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Non-biaryl Atropisomerism at C–B Bond in Sterically Hindered Aminoarylboranes

Mélodie Birepinte, Frédéric Robert, Sandra Pinet, Laurent Chabaud,* and Mathieu Pucheault*

Sterically hindered aminoarylboranes featuring atropisomerism about the C–B bond were prepared by addition of organomagnesium species onto readily accessible dialkylamine-borane complexes. Some of these aminoarylboranes, isosteres of vinyl styrene derivatives, were resolved by HPLC on chiral stationary phase. They are the first examples of non-biaryl type system which display slow rotation about a C–B bond.

Introduction

Atropisomers, which chirality results from a restricted rotation about a single bond, are an important class of compounds found in natural products,¹ ligands in organometallic catalysis,^{2, 3, 4, 5} and more recently in medicinal chemistry.^{6, 7, 8, 9, 10} Within this family, the biaryl scaffold is the most common structural motif,^{11, 12} although non-biaryl compounds that display a chiral axis have emerged as a new class of atropisomers.¹³ Slow rotation about a C(sp²)–C(sp²) single bond have been observed in styrenes **1**^{14, 15, 16, 17, 18, 19} or benzamides **2**,²⁰ as well as around the C(sp²)–Y bond (Y being a heteroatom N, P, S or O) in anilides **3**,^{21, 22, 23, 24, 25} phosphine oxides **4**,²⁶ sulfoxides **5**,²⁷ and diaryl anilines, sulfides, sulfones or ethers **6** (Figure 1 A).^{28, 29, 30, 31, 32, 33, 34} Organoboranes featuring a restricted rotation about the C–B bond has been scarcely explored, and limited to BN heterocyclic isosteres of biaryllic atropisomers.^{35, 36} However, the synthesis and separation of C–B atropisomers bearing a non-biaryl type system has never been reported.

In connection with our projects on the preparation and use of organoboron reagents,^{37, 38, 39, 40, 41, 42, 43} we were interested in the synthesis of aminoarylborane **7a**, as a surrogate of boronic acid derivatives in cross coupling reaction.⁴⁴ Aminoarylboranes are considered as BN isostere and isoelectronic of styrenes due to the delocalization of the π -electrons lone pair of the nitrogen into the empty orbital of the boron (*ie* **7b**). Thus, as in the styrene series, we envisioned that incorporating bulky substituents closed to the amino borane moiety could restrict the rotation about the C–B bond. Herein, we show for the first time that sterically hindered aminoarylboranes **7** disclose atropisomerism about the C–B bond, which enantiomers are resolvable by HPLC on chiral stationary phase (Figure 1, B). Such compounds can be viewed as chiral analogues of arylboronic acid derivatives.

Figure 1. Heteroatom-containing non-biaryl atropisomers.

Results and discussion

Synthesis and conformational studies on a model substrate

To test our hypothesis, we chose 2-methylnaphthalene aminoborane **10a** as a prototype substrate (Table 1). According to our previous synthesis of aminoarylboranes,^{40, 41} treatment of the *in situ* generated Grignard of **9a** with 1.1 equivalent of diisopropylaminoborane (DIPOB) gave the expected aminoborane **10a** in a good 62% yield (entry 1). However, the product was invariably contaminated with 2-methylnaphthalene, resulting from the hydrolysis of the Grignard reagent. Unfortunately, increasing the amount of DIPOB to 1.5 equivalent would not give a better isolated yield (entry 2). The air stable diisopropylamine-borane complex (DIPAB), is readily dehydrogenated into DIPOB by a catalytic amount of Grignard.⁴³ No improvement was observed when 5 mol% of PhMgBr were used (entry 3). In contrast, under Barbier conditions, a clean reaction occurred leading to aminoborane **10a** in 63% yield and 99% purity (entry 4).

A clear stereochemical fingerprint of an axially chiral aminoborane **10a** was observed by ¹H NMR spectrum. Indeed, two sets of sharp doublets for each isopropyl group of the amine were observed, indicating a slow rotation about both the B–N and C–B bonds on the NMR timescale (see supporting information). A variable temperature NMR spectroscopic analysis in [D₆]DMSO did not showed coalescence even at 105 °C, suggesting that enantiomers of **10a** could be separated. After extensive experimentations we managed to partially separate the enantiomers by HPLC on chiral stationary phase at 0 °C. The kinetic for racemization of the enantiomerically enriched sample was determined by circular dichroism spectroscopy, following the decay at λ max of its chiroptical signal in hexane at 10 °C. From these data, the half-life for racemization was estimated to 5 min, and the racemization barrier $\Delta G^{\ddagger}_{rac}$ to 83.4 kJ.mol⁻¹.

Table 1. Optimisation of borylation conditions.

Entry	Borylating agent (y equiv)	Additive (mol%)	Yield (%) ^a	Purity (%) ^b
1	DIPOB (1.1)	-	62	97
2	DIPOB (1.5)	-	55	96
3	DIPAB (1.1)	PhMgBr (5)	55	89
4	DIPAB (1.1)	-	63	99

^a Conversion 100%. Isolated yield. ^b Determined by ¹H NMR.

Scope of the borylation on hindered aromatic bromides

Having established for the first time that slow rotation around the C–B bond can be observed in aminoarylborane, the scope of the reaction was explored. The effect of the steric hindrance at both the aryl moiety and the nitrogen atom were evaluated to delineate the structural requirements for atropisomerism (Table 2).

Thus, aryl bromides **9b-n** were subjected to the established optimal reaction conditions in the presence of amine-borane complexes bearing bulky groups at the nitrogen. As expected, the reaction with DIPAB proceeded smoothly to afford in good yields 1-aminonaphthylborane **10b**, 2-alkyl- and 2-methoxy **10c-10f** substituted aminoboranes derivatives.

Table 2. Synthesis of sterically hindered aminoarylboranes **10b-n**.^a

^a Conversion 100%. Isolated yield, purity > 96%.

Likewise, the regioisomer **10g** with a methyl group in the *peri* position was isolated in 67% yield. The reaction was also tolerant to other borylating agents such as DICAB (dicyclohexylamine-borane) giving **10h-i** in yields ranging from 76% to 86%. Not surprisingly, when the highly hindered $\text{TMP}\cdot\text{BH}_3$ (tetramethylpiperidineamine-borane) was used, both **TMP** aminoborane **10j-k** were isolated in modest 49% and 43% yield respectively. The use of a boron reagent with two different alkyl groups on the nitrogen atom was also effective to furnish aminoborane **10l** in good yield (61%). Finally, two bromo phenyl congeners were tested, but only the mono substituted *tert*-butyl one led to aminoborane **10m** in an excellent 92% yield. The steric hindrance around the di-substituted aryl bromide presumably prevented the borylation reaction to afford **10n**.

Stereodynamic study of hindered aminoaryl boranes

With these substrates in hand we then investigated the stereodynamics behaviour of the C–B bond either by variable temperature NMR (VT NMR) for rapidly rotating atropisomers, or by circular dichroism spectroscopy for those that can be resolved by HPLC on chiral stationary phase (Table 3). Regarding the unsubstituted aminoborane **10b** (entry 2, table 3), ^1H NMR at low temperature (down to -65 °C) did not give any indication of slow rotation around the C–B bond. This result highlights the requirement of having a substituent, bulkier than a hydrogen atom,

next to the aminoborane to observe atropisomerism (compare entries 1 and 2). It was indeed confirmed, as compounds **10c-e** (entries 3-5) all exhibit a slow rotation about the C–B bond. As illustrated in Figure 2, both enantiomers of aminoborane **10e** were separated by chiral stationary phase HPLC. Study of the chiroptical signal over time of an enantiopur sample in hexane at 283 K, show a first-order decay to a racemic mixture.

Figure 2. (Top) Chiral Stationary phase HPLC chromatogram of compound **10e**. (Bottom) Decay of enantiopur compound **10e** (t_R 5.966 min) over time.

Thus, in that series **10c-e**, a general trend was observed with obviously the bulkier R group, the higher $\Delta G^\ddagger_{rac}$ and $t_{1/2}$ values; culminating with $\Delta G^\ddagger_{283} = 92.0 \text{ kJ.mol}^{-1}$ and $t_{1/2} = 187 \text{ min}$ at 10°C for the isopropyl derivative **10e**. The electronic nature of the R substituent has also a dramatic effect on the stereodynamic behaviour. For instance, aminoborane (**10f**) bearing a methoxy group rapidly interconverts with a 5 ms half-life time at 10°C .

This observation is probably due to the smaller size of the methoxy group compare to the methyl one. Furthermore, the lone pair delocalization of the methoxy group into the empty orbital of the boron atom, might stabilize the transition state for the interconversion of enantiomers. We also found that the substitution of the naphthyl moiety by a methyl group at the C8-position (*ie* **10g**) is much less efficient at restricting the rotation around the C–B bond. Evaluation of the configurational stability of more crowded aminoboranes **10h-i** revealed that changing the DIPAB by the dicyclohexylaminoborane slightly increases the $\Delta G^\ddagger_{rac}$ value up to 92.6 kJ.mol^{-1} with a half-life to racemization of 244 min at 10°C for **10i**. Unfortunately, when TMP derivatives **10j-k** were analysed by circular dichroism, partial decomposition was observed, which prevented the estimation of their barriers to rotation using this technic. In comparison, substrate **10l** bearing both an isopropyl and a *tert*-butyl at the nitrogen showed a good stability. Interestingly, the presence of this bulky aminoborane rises the barrier to rotation to 90.2 kJ.mol^{-1} ($t_{1/2} = 89 \text{ min}$), which are the highest values in the C2-methyl substituted series (*ie* **10a**, **10h**, **10l**). Finally, we found that a *tert*-butyl group at the *ortho* position of aminophenylborane **10m** is not sufficient to lock the rotation about the C–B bond.

Table 3. Rate of isomerization.

Entry	Compound	$t_{1/2}^a$	$\Delta G^\ddagger_{\text{rac}}(\text{exp})^b$	$\Delta G^\ddagger_{\text{rac}}(\text{calc})^c$
1	10a	5 min	83.4	97.1 ^d
2	10b	n.d. ^e	n.d. ^e	-
3	10c	14 min	85.9	102.2
4	10d	31 min	87.7	101.7
5	10e	187 min	92.0	104.7
6	10f	13 ms ^f	59.5 ^f	64.0 ^d
7	10g	19 ms ^f	61.9 ^f	71.6 ^d
8	10h	13 min	85.8	98.8 ^d
9	10i	244 min	92.6	105.1
10	10j	n.d. ^{g,h}	n.d. ^{g,h}	118.9
11	10k	n.d. ^{g,h}	n.d. ^{g,h}	134.8
13	10l	89 min	90.2	n.d. ^g
14	10m	< 1 ms ^f	52.2 ^f	56.0 ^d

^a Half-life for racemization determined by circular dichroism or estimated by VT NMR at 283 K. ^b Barrier to C–B bond rotation (kJ.mol⁻¹) determined by circular dichroism or estimated by VT NMR at 283 K. ^c Calculated barrier to C–B bond rotation (kJ.mol⁻¹) of the TS-*anti*. ^d Calculated barrier to C–B bond rotation (kJ.mol⁻¹) of the TS-*syn*. ^e Not determined, no coalescence observed by VT NMR at T = 208 K. ^f Estimated value at T = 283 K, determined by line-shape simulation at variable temperature. ^g Not determined. ^h Product partially decomposed during analysis.

DFT calculation: mechanism of racemization

The configurational stability of some of our aminoarylboranes is remarkable, when considering that the boron atom bears only one large dialkylamine substituent, the second one being a hydrogen atom. These results led us to explore the possible pathways for racemization using density functional theory run at the M06–2X/def2-TZVPP level of theory.⁴⁵ Although the calculated values are about 10–15 kJ/mol higher than the corresponding experimental one, we found that the calculated $\Delta G^\ddagger_{\text{rac}}$ of the transition state to racemization follow the same trend (Table 3). Interestingly, the highest $\Delta G^\ddagger_{\text{rac}}$ was calculated for the TMP derivatives **10j–k**, that were unfortunately not stable enough to be analyzed experimentally. Calculations also revealed that the mechanism to racemization is highly dependent on the nature of the substituent on the naphthyl group. Indeed, in most cases two transition states could be calculated, TS-*anti* and TS-*syn* with respect to the naphthyl substituent and the B–NR₂ bond (see supporting information). For instance, the calculated transitions states of compound **10a** show that the TS-*syn* is the lowest in energy by 3.3 kJ.mol⁻¹ (Figure 3). A closer look at the conformation of **10a** TS-*syn* reveals that the B–H bond is almost eclipsed to the aromatic ring with a distance of 1.849 Å between both hydrogens.

Figure 3. DFT calculated transition states for aminoarylboranes **10a** and **10e** with distances in Å between relevant hydrogen atoms. Other hydrogens are omitted for clarity.

On the other side, the C–H bond of the Ni-Pr group points towards the methyl substituent (distance HH = 1.882 Å), minimizing the steric repulsion. In comparison, a similar eclipsed conformation is observed in **10a** TS-*anti*. However, the shorter distance between hydrogens of the isopropyl and the *peri* position (distance HH = 1.587 Å) may account for a higher energy of TS-*anti* vs TS-*syn*. Thus, in this case the racemization occurs preferentially through the TS-*syn* by the rotation around the C–B bond.

By contrast, for the isopropyl substituted naphthyl aminoborane **10e**, only TS-*anti* could be modeled with a value of 104.7 kJ.mol⁻¹ for energy of rotational barrier. A particular structural feature of this conformation is the orientation of the isopropyl substituent of the naphthalene which projects its C–H bond towards the B–H bond to minimize the steric hindrance during the racemization process.

Conclusions

In summary, we have shown that sterically hindered aminoarylboranes can display atropisomerism about the C–B bond. Bulky substituents at both the dialkylaminoborane and the aromatic ring were required to observe restricted rotation around the C–B bond. Depending on the substitution pattern, both enantiomers can be resolved by HPLC on chiral stationary phase and their stereodynamic behaviour studied by circular dichroism spectroscopy. The experimental data were confirmed by DFT calculations, which also allowed to elucidate the mechanism of racemization. Our results pave the way to a new class of non-biaryl type atropisomers with axial chirality at the C–B bond. Further studies on the synthesis of this type of compounds and their applications are ongoing.

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