Homogeneous Catalysis

International Edition: DOI: 10.1002/anie.201703471
German Edition: DOI: 10.1002/ange.201703471

Rhodium-Catalyzed Addition of Aryl Boronic Acids to 2,2-Disubstituted Malononitriles

Christian A. Malapit, Donald R. Caldwell, Irungu K. Luvaga, Jonathan T. Reeves, Ivan Volchkov, Nina C. Gonnella, Zhengxu S. Han, Carl A. Busacca, Amy R. Howell, and Chris H. Senanayake*

Abstract: *β-Ketonitriles bearing a quaternary carbon at the 2-position were prepared through Rh-catalyzed addition of aryl boronic acids to 2,2-disubstituted malononitriles. In contrast to the previously described transnitrilative cyanation of aryl boronic acids with dialkylmalononitriles, the present reaction avoids retro-Thorpe collapse of the intermediate addition product through the use of a milder base. The reaction was amenable to a variety of aryl boronic acids and disubstituted malononitriles, providing a diverse array of β-ketonitriles. The products could be further derivatized to valuable chiral α,α-disubstituted-β-aminonitriles through addition reactions to the corresponding N-tert-butanesulfinyl imines.*

β-Ketonitriles are valuable compounds in organic synthesis.[1] They may be used in Knoevenagel condensations,[2] as building blocks for heterocycles,[3] and as components of copolymers with tunable hydrophilic or hydrophobic properties.[4] Stereoselective reduction of β-ketonitriles gives access to chiral β-hydroxynitriles or 1,3-aminoalcohols that have significant synthetic utility.[5] β-Ketonitriles or their derivatives are present in numerous natural products[6] and pharmaceuticals.[7]

β-Ketonitriles bearing 2,2-disubstitution are less prevalent than mono- and unsubstituted homologues, most likely due to the limited methods described for their preparation.[8] The addition of α,α-disubstituted nitrile anions to acylbenzotriazoles was reported by Katritzky and co-workers (Figure 1 A).[9] More recently, Skrydstrup and Beller described a Pd-catalyzed carbonylative arylation of nitrile anions to give β-ketonitriles (Figure 1 B).[10] We recently reported the Rh-catalyzed cyanation of aryl boronic acids by a transnitrilation with dimethylmalononitrile (Figure 1 C).[11] We postulated that this reaction proceeds through initial addition of the aryl boronic acid to one of the nitrile groups, and subsequent retro-Thorpe fragmentation of the N-protonated iminonitrile adduct **A** to give the aryl nitrile product as well as isobutyronitrile.[12] During optimization studies for this reaction, we found varying amounts of β-ketonitrile byproduct **B** were formed depending on the reaction conditions. The β-ketonitrile would result from either hydrolysis of adduct **A** prior to retro-Thorpe fragmentation, or from a lack of retro-Thorpe fragmentation of **A** and subsequent hydrolysis during workup.[13] Given the potential utility of a one-step synthesis of valuable 2,2-disubstituted β-ketonitriles from widely available aryl boronic acids and disubstituted malononitriles, we re-examined the reaction conditions employed for transnitrilation, with the goal of suppressing the retro-Thorpe fragmentation pathway and making β-ketonitrile **B** the exclusive product (Figure 1 D). Herein, we describe the development of reaction conditions that offer a new disconnection for accessing structurally diverse 2,2-disubstituted β-ketonitriles.

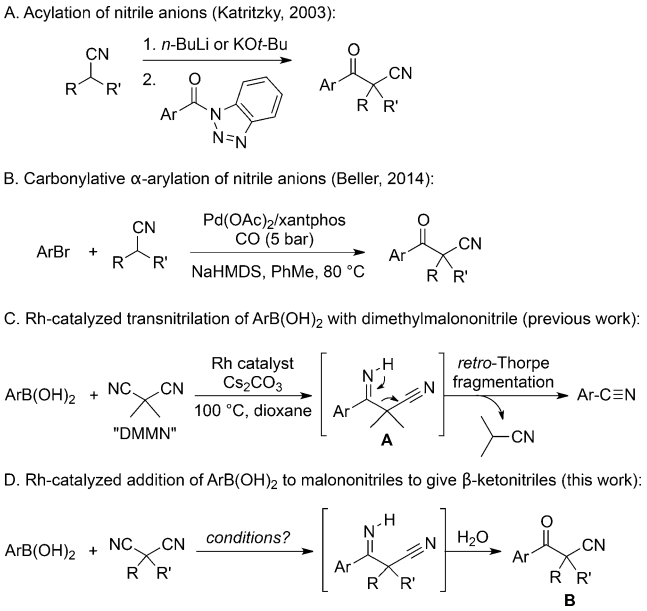
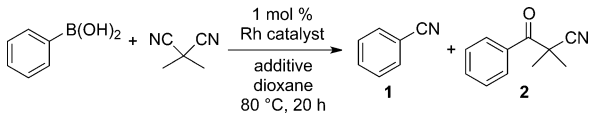


Figure 1. Methods for 2,2-disubstituted β-ketonitrile synthesis and reaction pathways for aryl boronic acid addition to malononitriles.

We began with a screen of parameters in the reaction of phenyl boronic acid with dimethylmalononitrile to give either benzonitrile (**1**) or 2,2-dimethyl-3-oxo-3-phenylpropanenitrile (**2**; Table 1). The optimized conditions for transnitrilation are given in entry 1 (1 mol% $[RhCl(cod)]_2$, 2 equiv Cs_2CO_3,

[*] Dr. J. T. Reeves, Dr. I. Volchkov, Dr. Z. S. Han, Dr. C. A. Busacca, Dr. C. H. Senanayake
Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road, Ridgefield, CT 06877-0368 (USA)
E-mail: jonathan.reeves@boehringer-ingelheim.com
Dr. N. C. Gonnella
Material and Analytical Sciences
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road, Ridgefield, CT 06877-0368 (USA)
C. A. Malapit, D. R. Caldwell, I. K. Luvaga, Prof. Dr. A. R. Howell
Department of Chemistry, University of Connecticut
55 North Eagleville Road, Storrs, CT 06269-3060 (USA)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201703471.

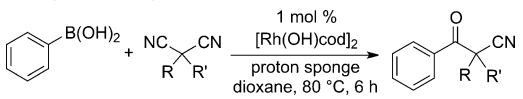
Table 1: Screening of catalysts and additives, and the effect of temperature.[a]

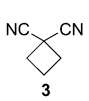
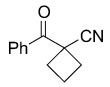
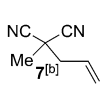
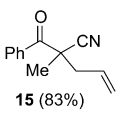
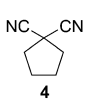
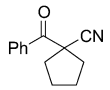
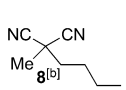
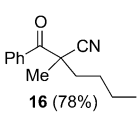
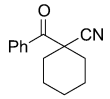
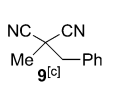
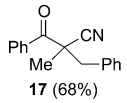
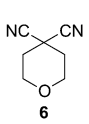
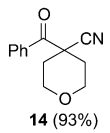
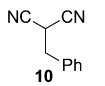
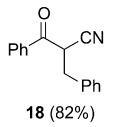


Entry	Catalyst	Additive (2 equiv)	Yield **1** [%][b]	Yield **2** [%][b]
1	$[RhCl(cod)]_2$	Cs_2CO_3; 100 °C	93 (89)	5
2	$[RhCl(cod)]_2$	K_3PO_4	25	71
3	$[RhCl(cod)]_2$	$ZnCl_2$	8	36
4	$[RhCl(cod)]_2$	CuI	7	30
5	$[RhCl(cod)]_2$	K_3PO_4; 1 equiv H_2O	8	55
6[c]	$Rh(nor)_2BF_4$	K_3PO_4; 1 equiv H_2O	3	28
7[c]	$Rh(cod)_2OTf$	K_3PO_4; 1 equiv H_2O	5	30
8	$[Rh(OH)(cod)]_2$	K_3PO_4; 1 equiv H_2O	5	68 (55)
9	$[Rh(OH)(cod)]_2$	*i*-Pr_2NEt	2	90
10	$[Rh(OH)(cod)]_2$	Proton sponge	0	98 (95)[d]
11	$[RhCl(cod)]_2$	Proton sponge	0	95[d]

[a] Reaction conditions: 0.75 mmol $PhB(OH)_2$, 0.50 mmol DMMN, 1 mol% catalyst and 1 mmol additive in 1 mL dioxane at 80 °C, 20 h. [b] HPLC assay yields; values in parentheses are isolated yields. [c] 2 mol% catalyst. [d] Reaction time of 4 h. cod = 1,5-cyclooctadiene, nor = norbornene, Proton sponge = 1,8-bis(dimethylamino)naphthalene.

Table 2: Scope with respect to the malononitrile.[a]



Dinitrile	Product (Yield)	Dinitrile	Product (Yield)
 **3**	 **11** (78%)	 **7**[b]	 **15** (83%)
 **4**	 **12** (92%)	 **8**[b]	 **16** (78%)
 **5**	 **13** (90%)	 **9**[c]	 **17** (68%)
 **6**	 **14** (93%)	 **10**	 **18** (82%)

[a] Reaction conditions: 1.5 equiv $PhB(OH)_2$, 1.0 equiv malononitrile, 1 mol% $[Rh(OH)cod]_2$ and 2.0 equiv proton sponge in 2 mL dioxane at 80 °C, 6 h; yields of isolated product are given. [b] Reaction was done at 100 °C. [c] Reaction time of 24 h.

dioxane, 100 °C). Under these conditions, the transnitrilation pathway is predominant, and **1** and **2** are formed in 93% and 5% assay yields, respectively.[11] It was noted that the use of K_3PO_4 as the base resulted in a shift towards favoring the β-ketonitrile product **2** (71% assay yield, entry 2). We thought the addition of water to the reaction mixture would facilitate hydrolysis of the putative iminonitrile adduct and potentially further increase the amount of β-ketonitrile formation. However, the inclusion of 1 equiv of water in reactions with different Rh catalysts resulted in reduced assay yields of **2** and **1** (entries 5–8). The use of $[RhOH(cod)]_2$ as the catalyst provided the best ratio of **2** to **1** of 68:5 (entry 8). A breakthrough in both yield and selectivity occurred when organic amine bases were employed instead of inorganic bases. When Hünig's base was used (entry 9), the β-ketonitrile product **2** was formed in 90% assay yield, while only 2% assay yield of **1** was detected. The best results were obtained with a proton sponge. Under these conditions, the reaction was completely selective for **2**. With either $[RhOH(cod)]_2$ or $[RhCl(cod)]_2$ as the catalyst, the reaction was complete after just 4 h, and **2** was formed in 98% and 95% assay yields, respectively (entries 10 and 11). Due to the slightly higher yield obtained with $[RhOH(cod)]_2$, the conditions of entry 10 were chosen as optimal.

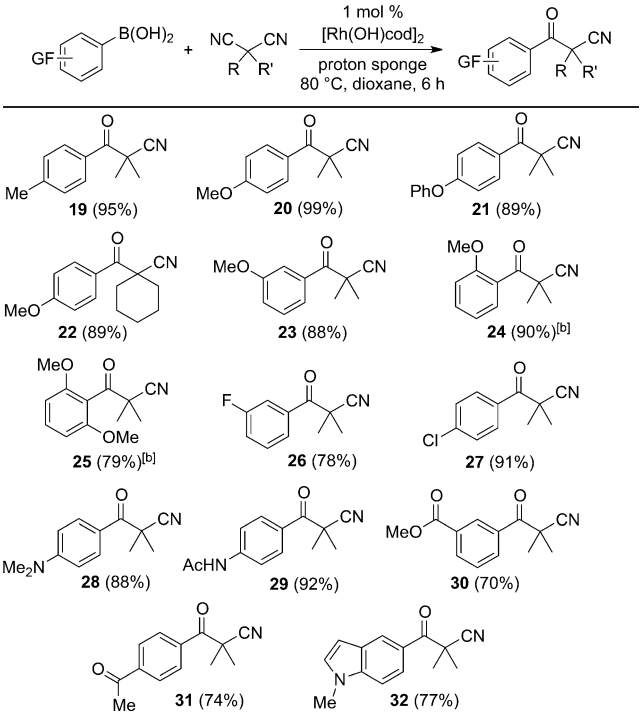
With the optimized reaction conditions in hand, the scope of β-ketonitrile formation was examined with respect to the dialkylmalononitrile (Table 2). The reaction was compatible with both cyclic (**3**–**6**) and acyclic (**7**–**10**) malononitriles, giving β-ketonitrile products in yields ranging from 68–93%. The reaction was sensitive to steric hindrance, since reduced yields were obtained with acyclic malononitriles relative to the tied-back cyclic malononitriles. The lowest yield of 68% was observed for the bulkiest malononitrile **9** (product **17**), for which the reaction time was extended from 6 to 24 h. Notably, the use of mono-substituted malononitrile **10**, which bears an acidic α-proton, was possible and gave β-ketonitrile **18** in 82% yield.

The reaction scope was next explored with respect to variation of the aryl boronic acid structure (Table 3). The presence of *p*-methyl, *p*-methoxy, *p*-phenoxy, or *m*-methoxy substituents on the aryl boronic acid resulted in excellent yields of products **19**–**23**. 2-Methoxy substitution of the boronic acid was tolerated (product **24**), though the reaction was run at increased temperature. The sterically hindered 2,6-disubstituted product **25** could also be formed in good yield at 100 °C. Halogens such as fluoride and chloride were amenable (products **26** and **27**), as were functional groups such as amine (**28**), acetamide (**29**), ester (**30**), and ketone (**31**) groups. Importantly, the presence of the ester and ketone functional groups would likely not be tolerated by the nitrile anion carbonylation method of Skrydstrup and Beller.[10] Finally, the reaction was possible with a heterocyclic boronic acid, giving indolyl product **32** in 77% yield.

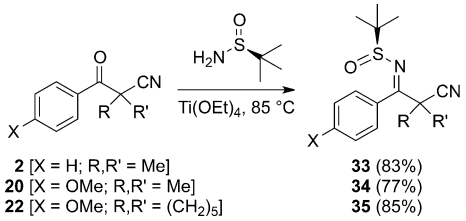
The utility of the β-ketonitrile products was demonstrated by diastereoselective additions to the derived *tert*-butanesulfinyl ketimines to give β-aminonitriles. The requisite ketimines were prepared through condensation of (*S*)-*tert*-butanesulfinamide with the β-ketonitrile in the presence of neat $Ti(OEt)_4$ (Scheme 1).[14] Imines **33**–**35** were obtained as single geometrical isomers in good yields.

With the β-ketiminonitriles in hand, the diastereoselective addition of nucleophiles was explored (Table 4). Reduction with $NaBH_4$ gave β-aminonitrile **36** in > 97:3 diastereoselectivity and 94% yield. The addition of MeLi proceeded in high yield and diastereoselectivity, giving the α-quaternary-β-quaternary aminonitrile **37**. The production of such a sterically hindered system in a diastereoselective manner is, to the best

Table 3: Scope with respect to the aryl boronic acid.[a]

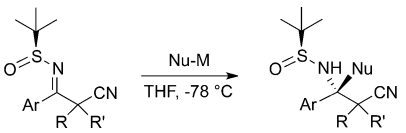


[a] Reaction conditions: 1.5 equiv aryl boronic acid, 1.0 equiv malononitrile, 1 mol% $[Rh(OH)cod]_2$ and 2.0 equiv proton sponge in 2 mL dioxane at 80 °C, 6 h; yields of isolated product are given. [b] Reaction was done at 100 °C.



Scheme 1. Conversion of β-ketonitriles into β-(*N-tert*-butanesulfinylimino)nitriles. Reaction conditions: 1.0 equiv β-ketonitrile, 1.5 equiv (*S*)-*tert*-butanesulfinamide, 6 equiv $Ti(OEt)_4$, 85 °C, 4 h; yields of isolated product are given.

Table 4: Diastereoselective additions to β-(*N-tert*-butanesulfinylimino)-nitriles.[a]



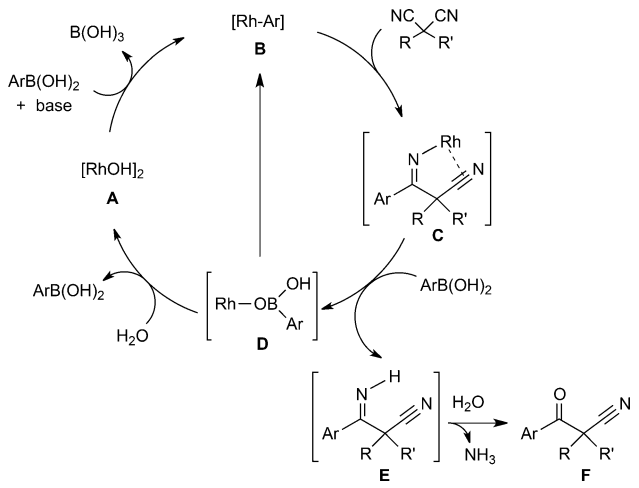
Nucelophile	Product (Yield, d.r.)[b,c]	Nucelophile	Product (Yield, d.r.)[b,c]
$NaBH_4$	**36** (94%, d.r. >97:3)		**40** (84%, d.r. 94:6)
MeLi	**37** (92%, d.r. >97:3)		**41** (79%, d.r. >97:3)
PhCCLi	**38** (97%, d.r. >97:3)		**42** (72%, d.r. >97:3)
PhLi	**39** (98%, d.r. >97:3)		**43** (89%, d.r. >97:3)

[a] Reaction conditions: 1.2–3.0 equiv Nu-M, 1.0 equiv *N-tert*-butanesulfinyl imine, THF, −78 °C; see the Supporting Information for details; yields of isolated product are given. [b] Yield of isolated product for the major diastereomer after purification. [c] Diastereomeric ratio as determined by ^1H NMR of the crude product.

of our knowledge, not easily accomplished by alternative methods. The addition of lithium phenylacetylide gave adduct **38** in near quantitative yield and >97:3 diastereoselectivity. Addition of PhLi gave the differentially arylated adduct **39** in excellent yield and selectivity. The addition of 2-thienyllithium gave heterocyclic adduct **40** in good yield with 94:6 diastereoselectivity. We described the highly diastereoselective addition of carbamoyl anions to *N*-sulfinyl aldimines and ketimines in 2013.[15] The present β-(*N-tert*-butanesulfinylimino)nitrile substrates were also compatible with carbamoyl anion nucleophiles. The addition of *N,N*-diisopropylcarbamoyllithium gave the sterically congested α-amino-β-cyano amide **41** in 79% yield and >97:3 diastereoselectivity. The stereochemistry of **41** was confirmed by X-ray crystal structure analysis and shown to be (*S*) for the newly formed stereocenter.[16] This mode of addition is consistent with our observations for the addition of carbamoyllithiums to *N*-sulfinyl ketimines.[15,17,18] The addition of a thiocarbamoyl anion was also possible, giving thioamide **42** in 72% yield and >97:3 diastereoselectivity. Finally, a Mannich-type addition of *tert*-butyl acetate lithium enolate proceeded smoothly to give the β-amino-γ-cyanoester **43** in 89% yield and >97:3 diastereoselectivity.

The proposed mechanism of the Rh-catalyzed β-ketonitrile formation is shown in Scheme 2. Transmetallation of the boronic acid with catalyst **A** would give the arylrhodium **B**. Carbometallation of the malononitrile with **B** would give the Rh-ketimine **C**. Protonolysis of the imine nitrogen would generate the β-iminonitrile **E** as well as the rhodium borate **D**. Species **D** could regenerate the arylrhodium **B** or undergo hydrolysis to give catalyst **A** and aryl boronic acid. Due to the use of a proton sponge as a base instead of Cs_2CO_3, retro-Thorpe fragmentation of **E** does not occur, and the N-H imine is hydrolyzed during workup to give the β-ketonitrile product **F**.

In conclusion, we have described the synthesis of β-ketonitriles through the Rh-catalyzed addition of arylboronic acids to 2,2-disubstituted malononitriles. This unique discon-



Scheme 2. Proposed mechanism for the rhodium-catalyzed addition of aryl boronic acids to malononitriles. Ligands on the rhodium were omitted to simplify the representation.

nection enables the synthesis of structurally diverse β-ketonitriles with sterically demanding α,α-disubstitution. The reaction was also possible with a mono-substituted malononitrile. The process offers complimentary starting materials compared with the Katritzky[9] and Skrydstrup/Beller[10] methods, and proceeds under less strongly basic reaction conditions. The addition of nucleophiles to the derived *N-tert*-butanesulfinyl imines gave access to sterically demanding α,α-disubstituted-β-aminonitriles with high diastereoselectivity.

Experimental Section

Typical procedure: Under a nitrogen atmosphere, a mixture of phenylboronic acid (366 mg, 3.0 mmol), DMMN (188 mg, 2.0 mmol), $[Rh(OH)cod]_2$ (9.1 mg, 0.02 mmol), and proton sponge (857 mg, 4.0 mmol) in dioxane (4 mL) was stirred at 80 °C for 4 h. After cooling, the reaction mixture was partitioned between aqueous 1M HCl (4 mL) and MTBE, and the layers were separated. The aqueous phase was extracted twice more with MTBE (4 mL), and the combined organic phases were dried with anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification of the crude residue by silica column chromatography using MTBE/hexane as the eluent afforded 2,2-dimethyl-3-oxo-3-phenylpropanenitrile **2** (328 mg, 95% yield) as a colorless oil.

Acknowledgements

We thank Dr. Heewon Lee for HRMS analysis.

Conflict of interest

The authors declare no conflict of interest.

Keywords: boronic acids · homogeneous catalysis · rhodium · sulfinimines · β-ketonitriles

[1] a) M. H. Elnagdi, M. R. H. Elmoghayar, G. E. H. Elgemeie, *Synthesis* **1984**, 1; b) I. Chataigner, A. Harrison-Marchand, J. Madduluno, *Sci. Synth.* **2005**, *26*, 1123; c) F. F. Fleming, P. S. Iyer, *Synthesis* **2006**, 893.
[2] a) B. K. Wilk, *Tetrahedron* **1997**, *53*, 7097; b) G. Jones, *Org. React.* **1967**, *15*, 204; c) S. J. Deshpande, P. R. Leger, S. R. Sieck, *Tetrahedron Lett.* **2012**, *53*, 1772.
[3] a) R. Aggarwal, V. Kumar, R. Kumar, S. P. Singh, *Beilstein J. Org. Chem.* **2011**, *7*, 179; b) S. Kambe, K. Saito, H. Kishi, *Synthesis* **1979**, 287; c) C. R. Hauser, C. J. Eby, *J. Am. Chem. Soc.* **1957**, *79*, 728; d) K. Gewald, *Chem. Ber.* **1965**, *98*, 3571.
[4] M. L. Lastra, M. S. Molinuevo, J. M. Giussi, P. E. Allegretti, I. Blaszczyk-Lezak, C. Mijangos, M. S. Cortizo, *Mater. Sci. Eng. C* **2015**, *51*, 256.
[5] a) O. Soltani, M. A. Ariger, H. Vazquez-Villa, E. M. Carreira, *Org. Lett.* **2010**, *12*, 2893; b) H. Ankati, D. Zhu, Y. Yang, E. R. Biehl, L. Hua, *J. Org. Chem.* **2009**, *74*, 1658; c) D. Zhu, H. Ankati, C. Mukherjee, Y. Yang, E. R. Biehl, L. Hua, *Org. Lett.* **2007**, *9*, 2561.
[6] F. Fleming, *Nat. Prod. Rep.* **1999**, *16*, 597.
[7] F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902.
[8] Selected approaches to β-ketonitriles: a) K. Kiyokawa, T. Nagata, S. Minakata, *Angew. Chem. Int. Ed.* **2016**, *55*, 10458; *Angew. Chem.* **2016**, *128*, 10614; b) H. Shen, J. Li, Q. Liu, J. Pan, R. Huang, Y. Xiong, *J. Org. Chem.* **2015**, *80*, 7212; c) J. Shen, D. Yang, Y. Liu, S. Qin, J. Zhang, J. Sun, C. Liu, C. Liu, X. Zhao, C. Chu, R. Liu, *Org. Lett.* **2014**, *16*, 350; d) Z. Yang, K. Son, S. Li, B. Zhou, J. Xu, *Eur. J. Org. Chem.* **2014**, 6380; e) A. Park, S. Lee, *Org. Lett.* **2012**, *14*, 1118; f) Y. Ji, W. C. Trenkle, J. V. Vowles, *Org. Lett.* **2006**, *8*, 1161.
[9] A. R. Katritzky, A. A. A. Abdel-Fattah, M. Wang, *J. Org. Chem.* **2003**, *68*, 4932.
[10] J. Schranck, M. Burhardt, C. Bornschein, H. Neumann, T. Skrydstrup, M. Beller, *Chem. Eur. J.* **2014**, *20*, 9534.
[11] C. A. Malapit, J. T. Reeves, C. A. Busacca, A. R. Howell, C. H. Senanayake, *Angew. Chem. Int. Ed.* **2016**, *55*, 326; *Angew. Chem.* **2016**, *128*, 334.
[12] J. T. Reeves, C. A. Malapit, F. G. Buono, K. P. Sidhu, M. A. Marsini, C. A. Sader, K. R. Fandrick, C. A. Busacca, C. H. Senanayake, *J. Am. Chem. Soc.* **2015**, *137*, 9481.
[13] Selected Rh-catalyzed additions of boronic acids to nitriles: a) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2005**, *7*, 2229; b) T. Miura, H. Nakazawa, M. Murakami, *Chem. Commun.* **2005**, 2855; c) K. Ueura, S. Miyamura, T. Satoh, M. Miura, *J. Organomet. Chem.* **2006**, *691*, 2821; d) H. Shimizu, M. Murakami, *Chem. Commun.* **2007**, 2855.
[14] a) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600; b) G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 1278.
[15] J. T. Reeves, Z. Tan, M. A. Herbage, Z. S. Han, M. A. Marsini, Z. Li, G. Li, Y. Xu, K. R. Fandrick, N. C. Gonnella, S. Campbell, S. Ma, N. Grinberg, H. Lee, B. Z. Lu, C. H. Senanayake, *J. Am. Chem. Soc.* **2013**, *135*, 5565.
[16] CCDC 1540107 (**41**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[17] D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1999**, *121*, 268.
[18] The stereochemistry of all products in Table 4 was assigned in analogy to the stereochemistry of adduct **41**.

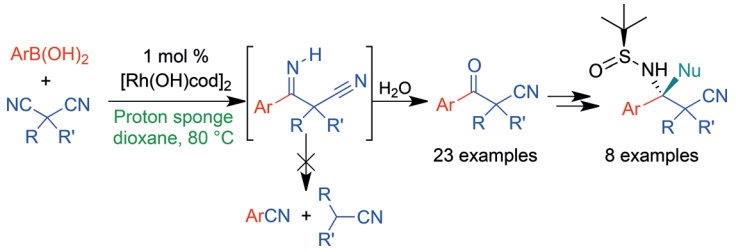
Manuscript received: April 3, 2017
Final Article published: ■■ ■■, ■■■■

Communications

Homogeneous Catalysis

C. A. Malapit, D. R. Caldwell, I. K. Luvaga, J. T. Reeves,* I. Volchkov, N. C. Gonnella, Z. S. Han, C. A. Busacca, A. R. Howell, C. H. Senanayake _____ ■■■■–■■■■

Rhodium-Catalyzed Addition of Aryl Boronic Acids to 2,2-Disubstituted Malononitriles



All about that base: In the presence of a Rh catalyst, aryl boronic acids add to 2,2-disubstituted malononitriles to give β-ketonitriles. A change of base from Cs_2CO_3, which was employed in a previous transnitrilation reaction, to a proton sponge prevents retro-Thorpe fragmentation of the intermediate β-iminonitrile. The utility of the β-ketonitriles was demonstrated by highly diastereoselective additions to the corresponding *N-tert*-butanesulfinyl imines.