# Boronic acid catalyzed ene carbocyclization of acetylenic dicarbonyl compounds†

Meiling Li,[a] Ting Yang[b] and Darren J. Dixon*[a]

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**The discovery and development of an efficient ene carbocyclization of 1,3-dicarbonyl compounds bearing pendent terminal alkyne substituents under 3-nitrobenzeneboronic acid catalysis is described. The reaction is efficient, easy to perform and general to a wide range of ketoester substrates.**

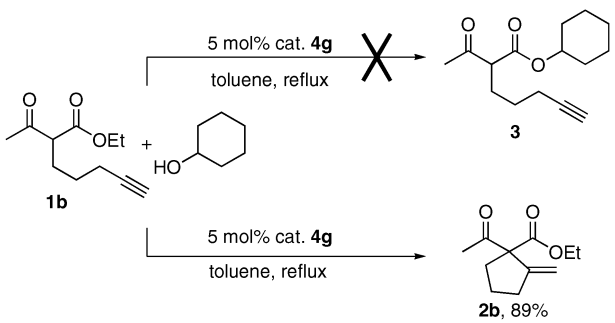
The carbocyclization of 1,3-dicarbonyl compounds to pendent alkyne functionality, first discovered by Eglinton and Whiting[1] and then developed by Conia and Perchec,[2] has received much attention in recent years.[3] The reaction allows the formation of cyclopentanes bearing a methylene substituent adjacent to the newly formed quaternary centre and can be conducted under thermal[2] conditions, strong mineral acid,[4] base,[1] or metal ion catalysis.[5–9] Nevertheless, the application of the ene carbocyclization of acetylenic dicarbonyl compounds in organic synthesis is limited because of the harsh experimental conditions that are often required. Recently, the use of transition metal catalysis has allowed a notable improvement to the reaction conditions. For example, Cu(I),[4,10] Au(I),[5] Ni(II)[6] all proved to be efficient catalysts for the cyclization of alkynoic esters.[11] Other than the use of strong mineral acids or alkoxide bases, to the best of our knowledge, no other transition-metal free method has been reported to efficiently catalyze the ene carbocyclization of acetylenic dicarbonyl compounds. Herein we wish to describe the discovery and development of the ene carbocyclization of acetylenic dicarbonyl compounds catalyzed by aryl boronic acids.

During some recent investigations in our laboratories,[10] we required β-ketoester derivative **3** and, to us, a direct route from **1b** was attractive. Following the report of Tale *et al.*, we attempted the transesterification of **1b** with cyclohexanol in the presence of 5 mol% 3-nitrobenzeneboronic acid **4g**.[12] To our surprise, the cyclized product **2b** was formed in 89% yield, and no evidence of the expected ester **3** was detected in the $^1$H-NMR spectrum of the crude reaction mixture (Scheme 1). Having uncovered a new catalytic process, we decided to explore the scope and mechanism of this reaction and herein we report our findings.

Initially a range of catalysts related to 3-nitrobenzeneboronic acid were screened for catalytic activity in the ene carbocyclization of **1a** and the results are summarised in Table 1. Indeed many benzeneboronic acids were catalytically active, as was the Lewis acid tris(pentafluorophenyl)borane **4f** which gave good conversion (95%) after 16 hours in boiling toluene. However, boric acid **4a** gave only 8% conversion under the same conditions. Of the benzeneboronic acids those bearing electron withdrawing groups afforded better reactivity than those with electron donating groups, presumably due to their increased acidity.[13] The most efficient was found to be 3-nitrobenzeneboronic acid (entry 7, Table 1). In order to identify the optimal conditions, a further screen of catalyst loading using 3-nitrobenzeneboronic acid was also performed. Complete conversion was achieved with 5 and 10 mol% boronic acid **4g** in 16 h and 20 h respectively. When 2 mol% of boronic acid **4g** was used, a slower reaction rate was observed (45% conversion after 48 h in boiling toluene).

With optimal conditions established, a range of α-pentynyl-β-ketoesters was readily prepared[14] and treated with 5 mol% of 3-nitrobenzeneboronic acid in boiling toluene. The results are presented in Table 2.

As expected from our initial discovery (Scheme 1) and the subsequent optimization study (Table 1), linear and α-branched aliphatic keto-esters were good substrates and were efficiently transformed to the corresponding carbocyclic products (Table 2, entries 1–4). Both electron rich and electron deficient aryl ketone substrates reacted smoothly and efficiently. However, prolonged reaction times were required for aryl ketones substituted with *para*-electron donating groups (Table 2, entry 11) while *ortho*- and *meta*-substituted aromatic substrates gave comparable reaction rates. The ester moiety had minimal influence on the reaction rate and methyl, ethyl, benzyl and *tert*-butyl esters were all well-tolerated. Also a keto-amide substrate **1o** proved to be an excellent substrate, affording the carbocyclic product in 75% isolated yield (Table 2, entry 15). The 3-nitrobenzeneboronic acid catalysis

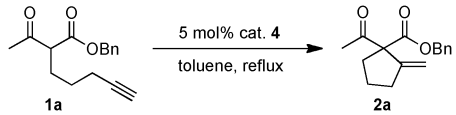


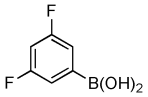
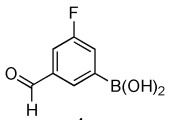
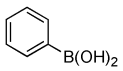
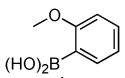
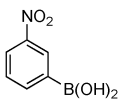

**Scheme 1** Discovery of the boronic acid catalyzed ene carbocyclization of acetylenic dicarbonyl compounds.

[a] *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK. E-mail: Darren.Dixon@chem.ox.ac.uk; Fax: +44 (0)1865 285002; Tel: +44 (0)1865 275648*
[b] *School of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK*

† Electronic supplementary information (ESI) available: Experimental procedures and spectral data for compounds **2a–q**. See DOI: 10.1039/b924899d

**Table 1** Identification of optimal catalysts and loading




| Entry | Catalyst | Loading/mol% | Time/h | Conv.[a] (%) |
|---|---|---|---|---|
| 1 | $B(OH)_3$ **4a** | 5 | 16 | 8 |
| 2 |  **4b** | 5 | 16 | 67 |
| 3 |  **4c** | 5 | 16 | 82 |
| 4 |  **4d** | 5 | 16 | 78 |
| 5 |  **4e** | 5 | 16 | 47 |
| 6 | $B(C_6F_5)_3$ **4f** | 5 | 16 | 95 |
| 7 |  **4g** | 5<br>2<br>10 | 16<br>48<br>20 | 100<br>45<br>100 |

[a] Conversion by $^1$H NMR analysis of crude reaction products.

was also effective in the case of 1,3-ketones; diketone **1p** was converted to methylene cyclopentane **2p** in an excellent 95% yield after 30 h (Table 2, entry 16).

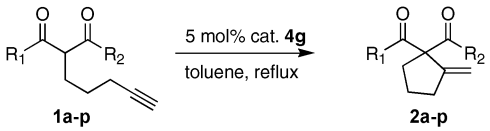
To further extend the scope of the reaction bis-keto ester **1q** was subjected to the optimal conditions and afforded **2q**, the product of two sequential carbocyclic reactions, in an excellent 95% yield after 17 h (Scheme 2).

As well as synthetically useful, the 3-nitrobenzeneboronic acid catalyzed ene carbocyclization of acetylenic dicarbonyl compounds was also interesting from a mechanistic point of view. Carbocyclization using deuterium labeled ketoester **5** with catalyst **4g** resulted in the production of (*E*)-**6** consistent with a concerted *syn*-addition step to the alkyne (Scheme 3).

Although a number of mechanistic pathways consistent with these data can be envisaged, the most likely role of the 3-nitrobenzeneboronic acid is to catalyze the enolization of the 1,3-dicarbonyl starting material. A subsequent concerted ene reaction of the enol form of the starting material would then afford the product with observed stereochemistry (Scheme 4). This pathway is consistent with the obtained data and is aligned to previous mechanistic proposals.[2,7]

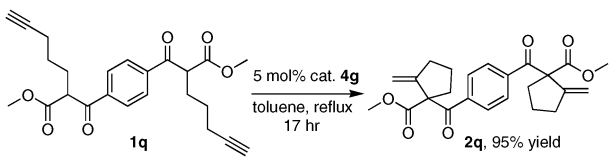
In summary, an attempted transesterification of a β-ketoester substrate bearing a pendent terminal alkyne substituent at the α-position led to the discovery of an efficient 3-nitrobenzeneboronic acid catalyzed ene carbocyclization of acetylenic dicarbonyl compounds. The reaction is easy to perform, efficient, broad in scope and provides a convenient

**Table 2** The scope of the ene carbocyclization of acetylenic dicarbonyl compounds catalyzed by **4g**

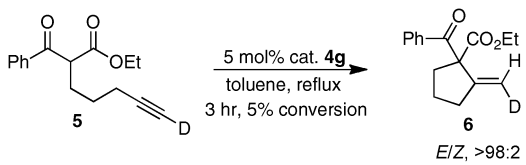



| Entry | Products | $R_1$ | $R_2$ | Time/h | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | **2a** | Me | –OBn | 16 | 90 |
| 2 | **2b** | Me | –OEt | 22 | 92 |
| 3 | **2c** | Et | –OMe | 54 | 56 |
| 4 | **2d** | *i*-Pr | –OMe | 23 | 88 |
| 5 | **2e** | Ph | –OEt | 18 | 97 |
| 6 | **2f** | Ph | –O*t*-Bu | 16 | 93 |
| 7 | **2g** | Ph | –OBn | 16 | 98 |
| 8 | **2h** | *o*-Me Ph | –OMe | 30 | 76 |
| 9 | **2i** | *m*-Me Ph | –OMe | 36 | 96 |
| 10 | **2j** | *m*-OMe Ph | –OMe | 24 | 98 |
| 11 | **2k** | *p*-OMe Ph | –OMe | 190 | 91 |
| 12 | **2l** | 3,4-Dichlorophenyl | –OMe | 16 | 95 |
| 13 | **2m** | *p*-Br Ph | –OMe | 70 | 90 |
| 14 | **2n** | *p*-Ph Ph | –OMe | 30 | 96 |
| 15 | **2o** | Ph | –NHPh | 40 | 75 |
| 16 | **2p** | Ph | –Me | 30 | 95 |

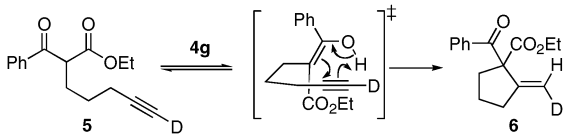
[a] Isolated yield after flash column chromatography.




**Scheme 2** Extension to a doubly substituted substrate.




**Scheme 3** Deuterium labelling study.




**Scheme 4** Postulated mechanistic pathway.

transition-metal free alternative to existing catalytic protocols. Further work to uncover new catalytic reactions using boronic acids is under investigation and will be reported in due course.

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## Notes and references

1 G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 1953, 3052.
2 J. M. Conia and P. L. Perchec, *Synthesis*, 1975, 1.
3 J. S. Fisk and J. J. Tepe, *J. Am. Chem. Soc.*, 2007, **129**, 3058.

 

4 M. A. Boaventura, J. Drouin and J. M. Conia, *Synthesis*, 1983, 801.
5 C. L. Deng, R. J. Song, S. M. Guo, Z. Q. Wang and J. H. Li, *Org. Lett.*, 2007, **9**, 5111.
6 J. J. Kennedy-Smith, S. T. Staben and F. D. Toste, *J. Am. Chem. Soc.*, 2004, **126**, 4526.
7 Q. Gao, B. F. Zheng, J. H. Li and D. Yang, *Org. Lett.*, 2005, **7**, 2185.
8 B. K. Corkey and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 17168.
9 C. L. Deng, T. Zou, Z. Q. Wang, R. J. Song and J. H. Li, *J. Org. Chem.*, 2009, **74**, 412.
10 T. Yang, A. Ferrali, F. Sladojevich, L. Campbell and D. J. Dixon, *J. Am. Chem. Soc.*, 2009, **131**, 9140.
11 For other examples, see references cited in references 9 and 10.
12 R. H. Tale, A. D. Sagar, H. D. Santan and R. N. Adude, *Synlett*, 2006, 415.
13 D. G. Hall, *Boronic Acids*, WILEY-VCH Verlag Gmbh & Co. KGaA, Weinheim, 2005.
14 D. Brillon and P. Deslongchamps, *Can. J. Chem.*, 1987, **65**, 43.