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Iridium-Catalyzed Allylic Amination Route to α -Aminoboronates: Illustration of the Decisive Role of Boron Substituents

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Abstract

The development of a new route to α -aminoboronates using an iridium-catalyzed allylic amination on boronated substrates is described. Unlike the boronate group, the trifluoroborato substituent was found to govern the regioselectivity exclusively in favor of branched products. The transformation of an allylic substitution product into an α -aminoboronic ester in an efficient way validated the implementation of this approach.

Keywords

allylic amination; α -aminoboronates; iridium; regioselectivity; trifluoroborates

The incorporation of α -aminoboronates into peptide chains has opened the route to new classes of very potent enzyme inhibitors.^[1] Their biological activities are based on the ability of nucleophilic residues, serine or threonine in most cases, located in the protease active site to bind to the electron-deficient boron atom. The tetrahedral adduct then mimics the transition structure formed during the course of natural substrate hydrolysis and strongly contributes to the observed potency of this class of inhibitors. Successful examples include Bortezomib (Velcade[®]), a highly selective reversible inhibitor of the 26S proteasome which was approved in May 2003 for treatment of patients with advanced multiple myeloma,^[2] and Val-boroPro (Talabostat), an orally-active inhibitor of dipeptidyl peptidases, which has been in phase II clinical trials for colorectal cancer (Figure 1).^[3]

Compared to the importance of their biological properties, relatively few methods have been explored for the synthesis of α -aminoboronic esters. They involve either the formation of a C–B bond (route A) or a C–N disconnection (route B, Figure 2).^[1a] The most popular approach is certainly the S_N2 displacement of a halogen α to a boron atom using amines and derivatives as nucleophiles, the diastereoselective insertion of a CHCl group into a carbon-

boron bond of a boronic ester being the cornerstone of this strategy.^[4a] More recently, another elegant diastereoselective method was also reported based on a copper-catalyzed addition of bis(pinacolato)diboron to *N-tert*-butanesulfinyl aldimines.^[4b] Other approaches are more limited in terms of generality by the nature of the starting products, such as borylation of organometallic compounds,^[4c] S_N2' reactions,^[4d,e] electrophilic amination^[4f] or [3,3]-sigmatropic rearrangements.^[4g]

In the past few years, our laboratory has been focusing on developing chemistry to prepare several boron analogues of carboxylic amino acids.^[5] We have now devised a new procedure for the synthesis of α -aminoboronic esters from γ -functionalized alkenylboron compounds based on an iridium-catalyzed allylic amination reaction. The allylic substitution catalyzed by transition metal complexes represents one of the most efficient and versatile methods for carbon-carbon and carbon-heteroatom bond formation.^[6] These reactions can be carried out with a variety of metals, substitution patterns of the allylic moiety, and nucleophiles. To the best of our knowledge, there have only been quite limited studies on substrates bearing a boron atom. Hall et al. reported the preparation of α -substituted allylboronates from 3-hydroxy-1-propenylboronate derivatives [Scheme 1, Eq. (1)],^[7] while 2-(pin)B-substituted allylic acetates have been recently used by Walsh et al. in the synthesis of trisubstituted allylic amines *via* a sequence including a palladium-catalyzed allylic amination followed by a Suzuki cross-coupling reaction [Scheme 1, Eq. (2)].^[8] On the basis of these precedents, we initiated a research program with the aim of exploring the reactivity of allylcarbonates **1** and **3** with amines as a new access to α -aminoboronic esters [Scheme 1, Eq. (3)]. Although remarkable results were reported with different allylic metal intermediates and chiral ligands,^[6] iridium complexes were chosen as catalysts in this preliminary study because of their high control of regioselectivity, their tolerance of a wide range of functional groups and the excellent results in terms of enantiocontrol.^[9]

We first selected compound **1** as a model substrate. This material was efficiently prepared in a stereochemically pure (*E*)-form by hydroboration of the propargyl ethyl carbonate using pinacolborane (Scheme 2). Under the standard reaction conditions initially described by Takeuchi et al.^[10] {[Ir(COD)Cl]₂ (2.5 mol%), P(OPh)₃ (P/Ir = 2), 3 equivalents of piperidine as nucleophile in refluxing CH₂Cl₂}, linear allylic amine **2b** was the only regioisomer observed in the ¹H NMR spectrum of the crude reaction mixture together with the starting material in a 78/22 ratio in favor of **2b**. Taking into account that the nature of the ligand can greatly influence the reactivity and the regioselectivity, the same reaction was performed with *N,N*-dimethyldinaphtho[2,1-*d*:1,2-*f*][1,3,2]dioxaphosphepin-4-amine **L**², a common ligand for this class of reaction,^[9] instead of triphenyl phosphite **L**¹. This modification gave disappointing results because the undesirable linear allylic amine **2b** is still predominantly obtained despite a full conversion, this time at room temperature.

In recent years, organotrifluoroborate salts have emerged as versatile reagents in a wide range of reactions.^[11] Besides their ability to allow chemical modifications of remote functional groups while retaining the synthetic potential of the carbon-boron bond, these surrogates of boronic acids^[12] also have the property of reversing the polarity of a double bond, in a hydroboration reaction, for example.^[13] On the other hand, it is also known that the enantioselectivity and regioselectivity of the iridium-catalyzed allylic amination are greatly influenced by many parameters, including the nature of the substituents at the allylic moiety.^[9] We therefore envisaged replacing the boronate moiety of **1** by a trifluoroborate group in the hope of promoting the exclusive formation of the branched product.

Trifluoroborate **3** was prepared by treatment of **1** with an aqueous solution of KHF₂ in methanol (82% yield). Having in hand this new substrate, we then performed its allylic amination with piperidine under the previously used conditions. We were pleased to observe

the exclusive formation of branched product, confirming the relevance of our approach. No linear product **5a** was detected in the ^1H NMR spectrum of the crude material. This inversion of regioselectivity can be attributed to the electronic effect of the trifluoroborate group on the (π -allyl)Ir intermediate. Compound **4a** was isolated by precipitation in a 50% yield (Scheme 3). It is worth noting that only the potassium aminomethyltrifluoroborates were hitherto known.^[14,15]

To optimize this reaction, we then evaluated the influence of other solvents (Table 1, entries 1–6). Except with a polar solvent (MeOH, entry 4), the branched product is always observed exclusively. The best yield of the desired product **4a** (65%) was obtained by using cyclopentyl methyl ether (CPME) (entry 6). The effect of an additional base was also examined. Although piperidine is usually basic enough to cause the C–H activation from $[\text{Ir}(\text{cod})\text{Cl}]_2$ and a phosphoramidite ligand, it was reported that the supplementary addition of a non-nucleophilic base can accelerate the reaction.^[16] Indeed, in our case, the reaction time for a full conversion is not only reduced from 48 h to 12 h at room temperature by the addition of a catalytic amount of DBU, but the yield of **4a** is also enhanced (entry 7).

With this information in hand, we assessed the scope and limitations of this reaction under our optimized catalyst system. In all cases, the regioselectivity of the reaction is exclusively in favor of α -aminotrifluoroborate **4** (Table 2, entries 1–10). Yields obtained using cyclic amines as nucleophiles are between 60 and 91%, except with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.^[17] This could be due to the fact that CH_2Cl_2 had to be used as a solvent because of solubility problems in CPME (entry 5). More interesting is to note the difference of reactivity with acyclic secondary amines (entries 10 and 11). We were disappointed to recover all of the starting trifluoroborate **3** when *N*-propylbenzylamine was used, while the reaction was complete with *N*-methylbenzylamine after 18 h at room temperature. A possible explanation for this phenomenon could be the value of the cone angle for *N*-propylbenzylamine, which is slightly larger than that of *N*-methylbenzylamine (estimated at $\sim 127^\circ$).^[18] Similarly, the use of dibenzylamine ($\theta = 140^\circ$) did not lead to the desired product. Finally, we also tested isobutylamine, a primary amine, ($\theta = 106^\circ$). After completion of the reaction (12 h, room temperature), ^1H NMR analysis indicated the presence of mono- and diallylation products with a ratio (70:30) in favor of the former. Unfortunately, we were unable to separate this mixture.

Our original aim being to provide access to α -aminoboronates, the transformation of trifluoroborates **4** into boronic esters was evaluated using **4a** as a model substrate (Scheme 4). Although different established procedures were attempted,^[12] we were unable to isolate any defined product. We attributed this failure to the presence of an allylic moiety that weakens the B–C bond, leading to facile protodeboronation. Circumvention of this problem was accomplished by reducing the double bond, generating **6**. Subsequently, treatment of **6** with 1,1,2,2-tetramethylethane-1,2-diol bis-(trimethylsilyl) ether in the presence of chlorotrimethylsilane in acetone at room temperature led to the formation of the hydrochloride **7** in 95% yield. This material can be stored several weeks in the freezer without decomposition, while the free base has a limited stability in air. A basic treatment furnished the deprotonated compound **8** in quantitative yield in a high purity (91% overall yield, three steps starting from **4a**).

In conclusion, we have reported in this preliminary letter a new means to access α -aminoboronates using an iridium-catalyzed allylic amination reaction as a key step. The use of a trifluoroborate group in place of a boronic ester has been the determining factor to control the regioselectivity of this approach. This complete inversion of regioselectivity, exclusively in favor of the branched product regardless of the used amine, deserves to be extended to diversely substituted allylic substrates and other nucleophiles, that should open

new perspectives in boron chemistry. Additionally, other future lines of investigation will be to find an efficient method to determine the enantiomeric excess of allylic substitution products^[19] and to test other boron derivatives, such as B-MIDA^[20] as directing group to control the regio- and enantioselectivity.

Experimental Section

General Procedure for the Preparation of **4** (Table 2)

In a flame-dried Schlenk tube under an argon atmosphere, chiral phosphoramidite ligand *N,N*-dimethyldinaphtho[2,1-*d*:1,2-*f*][1,3,2]dioxaphosphepin-4-amine, **L**² (7.6 mg, 0.021 mmol) and [Ir(cod)Cl]₂ (7.2 mg, 0.011 mmol) were dissolved in CPME (1 mL) at room temperature. The resulting orange solution was stirred for 10 min and treated with DBU (6.4 mL, 0.042 mmol). The color of the solution changed from orange to light yellow. This solution was stirred for 2 h. The organotrifluoroborate substrate **3** was added (100 mg, 0.424 mmol) followed by the addition of 3 mL of CPME. After few minutes, the desired amine was added (1.272 mmol) and the reaction mixture was stirred for the appropriate times (Table 2). After completion of the reaction, the solvent was evaporated and then treated with potassium carbonate (58.6 mg, 0.424 mmol) in a 1:1 mixture of acetone:acetonitrile (4 mL) at room temperature for 2 h. The insoluble salts were filtered off, and the filtrate was concentrated. The crude solid was dissolved in a minimal amount of acetone, and diethyl ether was added dropwise, leading to precipitation of the product. To aid the precipitation, the solution can be sonicated. The product was then filtered, collected, and dried for a few hours in vacuo to afford the desired compound.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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17. Because the purification of compounds **4** was achieved by simple precipitation from the crude mixture, and it was awkward to separate the starting material **3** from **4**, the reaction time has to be adapted to drive the allylic amination to completion. Nevertheless, we have not been able to obtain **4h** and **4i** in a pure form.
18. Piperidine has a cone angle of 121°. See: Seligson AL, Troglor WC. *J Am Chem Soc*. 1991; 113:2520–2527.
19. Despite numerous attempts (NMR with chiral shift reagents, HPLC), no method could be hitherto developed to determine the enantiomeric excess of trifluoroborates **4**. In addition, we encountered the same difficulties with the corresponding aminoboronic ester **8**, which lacked sufficient stability under tested conditions.
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Figure 1.
Some examples of bioactive boro-peptides.

Route A

- . addition to *N*-sulfinyl aldimines^[4b]
- . α -metalation and borylation^[4c]

Route B

- . S_N2 ^[4a] or S_N2' displacements^[4d,4e]
- . electrophilic amination^[4f]
- . [3,3]-sigmatropic rearrangements^[4g]

Figure 2.
Different approaches to the synthesis of α -aminoboronic esters.

Scheme 1.

Metal-catalyzed allylic substitution reaction with boronated substrates.

Scheme 2.
Allylic amination of boronate **1** with piperidine.

Scheme 3.
Inversion of regioselectivity with the trifluoroborate **3**.

Scheme 4.

Conversion of trifluoroborate **4a** into α -aminoboronate **8**.

Table 1Effect of solvent and additive on allylic amination of **3** (Scheme 3).^[a]

Entry	Solvent	Activator [mol%]	t [h]	Yield [%] ^[b]	Ratio ^[c] 4a/5a
1	THF	–	48	50	100/0
2	CH ₂ Cl ₂	–	48	31	100/0
3	toluene	–	48	25	100/0
4	methanol	–	48	20 ^[d]	54/46
5	TBME	–	48	30	100/0
6	CPME	–	48	65	100/0
7	CPME	DBU (10)	12	79	100/0

^[a]Reactions were conducted on a 0.5 mmol scale in 4 mL of solvent under an inert atmosphere.^[b]Isolated yield after precipitation.^[c]Determined by ¹H NMR spectroscopy of crude mixtures.^[d]Combined yield of branched and linear product.

Table 2

Synthesis of α -aminoallyltrifluoroborates **4**.^[a]

Entry	Amine R ⁴ R ⁵ NH	Product	<i>t</i> [h]	Yield [%] ^[b]
1		4a	12	79
2		4b	18	84
3		4c	18	72
4		4d	36	84
5		4e	36	40 ^[c]
6		4f	18	60
7		4g	24	82
8		4h	18	82 ^[d]
9		4i	18	91 ^[d]
10		4j	18	60 ^[d]

Entry	Amine R ⁴ R ⁵ NH	Product	<i>t</i> [h]	Yield [%] ^[b]
11		4k	18	–

^[a] A solution of [Ir(cod)Cl]₂ (2.5 mol%), **L**² (5 mol%) and DBU (10 mol%) was prepared, then carbonate (0.5 mmol) and amine were added.

^[b] Isolated yield after precipitation. Reactions conducted with 3 equivalents of amines.

^[c] Reaction was run in CH₂Cl₂.

^[d] Yield was calculated by ¹H NMR relative to an internal standard.