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Efficient one-pot synthesis of dan-substituted organo- and silyl-boron compounds†

Kazuki Tomota, Yuki Izumi, Kazuki Nakanishi, Masaaki Nakamoto and Hiroto Yoshida *

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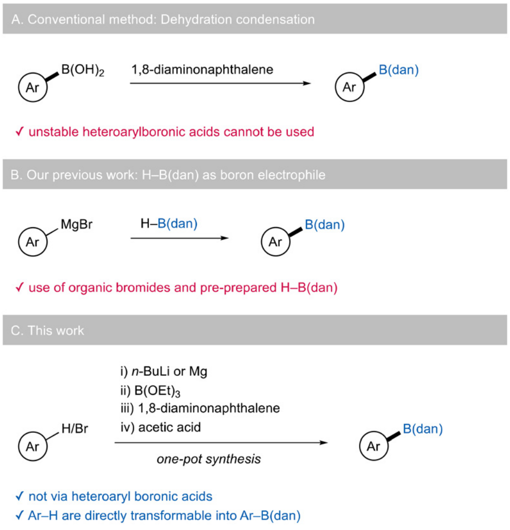
Direct, transition metal-free B(dan)-installation into organic frameworks has been developed. Heteroaryl–H bonds were transformable into the respective heteroaryl–B(dan) bonds through deprotonation. The resulting heteroaryl–B(dan) compounds, which are otherwise difficult to access, can undergo the direct Suzuki–Miyaura coupling. The method was demonstrated to apply to a silicon nucleophile, giving Lewis acidity-diminished stable silyl–B(dan) and –B(aam) in one pot.

Installation of a naphthalene-1,8-diaminato (dan) substituent on boron centers significantly diminishes the boron-Lewis acidity,[1] thus providing transmetalation-resistant properties to the respective organoboron compounds [R–B(dan)] that are conventionally synthesized by dehydration condensation of organoboronic acids [R–B$(OH)_2$] and 1,8-diaminonaphthalene ($danH_2$) (Scheme 1A).[2] The characteristic feature has been utilized for the boron-masking strategy in the iterative Suzuki–Miyaura coupling (SMC),[2] where the B(dan) moieties remain intact during the cross-coupling event at Lewis acidic B$(OH)_2$ or pinacol boronates [B(pin)]. On the other hand, we have disclosed that the B(dan) moieties can be activated toward transmetalation by treatment with *t*-BuOK, leading to the direct SMC of aryl–[3,4] and cyclopropyl–B(dan).[5] In addition to the inactive/active flexible properties in the SMC depending on bases, dan-installation also endows organoboron compounds with air- and water-resistant properties: protodeborylation is substantially suppressed with 2-pyridyl–B(dan),[3,6] and $PhMe_2Si$–B(dan)[7] becomes stable in air, while their B$(OH)_2$/B(pin) counterparts usually suffer from serious decomposition under these conditions.[8,9] In this regard, the development of a direct method of synthesizing dan-substituted organoboron compounds,[10] especially heteroaryl ones that are often unstable in their Lewis acidic –B$(OH)_2$ forms,[11] would be an important subject, since it could open the way to synthetic transformations with heteroaryl–B(dan). We have previously reported on a reaction of Grignard reagents with H–B(dan) that directly produces various R–B(dan) including 2-pyridyl– and 2-thienyl–B(dan) under transition metal-free conditions (Scheme 1B);[6] however, this reaction requires organic bromides (R–Br for preparing R–MgBr) and pre-prepared H–B(dan), which would leave something to be desired.[12] Hence, our attention was focused on the use of borates [R–B$(OR')_3{}^-$], one of the most common intermediates in the synthesis of organoboronic acid derivatives, generated from readily accessible B$(OR')_3$ and carbon nucleophiles (R–M, M = Li, MgX) for their direct conversion to R–B(dan). Here we disclose an improved approach to prepare R–B(dan) by using only commercially available reagents, wherein deprotonation of R–H moieties is also usable for generating the requisite carbon nucleophiles (Scheme 1C).

We first conducted a reaction (5 mmol scale) of 5-pyrazolyl lithium, prepared readily by deprotonation of 1-methyl-1*H*-pyr-



Scheme 1 Transition metal-free synthesis of Ar–B(dan).

Graduate School of Advanced Science and Engineering, Hiroshima University, Higashi-Hiroshima 739-8526, Japan. E-mail: yhiroto@hiroshima-u.ac.jp

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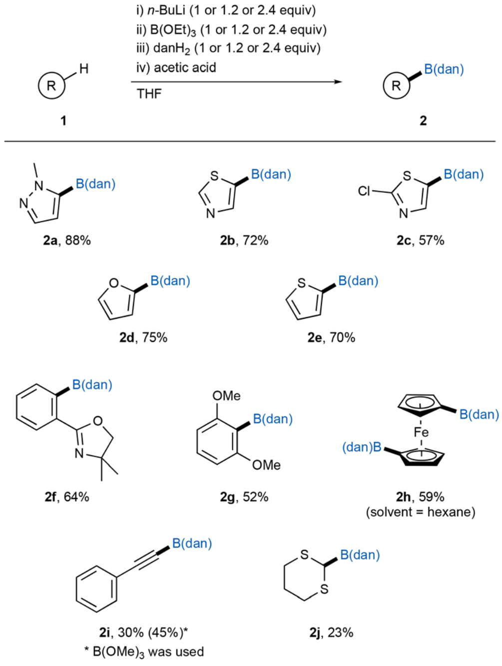
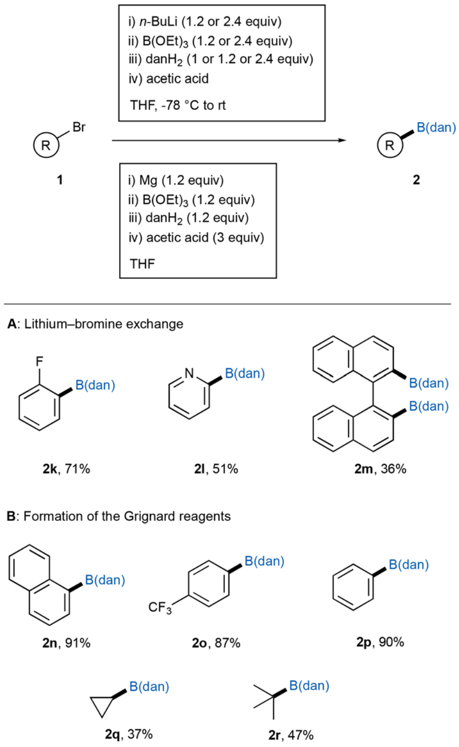
azole (**1a**), with triethylborate [$B(OEt)_3$]; subsequent treatment of the resulting pyrazoylborate [5-pyrazolyl–$B(OEt)_3^-$] with 1,8-diaminonaphthalene and acetic acid, in a similar way to the direct transformation of trialkyl borates [R–$B(OR')_3^-$] into pinacol boronates [R–B(pin)],[13] provided 5-pyrazolyl–B(dan) (**2a**) in 88% yield (Scheme 2).[14] Because the one-pot direct conversion of a heteroaryl–H bond into a heteroaryl–B(dan) bond can be carried out under non-aqueous conditions, 5-thiazolyl–B(dan) (**2b** and **2c**) could also be synthesized, avoiding the intermediary formation of their protodeborylation-prone $B(OH)_2$ counterparts.[11b] An acidic C–H moiety of furan (**1d**) or thiophene (**1e**) was also convertible into the respective C–B (dan) (**2d**: 75% and **2e**: 70%), and 4,4-dimethyl-2-phenyl-2-oxazoline (**1f**) and 1,3-dimethoxybenzene (**1g**) could participate in the reaction *via* directed *ortho* metalation. Owing to the diminished boron Lewis acidity, all the heteroaryl–B(dan) and other products mentioned below exhibit sufficient stability under ambient conditions, allowing for their isolation by column chromatography. The use of 1,1′-dilithioferrocene generated by dual deprotonation of ferrocene (**1h**) resulted in the formation of 1,1′-B(dan)-substituted ferrocene (**2h**) in 59% yield, and the procedure was also applicable to phenylacetylene (**1i**) or 1,3-dithiane (**1j**), giving phenylethynyl–B(dan) (**2i**) or 1,3-dithian-2-yl–B(dan) (**2j**) as air/water-stable compounds.[15]

Organic bromides (**1k–1q**) were naturally usable as starting materials (Scheme 3), and thus 2-fluorophenyl–B(dan) (**2k**), 2-pyridyl–B(dan) (**2l**) and 2,2′-B(dan)-substituted 1,1′-binaphthyl (**2m**) were produced through lithium–bromine exchange. In addition, various aryl–B(dan) (**2n–2p**)[16] and alkyl–B(dan) (**2q** and **2r**[17]) could be synthesized with the respective Grignard reagents.[18] A carbon nucleophile used for B(dan)-installation was also available by lithium–tin exchange of 2,5-bis(tributylstannyl)thiophene (**1s**) to afford a 63% yield of **2s** bearing B(dan) and $SnBu_3$ functionalities on the thiophene ring (Scheme 4).



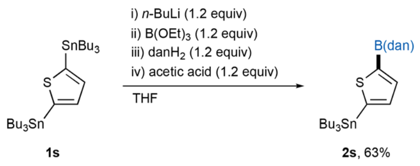
Scheme 2 Synthesis of R–B(dan) from R–H.



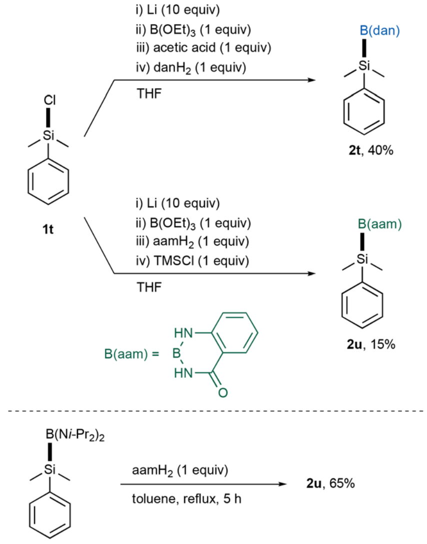
Scheme 3 Synthesis of R–B(dan) from R–Br.

It should be noted that the present method could also be applied to capturing a silicon nucleophile: air-resistant $PhMe_2Si$–B(dan) (**2t**) became straightforwardly accessible in 40% yield by treating $PhMe_2SiLi$ with $B(OEt)_3$ (Scheme 5),[19,20] while the previous multistep method[7] required the use of air/water-sensitive reagents and intermediates [BCl_3, $(i\text{-}Pr_2N)_2BCl$ and $PhMe_2Si$–$B(Ni\text{-}Pr_2)_2$]. A new air-resistant silylborane bearing an anthranilamide substituent on the boron center [$PhMe_2Si$–B(aam) (**2u**)] was generated by extending the direct synthesis, although the yield was relatively low.[21] According to the previous procedure using $PhMe_2Si$–$B(Ni\text{-}Pr_2)_2$, the yield was improved to 65%.

To gain insight into the reaction pathway, we carried out ^{11}B NMR experiments using *n*-BuLi as a carbon nucleophile (Fig. 1). Treatment of $B(OEt)_3$ (18.3 ppm, Fig. 1A) with *n*-BuLi resulted in the generation of an upfield-shifted species (3.0 ppm, Fig. 1B), being in a typical chemical shift range of a tetracoordinate borate.[22] The resulting borate [*n*-Bu–$B(OEt)_3^-$] remained unchanged upon mixing with 1,8-diaminonaphtha-



Scheme 4 B(dan)-installation *via* lithium–tin exchange.



Scheme 5 Synthesis of $PhMe_2Si–B(dan)$ and –B(aam).

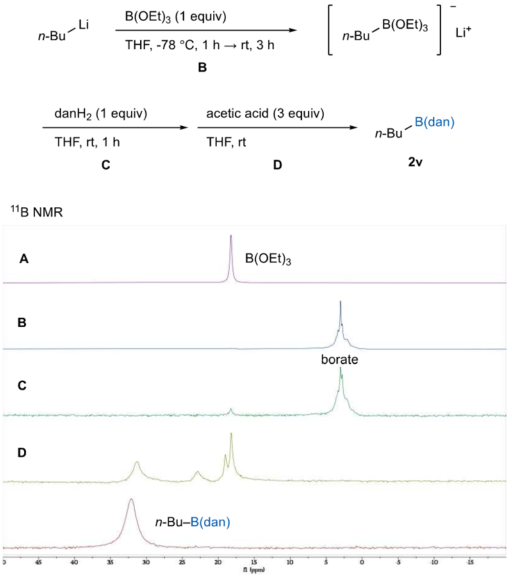
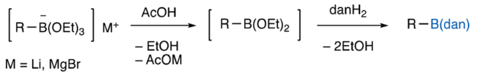


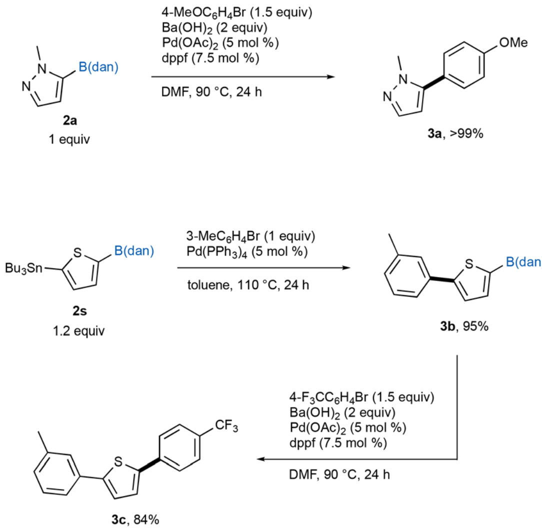
Fig. 1 ^{11}B NMR experiments on the reaction pathway.

lene (Fig. 1C), while further addition of acetic acid led to the formation of *n*-Bu–B(dan) (**2v**) with complete disappearance of the borate (Fig. 1D).[23] These results imply that dan-installation on the boron center does not occur at the tetracoordinate borate stage; the intermediary formed neutral species [R–B(OEt)$_2$] *via* protonation of the borates would immediately undergo ligand exchange to afford R–B(dan) (Scheme 6).



$$\left[R-\overset{-}{B}(OEt)_3\right]M^+ \xrightarrow[-\,EtOH \\ -\,AcOM]{AcOH} \left[R-B(OEt)_2\right] \xrightarrow[-\,2EtOH]{danH_2} R-B(dan)$$

Scheme 6 Proposed reaction pathway.



Scheme 7 Direct SMC of heteroaryl–B(dan).

Finally, the synthetic utility of heteroaryl–B(dan) was demonstrated by the direct SMC: treatment of **2a** with 4-bromoanisole and Ba(OH)$_2$ under Pd–dppf catalysis[3] quantitatively provided the coupling product (**3a**), which verifies the protodeborylation-resistant yet enough reactive property of the C–B(dan) bond (Scheme 7). Furthermore, chemoselective cross-coupling at the SnBu$_3$ moiety of **2s** gave a 95% yield of **3b**, whose thienyl–B(dan) bond was then coupled with 4-(trifluoromethyl)bromobenzene efficiently under the Ba(OH)$_2$ conditions.

Conclusions

We have developed a one-pot direct method for installing the B(dan) moiety without the intermediary formation of sometimes unstable organoboronic acids. The present transition metal-free method is superior to our previous H–B(dan) one[6] in that organolithium reagents directly generated by deprotonation are usable as carbon nucleophiles;[12] diverse R–B(dan) (R = heteroaryl, aryl, alkynyl, alkyl) endowed with air/water-resistant characters have become accessible in good yields. Moreover, the method was demonstrated to apply to a silicon nucleophile to lead to the direct synthesis of $PhMe_2Si–B(dan)$ and –B(aam). Further studies on the synthetic utilization of the resulting R–B(dan) especially for catalytic carbon–carbon bond-forming reactions are in progress.

Author contributions

K.T. and H.Y. conceived the concept and wrote the manuscript. K.T. conducted most of the experiments and data collection. Y. I. synthesized **2u** according to the previous method. K.N. performed the X-ray crystal structure analysis of **2u**. M.N. provided advice for the research. H.Y. directed the project. All authors have approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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14 Depending on the substrates, various reaction conditions (molar ratio, temperature, and time) were employed. See the ESI† for details.

15 The starting R–H were recovered when the yields were moderate.

16 Ph–B(dan) (**2p**) could also be synthesized from bromobenzene in 69% yield *via* lithium–bromine exchange.

17 A *tert*-butyl Grignard reagent was used as the starting material.

18 Isopropenyl–B(dan) was prepared according to a similar procedure by using isopropenyl–MgBr, $B(OMe)_3$, 1,8-diaminonaphthalene, and aqueous NH_4Cl. See: J. C. Lo, D. Kim, C.-M. Pan, J. T. Edwards, Y. Yabe, J. Gui, T. Qin, S. Gutiérrez, J. Giacoboni, M. W. Smith, P. L. Holland and P. S. Baran, *J. Am. Chem. Soc.*, 2017, **139**, 2484–2503.

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23 See the ESI† for the assignment of other 11B NMR signals.