

Arylboronic Acid-Catalyzed C-Allylation of Unprotected Oximes

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ABSTRACT: Unprotected keto- and aldoximes are readily C-allylated with allyl diisopropyl boronate in the presence of arylboronic acid catalysts to yield highly-substituted *N*- α -secondary (2°) and tertiary (3°) hydroxylamines. The method's synthetic utility is demonstrated with the total synthesis of the trace alkaloid *N*-methyl-euphococcine. Preliminary experimental and computational mechanistic studies point toward the formation of a boroxine as the active allylating species.

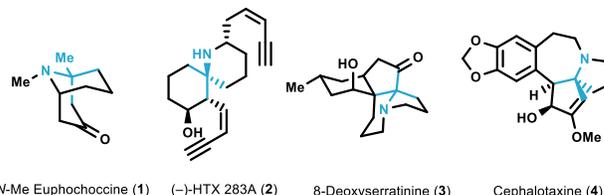
The α -tertiary amine moiety appears frequently as a key structural element in natural products (Scheme 1A).¹ Inspired by the abundance and importance of this structural motif, we considered α -tertiary homoallylic hydroxylamines as highly suitable precursors for their construction, since compared to α -tertiary homoallylic amines, they are capable of undergoing a wide range of further complexity-building transformations.² However, there are very few methods for constructing homoallylic α -tertiary hydroxylamines, and this severely limits the use of these compounds in target molecule synthesis.^{3a-e} Currently the chemoselective reduction (i.e., preserving the integrity of the N–O bond) of allylated aliphatic nitro compounds with aluminum amalgam remains the most general method for their preparation (Scheme 1B).^{3b-e} Synthetically, the direct C-allylation of unprotected ketoximes would be the ideal approach. Unfortunately, a general 1,2-addition of allylmetal reagents to unprotected ketoximes remains elusive due to concomitant deprotonations and rearrangements.⁴

Allyl boronates would conceptually be suitable candidates for such direct 1,2-addition reactions as these compounds are virtually non-Brønsted basic (Scheme 1C). Also, upon coordinating to the nitrogen atom of the unprotected oxime, their nucleophilicity increases, while the binding interaction simultaneously activates the oxime for the 1,2-addition. This choice of strategy is supported by a seminal work of R. W. Hoffman and co-workers in which simple aldoximes could be allylated in moderate to good yields (70–90%), using the highly reactive AlIB(OMe)_2 , under harsh conditions (10 days of reflux in tetrachloromethane).^{5,6}

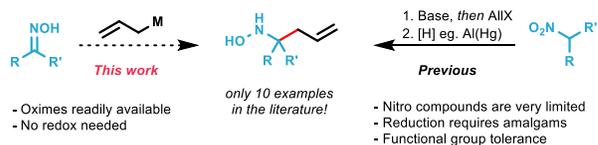
In our hands, only traces of allylation products were formed (<5% conversion), when the allylation of either benzaldehyde or acetophenone oxime was performed with commercially available AlIBpin or AlIB(OiPr)_2 reagents. During these initial studies, we serendipitously observed improved conversion (17%) when an older batch of AlIB(OiPr)_2 reagent was used. We attributed the improved conversion to the presence of boronate ester hydrolysis products, such as boronic acids. Following this logic, we repeated the allylation of acetophenone oxime (**5a**) with AlIB(OiPr)_2 (**6**) using 10 mol-% phenylboronic acid (**8a**) as a catalyst, and observed a markedly improved 51% conversion to **7a**. Further screening (see SI p. 12) identified 3,5-

difluorophenylboronic acid (**8b**) as best catalyst resulting in 64% conversion of **5a** to **7a**. Further optimization of catalyst loading, allyl boronate loading, as well as reaction time led to a 72% conversion (73% isolated yield) of **5a** to **7a**.

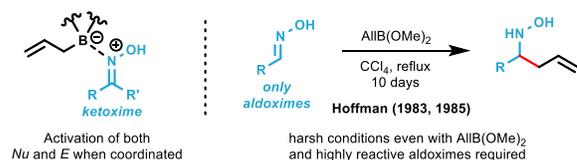
A α -Tertiary amines in natural products



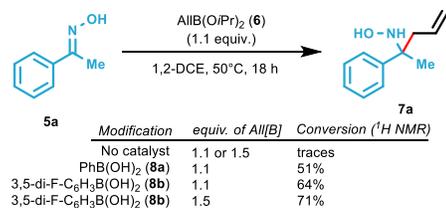
B Synthetic approaches to making α -trisubstituted hydroxylamines



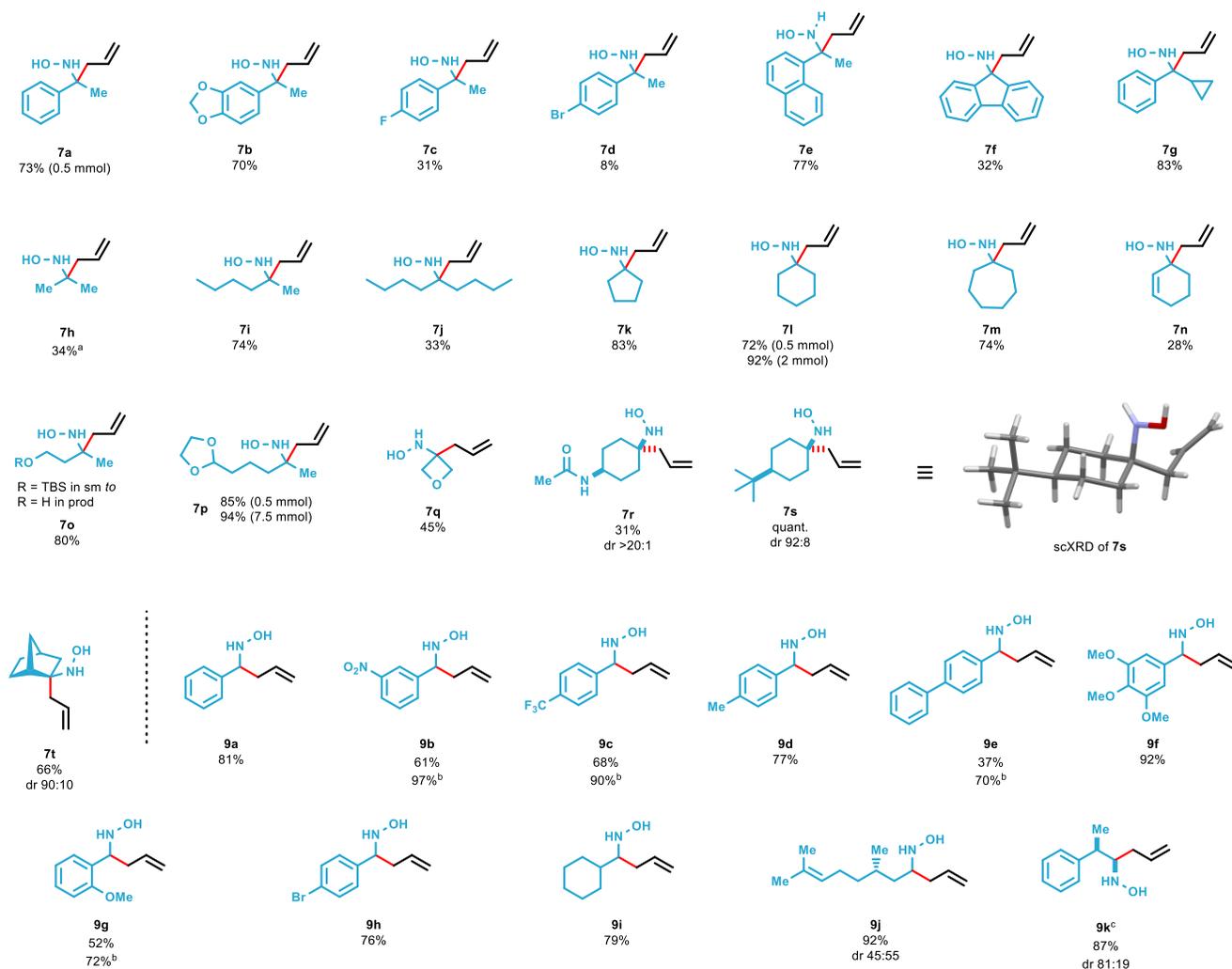
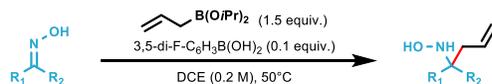
C Planned allylation of ketoximes using allyl boronates



D Discovery of boronic acid catalysis



Scheme 1: a) α -Tertiary amine moieties in alkaloids. b) Current state-of-the art for making α -fully substituted allylated hydroxylamines is troublesome c) Using allyl boronates under forcing conditions C-allylates reactive aldoximes but does not work with less reactive ketoximes d) Arylboronic acids catalyze the C-allylation of acetophenone oxime (**5a**).

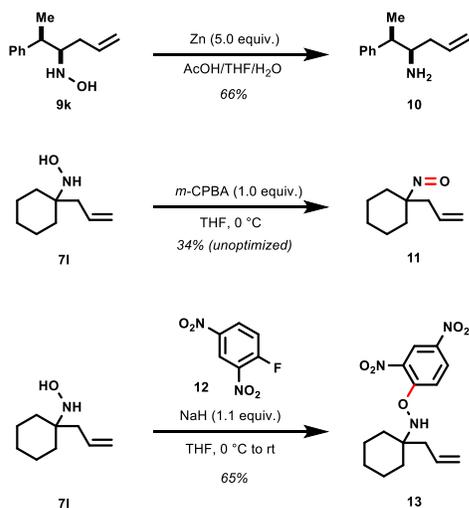


Scheme 2: Scope of substrates for the allylation reaction. Reagents and conditions: Oxime (**5**, 0.5 mmol unless otherwise noted, 1.0 equiv.), 3,5-*di*-F-C₆H₃B(OH)₂ (**8a**, 0.1 equiv.), AlIB(O*i*Pr)₂ (**6**, 1.5 equiv.) in 1,2-DCE (0.5 M) at 50 °C for 18 h. ^aFull conversion based on ¹H NMR, lowered isolated yield due to volatility of the product. ^b3,5-*di*-CF₃-C₆H₃B(OH)₂ (**8c**, 0.1 equiv.) used as a catalyst. ^cRelative stereochemistry determined by reduction to a known amine **10** (Scheme 3).

With the optimized catalytic conditions at hand, we proceeded to allylate a range of aliphatic and aromatic ketoximes to corresponding α -tertiary hydroxylamines (**7a–7t**) as shown in Scheme 2.⁷ Lower yields were observed for electron-withdrawing aryls such as **7c**, and **7d**. Cyclic and acyclic ketoximes (**7h–7m**) are mostly well tolerated (33–83% yields). The reaction is, however, sensitive to substrate bulkiness and 5-nonanone oxime gave a low 33% yield of **7j**, while menthone and camphor oximes could not be allylated (see SI p. 26). The allylation reaction is compatible with a range of functional groups, such as ethers **7q**, acetals **7p** and amides **7r**. Even α,β -unsaturated cyclohexanone oxime could be allylated to **7n** but with lower yield (28%). We were also surprised to find that a silyl protected alcohol (**5o**) undergoes desilylation under the reaction conditions, leading to hydroxylamine product **7o** in good yield. In addition, the relative configuration of hydroxylamine **7s** could be established by single crystal x-ray diffraction.⁸

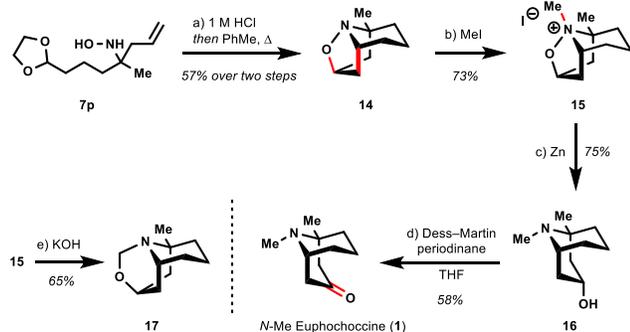
Similarly, a range of aliphatic and aromatic aldoximes could also be successfully allylated using the method to form the corresponding α -secondary homoallylic hydroxylamines (**9a–9k**). Compared to ketoximes, the aldoximes were much less effected by electronic effects (*p*-Br **9h** 76% yield vs **7d** 8% yield). We were also pleased to find that the allylation proceeds under acyclic stereocontrol (dr 81:19) in the case of **9k**. In addition, for several low-yielding cases (**9b**, **9c**, **9e**, **9g**), we found that using 3,5-*di*-trifluoromethyl phenylboronic acid (**8c**) as the catalyst improved the yields, even though with acetophenone oxime **8b** performed better than **8c** (see SI, page 12).

The product hydroxylamine **9k** could be readily reduced with zinc powder to give the corresponding homoallylic amine **10**. In addition hydroxylamine **7l** could be oxidized to the corresponding nitroso compound **11** using *m*-CPBA (34% unoptimized yield),⁹ and converted to the corresponding activated *O*-(2,4-dinitrophenyl)hydroxylamine derivative **13** in 65% yield.



Scheme 3: Synthetic utility of the hydroxylamine products. Reagents and conditions a) Zn (5.0 equiv.), AcOH/THF/H₂O, rt, 16 h, 66% b) *m*-CPBA (1.0 equiv.), THF, 0 °C, 34% c) NaH (1.1 equiv.), 1-fluoro-2,4-dinitrobenzene (**12**) (1.1 equiv.), THF, 0 °C to rt, 65%.

To further demonstrate the synthetic utility of the products, we embarked on the total synthesis of *N*-methyl Euphococcine (**1**), a trace homotropane alkaloid isolated from Colorado blue spruce, *Picea pungens*.¹⁰ Acetal protected hydroxylamine **7p** was hydrolyzed in aqueous hydrochloric acid and the formed nitron heated in toluene to induce a 1,3-dipolar cycloaddition forging the homotropane alkaloid core **14** in 57% yield over two steps.¹¹ We then installed the *N*-methyl group by alkylating **14** with an excess of MeI to form the corresponding ammonium salt **15** in 73% yield. Attempts at direct base-induced Hoffmann-type fragmentation of the salt **15** to form *N*-Me Euphococcine directly were hampered by formation of 1,3-oxazine **17** (see Scheme 4, inset). With weaker bases such as Ag₂O, Et₃N, K₂CO₃ the ammonium salt **15** remained unchanged, and with more basic KOH/MeOH the ammonium salt **15** rearranged to tetrahydro-1,3-oxazine **17** together with traces of *N*-Me-euphococcine (**1**).¹² Therefore, a two-step reduction-oxidation sequence was employed.¹³ The *N*-O bridge of **15** was reduced with zinc, and the resulting aminoalcohol **16** oxidized with Dess–Martin periodinane to deliver *N*-Me Euphococcine (**1**). The spectroscopic data for synthetic *N*-Me Euphococcine (**1**) corresponded to those reported for semisynthetic material.¹⁰



Scheme 4: Total synthesis of *N*-Me Euphococcine (**1**). Reagents and Conditions: a) 1 M HCl(aq), rt, 30 min then PhMe, 100 °C, 10 h, 57% over two steps b) MeI (5.0 equiv.), Et₂O, 24 h, 73% c) Zn (5.0 equiv.), AcOH/THF/H₂O, 30 °C, 6 h, 75% d) Dess–Martin periodinane, THF, 58% e) KOH, 65%

Dess–Martin periodinane (2.0 equiv.), NaHCO₃ (4.0 equiv.), THF, 0 °C to rt, 58% e) KOH 10% MeOH, rt, 3 h, 65%.

We then turned our attention to understanding the role of the aryl boronic acid catalyst in the allylation process. As the stability of C–O bonds in boronic acids and their esters is comparable, the arylboronic acid **8b** can be expected to undergo a ligand-exchange reaction with the diisopropyl allyl boronate (**6**), liberating allylboronic acid (**17**) (Scheme 5).¹⁴ For this ligand-exchange reaction to take place, free boronic acid **8b** is needed.¹⁵ Compared to electron-donating aryl boronic acids which readily form boroxines, electron-deficient aryl boronic acids exist predominantly as free boronic acids.¹⁶ This is in line with the experiments, as higher conversions in the allylation of acetophenone oxime (**5a**) were observed with electron deficient arylboronic acids: OMe ($\sigma_p = -0.27$), H ($\sigma_p = 0$), NO₂ ($\sigma_p = +0.78$) resulting in 40, 50 and 63% conversions, respectively (see SI, p. 12). This trend is also supported by faster ligand-exchange of electron-deficient arylboronic acids.¹⁷

To assess whether the formation of allyl boronic acid (**17**) *via* ligand exchange alone is enough to explain the improved yields, the allyl-transfer transition states for both allyl boronate ester and allylboronic acid pathways were computationally studied at B97D3/def2-TZVP level of theory using a CPCM solvent model (see SI for details). The conformational flexibility was restricted by using dimethyl allyl boronate as the allylating reagent, and acetone oxime as the oxime.¹⁸

The reaction path corresponding to allylation of acetone oxime in the absence of catalyst, results in a loose reactant complex (d_{B-N} 3.28 Å) at +9.3 kcal/mol with respect to separated starting materials, and the barrier for allylation lies at +29.8 kcal/mol. Computationally, allylation with AllB(OH)₂ resulted in a slightly more stable reactant complex (d_{B-N} 3.11 Å, +7.5 kcal/mol) yet the transition state remained almost equally high in energy (+29.4 kcal/mol).

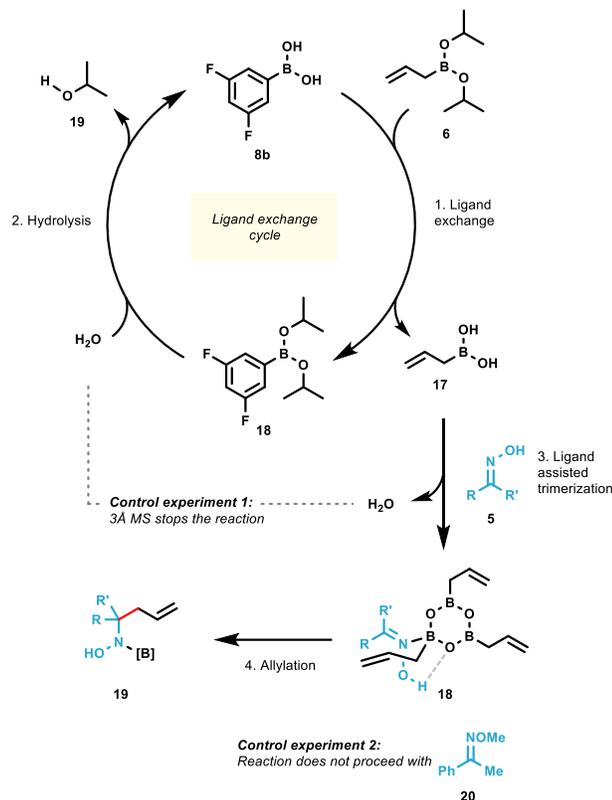
These results suggest hydrolysis alone does not result in significantly lower transition state energies for the C–C bond formation, and cannot explain the increase in reactivity. Inspired by the work of the Szabó group, we considered the involvement of allyl boroxines of the type **18**.^{19a,b} Formation of boroxines is known to be assisted by nitrogenous ligands, in our case the oxime substrate **5**, *via* ligand-assisted trimerization in aprotic and non-coordinating solvents such as 1,2-DCE.^{20a,b}

Computationally, the triboroxine-acetone oxime reactant complex corresponding to **18** is tighter (d_{B-N} 1.71 Å, +5.4 kcal/mol) when compared to either of the boronate species, and displays an internal N=O–H ⋯ O–B hydrogen bond. The TS_{CC} for triallylboroxine lies significantly lower at +23.3 kcal/mol. Which is also in-line with the computational observations made by the Szabó group.^{19a,b}

To assess the importance of the computationally observed hydrogen bond, a control experiment with *O*-methoxy acetophenone (**20**), where the hydrogen bonding site is blocked, yielded no product under reaction conditions and the starting material was fully recovered.

These results would point toward a mechanistic proposal as described in Scheme 5. The reaction initiates by ligand exchange between AllB(O*i*Pr)₂ (**6**) and the aryl boronic acid catalyst **8a**, releasing allyl boronic acid **17**. The released allylboronic acid **17** is trimerized in a ligand-assisted condensation to form **18**, and the released water hydrolytically regenerates the arylboronic catalyst from ester **18**. This is further supported by a

control experiment with 3 Å MS giving only traces of allylated product with acetophenone oxime (**5a**) (<5% conversion). A homoboroxime triallyl species **18** instead of a heteroboroxime species is likely as Tokunaga group has demonstrated that electron deficient arylboronic acids, such as our catalyst **8a**, disfavor the formation of heteroboroximes.¹⁶ The reactant complex **19** undergoes an allyl transfer forming the aminoborane adduct **19**. As the reaction performs in quantitative yield with only 1.5 equivalents of the allylating species (Scheme 2, **7s**), the terminal species **19** must also be an active allyl transfer agent.



Scheme 5: Proposed mechanism for the catalytic activity of arylboronic acids. 1) Ligand-exchange between **6** and catalyst **8b** releases allylboronic acid (**17**) 3) Allylboronic acid (**17**) is trimerized in a ligand assisted condensation to form adduct **18** and release water 2) Released water hydrolytically regenerates the catalyst **8b** from ester **18** 4) Allyl transfer forms the product **19**, which is expected to still be an active allylating species.

In conclusion, we have uncovered an arylboronic acid catalyzed allylboration of unprotected oximes. The homoallylic hydroxylamine products show promising functionalization possibilities as demonstrated by a short total synthesis of the homotropane alkaloid *N*-methyl euphococcine, as well as other manipulations on the hydroxylamine functionality. Based on initial mechanistic studies, we propose the catalytic activity to be due to ligand exchange between the arylboronic acid and the allyl boronate ester.

ASSOCIATED CONTENT

Complete experimental procedures and characterization data including computational details is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- Crystallographic data for hydroxylamine **7s** have been deposited with the deposition number CCDC 1948852, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.
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