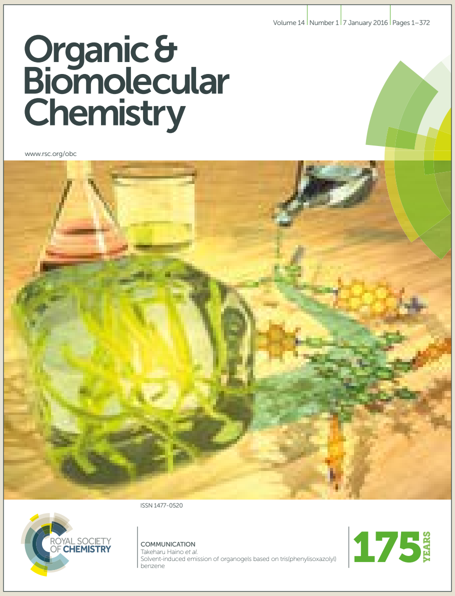
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: X. Ou, R. Labes, C. Battilocchio and S. V. Ley, *Org. Biomol. Chem.*, 2018, DOI: 10.1039/C8OB01831F.



Volume 14 | Number 1 | 7 January 2016 | Pages 1–372

Organic & Biomolecular Chemistry

www.rsc.org/obc

ISSN 1477-0520

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION
Takeharu Haino et al.
Solvent-induced emission of organogels based on tris(phenylisoxazolyl)benzene

175 YEARS

View Article Online
DOI: 10.1039/C8OB01831F

Journal Name

COMMUNICATION

Preparation of homoallylic amines via a three-component coupling process†

Xiaoxu Ou,[a] Ricardo Labes,[a] Claudio Battilocchio,[a,b]* Steven V. Ley[a]*

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

A three-component synthesis of homoallylic amines is described. The allylboronic species were generated in situ by homologation of vinyl boroxines with trimethylsilyldiazomethane, then followed by trapping of the allylboron intermediate with imines. Twenty-seven compounds were successfully prepared in moderate to high yields. Imines bearing various functional groups were tolerated, including aliphatic, aromatic and heteroaromatic substituents. Further elaboration of some of the homoallylic amines to form azeditines is also reported.

Homoallylic amines occur as a structural feature in various alkaloids and anti-cancer agents (Figure 1).[1] As a result, there is interest in developing efficient strategies for the formation of these particular entities.

Of special merit for their preparation is the addition of allylboronic derivatives to imines.[2-5] The first diastereoselective allylboration of acyclic imines by allylic boroxines under anhydrous conditions was reported in 2014.[2] In this particular case, the authors selected three boroxines, which were prepared via a Pd-catalysed procedure.[6] Despite the lack of stability and the limited scope of the boroxine component, the method has broad imine scope.

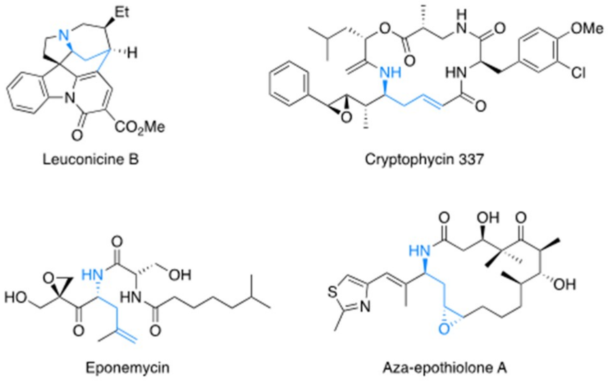


Figure 1 Natural products containing the homoallylic amine motif.

Concerning the allylation of imines to afford homoallylic amines, although there are many reported studies to show applicability of the various methods, there is however a need for a complementary, more general method which would result in a broader scope of the boronic precursors.

Recently we have described a metal-free route to afford homoallylic alcohols via in situ generation of allyl boronic species, which are initially formed from (trimethylsilyl)diazomethane (TMSCHN$_2$) and a vinyl boronic acid, and trapped with aldehydes.[7] In addition to this, recent DFT studies[8] have shed light on the role that boroxines play in the reactivity of this system.

Based on this previous work, we explored the use of boroxines as reactive species to afford a broad class of homoallylic amines, via homologation with TMSCHN$_2$ followed by combination with a variety of substituted imines.

In Table 1, *N*-methyl benzaldimine **2** and chloro-methylvinyl boroxine **1** were selected as model substrates for initial studies. The reaction was performed under anhydrous conditions, to avoid hydrolysis of the boroxine, and a 1:1 ratio of trimethylsilyldiazomethane vs boroxine was initially investigated. When 1 equivalent of imine and boroxine were reacted with trimethylsilyldiazomethane in CH$_2$Cl$_2$ at room temperature for 24 hrs (Table 1, entry 1), we could isolate the homoallylic amine 3 as a single diastereomer, but only in 13% yield, alongside unreacted starting material and homoallylic alcohol byproduct **4**.

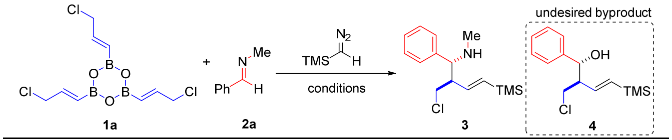
A series of further experiments highlighted that the yield and reaction rate were affected by the stoichiometry of the boroxine (Table 1, entry 3-5), whereby increasing the equivalent of boroxine to 1.5 drove the reaction to completion. Employing strictly anhydrous conditions, at 85°C, it was possible to obtain the product in 94% yield, over 6h (Entry 11).

---

[a] *Innovative Technology Centre, Department of Chemistry, University of Cambridge, Lensfield Road, CB2 1EW, Cambridge, UK. E-mail: svl1000@cam.ac.uk*
[b] *Current address: Syngenta Crop Protection, Process Research, Schaffhauserstrasse 101, CH-4332, Switzerland.*

† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx0000 Additional data is available from the University of Cambridge Data Repository Web site: https://doi.org/10.17863/CAM.26332

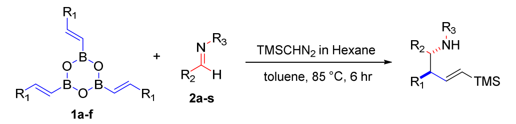
Table 1 Allylboration of arylimines with allylboroxines

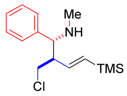


Entry	Eq. Monomeric Boroxine	Solvent	Temp	Time(h)	Additive	Yield 3 (%)
1	1	CH_2Cl_2	rt	24	-	13
2	1	CH_2Cl_2	rt	48	-	17
3	1.3	CH_2Cl_2	rt	48	-	20
4	1.5	CH_2Cl_2	rt	48	-	29
5	2	CH_2Cl_2	rt	48	-	30
6	1.5	toluene	rt	48	-	55
7	1.5	toluene	rt	48	Et_3N	0
8	1.5	toluene	rt	48	Na_2SO_4	73
9	1.5	toluene	85˚C	12	Na_2SO_4	86
10	1.5	toluene	85˚C	12	-	87
11	1.5	toluene	85˚C	6	-	94
12	1.5	toluene	85˚C	3	-	43

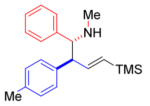
Next we explored and the scope of the method, initially varying the boroxine component. Both electron-rich (Table **2**, entry 4) and electron-deficient (Table 2, entry 5 and 6) all reacted in high yields. Alkyl and vinyl boroxines were also tolerated affording good yields of the corresponding products (Table **2**, entries 7,13,15-18 and 21-23).

Table 2 Allylboration of arylimines with allylboroxines

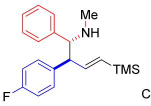




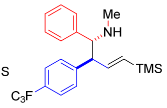
3, 94 %
d.r. = 100:1



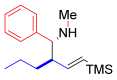
4, 86 %
d.r. = 100:1



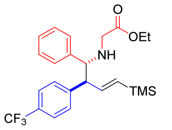
5, 75%
d.r. = 100:1



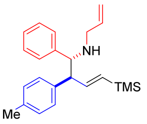
6, 64%
d.r. = 100:1



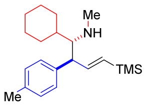
7, 66%
d.r. = 6:4



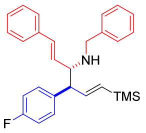
8, 63%
d.r. = 100:1



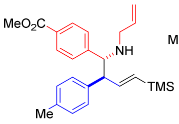
9, 67%
d.r. = 100:1



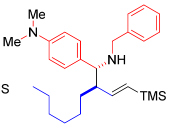
10, 81%,
d.r. = 100:1



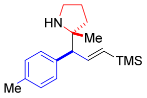
11, 69%,
d.r. = 100:1



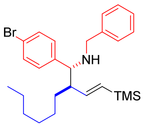
12, 81%
d.r. = 100:1



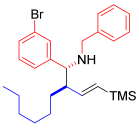
13, 96%
d.r. = 100:1



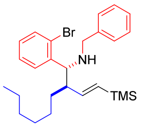
14, 89%
d.r. = 100:1



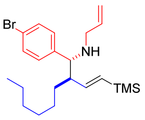
15, 81%
d.r. = 3:1



16, 63%
d.r. = 6:1



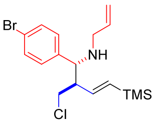
17, 73%
d.r. =6:1



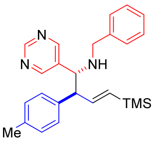
18, >99%
d.r. = 100:1

Table 2 Continued

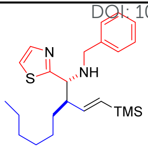
View Article Online
DOI: 10.1039/C8OB01831F



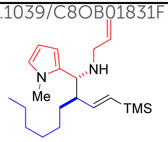
19, 94%
d.r. = 100:1



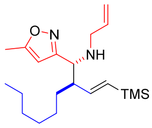
20, 67%
d.r. = 1.5:1



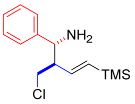
21, >99%
d.r. = 1.5:1



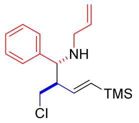
22, 98%
d.r. = 100:1



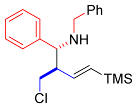
23, 94%
d.r. = 2:1



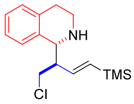
24, 65%
d.r. = 100:1



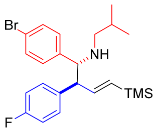
25, 73%
d.r. = 100:1



26, 76%
d.r. = 100:1



27, 41%
d.r. = 100:1



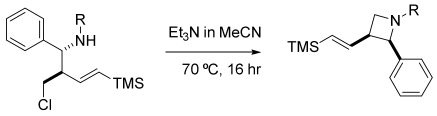
28, 48%
d.r. = 100:1

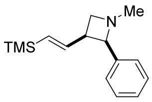
The examples demonstrate wide reaction scope tolerating heterocycles, esters, alkenes, halides and anilines. In most cases, the reactions are highly diastereoselective while in some cases moderate d.r. were observed. Yields are generally good to excellent.

This very general and mild protocol clearly sets the scene for further product transformations. One can envisage various cross-couplings, cross metathesis, deprotection and ring forming reactions for example. Similarly, the vinyl trimethylsilyl substituent can serve as a precursor for protodesilylation or halodesilylation following known procedures.[9-10]

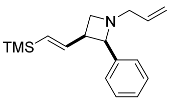
By way of an illustration, we report three examples whereby the chloromethylated precursors 3, 25 and 26 were readily converted using triethylamine to the corresponding azetidines 29-31 in essentially quantitative yields (Table 3).

Table 3 Synthesis of azetidines from homoallylic amines

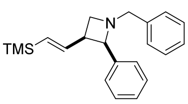




29, >99%



30, >99%



31. >99%

It is clear that this new three component coupling approach rapidly builds molecular complexity and attractively leads to a wide range of useful homoallylic amines, some of which precursors for azetidine preparation. One can anticipate further elaboration and in particular employing other reactive more substituted diazo species.

We are grateful to Syngenta Crop Protection (CB) and the EPSRC (SVL, grant # EP/K009494/1, EP/M004120/1 and EP/K039520/1) for financial support.

View Article Online
DOI: 10.1039/C8OB01831F

Conclusions

In conclusion, the method efficiently generates a wide range of potentially useful homoallylic amines through a 3-component coupling approach, involving the reaction with vinyl substituted boroxines, which were homologated in situ with trimethylsilyl diazomethane prior to being intercepted with various imines to afford a range of useful building blocks including azetidines.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 a) U. Schmidt and J. Schmidt, *Synthesis*, 1994, 300. b) R. M. Borzilleri, X. Zheng, R. J. Schmidt, J. A. Johnson, S. H. Kim, J. D. DiMarco, C. R. Fairchild, J. Z. Gougoutas, F. Y. F. Lee, B. H. Long and G. D. Vite, *J. Am. Chem. Soc.*, 2000, **122**, 8890–8897. c) A. M. Doherty, I. Sircar and B. E. Kornberg, *J. Med. Chem.*, 1992, **35**, 2–14. d) D. L. Silverio, S. Torker, T. Pilyugina, E. M. Vieira, M. L. Snapper, F. Haeffner and A. H. Hoveyda, *Nature*, 2013, **494**, 216–221.

2 R. Alam, A. Das, G. Huang, L. Eriksson, F. Himo and K. J. Szab., *Chem. Sci*., 2014, **5**, 2732–2737.

3 S. Lou, P. N. Moquist and S. E. Schaus, *J. Am. Chem. Soc.,* 2007, **129**, 15398–15404.

4 Y. Jiang and S. E. Schaus, *Angew. Chem. Int. Ed.*, 2017, **129**, 1566–1570.

5 J. L. Y. Chen and V. K. Aggarwal, *Angew. Chem. Int. Ed*., 2014, **53**, 10992–10996.

6 M. Raducan, R. Alam and K. J. Szabo., *Angew. Chem. Int. Ed.*, 2012, **51**, 13050–13053.

7 J. S. Poh, S. H. Lau, I. G. Dykes, D. N. Tran, C. Battilocchio and S. V. Ley, *Chem. Sci.*, 2016, **7**, 6803–6807.

8 C. Bomio, M. A. Kabeshov, A. R. Lit, S. H. Lau, J. Ehlert, C. Battilocchio and S. V. Ley, *Chem. Sci.*, 2017, **8**, 6031-6075.

9 W. Adam, C. R. Saha-Möller and K. S. Schmid, *J. Am. Chem. Soc.,* 2011, **22**, 7365-7371.

10 R. B. Miller and G. McGarvey, *J. Org. Chem*., 1978, **23**, 4424-4431.