ARTICLE

Straightforward synthesis of chiral non-racemic α-boryl isocyanides

Received 00th January 20xx,
Accepted 00th January 20xx

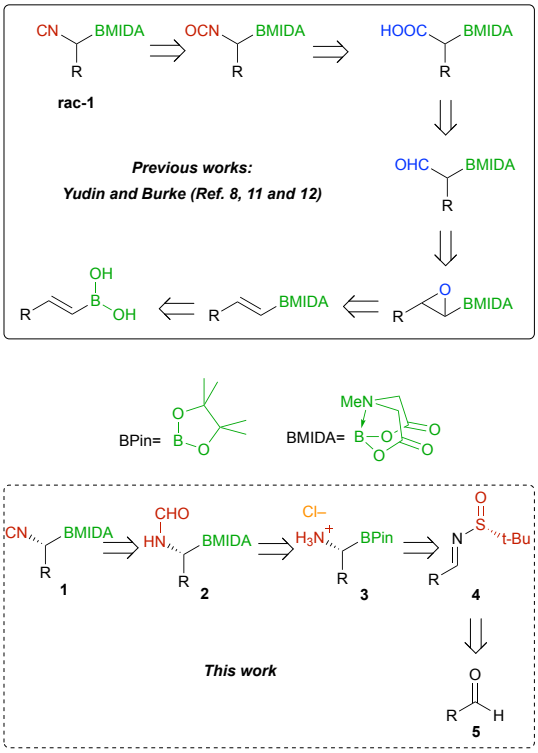
DOI: 10.1039/x0xx00000x

Francesco Fini,*[a] Alessandro Zanni,[a] Maria Luisa Introvigne,[a,b] Mattia Stucchi,[a] Emilia Caselli[a] and Fabio Prati*[a]

A straightforward concise synthesis of chiral non-racemic aliphatic α-boryl isocyanides, relay intermediates for boron-based bioactive molecules by using multicomponent reaction, is presented. The short synthetic sequence comprises as key steps copper-catalysed asymmetric borylation of imine, simultaneous nitrogen formylation/boron-protecting group interconversion and final formamide dehydration reaction.

Introduction

Boron containing molecules (BCMs) gained much attention due to their usefulness as building blocks in organic synthesis, mainly as preferred reagents in palladium-catalysed C–C bond forming reactions.[1] In addition, in the last decade, several BCMs with biological activity have been surfaced from academia and pharmaceutical companies as new therapeutic agents. Indeed, a cyclic boronic acid (vaborbactam) has been approved as novel β-lactamase inhibitor to fight bacterial antibiotic resistance and two dipeptidyl boronic acids (bortezomib and ixazomib) have been approved as proteasome inhibitors for the treatment of multiple myeloma.[1b,2] The latter type of BCMs belongs to the boron-containing peptides, where the carboxylate of the last AA is replaced by a boronic acid group. The boropeptide synthesis carried out started with the synthesis of chiral enantiopure α-aminoboronic unit obtained by the Matteson homologation protocol,[1b,3] or by borylations of chiral sulfinylimines.[1b,4] These α-aminoboronates are then sequentially coupled with the corresponding amino acids or simple carboxylic acids, through the traditional peptide coupling chemistry.[5] Recently, an attractive methodology appeared in literature, where the boropeptide has been synthesised exploiting a multicomponent reaction (MCR),[6] thus envisioning a rapid exploration of chemical space for such peptidomimetics. As a matter of fact, Yudin and co-workers introduced for the first time the synthesis of stable[7] α-boryl isocyanide **rac-1**,[8] as a suitable reagent for the Passerini (P3CR),[9] and Ugi (U4CR)[10] multicomponent reactions. Remarkably, protected racemic bortezomib was synthesised in one step from the selected carboxylic acid, aldehyde, ammonia and α-boryl isocyanide **rac-1** under U4CR condition. In addition, α-acyloxy carboxamides were successfully obtained from **rac-1**, under P3CR condition.[8] Given the high atom economy, the operational simplicity and the high convergent character of this synthetic approach, the accessibility of α-boryl isocyanides **1** in enantiopure form should maximise the efficiency of the overall process**.** In the cited work, racemic α-Boryl isocyanides **rac-1** were synthesised by a six steps synthetic sequence starting from the corresponding alkenylboronic acid (**Scheme 1**, top).[11]



Scheme 1. Rational design behind the synthesis of chiral enantiopure α-Boryl isocyanides **1**.

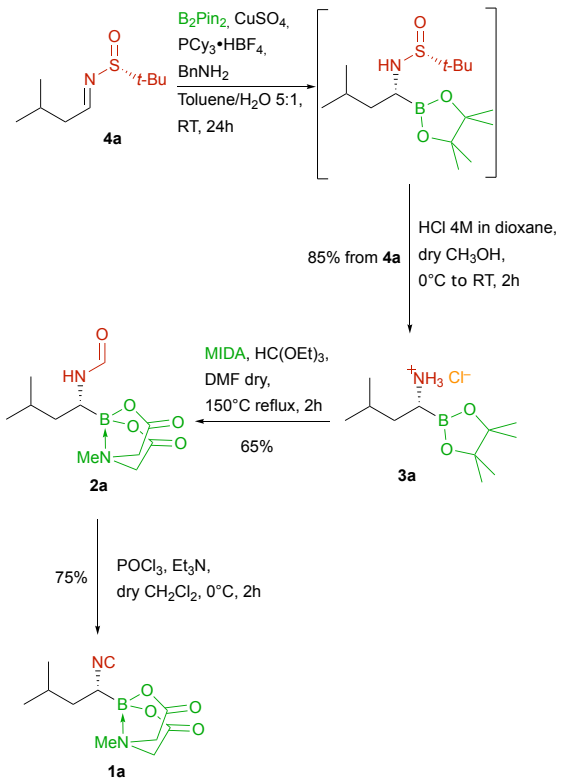
[a] Department of Life Sciences, Università degli Studi di Modena e Reggio Emilia, via G. Campi 103, 41125, Modena, Italy. E-mail: francesco.fini@unimore.it, fabio.prati@unimore.it.
[b] International Doctorate School in Clinical and Experimental Medicine (CEM), Università degli Studi di Modena e Reggio Emilia, via G. Campi 287, 41125, Modena, Italy

Electronic Supplementary Information (ESI) available: [Experimental details, analytical data, characterisation data and NMR spectra]. See DOI: 10.1039/x0xx00000x

Despite the chiral version of MIDA (*N*-methyl iminodiacetic acid), pinene-derived iminodiacetic acid, PIDA,[11,12] might be used to attain chiral enantiopure α-boryl isocyanides, no examples have been reported so far. Herein we report a straightforward synthesis of chiral non-racemic α-boryl isocyanide **1** starting from simple aldehyde in four synthetic steps by using very few chromatographic purifications (**Scheme 1**, bottom). The retrosynthetic analysis depicts the synthesis of **1** from the corresponding formamide **2** by a dehydration reaction. By using functional groups interconversion and C–N bond forming reactions, key intermediate **2** is directly synthesised from α-ammoniumboronic acid pinacol ester **3**. Finally, the boronic acid ester **3** may be afforded by the diastereoselective borylation of imines **4**, conveniently attained by the corresponding aldehyde **5**, prior the *N*-sulfinyl protecting group removal (**Scheme 1**, bottom).

Results and discussion

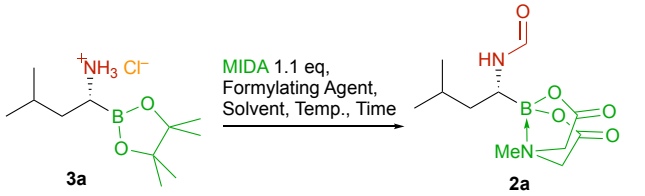
For the isobutyl derivative, the synthetic sequence commenced with the borylation of the *t*-butylsulfinyl imine **4a**,[13] as chiral enantiopure auxiliary used for the diastereomeric borylations in the optimised condition reported by Ellman and co-workers in 2014 (**Scheme 2**).[4] The crude borylated adduct was directly hydrolysed with HCl 4M in dioxane, in dry methanol for 2h to attain **3a** in very good yield from the sulfinyl imine **4a** by simple trituration (85%, **Scheme 2**).



Scheme 2. Optimised synthetic sequence for the synthesis of chiral non-racemic α-boryl isocyanide **1a**, starting from *t*-butylsulfinylimine **4a**.

The next step involved a one pot/two–steps procedure where the ammonium salt **3a** underwent a simultaneous boron-protecting group interconversion and C–N bond formation to obtain the related *N*-formyl – *B*-MIDA adduct **2a**.
An extensive optimisation was conducted, and representative resulted are reported in **table 1**: formylating agent and the use of a DMF in combination with the increase of temperature were screened.

Table 1. Representative results from the optimisation of compounds **2a**.

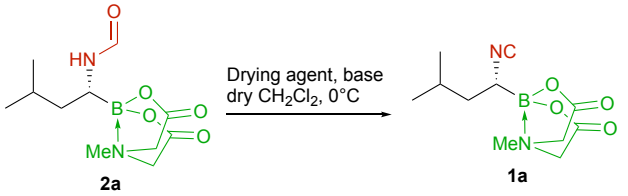


Entry	Formylating Agent	Solvent	Temp. (°C)	Time (h)	Conv. (%)
1	$CH(OMe)_3$ 6eq.	--	105	6	20
2	$CH(OEt)_3$ 6eq.	--	150	6	70
3	$CH(OEt)_3$ 4eq.	DMF dry[a]	150	3	>95 (65)[b]

[a] 0.5 ml of DMF per mmol of **3a** was used [b] In parenthesis is reported the isolated yield of compound

After the optimization we were able to merge both the *N*-formylating and B-Pin → *B*-MIDA processes in a one pot fashion by using triethylortoformate as formylating/mild dehydrating agent and MIDA, in DMF, obtaining **2a** with 65% yield, by simple precipitation (**Scheme 2**, centre).
The final step involved the dehydration of the formyl derivative **2a**. In **Table 2** a short optimisation performed for the dehydration step is shown.

Table 2. Representative results for the dehydration of **2a** to obtain isocyanide **1a**.



Entry	Drying agent	Base	Time (h)	Yield (%)
1	TsCl	Pyridine (2eq.)	3	61
2	Triphosgene (0.35 eq.)	NMM (2 eq.)	2	63
3	Triphosgene (0.35 eq.)	Et_3N (2.5 eq.)	2	65
4	$POCl_3$ (1.5 eq.)	Et_3N (5 eq.)	3	75

$POCl_3$ in combination with Et_3N proved to be the reagents of choice for the synthesis of the corresponding isocyanide **1a**, with good results in terms of yield and easy to handle purification. As highlighted in **Scheme 2** (bottom) performing the reaction with an excess of $POCl_3$ and triethylamine at 0 °C afforded the isocyanide **1a** with 75 % yield, by extracting with CH_2Cl_2 and washing the organic phase with saturated $NaHCO_3$. The isocyanide was found spectroscopically pure and quite

suitable for a multicomponent reaction. To address a possible racemisation during the last two–steps, compound **1a** was analysed by using Pirkle's alcohol as CSA (Chiral Shifts Agents) with ^{1}H NMR technique (See ESI for more details). ^{1}H doublet at 4.12 ppm, belonging to one of the diastereotopic hydrogen of the MIDA group, was chosen as a suitable signal for the CSA splitting (enlargement **b**, **Figure 1**). The enlargement **c** (**Figure 1**) shows a 98:2 ratio between **1a** and **ent-1a**, this result has been validated by adding a small amount of **ent-1a** to the sample **1a** : Pirkle's alcohol 1:20 (enlargement **d**, **Figure 1**). The enantiomeric ratio of **1a** remained 98:2 along the synthetic sequence confirming the mild reaction conditions of the two final steps.

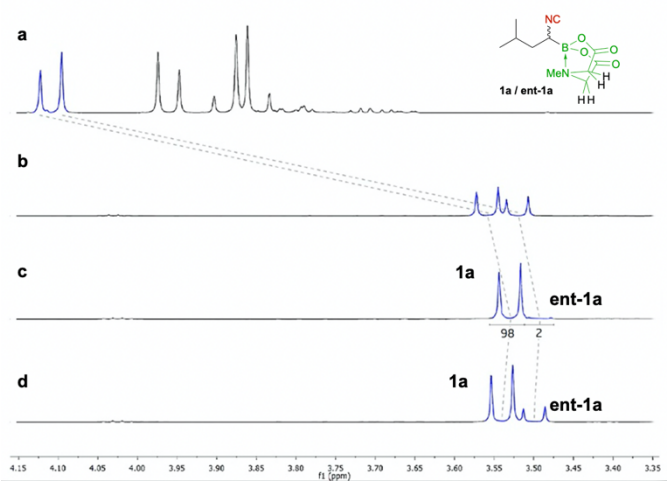
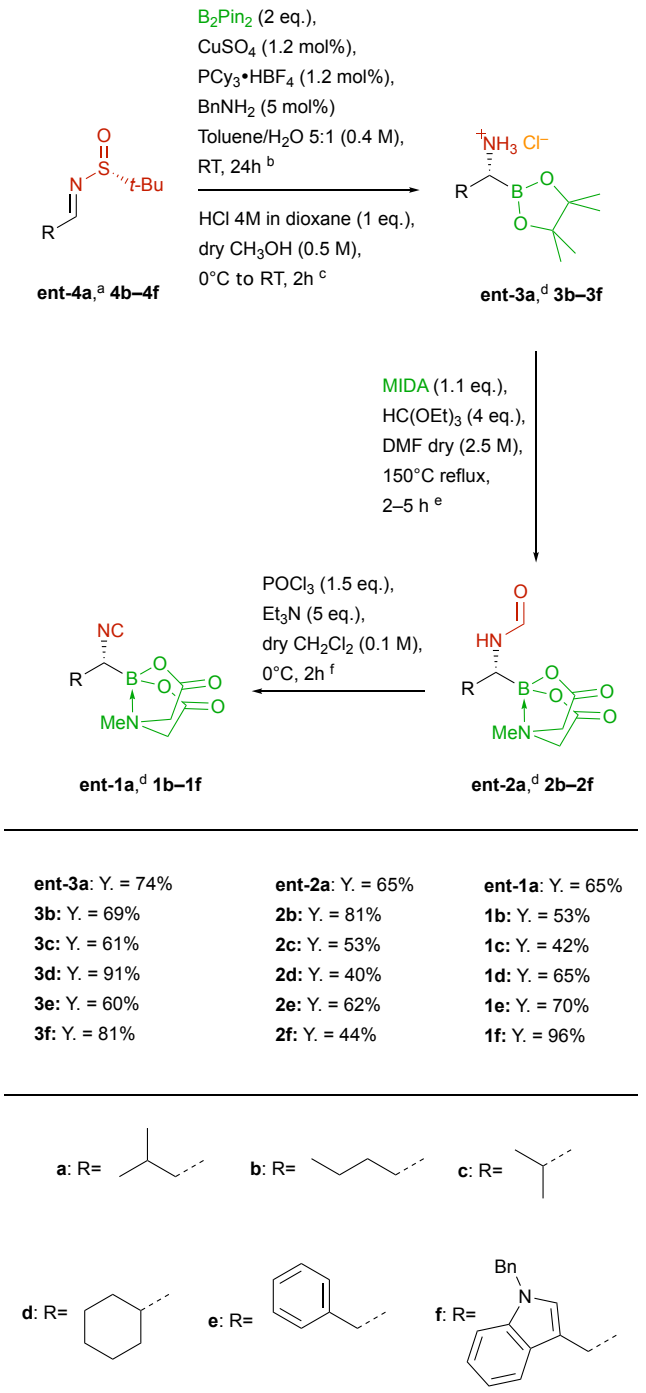


Figure 1. Determination of enantiomeric ratio. ^{1}H NMR spectra (600 MHz, $CDCl_3$): **a)** racemic; **b)** racemic : Pirkle 1:20; **c) 1a** : Pirkle 1:20; **d)** (**1a** : Pirkle 1:20) + **ent-1a**.

Starting from imine **4a**, chiral enantiopure isocyanide **1a** was synthesised for the first time in three synthetic steps, with an overall yield of 41%, overcoming late-stage column chromatography purification, potentially detrimental for the efficiency of the process.

With the overall synthetic sequence established, several substrates have been chosen to broaden the scope of the process (**Scheme 3**). The diastereomeric borylation/hydrolysis resulted to be quite robust, the corresponding ammonium salts **ent-3a**, **3b–f** were isolated by simple trituration of the crude with a minimum amount of MTBE/*n*-hexane, a relatively non-toxic mixture. Several substrates have been used bearing an alkyl chain with different degree of steric hindrance and in presence of aromatic or heteroaromatic rings. Primary and secondary β-branching aliphatic α-ammoniumboronic acid pinacol esters **ent-3a**, **3b–f** were obtained in satisfactory to excellent yields over two synthetic steps from the imines **ent-4a**, **4b–f**[14] (**Scheme 3**, top). This two–steps procedure was suitable even for an aromatic substituent directly attached to the carbon–boron moiety with 84% yield; unfortunately, this compound was not suitable for further modification (*vide infra*). In addition, the borylation of tertiary α-branched imine, under aqueous condition, did not take place, probably due to steric hindrance.[15]



Scheme 3. Substrate scope for the synthesis of chiral non-racemic α-boryl isocyanide **ent-1a**, **1b–f**, starting from *t*-butylsulfinylimine **ent-4a**, **4b–f**. [a] Opposite enantiomer **ent-4a** was obtained from the condensation of isovaleraldehyde with (*S*)-sulfinyl amide. [b] Reaction conditions. Borylation: reactions were carried out using 1.8–7.1 mmol of **ent-4a**, **4b–f**. [c] Reaction conditions. Hydrolysis: reactions were carried out using crude *N*-protected B-pin adducts. [d] Opposite enantiomer. [e] Reactions were carried out using 0.4–1.4 mmol of **3a–f**. [f] Reactions were carried out using 0.1–0.4 mmol of **2a–f**.

The subsequent step involved the transformation of ammonium salts **ent-3a**, **3b–f** into *N*-formyl–*B*-MIDA adducts **ent-2a**, **2b–f**. The procedure was quite sturdy for substrates bearing an aliphatic group attached to the alpha carbon: **ent-2a**, **2b–f** were

attained at reflux (150 °C), after the stated time (2–5 h), with moderated to good yields, by precipitating the crude mixture by using CH_2Cl_2/diethyl ether mixture (**Scheme 3**, centre). Aromatic substrate was not suitable for the formylation/B-MIDA transformation conditions and only deboronated side products were recovered at the end of several attempts.

The final step for the synthesis of α-boryl isocyanide **ent-1a**, **1b–f** regarded an easy-to-handle dehydration of formyl derivatives **ent-2a**, **2b–f** by using and excess of $POCl_3$ and Et_3N.[16] The corresponding products were isolated from the crude by extracting with CH_2Cl_2 and washing the organic phase with saturated $NaHCO_3$. The isocyanides were found spectroscopically pure and suitable for a multicomponent reaction.

Conclusions

Straightforward concise reaction sequence is introduced to access chiral non-racemic α-boryl isocyanides **ent-1a**, **1a–f** with overall 17–37% yield over four synthetic steps from the corresponding aldehyde, with convenient purification procedures. Several α-ammonium boronic acid pinacol esters **3a–f** were easily attained, and then by introducing a novel simultaneous functional group interconversion at the boron atom and a *N*–formylation reaction we opened a new path towards the synthesis of chiral non-racemic aliphatic α-boryl isocyanide **1**, one of the most desired relay building blocks to use in MCR, for the synthesis of boron-based β-lactamases and proteasome inhibitors. The straightforward synthetic sequence could trigger the design and the easy access of several boron containing inhibitor libraries.

Experimental

General Synthetic procedures

Borylation of imines 4a–f and subsequent hydrolysis for the synthesis of 3a–f.

In a 25 ml round bottomed flasks with magnetic stirring bar, $PCy_3{\cdot}HBF_4$ (1.2 mol%) in toluene (0.06 M) was added. Then an aqueous solution of $CuSO_4$ (1.2 mol%, 0.03M) and benzylamine (5 mol%) were added. The flask is closed and left under stirring for 15 minutes. Afterward *t*-butylsulfinylimine **4a–f** (1 eq., 1.8 – 7.1) in toluene (0.5 M) and B_2Pin_2 (2 eq.) were sequentially added. The flask is kept stirring with a refrigerator at 20°C for 24h. Water (10ml per mmol of imine) was poured in the crude mixture and extracted with AcOEt (3x10ml per mmol of imine). The organic phase was washed with water (10ml per mmol of imine) and brine (10ml per mmol of imine), dried over $MgSO_4$, filtered and evaporated under reduced pressure.

The crude mixture was dissolved in dry CH_3OH (0.5 M) and cooled down to 0°C and treated with anhydrous HCl 4M in dioxane (1 eq.) under argon. The resulting solution is left for 2h at 20 °C. After the stated time the crude mixture was evaporated under reduced pressure and the crude ammonium salts was triturated with MTBE/n-hexane to afford **3a–f** as pale yellow solid and then used for the next step.

Direct one pot/two–steps C–N bond formation and FGI from compounds 3a–f to *N*-formyl adducts 2a–f.

In a Schlenk tube, with magnetic stirring bar, were added **3a–f** (1eq.) and MIDA (1.1 eq.) under argon. Then triethylortoformate (4.0 eq.) and dry DMF (2.5 M) were sequentially added. The resulting mixture is warmed up until reflux (150°C). After the stated time (2–5 h) the reaction mixture is cooled down, diluted with CH_2Cl_2 and solvents were evaporated under reduced pressure. The is then solubilised with the minimum amount of CH_2Cl_2 and precipitated with diethyl ether. The pale-yellow solid is further triturated with diethyl ether to obtain spectroscopically pure N-formyl adducts **2a–f**.

Synthesis of α-boryl isocyanide 1a–f from *N*-formyl adducts 2a–f by using $POCl_3$ and Et_3N.

In a pear-shaped flask, with magnetic stirring bar, compounds **2a–f** (1 eq., 0.1–0.67 mmol) and CH_2Cl_2 (0.1 M) were sequentially added. The solution was kept at 0°C for 5 minutes. Then Et_3N (5.0 eq.) was slowly added followed by $POCl_3$ (1.5 eq.). The reaction mixture was stirred at 0°C for 1.5 h. Afterwards the reaction was quenched with saturated $NaHCO_3$ (3 ml) and stirred for 10 minutes. The organic layer was separated and the aqueous one was extracted with CH_2Cl_2 (3 x 3 ml). The reunited organic phases were added 500 ml of Et_3N, washed with saturated $NaHCO_3$ (3 x 10 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain a-boryl isocyanide **1a–f**. Compounds **1a–f** resulted to be spectroscopically pure.

Author Contributions

F.F. and A.Z. conducted most of the experiments and developed the method. M.L.I., M.S. and E.C. repeated some of the reactions and checked the data. F. F. and F.P. conceived the project, directed the research work, and wrote the manuscript with the feedback from other authors.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

The authors acknowledge Giulia Avino for helpful discussions and Centro Interdipartimentale Grandi Strumenti (CIGS) of the University of Modena and Reggio Emilia for technical assistance. LC-MS/MS instruments at CIGS were granted by the Foundation "Fondazione Cassa di Risparmio di Modena – FCRM."

Research reported in this publication was supported by facilities and funds provided by Department of Life Sciences, Università degli Studi di Modena e Reggio Emilia and Ministry of University and Research (MUR) to F.F. (FAR-DSV 2019, FFABR N° E51I17000660005) and E.C. (FAR-DSV 2016, FFABR N° E51I17000650005).

Notes and references

1 (a) *Synthesis and Application of Organoboron Compounds*, ed. E. Fernandez, A. Whiting, Springer International, Cham, 2015; (b) *Boronic acids: Preparation and Application in Organic Synthesis, Medicine and Materials*, ed. D. G. Hall., Wiley, Weinheim, 2nd rev. edition, 2011.

2 D. B. Diaz and A. K. Yudin, *Nat. Chem.* 2017, **9**, 731.

3 (a) D. S. Matteson *Chem. Rev.* 1989, **89**, 1535; (b) D. S. Matteson *Acc. Chem. Res.* 1988, **21**, 294.

4 a) M. Beenen, C. An, J. Ellman, *J. Am. Chem. Soc.* 2008, **130**, 6910; b) A. Buesking, V. Bacauanu, I. Cai, J. Ellman, *J. Org. Chem.* 2014, **79**, 3671.

5 (a) J. Adams, M. Behnke, A. A. Cruickshank, L. R. Dick, L. Grenier, J. M. Klunder, J.-M. Ma, L. Plamondon, R. L. Stein *Bioorg. Med. Chem. Lett.* 1998, **8**, 333; (b) Y. Li, M. Plesescu, P. Sheehan,J. S. Daniels, S. R. Prakash, *J. Labelled Compd. Radiopharm.* 2007, **50**, 402; (c) I. F. Pickersgill, J. Bishop, C. Koellner, J.-M. Gomez, A. Geiser, R. Hett, V. Ammoscato, S. Munk, Y. Lo, F.-T. Chui, V. R. Kulkarni, WO Patent Appl., 2005097809, 2005; d) A. S. Ivanov, A. A. Zhalnina, S. V. Shishkov, *Tetrahedron*, 2009, **65**, 7105 e) J. Tan, J. J. Grouleff, Y. Jitkova, D. B. Diaz, E. C. Griffith, W. Shao, A. F. Bogdanchikova, G. Poda, A. D. Schimmer, R. E. Lee and Andrei K. Yudin *J. Med. Chem* 2019, **62**, 6377.

6 a) *Multicomponent Reactions*, ed J. Zhu, H. Bienaymé, Wiley-VCH, Weinheim, 2005; b) R. Riva, L. Banfi, A. Basso in *Science of Synthesis: Multicomponent Reaction*; ed. T. J. J. Müller; Thieme: Stuttgart, Germany, vol. 1, 2012.

7 In 1995 Van Leusen reported the first α-boryl isocyanide with tricoordinated boron atom stable up to -30°C: J. Versleijen, P. Faber, H. Bodewes, A. Braker, D. van Leusen, A. van Leusen, *Tetrahedron Lett.* 1995, **36**, 2109;

8 A. Zajdlik, Z. Wang, J. L. Hickey, A. Aman, A. D. Schimmer, A. K. Yudin *Angew. Chem. Int. Ed.* 2013, **52**, 8411.

9 a) M. Passerini, L. Simone *Gazz. Chim. Ital.* 1921, **51**, 126, b) M. Passerini, G. Ragni *Gazz. Chim. Ital.* 1931, **61**, 964 c) R. H. Baker, A. H. Schlesinger, *J. Am. Chem. Soc.* 1945, **67**, 1499; d) S.-X. Wang, M.-X. Wang, D.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* 2008, **47**, 388; e) I. Ugi, *Angew. Chem. Int. Ed.* 1962, **1**, 8; f) R. Ramozzi, K. Morokuma, *J. Org. Chem.* 2015, **80**, 5652.

10 a) I. Ugi, F. K. Rosendahl, F. Bodesheim, *Justus Liebigs Ann. Chem.* 1963, **666**, 54; b) S. Lehnhoff, M. Goebel, R. M. Karl, R. Klçsel, I. Ugi, *Angew. Chem. Int. Ed.* 1995, **34**, 1104; c) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* 2000, **39**, 3168; d) M. Waki, J. Meienhofer, *J. Am. Chem. Soc.* 1977, **99**, 6075; e) E. Ruijter, R. Scheffelaar, R.V.A. Orru, *Angew. Chem. Int. Ed.* 2011, **50**, 6234. F) J. Zhang, P Yu, S.-Y. Li, H. Sun, S.-H. Xiang, J. Wang, K. N. Houk, B. Tan, *Science*, 2018, **361**, 1087.

11 a) Z. He, A. K. Yudin, *J. Am. Chem. Soc.* 2011, **133**, 13770; b) Z. He, A. Zajdlik, J. D. St. Denis, N. Assem, A K. Yudin *J. Am. Chem. Soc.* 2012, **134**, 13774.

12 J. Li, M. D. Burke, *J. Am. Chem. Soc.* 2011, **133**, 13774

13 a) G. Liu, D. Cogan, J. Ellman, *J. Am. Chem. Soc.* 1997, **119**, 9913; b) J. Ellman, T. Owens, T. Tang, *Acc. Chem. Res.* 2002, **35**, 984; c) M. Robak, M. Herbage, J. Ellman, *Chem. Rev.* 2010, **110**, 3600.

14 See Electronic Supporting Information (ESI) for more details.

15 W. Ye. C. Ni, J. Hu, J. Fluor. Chem. 2020, **231**, 109451.

16 Other *N*-formyl aromatic derivatives containing pinandiolyl or *N*-methyldiethanolamine boron protection were synthesised using Matteson homologation protocol. Unfortunately, these substrates were not suitable for simple dehydration at 0 °C, -20°C or -78°C with the most common dehydrating agents, and only deboronated side products or complex reaction mixtures were obtained.