

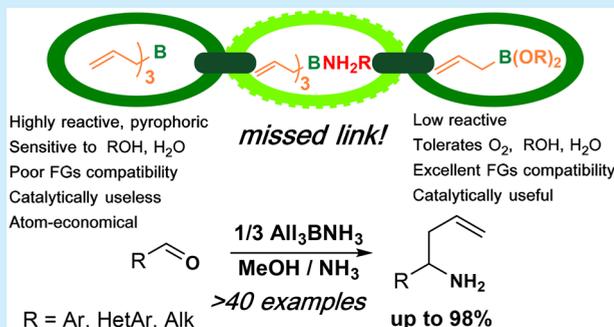
Adducts of Triallylborane with Ammonia and Aliphatic Amines as Stoichiometric Allylating Agents for Aminoallylation Reaction of Carbonyl Compounds

Nikolai Yu. Kuznetsov,*^{ORCID} Rabdan M. Tikhov, Tatiana V. Strelkova, and Yuri N. Bubnov

A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov 28, 119991 Moscow, Russian Federation

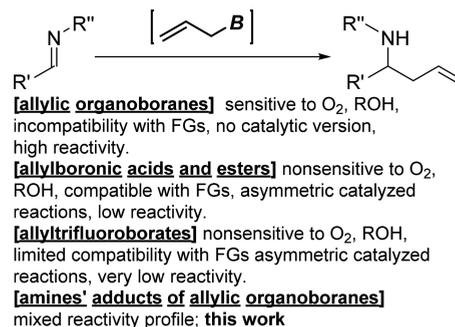
S Supporting Information

ABSTRACT: Triallylborane–amines adducts are effective stoichiometric allylating agents in the aminoallylation reaction of carbonyl compounds in methanol. Moreover, copper-catalyzed diastereoselective allylation of Ellman's imine was achieved with triallylborane–methylamine adduct.



Since the time of their discovery,¹ allylboranes and allylboration reactions have become extremely important synthetic tools.² A survey of the amazing progress achieved in the synthesis and application of allylboron species has been published recently.^{2c} Among the multiple allylborane-mediated transformations, particular attention is paid to the synthesis of homoallylamines via allylation of C=N bonds of imines.³ Homoallylamines are versatile and useful synthetic intermediates in the pharmaceutical chemistry and in the synthesis of natural products and heterocyclic compounds.⁴ The most powerful allylborating agents for synthesis of homoallylamines are tri- and monoallylic organoboranes, which are capable of allylborating an array of compounds with multiple C–N bonds.^{5–12} Allylic organoboranes are highly reactive and react with imines at temperatures as low as –100 °C, providing excellent enantioselectivity with chiral organoboranes.^{5b} One of the most important advantages of triallylic boranes along with their activity is their atomic efficiency. The main disadvantages of the allylic organoboranes is that they are sensitive to different factors: oxygen of air, proton-donor compounds (water, alcohols etc.) and poor compatibility with many FGs; in addition they cannot be used in catalysis due to self-catalytic properties.¹³ As alternatives to organoboranes for allylation of imines, low-active allylboronic acids, their esters, and trifluoroborate salts, which are generally free of the above disadvantages, are widely applied (Scheme 1). Following the Petasis-type¹⁴ α -aminoallylation procedure, even carbonyl compounds can be transformed in “one-pot” to homoallylamines with allylboronic acids.¹⁵ The low activity of allylboronic acid derivatives arising due to neutralization of Lewis acidity of boron by the lone pairs of oxygen atoms and their low atomic efficiency both are

Scheme 1. Boranes for Allylation of Imines



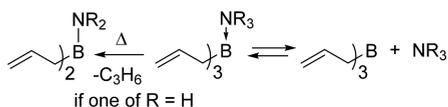
compensated by the possibility of catalytic asymmetric transformations, proceeding highly stereo- and enantioselectively.^{2c}

Enhancement of the reactivity of allylboronates is achieved by their conversion into more active borinate derivative, making them closer to organoboranes.¹⁶ Similar improvement of reactivity of allylboronic acids occurs upon dehydration and trimerization into boroxines.¹⁷ Despite the success achieved with the use of allylboronates, the lack in the reactivity limits the spectrum of the possible substrates and catalysts. On the other hand, shortcomings inherent in allylic organoboranes hamper the development of modern chemistry on their basis. Therefore, it would be useful to have allylboranes with intermediate activity possessing the advantages of both classes of compounds. According to our results, amine adducts of allylic organoboranes can be such promising reagents.

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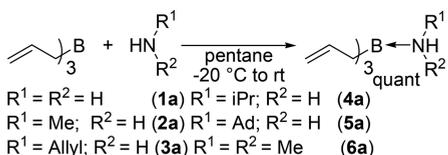
Until this present work, no specific studies of adducts as allylborating agents have been undertaken. We believe that such inattention is objectively conditioned by the data obtained in previous years, which unequivocally pointed to the lability of adducts with ammonia and amines. Triallylborane (TAB), as Lewis acid, forms sufficiently stable adducts with few tertiary amines, which can be even distilled in vacuum without decomposition. However, when treated with alcohols or water these complexes are readily decomposed with propylene evolution except for β - and γ -substituted pyridines.¹⁸ Pyridine complexes of TAB and other triallylic boranes upon heating with proton-donor compounds (water, alcohols, amines) undergo intramolecular allylboration, yielding 2,6-diallylated tetrahydropyridines.¹⁰ Interaction of TAB with NH_3 , primary, and secondary amines produces aminoboranes, although the formation of adducts is always assumed.¹⁹ Allylborane adducts can follow two decomposition routes — through dissociation (with tertiary amines) and proto-deallylation (for primary, secondary amines) or both routes in the case of bulky amines with an NH group (Scheme 2).

Scheme 2. Decomposition of Allylborane–Amine Adducts



Clearly, such properties did not stimulate additional studies of amine adducts in allylation reactions. We proposed that careful temperature control during the synthesis of adducts with NH-group and the use of the amine in excess can prevent their undesirable decomposition. A three-component aminoallylation of carbonyl compounds in methanol was chosen as a model reaction.¹⁵ Although this process works well with allylboronic acid derivatives, the same reaction with TAB adducts might be complicated by protonolysis of allyl–B bonds that is, in fact, a textbook example. Indeed, very vigorous reaction occurs upon addition of TAB to methanol solution of NH_3 even at -60°C , leading to a mixture of di- and triallylborane–ammonia adducts (1:1.2). To eliminate the protonolysis process, a flow of dry ammonia was passed through the solution of TAB in pentane at -20°C (Scheme 3).

Scheme 3. Synthesis of Triallylborane–Amine Adducts



Under these conditions, ammonia complex (1a) is formed in quantitative yield. Adduct 1a is a solid and can be handled without argon, although it is slowly oxidized on air. Adducts 2a–6a were synthesized similarly. It should be noted that triallylboranes form similar adducts with NH_3 and some amines. Adducts with higher boranes are less stable and readily dissociate into the initial reagents that are successfully used in reactions of radical polymerization.²⁰

The stability of 1a was tested by heating its solution in benzene. Gradual transformation of 1a into the amino(diallyl)borane at 40°C (Scheme 2) was detected by NMR, while the

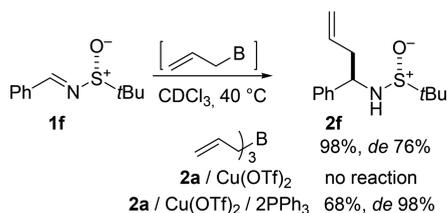
deallylation process was accelerated at 60°C (31% for 1 h, 54% for 4 h). Switching to the proton media demonstrates a surprising effect of stabilization of 1a. The destruction of 1a in iPrOH for 1 h was 14%, in EtOH 19%, and MeOH 38%. However, this stabilizing effect is limited, and more acidic alcohols, 2,2,2-trifluoroethanol and HFIP, rapidly decompose 1a even at 25°C . The observed stability of 1a in iPrOH is superior, but we were interested in MeOH, in which higher yields of homoallylamines were observed.^{15c,d} We found also the stability of 1a in methanolic NH_3 solution increases significantly: the half-life time of 1a at 60°C is 24 h and at 25°C 36 days, and it can be stored for months without any changes at -18°C . Such an excellent stability profile of the complex is totally fit to the potential use of 1a as an allylborating reagent. Experimentally, the three-component aminoallylation procedure consists of two steps: first, an aldehyde is dissolved in methanolic NH_3 (3–15 equiv) and held for 30–60 min, during which time almost all amount of the aldehyde is converted to the so-called imine trimer (hydrobenzamide),²¹ followed by the addition of 1a. The reaction was conveniently monitored by ^1H and ^{11}B NMR, where the boron chemical shift of 1a at -8.56 ppm (value can vary a little) smoothly transforms to the signal of boric acid at 4.7 ppm. There are signals of intermediates: mono- and diallylated boranes are usually in a range of 0–10%.

Aminoallylation of benzaldehyde 1b with 1a proceeds quickly at the beginning of the reaction, giving rise to amine 1c (Scheme 4) and its Schiff base with 1b in a 1:1 ratio (see the SI for mechanistic details). Further reaction is practically stopped at 25°C ; various additives (ZnCl_2 , $\text{Zn}(\text{OTf})_2$, MgCl_2 , $\text{In}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$, $\text{Y}(\text{OTf})_3$, CuCl_2 , NH_4Cl) have no effect on the ratio of the products. The reaction is markedly accelerated at 40°C and complete after 4 h. The most remarkable thing is that *unproductive protonolysis of 1a is completely absent under these conditions, and consumption of all allyl groups takes place only via allylation of the C=N bond!* The amine 1c was conveniently isolated as hydrochloride salt (88%) after treatment with HCl without chromatography (Scheme 4). On a series of substituted benzaldehydes (2b–26b), it was shown that aldehydes enter the aminoallylation reaction irrespective of the nature of the substituent. The reaction involves aromatic aldehydes containing a variety of FGs to nitro (22b, 23b) and cyano (24b) groups; these are acetylene (25b), ester group (26b), azaheterocycles (pyridine (27b), pyrazole (29b), indole (28c)), and furan (30c); however, the adduct 1a (unlike pure triallylborane) selectively allylates only the C=N bond of imines, leaving virtually all FGs unaffected. All homoallylamines were isolated as hydrochlorides or oxalates in high yields, with the exception of 28c (84%), which was isolated by chromatography. It is necessary to note the peculiarity of the reaction of acetylene 32b with 1a where 32c was obtained instead of the expected homoallylamine. Initially, from the aldehyde 32b and NH_3 isoquinoline 33b is formed, which undergoes reductive allylboration upon addition of 1a in the same way as with neat TAB.

Apparently, 33b is the only azaheterocycle that is allylborated under these conditions because neither indole, pyridine, nor quinoline reacts with 1a (Scheme 5).

Along with ammonia adduct 1a, adducts 2–6a (Scheme 3) were also tested in the aminoallylation reaction with different carbonyl compounds (Table 1).

Diastereomer ratios in 36c and 40c (entries 3 and 7) are close to the previously obtained values.^{15a,22} Generally, compounds with a branching site adjacent the carbonyl group (entries 2–4 and 7) react more slowly, demonstrating the great importance of

Scheme 7. Copper-Catalyzed Allylation of **1f** with **2a**

phosphine or phosphite-type ligands.²⁵ In our case, allylation of **1f** with TAB in CDCl₃ at 40 °C (5 min) quantitatively gives homoallylamide **2f** with *de* 76%; similarly, allylation with adduct **2a** in the presence of Cu(OTf)₂/PPh₃ leads to **2f** (68%) with *de* 98%. In the blank experiment without the phosphine, allylation of **1f** does not occur at all. This is the first and promising example of catalytic allylation via derivatives of triallylic organoboranes. The study of the scope of various triallylic boranes adducts in imine allylation reactions, including catalytic versions, is currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01317.

Full experimental procedures, study of the mechanism and spectroscopic data for **1–6a**, **1–32c**, **34–40c**, **1–3d**, **2f**, and chiral HPLC analysis data of *N*-Boc-derivatives **1c** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nkuznff@ineos.ac.ru.

ORCID

Nikolai Yu. Kuznetsov: 0000-0003-2702-5366

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Masao, K.; Kunihiko, I. Jpn Patent 7019, 1954; *Chem. Abstr.* **1956**, *50*, 4196. (b) Mikhailov, B. M.; Tutorskaya, F. B. *Dokl. Akad. Nauk SSSR* **1958**, *123*, 479. (c) Mikhailov, B. M.; Bubnov, Yu. N. *Izv. Akad. Nauk SSSR* **1964**, *10*, 1874.
- (2) (a) Bubnov, Yu. N. *Sci. Synth.* **2004**, *6*, 945. (b) Hall, D.; Lachance, H. *Allylboration of Carbonyl Compounds*; Wiley: Hoboken, NJ, 2012. (c) Hall, D. G. *Boronic Acids*; Wiley: Weinheim, 2011. (d) Jonnalagadda, S. C.; Suman, P.; Patel, A.; Jampana, G.; Colfer, A. Allylboration. In *Boron Reagents in Synthesis*; Coca, A., Ed.; ACS Symposium Series, 2016; Vol. 1236, Chapter 3, pp 67–122. (e) Diner, C.; Szabo, K. J. *J. Am. Chem. Soc.* **2017**, *139*, 2.
- (3) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (d) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. (e) Ramadhar, T. R.; Batey, R.

A. *Synthesis* **2011**, *2011*, 1321. (f) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595. (g) Huo, H.-X.; Duvall, J. R.; Huang, M.-Y.; Hong, R. *Org. Chem. Front.* **2014**, *1*, 303.

(4) (a) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, UK, 2004. (b) *Chiral Amine Synthesis: Methods, Developments and Applications*; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, 2010. (c) Puentes, C. O.; Kouznetsov, V. J. *Heterocycl. Chem.* **2002**, *39*, 595.

(5) Imines: (a) Itsuno, S.; Watanabe, K.; Matsumoto, T.; Kuroda, S.; Yokoi, A.; El-Shehawy, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, *1*, 2011. (b) Ramachandran, P. V.; Burghardt, T. E. *Chem. - Eur. J.* **2005**, *11*, 4387. (c) Canales, E.; Hernandez, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 8712. (d) Lee, J. H.; Gupta, S.; Jeong, W.; Rhee, Y. H.; Park, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10851. (e) González, J. R.; Soderquist, J. A. *Org. Lett.* **2014**, *16*, 3840. (f) Review: Ramachandran, P. V.; Burghardt, T. E. *Pure Appl. Chem.* **2006**, *78*, 1397.

(6) Aluminium–imines: (a) Watanabe, K.; Kuroda, S.; Yokoi, A.; Ito, K.; Itsuno, S. *J. Organomet. Chem.* **1999**, *581*, 103. (b) Ramachandran, P. V.; Burghardt, T. E.; Bland-Berry, L. *J. Org. Chem.* **2005**, *70*, 7911. (c) Ramachandran, P. V.; Biswas, D.; Krzeminski, M. P.; Chen, G.-M. *Tetrahedron Lett.* **2010**, *51*, 332.

(7) Boron–imines: Ramachandran, P. V.; Biswas, D. *Org. Lett.* **2007**, *9*, 3025.

(8) Nitriles: (a) Mikhailov, B. M.; Bubnov, Yu. N.; Tsyban', A. V.; Grigoryan, M. Sh. *J. Organomet. Chem.* **1978**, *154*, 131. (b) Kuznetsov, N. Yu.; Maleev, V. I.; Khrustalev, V. N.; Mkrtchyan, A. F.; Godovikov, I. A.; Strelkova, T. V.; Bubnov, Yu. N. *Eur. J. Org. Chem.* **2012**, *2012*, 334.

(9) Amides: Bubnov, Yu. N.; Pastukhov, F. V.; Yampolsky, I. V.; Ignatenko, A. V. *Eur. J. Org. Chem.* **2000**, *2000*, 1503.

(10) Pyridines: Bubnov, Yu. N. *Pure Appl. Chem.* **1994**, *66*, 235.

(11) Isoquinolines: (a) Bubnov, Yu. N.; Evchenko, S. F.; Ignatenko, A. V. *Russ. Chem. Bull.* **1993**, *42*, 1268. (b) Kuznetsov, N. Yu.; Lyssenko, K. A.; Peregodov, A. S.; Bubnov, Yu. N. *Russ. Chem. Bull.* **2007**, *56*, 1569.

(12) Pyrrole and indole: Bubnov, Yu. N.; Lavrinovich, L. L.; Zykov, A. Yu.; Klimkina, E. V.; Ignatenko, A. V. *Russ. Chem. Bull.* **1993**, *42*, 1269.

(13) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518.

(14) (a) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.

(15) (a) Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182. (b) Kobayashi, S.; Hirano, K.; Sugiura, M. *Chem. Commun.* **2005**, *104*. (c) Sugiura, M.; Mori, C.; Hirano, K.; Kobayashi, S. *Can. J. Chem.* **2005**, *83*, 937. (d) Dhudshia, B.; Tiburcio, J.; Thadani, A. N. *Chem. Commun.* **2005**, 5551.

(16) Chen, J. L.-Y.; Aggarwal, V. K. *Angew. Chem.* **2014**, *126*, 11172.

(17) Alam, R.; Das, A.; Huang, G.; Eriksson, L.; Himo, F.; Szabo, K. J. *Chem. Sci.* **2014**, *5*, 2732.

(18) (a) Bogdanov, V. S.; Barishnikova, T. K.; Kiselev, V. G.; Mikhailov, B. M. *Zh. Obsch. Khim.* **1971**, *41*, 1533. (b) Schroeder, S.; Thiele, K. H. Z. *Anorg. Allg. Chem.* **1977**, *428*, 225.

(19) Mikhailov, B. M.; Tutorskaya, F. B. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1961**, *10*, 1076.

(20) (a) Ramachandran, P. V.; Drolet, M. P.; Kulkarni, A. S. *Chem. Commun.* **2016**, *52*, 11897. (b) Erdyakov, S. Yu.; Mel'nik, O. A.; Gurskii, M. E.; Ignatenko, A. V.; Vygodskii, Ya. S. *Russ. Chem. Bull.* **2004**, *53*, 2215.

(21) Nielsen, A. T.; Atkins, R. L.; DiPol, J.; Moore, D. W. *J. Org. Chem.* **1974**, *39*, 1349.

(22) Thadani, A. N.; Dhudshia, B. Patent WO 2008119162, 2008.

(23) Hernandez, E.; Canales, E.; Gonzalez, E.; Soderquist, J. A. *Pure Appl. Chem.* **2006**, *78*, 1389.

(24) (a) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853. (b) Jiang, Y.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2017**, *56*, 1544. (c) Jiang, L.; Cao, P.; Wang, M.; Chen, B.; Wang, B.; Liao, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 13854.

(25) Zhao, Y.-S.; Liu, Q.; Tian, P.; Tao, J.-C.; Lin, G.-Q. *Org. Biomol. Chem.* **2015**, *13*, 4174.