STUDY ON THE REGIOSELECTIVITY OF RHODIUM-CATALYZED RING OPENING REACTIONS OF C1-SUBSTITUTED 7-OXABENZONORBORNADIENES WITH BORONIC ACIDS

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GRAPHICAL ABSTRACT

Abstract An optimized condition for the rhodium-catalyzed ring-opening reaction of C1-substituted oxabicyclic alkenes with aryl boronic acids was developed and the effect of aryl boronic acid as well as the effect of C1 substitution on the oxabicyclic alkenes was studied. Aryl boronic acids carrying electron-donating substituents provided the ring-opened products in excellent yields regardless of the position, while electron-withdrawing substituents were more susceptible to steric interactions. Although two different regioisomers are possible, all the rhodium-catalyzed ring-opening reactions of C1 substituted oxabicyclic alkenes studied with aryl boronic acids were found to be highly regioselective, giving single regioisomers in all cases.

Keywords Boronic acids; 7-oxabenzonorbornadienes; regioselectivity; rhodium catalysis; ring-opening reactions

INTRODUCTION

Oxabicyclic alkenes are a synthetically useful class of compounds central to the construction of highly functionalized cyclic and acyclic systems. Exploration into the transition-metal-catalyzed reactions of these compounds has led to many...
interesting discoveries.[2] One such reaction, nucleophilic ring opening, has become well recognized for its ability to generate multiple stereocenters while simultaneously forging new bonds in a single step.[3,4] A good example of the utility of this reaction was provided by Lautens and coworkers in their asymmetric synthesis of sertraline 2 from oxabenzonorbornadiene 1 (Scheme 1).[5]

The nucleophilic ring opening of 1 provides a wide variety of products depending on both the metal catalyst and nucleophile used (Scheme 2). Unsubstituted ring-opened products 3 can be accessed through the reductive opening with hydride nucleophiles and nickel catalysis.[6] Anti stereoisomeric ring opened products 4 and 5 are produced through the addition of a heteroatomic nucleophile under rhodium catalyst[7] or through copper-catalyzed addition of an alkyl nucleophile.[8] Syn stereoisomeric ring opened products 6–8 are afforded through the nucleophilic addition of arene nucleophiles under rhodium,[9] palladium,[10] or nickel[11] catalysis, and also

Scheme 1. Synthesis of sertraline.

Scheme 2. Transition-metal–catalyzed nucleophilic ring opening reactions of 7-oxabenzonorbornadiene 1.
through the addition of alkyl nucleophiles when under nickel\textsuperscript{[12]} or palladium\textsuperscript{[13]} catalysis. In each instance, the dihydronaphthol produced serves as a valuable template by which syntheses toward more complex compounds can take place.

Although there has been much research directed to the ring opening of oxabicyclic alkenes, very little has been reported on the regioselective effect proximal substitution has on the reaction. Palladium-catalyzed reactions on \( \text{C}_1 \) methylated oxabenzonorbornadiene 9 (\( \text{R} = \text{Me} \), Scheme 3) demonstrated a preference for the formation of a tertiary alcohol dihydronaphthol product 10 through nucleophilic addition to \( \text{C}_2 \).\textsuperscript{[14]} The opposite was observed for rhodium-catalyzed ring openings with heteroatom\textsuperscript{[15]} and aryl nucleophiles\textsuperscript{[16]} showing a strong preference for nucleophilic addition to \( \text{C}_3 \), producing the secondary alcohol dihydronaphthol product (11 and 12). Our investigation into the effect of \( \text{C}_1 \) substitution on ruthenium-catalyzed isomerizations showed that one regioisomeric product could be formed in preference to the other depending on the substitution type.\textsuperscript{[17]} With an electron-donating \( \text{C}_1 \) methyl substituent (\( \text{R} = \text{Me} \)), Ru-catalyzed isomerization of 9 led to the formation of one regiosiomer 13a. On the other hand, with an electron-withdrawing methyl ester substituent (\( \text{R} = \text{COOMe} \)), Ru-catalyzed isomerization of 9 led to the formation of the opposite regiosiomer 13b. To the best of our knowledge, no systematic study had investigated the effect of \( \text{C}_1 \) substitution beyond methyl groups and it was interesting.

\begin{center}
\textbf{Scheme 3.} Regioisomeric products arising from nucleophilic ring opening of \( \text{C}_1 \)-substituted oxabenzonorbornadienes.
\end{center}
to us to see if these regioselective effects would be observed in the rhodium-catalyzed ring opening with aryl boronic acids as well. Exploration into the effects of remote substitution on a similar rhodium-catalyzed ring-opening reaction had shown that electronics may exert an influence on which side the rhodium metal approaches (Scheme 4). Based on these results we envisioned two possible regioisomers, 14 with the nucleophile attacking C3 and 15 with the nucleophile attacking C2 (Scheme 5). Our group had recently published a paper outlining the synthesis of a variety of C1-substituted oxabenzonorbornadienes. Armed with this knowledge, we set out to investigate the effect these various C1-substituted substrates had on the rhodium-catalyzed nucleophilic ring opening with aryl boronic acids.

RESULTS AND DISCUSSION

C1-Substituted oxabenzonorbornadienes were prepared by a Diels–Alder reaction between variously substituted furans and in situ-generated benzyne. For simplicity’s sake all optimization trials were carried out on 1-ethylxabenzonorbornadiene (9a) which was easily derived in gram scale from commercially available 2-ethyl furan. The effects of rhodium(I) catalyst and silver salt additive are summarized in Table 1. Wilkinson’s catalyst, RhCl(PPh3)3 (entry 1), failed to provide any product. [Rh(C2H4)2Cl]2 and [Rh(C8H14)2Cl]2 (entries 2 and 3) both produced the ring-opened product but in poor yields (26 and 34%, respectively). Moderate to good yields were afforded with [Rh(C8H12)2][SO3CF3] and [Rh(CO)2Cl]2 (entries 4 and 5), yet they proved less effective at catalyzing the reaction than [Rh(COD)Cl]2 (entry 6), which provided the greatest yield of 86%.

Previous studies undertaken by our group had demonstrated that an increase in yield was possible when promoting the cationic state of the rhodium catalyst through addition of silver salt. Additions of AgOTf, AgClO4, AgBF4, AgSbF4, and AgNO3 (entries 7–11), however, all failed to provide any increase in yield. In each
Table 1. Optimization of rhodium(I) catalyst and silver salt

| Entry | Rh catalyst                   | AgX      | Yield (%)<sup>a</sup> |
|-------|------------------------------|----------|-----------------------|
| 1     | RhCl(PP3)<sub>3</sub>        | —        | 0                     |
| 2     | [Rh(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub>Cl]<sub>2</sub> | —        | 26                    |
| 3     | [Rh(C<sub>8</sub>H<sub>12</sub>)<sub>2</sub>Cl]<sub>2</sub> | —        | 34                    |
| 4     | [Rh(C<sub>8</sub>H<sub>12</sub>)<sub>2</sub>[SO<sub>3</sub>CF<sub>3</sub>]<sub>2</sub> | —        | 66                    |
| 5     | [Rh(CO)<sub>2</sub>Cl]<sub>2</sub> | —        | 78                    |
| 6     | [Rh(COD)Cl]<sub>2</sub>      | —        | 86                    |
| 7     | [Rh(COD)Cl]<sub>2</sub>      | AgOTf    | 71                    |
| 8     | [Rh(COD)Cl]<sub>2</sub>      | AgClO<sub>4</sub> | 70          |
| 9     | [Rh(COD)Cl]<sub>2</sub>      | AgBF<sub>4</sub> | 68            |
| 10    | [Rh(COD)Cl]<sub>2</sub>      | AgSbF<sub>6</sub> | 63            |
| 11    | [Rh(COD)Cl]<sub>2</sub>      | AgNO<sub>3</sub> | 63            |

<sup>a</sup>Yields based on <sup>1</sup>H NMR with internal toluene standard.

Table 2. Optimization of base, phosphine, and temperature

| Entry | Base (2 eq.) | Phosphine | Temp (°C) | Yield (%)<sup>a</sup> |
|-------|--------------|-----------|-----------|-----------------------|
| 1     | NaHCO<sub>3</sub> | P(OEt)<sub>3</sub> | 65        | 86                    |
| 2     | NaHCO<sub>3</sub> | —         | 65        | 84                    |
| 3     | NaO'Bu       | —         | 65        | 0                     |
| 4     | KO'Bu        | —         | 65        | 0                     |
| 5     | K<sub>2</sub>P<sub>2</sub>O<sub>4</sub> | —        | 65        | 78                    |
| 6     | K<sub>2</sub>CO<sub>3</sub> | —        | 65        | 83                    |
| 7     | KF           | —         | 65        | 84                    |
| 8     | NaHCO<sub>3</sub> | —        | 95        | 63                    |
| 9     | NaHCO<sub>3</sub> | —        | 45        | 78                    |
| 10    | NaHCO<sub>3</sub> | —        | 25        | 91                    |
| 11    | NaHCO<sub>3</sub> | —        | 25        | 96                    |

<sup>a</sup>Yields based on <sup>1</sup>H NMR with internal toluene standard.

<sup>b</sup>1 equivalent of base was used.
case the ring-opened product was produced at lower yields than those produced with a neutral rhodium catalyst.

The effect of phosphine, base, and temperature are summarized in Table 2. Previous iterations of the ring-opening reaction of oxabicycles had focused on desymmetrizing compounds and had subsequently required the addition of chiral phosphines to increase ee. By working with unsymmetrical C₁ substituted oxabenzonorbornadienes, the need for a phosphine ligand was questionable. As no control reactions had previously been carried out, a trial excluding the phosphine was undertaken. Relative to the phosphine-containing reaction (entry 1) no significant difference in yield was observed (entry 2) and thus all future trials excluded phosphine ligands. Using these modified conditions, we explored the effectiveness of various bases and temperatures. Both NaO'TBu and KO'Bu failed to provide any product in the protic MeOH solvent (entries 3 and 4). Other bases commonly used to promote similar reactions, KF, K₂CO₃, K₃PO₄, and NaHCO₃, proved much more successful, giving excellent yields in each instance. The lowest yield, 78%, was provided by K₃PO₄ (entry 5), while the other three bases provided similar yields ranging from 83% to 84% (entries 6 and 7). NaHCO₃ (entry 2) was chosen for all further investigations; however, substitution of KF or K₂CO₃ in cases where the substrate requires a solvent in which NaHCO₃ is insoluble could still prove fruitful.

A significant effect was observed for temperature. Increasing the temperature to 90 °C (Table 2, entry 8) provided the lowest yield at 63%. Lowering the temperature to 45 °C provided a slightly lower yield at 78% (entry 9). When run at room temperature (entry 10), a modest increase to 91% yield was observed. Interestingly, this yield was further improved by reducing the amount of base in the reaction to 1 equivalent (entry 11), an observation contrary to previous studies requiring excess base.

With the optimized reaction conditions in hand the effect of substitution on the arylboronic acid was then studied (Table 3). Relative to the unsubstituted aryl

Table 3. Effect of substitution on the aryl boronic acid

| Entry | R₁  | R₂  | R₃  | Time (h) | Product | Yield (%)<sup>a</sup> |
|-------|-----|-----|-----|---------|---------|---------------------|
| 1     | H   | H   | H   | 0.5     | 16a     | 96                  |
| 2     | Me  | H   | H   | 0.5     | 16b     | 96                  |
| 3     | H   | Me  | H   | 0.5     | 16c     | 97                  |
| 4     | H   | H   | Me  | 0.5     | 16d     | 87                  |
| 5     | OMe | H   | H   | 0.5     | 16e     | 92                  |
| 6     | H   | OMe | H   | 0.5     | 16f     | 99                  |
| 7     | H   | H   | OMe | 2.5     | 16g     | 85                  |
| 8     | Cl  | H   | H   | 0.75    | 16h     | 64                  |
| 9     | H   | Cl  | H   | 0.5     | 16i     | 98                  |

<sup>a</sup>Isolated yields after column chromatography.
boronic acid (entry 1), meta- and para-methyl substituted boronic acids provided excellent yields of the ring-opened product (entries 2 and 3). A sharp drop in yield was noted for the ortho-substituted methyl aryl boronic acid (entry 4), an effect likely arising from steric interactions. A similar trend was observed for methyloxy-substituted boronic acids, with a more pronounced effect on time when ortho to the boronic acid (entry 7). A stark difference was observed in the chloro-substituted boronic acids. When situated para to the boronic acid, the yield was drastically lowered to 64% (entry 8). Surprisingly, when the chloro group was in the meta position, an opposite effect on yield was observed, affording the ring-opened product in 98% yield (entry 9).

The results of the ring-opening reactions of C1-substituted oxabenzonorbornadienes are summarized in Table 4. Both methyl (entry 1) and ethyl (entry 2) substitutions provided good yields, 94% and 96% respectively, in comparable time. The more sterically bulky iPr (entry 3) group provided a much lower yield at 25%. Interestingly, the steep drop in yield was not observed when a phenyl group was substituted (entry 4), instead providing an increase in yield to 96% in the shortest reaction time observed. Both of the electron-withdrawing methyl ester (entry 5) and carboxylic acid (entry 6) functional groups provided moderate yields of 77 and 66% respectively. The tertiary alcohol (entry 7) ring-opened product was afforded in 55% yield with a reaction time of 140 h. The silyl group (entry 8) provided a yield of 54%. In all cases, the Ph group of phenylboronic acid was added to the sterically less hindered C3 (instead of C2). The general trend is the bulkier the C1 R group, the lower the yields (e.g. compare entries 1 and 2 with entry 3).

**CONCLUSION**

In summary, we have investigated the effect of substitution on the aryl boronic acid and the C1 position of oxabenzonorbornadiene toward nucleophilic ring opening. The use of a Pd catalyst provided syn ring-opening products exclusively
instead of the anti products when other catalysts such as Rh and Cu catalysts were used, thus providing complementary methods for generating different stereoisomers in the ring-opening reactions. Electron-rich aryl boronic acids produced excellent yields of the ring-opened product in all cases, whereas electron-poor boronic acids were more dependent on the substituent location. A wide range of C1-substituted oxabenzenonorbornadienes were subjected to ring opening and in each case produced the regioisomer resulting from carborhodation on the carbon beside the C1 substituent as dictated by steric interactions.

EXPERIMENTAL

All ring-opening reactions were carried out under inert atmospheric conditions. All glassware was oven dried overnight before use. Flash column chromatography was performed on 230- to 400-mesh silica gel purchased from Silicycle. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 250µm 60 F254 aluminum plates purchased from Silicycle. TLC visualization was carried out under ultraviolet light and p-anisaldehyde stain. 1H and 13C NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer (CDCl3: δ 7.24 ppm (1H at 400 MHz) or δ 77.0 ppm (13C at 100 MHz)). High-resolution mass spectrometry (HRMS) analyses were performed at the Queen's Mass Spectrometry and Proteomics Unit, Kingston, Ontario. The samples were ionized by electron impact (EI) or electrospray ionization (ESI) as specified and detection of the ions was performed by time of flight (TOF).

General Procedure for Rh-Catalyzed Reaction Between 1-Substituted-7-oxabenzenonorbornadiene and Boronic Acids

Inside an inert atmospheric glove box system, [Rh(COD)Cl]2 (5 mol%), NaHCO3 (1 equiv.), and boronic acid (1.1 equiv.) were weighed and added to a screw-capped vial equipped with a stir bar. To this mixture was charged substituted oxabenzenonorbornadiene 9a (0.35 mmol) and methanol (2 mL). The vial was then capped and left to stir at room temperature. Upton reaction completion, the vial was removed from the dry box, diluted with dichloromethane (DCM), and passed through a silica plug. The crude product was then subjected to flash column chromatography, eluting with mixtures of EtOAc/hexanes to provide the product 16a. Yield: 96% (38.2 mg, 0.152 mmol), light brown oil. Rf = 0.44 (EtOAc/hexanes, 3:7). IR (CH2Cl2): 3564, 3054, 2986, 1602, 1452, 1422, 1265, 896, 739 cm\(^{-1}\). 1H NMR (400 MHz, CDCl3): δ 1.17 (t, J = 7.4 Hz, 3H), 1.41 (d, J = 8.4 Hz, 1H), 2.52 (dq, J = 1.3, 7.4 Hz, 2H), 3.76 (dd, 5.8, 4.4 Hz, 1H), 4.81 (dd, J = 8.3, 5.9 Hz, 1H), 5.87 (d, J = 4.4 Hz, 1H), 7.12–7.35 (m, 9H). 13C NMR (100 MHz, CDCl3): δ 12.9, 25.1, 47.0, 71.5, 122.9, 124.3, 126.6, 127.3, 127.5, 128.1, 128.5, 129.3, 133.6, 136.9, 138.2, 138.5. HRMS (EI) calcd. for C18H18O (M\(^+\)): 250.1358; found: 250.1354.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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