 3H6 (Canada)
E-mail: ayudin@chem.utoronto.ca

[**] We would like to thank the Natural Science and Engineering Research Council (NSERC) and the Canadian Institutes of Health Research (CIHR) for financial support.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201504271>.

Table 1: Preparation of boron-containing 1,4-dicarbonyl compounds.^[a]

Bromide	R	Product	Conv. ^[b] [%]	Selectivity ^[b] [%]	Yield ^[c] [%]
2a		3a	92	97	48
2b ^[d]		3b	90	> 99	69
2c		3c	93	> 99	64
2d		3d	100	66	44
2e ^[d]		3e	81	> 99	41
2f		3f	95	> 99	47
2g ^[d]		3g	95	> 99	51

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.0 equiv), pyrrolidine (50 mol %), 2,6-lutidine (1.0 equiv), [Ru(bpy)₃]Cl₂ (5 mol %) in DMF (0.7 M), RT, N₂ atmosphere, 24 h, under irradiation with 23 W CF light. [b] Conversions and selectivities were determined by ¹H NMR analysis of the crude reaction mixtures. For details on the determination of the selectivity, see the Supporting Information. [c] Yields of isolated products after column chromatography on silica gel. [d] Pyrrolidine (70 mol %). bpy = 2,2'-bipyridine.

not only with electron-neutral (**2a** and **2b**) and electron-deficient (**2c** and **2d**) aryl bromoketones, but also with electron-rich (**2e** and **2f**) aryl derivatives. Analogous results were obtained with heteroaryl bromoketone **2g**, which effectively led to the formation of the corresponding heteroaryl-substituted 1,4-dicarbonyl boronate **3g**. Importantly, the synthesis of the dicarbonyl boronates proved to be amenable to scale-up. The reaction was performed on 1.0–1.5 g scale with various α -bromoketones without significant effect on the yield of the final products.^[6]

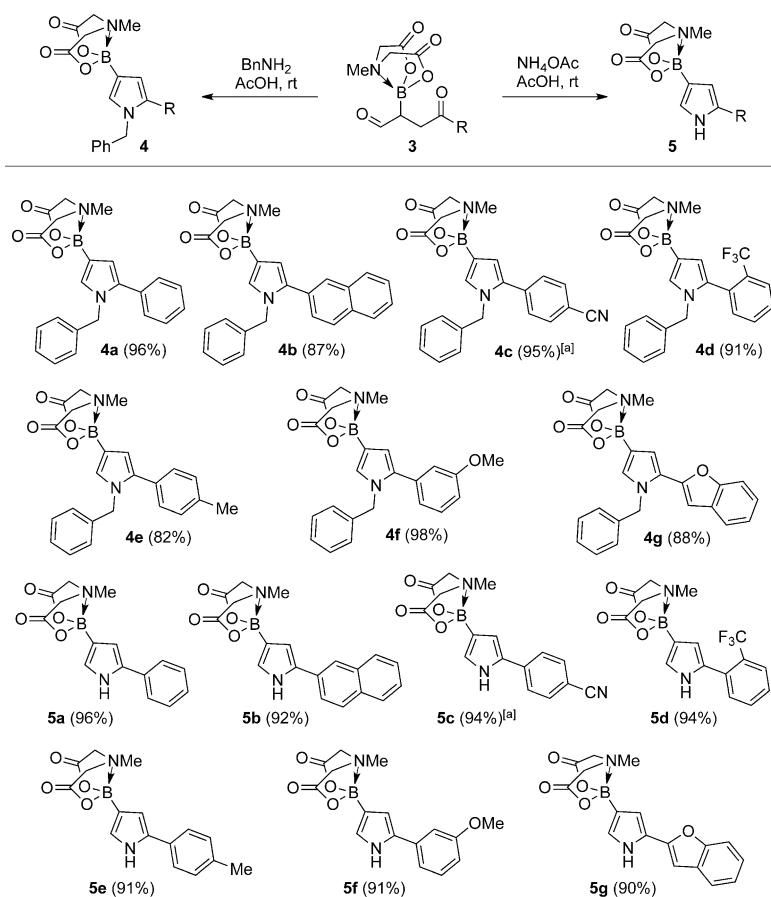
Having secured access to 1,4-dicarbonyl boronates, we investigated the synthetic utility of this previously unexplored structural motif. We reasoned that exploiting the presence of the two carbonyl groups in a double condensation reaction might help us to devise a general method for the regioselective synthesis of a variety of borylated heterocycles. This strategy is distinctly different from the traditional borylation of pre-formed heterocycles and complements it in terms of the regiochemical pattern of the final products. Indeed, the synthesis of borylated pyrroles, furans, and thiophenes is typically accomplished by borylation of pre-formed heteroarenes through either indirect strategies that involve heteroaryl halide intermediates or directed C–H lithiation/borylation.^[7] Whereas the indirect methods require multistep procedures and display limited functional-group compatibil-

ity, the directed C–H lithiation/borylation is only applicable to the synthesis of C2-borylated heterocycles. Considerable progress has also been reported in both the areas of transition-metal-catalyzed C–H borylation^[8] and electrophilic borylation.^[9] However, the borylation occurs exclusively at the C2 position, with reversal of regioselectivity observed only for pyrroles that bear a large protecting group on the nitrogen atom and heterocycles that are pre-functionalized with a directing group. To the best of our knowledge, there are just two literature examples of the selective borylation of NMe and NH pyrroles at the C3 position without the preliminary installation of protecting/directing groups, both of which use the parent unsubstituted rings.^[9e,10] Few approaches have been described that make use of boron-containing starting materials to access C3-borylated heterocycles. Recently, Gevorgyan and co-workers reported an elegant synthesis of C3-borylated furans by a cycloisomerization reaction of boron-containing alkynyl epoxides. However, this method is only applicable to the synthesis of the five-membered oxygen heterocycle.^[11] Moreover, two strategies for the synthesis of C3-borylated pyrroles have been described, but they exclusively led to unsubstituted *N*-aryl and *N*-alkyl pyrroles or exhibited poor selectivity.^[12,13] Therefore, the development of new procedures for the general and selective synthesis of a variety of C3-borylated heterocycles is highly desirable, especially for medicinal chemistry, where heterocycles are routinely called upon to map out the accessible chemical space.

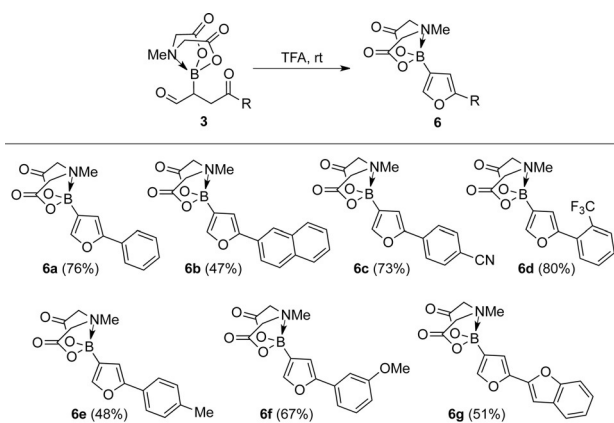
Initially, we explored the synthesis of C3-borylated pyrroles by a double-condensation reaction of various 1,4-dicarbonyl boronates with benzylamine. We were pleased to observe that by simply stirring our substrates in acetic acid in the presence of the amine at room temperature, we could easily access the desired C3-borylated *N*-benzyl 5-aryl pyrroles **4** (Scheme 2). Reactions proceeded with complete conversion and led to the formation of the products in under two hours with no observable cleavage of the B–C bond. Replacement of benzylamine with an excess of ammonium acetate resulted in the smooth generation of C3-borylated NH pyrroles **5** (Scheme 2). C3-borylated pyrroles featuring analogous ring substitution patterns to our products have never been reported.

The facile access to borylated pyrroles encouraged us to examine the versatility of the 1,4-dicarbonyl boronates in the synthesis of other heterocycles. After testing a range of reaction conditions, stirring the substrates in trifluoroacetic acid was found to be the easiest and most selective procedure to effectively prepare the C3-borylated furans **6** (Scheme 3). On the other hand, the synthesis of C3-borylated thiophene derivatives turned out to be a more challenging task owing to the formation of furan side products. Routes to the selective synthesis of thiophene analogues are still under development.

Finally, we were attracted by the possibility of using our 1,4-dicarbonyl boronates for the synthesis of 4-borylated pyridazines. Given their affinity for a great number of receptor proteins, pyridazine derivatives are considered to be privileged structures.^[14] This fact, together with the limited availability of synthetic procedures to borylated pyridazines, makes these compounds of particular interest.



Scheme 2. Preparation of C3-borylated *N*-benzyl and NH pyrroles. Reaction conditions for the synthesis of **4**: **3** (1.0 equiv), BnNH₂ (1.0 equiv) in AcOH (0.1 M), RT, 1–2 h. Reaction conditions for the synthesis of **5**: **3** (1.0 equiv), NH₄OAc (16 equiv) in AcOH (0.1 M), RT, 1–2 h. All yields in parentheses correspond to the yields of isolated products after column chromatography on silica gel. [a] The reaction was stirred overnight. Bn = benzyl.



Scheme 3. Preparation of C3-borylated furans. Reaction conditions: **3** (1.0 equiv) in TFA (0.1 M), RT, 1–2 h. All yields in parentheses correspond to the yields of isolated products after column chromatography on silica gel.

A reported method for accessing 4-borylated pyridazines relies on the directed *ortho* metalation/boronation of pre-formed pyridazines, thus making it necessary to pre-functionalize the ring with a directing group.^[15] Alternatively, an inverse-electron-demand Diels–Alder reaction of tetrazines with alkynyl boronic esters has been described by Harrrity and co-workers.^[16] However, 4-borylated 6-aryl pyridazines that are unsubstituted in the other positions of the ring are unknown in the literature.

1,4-Dicarbonyl boronates were treated with hydrazine in acetic acid at room temperature, and after two hours, we observed complete conversion of the starting material into two new MIDA-containing compounds: the desired pyridazines (minor) and the corresponding *N*-amino pyrroles (major), which are typical side products of this reaction arising from a Paal–Knorr-type mechanism. Gratifyingly, longer reaction times resulted in the complete disappearance of the side products in favor of the thermodynamically more stable pyridazines **7** (Scheme 4).

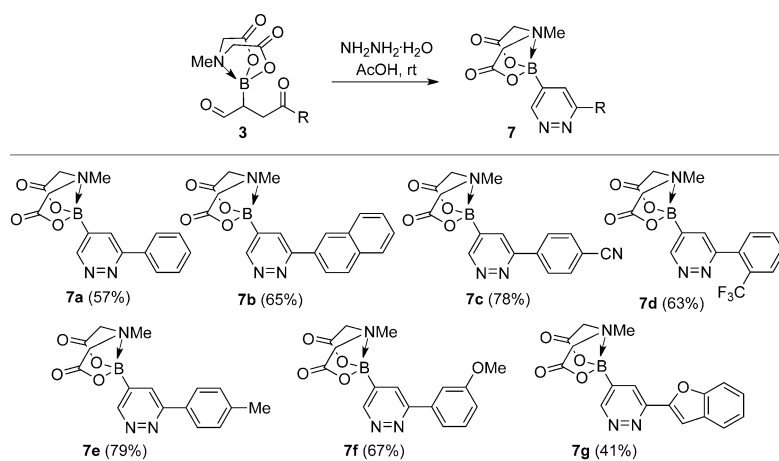
Significantly, the condensation reactions of our dicarbonyl boronates with all of the tested nucleophiles worked well on both small (0.1 mmol) and large (2.0 mmol) scale, providing the desired heterocycles in moderate to excellent yields.

The synthetic value of our method to borylated heterocycles was further underscored by the positive results obtained when a crude sample of the dicarbonyl boronate **3a** was directly employed in the condensation reactions. The corresponding pyrroles, furan, and pyridazine were effectively prepared without starting-material purification, leading to better overall yields of the final heterocycles.

In summary, guided by the intention to design topologically distinct amphoteric environments, we have realized the synthesis of previously inaccessible boron-containing 1,4-dicarbonyl compounds. These novel amphoteric molecules have proven their versatility as starting materials for the preparation of a wide range of boron-containing pyrroles, furans, and pyridazines. Importantly, through the synthesis of C3-borylated five-membered heterocycles, our strategy has overcome a longstanding challenge in this area. Considering our documented success in multicomponent reactions driven by amphoteric reagents of different topologies,^[17] we anticipate to make additional gains in accessing skeletal diversity using the amphoteric molecules reported in this paper. Studies along these lines are being actively pursued.

Keywords: amphoteric molecules · borylated heterocycles · condensation · 1,4-dicarbonyl compounds · MIDA boronates

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 9038–9041
Angew. Chem. **2015**, *127*, 9166–9169



Scheme 4. Preparation of C4-borylated pyridazines. Reaction conditions: **3** (1.0 equiv), hydrazine monohydrate (1.3 equiv) in AcOH (0.1 M), RT, 16 h.

- [1] Z. He, A. Zajdlik, A. K. Yudin, *Acc. Chem. Res.* **2014**, *47*, 1029–1040.
- [2] a) T. Mancilla, R. Contreras, *J. Organomet. Chem.* **1986**, *307*, 1–6; b) B. Garrigues, M. Mulliez, A. Raharirina, *J. Organomet. Chem.* **1986**, *302*, 153–158; c) Q. I. Churches, *Aust. J. Chem.* **2011**, *64*, 1474; d) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717; e) E. P. Gillis, M. D. Burke, *Aldrichimica Acta* **2009**, *42*, 17–27; f) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963; g) G. R. Dick, E. M. Woerly, M. D. Burke, *Angew. Chem. Int. Ed.* **2012**, *51*, 2667–2672; *Angew. Chem.* **2012**, *124*, 2721–2726.
- [3] Z. He, A. Zajdlik, A. K. Yudin, *Dalton Trans.* **2014**, *43*, 11434–11451.
- [4] J. D. St. Denis, A. Zajdlik, J. Tan, P. Trinchera, C. F. Lee, Z. He, S. Adachi, A. K. Yudin, *J. Am. Chem. Soc.* **2014**, *136*, 17669–17673.
- [5] a) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77–80; b) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877; c) H.-W. Shih, M. N. Vander Wal, R. L. Grange, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 13600–13603; d) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363; e) P. Melchiorre, *Angew. Chem. Int. Ed.* **2009**, *48*, 1360–1363; *Angew. Chem.* **2009**, *121*, 1386–1389; f) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527–532; g) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102–113.
- [6] The observed high conversion and selectivity of the reaction are not reflected in the yields of isolated products, thus indicating product loss during purification. However, given the high purity of the dicarbonyl compounds in the crude samples, reactions to evaluate the applicability of the unpurified products in subsequent transformations were performed with positive results (see below).
- [7] a) *Boronic Acids: Preparation and Applications in Organic Synthesis Medicine and Materials*, 2nd ed. (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2011**; b) *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**; c) E. Tyrrell, P. Brookes, *Synthesis* **2003**, 0469–0483; d) K. Billingsley, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366; e) C. Moldoveanu, D. A. Wilson, C. J. Wilson, P. Leowanawat, A.-M. Resmerita, C. Lui, B. M. Rosen, V. Percec, *J. Org. Chem.* **2010**, *75*, 5438–5452; f) J. W. Clary, T. J. Rettenmaier, R. Snelling, W. Bryks, J. Banwell, W. T. Wipke, B. Singaram, *J. Org. Chem.* **2011**, *76*, 9602–9610; g) G. A. Molander, S. L. J. Trice, S. M. Kennedy, *Org. Lett.* **2012**, *14*, 4814–4817.
- [8] a) I. A. I. Mkhaliid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890–931; b) T. Ishiyama, N. Miyaara, *J. Organomet. Chem.* **2003**, *680*, 3–11; c) T. Ishiyama, N. Miyaara, *Chem. Rec.* **2004**, *3*, 271–280; d) T. Ishiyama, N. Miyaara, *Pure Appl. Chem.* **2006**, *78*, 1369–1375; e) T. Ishiyama, J. Takagi, Y. Yonekawa, J. F. Hartwig, N. Miyaara, *Adv. Synth. Catal.* **2003**, *345*, 1103–1106; f) V. A. Kallepalli, F. Shi, S. Paul, E. N. Onyeozili, R. E. Maleczka, Jr., M. R. Smith III, *J. Org. Chem.* **2009**, *74*, 9199–9201; g) S. Kawamorita, H. Ohmiya, M. Sawamura, *J. Org. Chem.* **2010**, *75*, 3855–3858.
- [9] a) A. Del Grosso, C. A. Muryn, R. G. Pritchard, M. J. Ingleson, *Organometallics* **2010**, *29*, 241–249; b) A. Del Grosso, M. D. Helm, S. A. Solomon, D. Caras-Quintero, M. J. Ingleson, *Chem. Commun.* **2011**, *47*, 12459–12461; c) A. Del Grosso, P. J. Singleton, C. A. Muryn, M. J. Ingleson, *Angew. Chem. Int. Ed.* **2011**, *50*, 2102–2106; *Angew. Chem.* **2011**, *123*, 2150–2154; d) A. Prokofjevs, J. W. Kampf, E. Vedejs, *Angew. Chem. Int. Ed.* **2011**, *50*, 2098–2101; *Angew. Chem.* **2011**, *123*, 2146–2149; e) V. Bagutski, A. Del Grosso, J. A. Carrillo, I. A. Cade, M. D. Helm, J. R. Lawson, P. J. Singleton, S. A. Solomon, T. Marcelli, M. J. Ingleson, *J. Am. Chem. Soc.* **2013**, *135*, 474–487.
- [10] S. M. Preshlock, D. L. Plattner, P. E. Maligres, S. W. Krska, R. E. Maleczka, Jr., M. R. Smith III, *Angew. Chem. Int. Ed.* **2013**, *52*, 12915–12919; *Angew. Chem.* **2013**, *125*, 13153–13157.
- [11] R. K. Shiroodi, O. Koleda, V. Gevorgyan, *J. Am. Chem. Soc.* **2014**, *136*, 13146–13149.
- [12] A. Hercouet, A. Neu, J.-F. Peyronel, B. Carboni, *Synlett* **2002**, 0829–0831.
- [13] H. Wang, C. Grohmann, C. Nimphius, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 19592–19595.
- [14] C. G. Wermuth, *MedChemComm* **2011**, *2*, 935–941.
- [15] K. M. Clapham, A. S. Batsanov, R. D. R. Greenwood, M. R. Bryce, A. E. Smith, B. Tarbit, *J. Org. Chem.* **2008**, *73*, 2176–2181.
- [16] a) M. D. Helm, J. E. Moore, A. Plant, J. P. A. Harrity, *Angew. Chem. Int. Ed.* **2005**, *44*, 3889–3892; *Angew. Chem.* **2005**, *117*, 3957–3960; b) M. D. Helm, A. Plant, J. P. A. Harrity, *Org. Biomol. Chem.* **2006**, *4*, 4278–4280; c) J. F. Vivat, H. Adams, J. P. A. Harrity, *Org. Lett.* **2010**, *12*, 160–163; d) M. D. Helm, A. Plant, J. P. A. Harrity, *Synlett* **2007**, 2885–2887.
- [17] a) A. Zajdlik, Z. Wang, J. L. Hickey, A. Aman, A. D. Schimmer, A. K. Yudin, *Angew. Chem. Int. Ed.* **2013**, *52*, 8411–8415; *Angew. Chem.* **2013**, *125*, 8569–8573; b) A. P. Treder, M.-C. Tremblay, A. K. Yudin, E. Marsault, *Org. Lett.* **2014**, *16*, 4674–4677; c) L. Belding, S. Zaretsky, B. R. Rotstein, A. K. Yudin, T. Dudding, *J. Org. Chem.* **2014**, *79*, 9465–9471; d) S. Zaretsky, S. Adachi, B. H. Rotstein, J. L. Hickey, C. C. G. Scully, J. D. St. Denis, R. Courtemanche, J. C. Y. Yu, B. K. W. Chung, A. K. Yudin, *J. Org. Chem.* **2014**, *79*, 9948–9957.

Received: May 10, 2015

Published online: June 25, 2015