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γ -, Diastereo-, and Enantioselective Addition of MEMO-Substituted Allylboron Compounds to Aldimines Catalyzed by Organoboron–Ammonium Complexes

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Abstract

The first catalytic, broadly applicable, efficient, γ -, diastereo-, and enantioselective method for addition of O-substituted allyl–B(pin) compounds to phosphinoylimines (MEM = methoxyethoxymethyl, pin = pinacolato) is presented. The identity of the most effective catalyst and the optimal protecting group for the organoboron reagent were determined by consideration of the steric and electronic requirements at different stages of the catalytic cycle, namely, the generation of the chiral allylboronate, the subsequent 1,3-borotropic shift, and the addition step. Aryl-, heteroaryl-, alkenyl- and alkyl-substituted vicinal phosphinoylamido MEM-ethers were thus accessed in 57–92% yield, 89:11 to >98:2 γ : α selectivity, 76:24–97:3 diastereomeric ratio, and 90:10–99:1 enantiomeric ratio. The method is scalable, and the phosphinoyl and MEM groups may be removed selectively or simultaneously. Utility is highlighted by enantioselective synthesis of an NK-1 receptor antagonist.

Graphical Abstract

Keywords

allylic ethers; amino alcohols; boron; enantioselective catalysis; diastereoselective synthesis; homoallylic amines

Vicinal amino alcohol fragments reside within many biologically active compounds (Scheme 1a).^[1,2] Among the catalytic strategies for enantioselective synthesis of such entities,^[3,4,5,6] one attractive possibility involves addition of an alkoxy-substituted allyl group to aldimines.^[7] However, while additions of *O*-substituted enolate equivalents to aldimines (i.e., Mannich-type reactions) have been reported,^[8] just one example of a catalytic enantioselective allyl addition has been disclosed by Kobayashi et al.^[9] It was shown that an electronically activated hydrazono ester (Scheme 1b) reacts with 3-benzyloxy-substituted allyl–B(pin) (pin = pinacolato) in the presence of 5.0 mol % of a Zn–diamine complex, generating the desired product in >99:1 diastereomeric ratio (d.r.) and 91:9 enantiomeric ratio (e.r.). However, two days at –20 °C were needed for high conversion.

Moreover, conversion to the derived *t*-butyl carbamate demanded three steps; one operation required costly SmI₂, and removal of the benzyl ether led to concomitant loss of the alkene (Pd/C, H₂). In a non-catalytic approach, Xu, Lin and co-workers demonstrated that in situ-generated γ -benzoyloxy-substituted allyl–ZnBr compounds can add to enantiomerically pure *N*-*tert*-butanesulfinyl imine with high efficiency and diastereoselectivity.^[10] However, HMPA had to be used as the solvent for optimal stereoselectivity.

To address the above shortcoming, we considered the use of a class of catalysts, generated in situ from an aminophenol and an organoboron compound,^[11] for γ -, diastereo- and enantioselective addition of an *O*-substituted allylboronate species to phosphinoylimines (Scheme 1c). The following key questions needed to be addressed:

1) What would be the optimal aminophenol? Previous investigations show that, depending on the transformation, aryl substituents (G) as large as a triphenylsilyl moiety,^[12] or as small as a trifluoromethyl^[13] or a methyl group,^[12b] might deliver the highest e.r. Would the same be true here, or would such alterations also impact γ -and/or diastereoselectivity?

2) What would be the optimal protecting/activating group (pag) for the *O*-substituted allylboronate? Not only should removal of the oxygen-based pag unit – alone or together with the phosphinoyl unit – be feasible, it should be possible to unmask the N-H selectively.

The electronic characteristics of an allylboronate's pag group can exert an influence at two different stages of the catalytic cycle (Scheme 2): The formation of the enantiomerically enriched allylboronate **IV** (from **I** via **III**), and the subsequent reaction with an aldimine. That is, the pag group needs to be sufficiently electron withdrawing to disfavor the charge distribution (**II** vs. **I**) that can diminish the rate of allyl transfer (formation of **IV**). Further, the stronger the contribution of **V**, the slower the addition of an aminophenol-derived allyl–boron to a phosphinoylimine.

For further insight, we computed the charges at C γ of several *O*-substituted allyl–B(pin) compounds (Table 1). This indicated that, compared to a methyl ether, there is a higher degree of electron density at the C γ of an allyl–B(pin) compound bearing a methoxyethoxymethyl (MEM) or a trimethylsilyl (TMS) unit, a favorable attribute. It remained to be determined whether a larger silyl group would be detrimental to the rate of allyl transfer and/or addition.

We synthesized several allyl–B(pin) compounds (**1a–c**),^[14] and investigated their catalytic additions to imine **2a** with **ap-1** (Table 2). The transformations involving methoxy-substituted allylboronates *E*- and *Z*-**1a** and imine **2a** were severely inefficient at ambient temperature (entries 1–2), which is consistent with the observations of Hoffmann et al. in their pioneering studies regarding the reactivity of this class of organoboron compounds.^[15] Still, reaction with *Z*-**1a** was appreciably γ -, diastereo- and enantioselective (entry 2). At 60 °C, there was <5% conversion with *E*-**1a** (entry 3), and when *Z*-**1a** was used (entry 4), there was 33% conversion to methyl ether **3a**, which was generated with >98:2 γ : α selectivity, and in 92:8 d.r., and 92:8 e.r.

In line with the above analysis (cf. Scheme 2, Table 1), the catalytic process was considerably more efficient with MEMO-substituted **1b** (83% and >98% conv., 56% and 78% yield; entries 5–6); **4a** was generated with nearly identical enantioselectivity, although γ selectivity and d.r. were noticeably higher when *Z*-**1b** was used (90:10 and 94:6 γ : α , and 89:11 and 95:5 d.r. for *E*- and *Z*-**1b**, respectively). At 22 °C, under otherwise the same conditions as shown in entry 5, which is the same as that used for crotyl–B(pin) additions, [16a] there was <2% conversion to **4a**. With the bulkier silyl ether (**1c**; entry 7), there was a greater preference for the γ isomer, but the transformation was slower and d.r. and e.r. were lower (compared to *E*- and *Z*-**1b**). The higher yield for trimethylsilyl ether **5a** compared to the much smaller, but more electron donating, methyl ether **3a** underscores the importance of electronic effects (66% vs. 33% conv., entries 7 and 4, respectively).

We then set out to identify the optimal aminophenol (Scheme 3). With **2a** as the limiting agent (1.5:1 *Z*-**1b**:**2a**), there was a clear trend vis-à-vis the effect of the aryl substituent on γ selectivity and e.r. (Scheme 3a). In the case of a larger catalyst substituent (i.e., **ap-2**), the γ : α ratio dropped significantly (83:17 vs. 94:6 for *t*Bu-substituted **ap-1**). Conversely, with a smaller aryl substituent (i.e., **ap-3-4**), γ selectivity improved (γ : α 98:2 vs. 94:6 for **ap-1**), but there was a notable lowering of e.r. (84:16–89:11 vs. 92:8 for **ap-1**).

The variation in γ : α selectivities for the reactions with **ap-1** (94:6) versus those involving **ap-3** and **ap-4** (98:2) correspond to a significant energy difference, especially when the transformation with **ap-2** (83:17) is included. The origin of these changes may be because a bulkier catalyst substituent hinders 1,3-borotropic shift,^[16] which must be faster than direct addition to an aldimine for the *g*-addition product to be formed preferentially (Scheme 3b). The deleterious effect on the rate with which **III** can convert to the sterically less congested and lower energy allylboronate intermediate **IV**^[16] might have two origins: 1) increased steric pressure in the transition state, engendered by a bulkier catalyst (**VIa** vs. **VIb**) en route to **IVa-b**, which can then be transformed to the anti product,^[16a] and 2) weaker association of the Lewis acidic Zn(II)-based co-catalyst, needed to accelerate the boryl shift via **VI**. The first scenario is supported by DFT studies (Scheme 3b; *t*-Leu-based complex and methyl ether used to facilitate computation), showing that, due to a change in hybridization at the boron center during the 1,3-borotropic shift, as the transformation proceeds via **VI**, there is greater proximity between the allyl and the catalyst's aryl fragments (G). The borotropic shift transition state with **ap-2** would thus be higher in energy compared to **ap-3**. An increase in the relative concentration of the phosphinoylimine thus led to lower γ : α ratios (Scheme 3c); this is likely because addition of the initially generated complex (**III**) to the substrate becomes more competitive with the borotropic shift (i.e., reaction of **VI** with **2a**). The idea that weaker catalyst–Lewis acid interaction results in less borotropic shift and lower γ selectivity is supported by the finding that with the bulkier Zn(O*t*Bu)₂ and **ap-2** (1:2 *Z*-**1b**:**2a**), γ : α selectivity plummeted to 55:45. Further screening revealed that with 7.5 mol % *t*-Leu-derived **ap-5** (e.r. may be significantly increased, without adversely impacting γ selectivity or d.r., consistent with the original stereochemical model.^[11a] By utilizing **ap-5**, we were able to obtain **4a** in 86% yield, 98:2 γ : α ratio, 93:7 d.r., and 97:3 e.r. (Scheme 4a).^[17]

The method is broadly applicable (Scheme 4a). Different *ortho*-substituted aryl-substituted products (**4b-f**), including the sterically hindered *o*-tolyl- and 1-naphthyl-substituted products **4e** and **4f**, were isolated in 84–89% yield, 94:6–99:1 γ : α ratio, 89:11–93:7 d.r. and 97:3–99:1 e.r. Typically, the electronics of the aryl group had little effect on selectivity, as electron-rich *para*-dimethylaminophenyl- and electron-poor *para*-trifluoromethylphenyl-substituted **4h** and **4k** were isolated in 83% and 92% yield, 98:2 and 95:5 γ : α selectivity, 93:7 d.r., and 97:3 and 99:1 e.r., respectively. Synthesis of the more electron-rich **4h** required a higher loading of Zn(OMe)₂ (15 mol %) and more MeOH (2.5 vs. 1.5 equiv.). In the case of *para*-carbomethoxyphenyl-substituted **4l**, where electron withdrawal is probably stronger, the reaction was efficient and highly γ - and enantioselective, but the d.r. was lower (88:12).

Heteroaryl-substituted phosphinoylimines were equally effective (Scheme 4b), as indicated by the synthesis of 2- and 3-furyl and thienyl-substituted products (**4m-p**), and 3-pyridyl-substituted **4q**. A reason for the lower e.r. for the 2-substituted furyl substrate (cf. **4m** vs. **4n**) has been provided^[12a] (electrostatic attraction between the heterocycle O atom and the catalyst's ammonium group). However, why, unlike previous cases,^[12a,c] the reaction with thienyl-substituted imine are similarly enantioselective (cf. **4o** vs. **4p**), and what might be the reason for the lower d.r. for **4m** and **4o**, is unclear.

Reactions with alkenyl- and alkyl-substituted imines were efficient (**4r-u**, Scheme 4c), although selectivities were lower in some cases. The decrease in γ selectivity for **4t** may be because the less hindered phosphinoylimine binds to the boron center of the chiral catalyst more readily, negatively impact the rate of borotropic shift (cf. Scheme 4b). It is also possible that the lower d. r. and e.r. in the formation of **4t** and **4u** might be because with a smaller alkyl moiety, reaction via a *Z*-phosphinoylimine is more competitive.^[18]

A transformation was successfully carried out on gram scale at 3.5 mol % loading (Scheme 5a). The MEM group was removed with reasonable efficiency by using a CeCl₃/NaI combination^[19] (e.g., **6** in 69% yield, Scheme 5b). The resulting allylic alcohol was converted to **7** (73% yield), a process that improves diastereomeric purity (from 93:7 to 96.5:3.5 d.r.), likely due to faster ring closure to generate the lower energy *anti* isomer; this type of vinyl aziridine has been used in regio-controlled allylic substitutions.^[20] Selective removal of the phosphinoyl unit was less efficient, as represented by the formation of homoallylic amine **8** (43% yield), involved a combination of HPO(OPh)₂ and triphenylphosphite.^[21] Treatment of **4a** with 12 M HCl/EtOH for four hours at ambient temperature (Scheme 5c), followed by subjection of the resulting amino alcohol **9** (unpurified) to chloroacetyl chloride/Et₃N for an additional hour led to the formation of amido-alcohol **10** (67% overall yield). Ensuing treatment with base, to afford **11** (86% yield), and catalytic cross-metathesis afforded the compound reported as the aforementioned (Scheme 1a) NK-1 receptor antagonist, and precursor to its more potent epoxide derivative^[2a-b] (65% yield, >98% *E*). Synthesis of amino alcohol **9** in high e.r. would require a lengthier pathway if the other available catalytic methods were to be adopted.^[3,4,6,8]

These studies shed new light on the inner workings of an emerging class of organoboron–ammonium catalysts;^[11–13,16] it demonstrates that adjustment of the size and electronic

attributes of the *O*-based substituent of the allyl boronate reagent can lead to efficient generation of an enantiomerically pure allylboronate and its subsequent addition to an imine. The new method entails a catalyst and substrates that are readily accessible, and delivers differentially protected vicinal amino alcohols in generally high yields and stereoselectivities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References & Footnotes

- [1]. For reviews and overviews regarding stereoselective preparation of vicinal amino alcohol and derivatives, see: Bergmeier SC, *Tetrahedron* 2000, 56, 2561–2576; Lee H-S, Kang SH, Synlett 2004, 1673–1685; Karjalainen OK, Koskinen AMP, *Org. Biomol. Chem* 2012, 10, 4311–4326. [PubMed: 22535485]
- [2]. For the NK-1 receptor antagonist, see: Ladduwahetty T, Keown L, Cascieri MA, Sadowski S, *Bioorg. Med. Chem* 1994, 4, 1917–1920; Dorn CP, Finke PE, Hale JL, Mills SG, Shah S, Chambers MS, Harrison T, Ladduwahetty T, Williams BJ, 1995, International Patent WO 95/16679. For 6-hydroxy-4-sphingene, see: Kolesnick RN, Goñi FM, Alonso A, *J. Cell. Physiol* 2000, 184, 285–300; [PubMed: 10911359] Mori K, Masuda Y, *Tetrahedron Lett* 2003, 44, 9197–9200; Brodesser S, Sawatzki P, Kolter T, *Eur. J. Org. Chem* 2003, 2021–2034; Masuda Y, Mori K, *Eur. J. Org. Chem* 2005, 4789–4800. For hapalosin, see: Stratmann K, Burgoyne DL, Moore RE, Patterson GML, Smith CD, *J. Org. Chem* 1994, 59, 7219–7226; Okuno T, Ohmori K, Nishiyama S, Yamamura S, Nakamura K, Houk KN, Okamoto K, *Tetrahedron* 1996, 52, 14723–14734.
- [3]. For synthesis of vicinal amino alcohols (with secondary C–O and C–N bonds) by catalytic enantioselective additions of hydroxyl-amines to alkenes, see: Li G, Angert HH, Sharpless KB, *Angew. Chem. Int. Ed. Engl* 1996, 35, 2813–2817; Donohoe TJ, Callens CKA, Flores A, Lacy AR, Rathi AH, *Chem. Eur. J* 2011, 17, 58–76. [PubMed: 21207600] By catalytic enantioselective hydrogenation: Klingler FD, *Acc. Chem. Res* 2007, 40, 1367–1376; [PubMed: 18052332] Jiang Y, Chen X, Zheng Y, Xue Z, Shu C, Yuan W, Zhang X, *Angew. Chem. Int. Ed* 2011, 50, 7304–7307; Goodman CG, Do DT, Johnson JS, *Org. Lett* 2013, 15, 2446–2449. [PubMed: 23631467]
- [4]. For preparation of vicinal amino alcohols (with secondary C–O and C–N bonds) by additions to aldehydes and imines, and with enantiomerically pure substrates or reagents, see: Additions to carbonyl-containing compounds: Coleman RS, Carpenter AJ, *Tetrahedron Lett* 1992, 33, 1697–1700; Barrett AGM, Seefeld MA, *J. Chem. Soc., Chem. Commun* 1993, 339–341; Reetz MT, *Chem. Rev* 1999, 99, 1121–1162; [PubMed: 11749442] Buesking AW, Ellman JA, *Chem. Sci* 2014, 5, 1983–1987; Silveira-Dorta G, Donadel OJ, Martín VS, Padrón JM, *J. Org. Chem* 2014, 79, 6775–6782; [PubMed: 24708186] Zamani F, Pyne SG, Hyland CJT, *J. Org. Chem* 2017, 82, 6819–6830; [PubMed: 28557457] Liu C, Weng J, Lin Z-H, Huang W-J, Guo J, Huang L-J, Liu G, *Tetrahedron: Asymmetry* 2017, 28, 41–46. Additions to imines: Muñoz-Hernández L, Soderquist JA, *Org. Lett* 1999, 11, 2571–2574; Ramachandran PV, Burghardt TE, *Chem. Eur. J* 2005, 11, 4387–4395; [PubMed: 15880541] Louvel J, Chemla F, Demont E, Ferreira F, Pérez-Luna A, Voituriez A, *Adv. Synth. Catal* 2011, 353, 2137–2151; Muñoz-Hernández L, Seda LA, Wang B, Soderquist JA, *Org. Lett* 2014, 16, 4052–4055; [PubMed: 25014710] Zhao Y-H, Liu H-W, *Synth. Commun* 2014, 44, 1012–1018.
- [5]. Vicinal amino alcohols (with secondary C–O and C–N bonds) may be prepared by catalytic enantioselective addition of N-based nucleophiles to meso epoxides. For representative examples

see: Bartoli G, Bosco M, Carlone A, Locatelli M, Massaccesi M, Melchiorre P, Sambri L, Org. Lett 2004, 6, 2173–2176; [PubMed: 15200313] Carrée F, Gil R, Collin J, Org. Lett 2005, 7, 1023–1026; [PubMed: 15760129] Azoulay S, Manabe K, Kobayashi S, Org. Lett 2005, 7, 4593–4595; [PubMed: 16209487] Shivani, Pujala B, Chakraborti AK, J. Org. Chem 2007, 72, 3713–3722; [PubMed: 17411096] Bonollo S, Fringuelli F, Pizzo F, Vaccaro L, Synlett 2008, 1574–1578; Birrell JA, Jacobsen EN, Org. Lett 2013, 15, 2895–2897; [PubMed: 23742206] Kumar M, Kureshy RI, Saravanan S, Verma S, Jakhar A, Khan NH, Abdi SHR, Bajaj HC, Org. Lett 2014, 16, 2798–2801; [PubMed: 24828318] Tak R, Kumar M, Kureshy RI, Choudhary MK, Khan NH, Abdi SHR, Bajaj HC, RCS Advances 2016, 6, 7693–7700; Tak R, Kumar M, Menapara T, Choudhary MK, Kureshy RI, Khan NH, ChemCatChem 2017, 9, 322–328.

- [6]. For photocatalytic enantioselective synthesis of vicinal amino alcohols (with secondary C–O and C–N bonds), see: Rono LJ, Yayla HG, Wang DY, Armstrong MF, Knowles RR, J. Am. Chem. Soc 2013, 135, 17735–17738; [PubMed: 24215561] Ye C-X, Melcamu YY, Li H-H, Cheng J-T, Zhang T-T, Ruan Y-P, Zheng X, Lu X, Huang P-Q, Nat. Commun DOI: 10.1038/s41467-017-02968-4.
- [7]. For a review on enantioselective additions of allyl groups to imines, see: Yus M, González-Gómez JC, Foubelo F, Chem. Rev 2011, 111, 7774–7854. [PubMed: 21923136] For an overview regarding additions of organoboron compounds in various addition reactions, see: Diner C, Szabó K, J. Am. Chem. Soc 2017, 139, 2–14. [PubMed: 27966922]
- [8] a). Kobayashi S, Ishitani H, Ueno M, J. Am. Chem. Soc 1998, 120, 431–432; b) Trost BM, Terrell LR, J. Am. Chem. Soc 2003, 125, 338–339; [PubMed: 12517138] c) Matsunaga S, Yoshida T, Morimoto H, Kumagai N, Shibasaki M, J. Am. Chem. Soc 2004, 126, 8777–8785; [PubMed: 15250731] d) Ramasastry SSV, Zhang H, Tanaka F, Barbas CF, III, J. Am. Chem. Soc 2007, 129, 288–289; [PubMed: 17212404] e) Trost BM, Jaratjaroonphong J, Reutrakul V, J. Am. Chem. Soc 2006, 128, 2778–2779; [PubMed: 16506738] f) Wu C, Fu X, Li S, Tetrahedron: Asymmetry 2011, 22, 1063–1073.
- [9]. Fujita M, Nagano T, Schneider U, Hamada T, Ogawa C, Kobayashi S, J. Am. Chem. Soc 2007, 130, 2914–2915.
- [10]. Liu M, Sun X-W, Xu M-H, Lin G-Q, Chem. Eur. J 2009, 15, 10217–10224. [PubMed: 19711382]
- [11] a). Silverio DL, Torker S, Pilyugina T, Vieira EM, Snapper ML, Haefner F, Hoveyda AH, Nature 2013, 494, 216–221; [PubMed: 23407537] b) Wu H, Haefner F, Hoveyda AH, J. Am. Chem. Soc 2014, 136, 3780–3783. [PubMed: 24588835]
- [12] a). Lee K, Silverio DL, Torker S, Robbins DW, Haefner F, van der Mei FW, Hoveyda AH, Nat. Chem 2016, 8, 768–777; [PubMed: 27442282] b) Robbins DW, Lee K, Silverio DL, Volkov A, Torker S, Hoveyda AH, Angew. Chem. Int. Ed 2016, 55, 9610–9614; c) van der Mei FW, Qin C, Morrison RJ, Hoveyda AH, J. Am. Chem. Soc 2017, 139, 9053–9065. [PubMed: 28648084]
- [13]. Mszar NW, Mikus MS, Torker S, Haefner F, Hoveyda AH, Angew. Chem. Int. Ed 2017, 56, 8736–8741.
- [14]. Preparation of alkoxy- and siloxy-substituted allyl–B(pin) compounds were based on procedures outlined previously. See: Hoffmann RW, Metternich R, Lanz JW, Liebigs Ann. Chem 1987, 881–887; Yamamoto Y, Fujikawa R, Yamada A, Miyaura N, Chem. Lett 1999, 1069–1070; Murata M, Watanabe S, Masuda Y, J. Chem. Research (S) 2002, 142–143; Zhang P, Roundtree IA, Morken JP, Org. Lett 2012, 14, 1416–1419. [PubMed: 22375950] See the Supporting Information for details.
- [15] a). Hoffmann RW, Kemper B, Metternich R, Lehmeier T, Liebigs Ann. Chem 1985, 2246–2260; b) Hoffmann RW, Metternich R, Liebigs Ann. Chem 1985, 2390–2402.
- [16] a). van der Mei FW, Miyamoto H, Silverio DL, Hoveyda AH, Angew. Chem. Int. Ed 2016, 55, 4701–4706. For key reports regarding 1,3-boryl shift processes, see: Hancock KG, Kramer JD, J. Am. Chem. Soc 1973, 95, 6463–6465; Hancock KG, Kramer JD, J. Organomet. Chem 1974, 64, C29–C31; Henriksen U, Snyder JP, Halgren TA, J. Org. Chem 1981, 46, 3767–3768; Bühl M, von Ragué Schleyer P, Ibrahim MA, Clark T, J. Am. Chem. Soc 1991, 113, 2466–2471; Gridnev ID, Gursky ME, Bubnov YN, Organometallics 1996, 15, 3696–3702; Bubnov YN, Pure Appl. Chem 1987, 59, 895–906; Choi JY, Kim CK, Kim CK, Lee I, J. Phys. Chem. A 2002, 106, 5709–5715; Gurskii ME, Belyakov PA, Lyssenko KA, Semenova AL, Bubnov YN, Russian Chem. Bull. Int. Ed 2014, 63, 480–486.

- [17]. When the t-Bu-substituted analogue of ap-1 (i.e., derived from t-Leu) was used, under otherwise identical conditions, 4a was generated in 77% yield, 89:11 g:a selectivity, 93:7 d.r., and 95:5 e.r. (for the g product). These data confirm that by proper combination of the optimal catalyst substituents (i.e., ap-5), high g selectivity and e.r. can be attained.
- [18]. We were unable to challenge the veracity of this latter possibility by examining the reactions with phosphinoylimines that contain a larger alkyl group. This is mostly because such entities (unlike, aryl-, heteroaryl- or alkenyl-substituted derivatives) must be generated by in situ elimination of the corresponding p-tosyl-substituted diphenylphosphorylamine (for example, see: N. W. Mszar, F. Haeffner, A. H. Hoveyda, J. Am. Chem. Soc. 2014, 136, 3362–3365), a process that is often inefficient and forms unidentifiable byproducts that are detrimental to the subsequent catalytic enantioselective addition. This is indeed a shortcoming of the state-of-the-art vis-à-vis protocols that involved alkyl-substituted phosphinoylimines.
- [19]. Sabitha G, Babu RS, Rajkumar M, Srividya R, Yadav JS, Org. Lett 2001, 3, 1149–1151. [PubMed: 11348181]
- [20]. Jarvis AN, McLaren AB, Osborn HMI, Sweeney J, Beilstein J Org. Chem 2013, 9, 852–859.
- [21] a). Li P, Wischert R, Metivier P, Angew. Chem. Int. Ed 2017, 56, 15989–15992. The following methods were less effective: Li Y, Das S, Zhou S, Junge K, Beller M, J. Am. Chem. Soc 2012, 134, 9727–9732; [PubMed: 22480270] Han ZS, Goyal N, Herbage MA, Sieber JD, Qu B, Xu Y, Li Z, Reeves JT, Desrosiers J-N, Ma S, Grinberg N, Lee H, Mangunuru HPR, Zhang Y, Krishnamurthy D, Lu BZ, Song JJ, Wang G, Senanayake CH, J. Am. Chem. Soc 2013, 135, 2474–2477; [PubMed: 23369026] Chen W, Yang X-D, Tan W-Y, Zhang X-Y, Liao X-L, Zhang H, Angew. Chem. Int. Ed 2017, 56, 12327–12331; Li B-J, Simard RD, Beauchemin AM, Chem. Commun 2017, 53, 8667–8670.

a. Representative bioactive compounds with a vicinal amino alcohol moiety (secondary carbon centers):

b. Relevant previous findings:

2007 (Kobayashi, et al.)

Shortcomings:

1. Only one example reported, and involves an activated aldimine
2. Hydrazone ester removal requires three steps and several equivalents of costly Sml₂
3. Removal of Bn group causes concomitant alkene hydrogenation

2009 (Xu & Lin, et al.)

Shortcoming: Dry HMPA required as the solvent

c. Objectives of this study:

Scheme 1.

Examples of biologically active compounds with vicinal amino alcohol moiety (or a derivative), the only previous example of a catalytic enantioselective, and a relevant non-catalytic and diastereoselective, addition of *O*-substituted allyl moieties to aldimines, and the objectives of this study. HMPA, hexamethylphosphoramide.

Scheme 2.

The *O*-protecting/activating (pag) group in an allylboronate compound can impact the process at two different stages.

a. Probing the effect of the catalyst's aryl substituent (G):

b. DFT studies suggest a lower barrier to 1,3-borotropic shift with a smaller G in the catalyst:

c. Variations in γ selectivity due to a change in imine concentration:

With 1:2 Z-1b:2a :			
98% conv., 65% yield, 90:10 $\gamma:\alpha$, 93:7 d.r., 92:8 e.r.	85% conv., 54% yield, 65:35 $\gamma:\alpha$, 92:8 d.r., 89:11 e.r.	98% conv., 67% yield, 91:9 $\gamma:\alpha$, 95:5 d.r., 88:12 e.r.	98% conv., 71% yield, 94:6 $\gamma:\alpha$, 93:7 d.r., 82:18 e.r.

Scheme 3.

Examination of different aminophenol ligands, aided by DFT studies, indicated that the optimal combination of efficiency, γ - and stereoselectivity can be obtained by one containing a smaller aryl substituent (G). See the Supporting Information for details.

a) With aryl-substituted imines:

b) With heteroaryl-substituted imines:

c) With alkenyl- and alkyl-substituted imines:

Scheme 4.

Aryl-, heteroaryl-, alkenyl- and alkyl-substituted phosphinoyl imines may be used (>98% conv. in all cases). [a] 7.5 mol % **ap-5**, 15 mol % $\text{Zn}(\text{OMe})_2$, 2.5 equiv. MeOH used. See the Supporting Information for details.

a. Reaction on gram scale: **b. Selective unmasking of MEM ether or phosphinoyl amide:** **c. Application to synthesis of a bioactive compound via an unprotected amino alcohol:** **Scheme 5.**

The catalytic process may be carried out on gram scale, and the corresponding differentially or fully unprotected derivatives can be accessed for application to synthesis of biologically active molecules. diad = di(*i*-propoxy)azadicarboxylate.

Table 1:Charge at C γ of *O*-substituted allylboronates.^[a]

pag = protecting/activating group

pag = Me	pag = MEM	pag = TMS
-0.12685	-0.15882	-0.16836

^[a]Values obtained based on analysis of the Fukui function. Calculations were performed at ω B97×D/Def2TZVPP// ω B97×D/Def2SVP level in the gas phase. See the Supporting Information for details. MEM, CH₂O(CH₂)₂Me; TMS, SiMe₃.

Table 2:

Initial evaluation/optimization of values organoboron reagents and conditions.^[a]

Entry	pag, stereochem.	T (°C); t (h)	Conv. (%); ^[b]	Yield (%) ^[c]	γ : α ^[b]	d.r. ^[b]	e.r. ^[d]
1	a Me, <i>E</i>	22; 18	<5; NA		NA	NA	NA
2	a Me, <i>Z</i>	22; 18	12; ND		>98:2	96:4	94:6
3	a Me, <i>E</i>	60; 14	<5; NA		NA	NA	NA
4	a Me, <i>Z</i>	60; 14	33; 21		>98:2	92:8	92:8
5	b MEM, <i>E</i>	60; 14	83; 56		90:10	89:11	91:9
6	b MEM, <i>Z</i>	60; 14	>98; 78		94:6	95:5	92:8
7	c TMS, <i>Z</i>	60; 14	66; 45 ^[e]		>98:2	89:11	90:10

^[a] Performed with 1.5 equiv. organoboron reagent under N₂ atm.^[b] Conv., d.r., and g:a ratios were determined by analysis of ¹H NMR spectra of unpurified mixtures; conv. ($\pm 2\%$) refers to disappearance of the **2a**.^[c] Yield of isolated and purified product and the corresponding α -addition byproduct ($\pm 5\%$).^[d] E.r. values were determined by HPLC analysis ($\pm 1\%$).^[e] The corresponding alcohol was isolated (silyl removal occurred upon work-up). See the Supporting Information for details. MEM, CH₂O(CH₂)₂OMe; TMS, SiMe₃; NA, not applicable; ND, not determined.