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Ruthenium- and palladium-catalyzed consecutive coupling and cyclization of aromatic sulfoximines with phenylboronic acids: an efficient route to dibenzothiazines[†]

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A ruthenium-catalyzed *ortho* arylation of aromatic sulfoximines with aromatic boronic acids followed by intramolecular cyclization in the presence of a palladium catalyst, providing dibenzothiazine derivatives in two consecutive steps, is described.

Sulfoximine is a pivotal structural motif which is present in various biologically active molecules, pharmaceuticals and agrochemicals (eqn (1)).¹ The sulfoximine derivatives are also successfully used as chiral auxiliaries and ligands in asymmetric synthesis of various chiral organic molecules.² Several methods are available in the literature to synthesize linear sulfoximine derivatives.³ But, the synthesis of cyclic sulfoximines is limited in the literature.⁴ Recently, the synthesis of cyclic sulfoximines has gained much attention in organic synthesis due to their usefulness as scaffolds in drug development and as chiral ligands in enantioselective reactions.⁵ Meanwhile, sulfoximine derivatives also serve as key synthetic intermediates in various organic transformations.⁵⁻⁷



Harmata's group reported the synthesis of bicyclic sulfoximine derivatives such as 1,2-benzothiazine and 2,1-benzothiazine by palladium-catalyzed cyclization of 2-bromo benzaldehydes or 2-alkenylated aromatic bromides with sulfoximines, AlCl₃-mediated cyclization of sulfonimidoyl chlorides with alkynes or alkenes and electrophilic cyclization of 2-bromophenyl substituted sulfoximines with terminal alkynes in the presence of palladium and copper catalysts.⁶ Very recently, Bolm's group reported the synthesis of bicyclic 1,2-benzothiazine derivatives *via* rhodium-catalyzed oxidative cyclization^{7a} of phenyl sulfoximines with

alkynes *via* a chelation-assisted C–H bond activation reaction.⁸⁻¹⁰ Subsequently, sulfoximine directed *ortho* alkenylation of phenyl sulfoximines with alkenes in the presence of a metal catalyst was also disclosed.^{7b–e} In all these reports, sulfoximine containing bicyclic benzothiazine derivatives were synthesized efficiently.

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Herein, we report the synthesis of tricyclic dibenzothiazines by a ruthenium-catalyzed *ortho* arylation of phenyl sulfoximines with aromatic boronic acids followed by intramolecular cyclization in the presence of a palladium catalyst in two consecutive steps. The present reaction was compatible with various sensitive and useful functional group substituted phenyl sulfoximines and aromatic boronic acids. An enantioselective version of *ortho* arylation of phenyl sulfoximines with phenylboronic acids followed by cyclization, and this transformation leads to chiral dibenzothiazines with an excellent ee ratio of 99%.

Initially, the *ortho* arylation of phenyl sulfoximine (**1a**) with phenylboronic acid (**2a**) (1.5 equiv.) in the presence of [{RuCl₂-(p-cymene)}₂] (5 mol%), AgSbF₆ (20 mol%) and Cu(OAc)₂·H₂O (1.5 equiv.) in THF at 100 °C for 16 h was investigated (Scheme 1). In the reaction, *N*-arylated phenyl sulfoximine **3a** in 35% yield, mono *ortho* arylated phenyl sulfoximine **5a** in 15% yield were observed, respectively (Scheme 1). It is known that the free N–H group of **1a** is acidic in nature and smoothly undergoes *N*-arylation with aromatic electrophiles or organometallic reagents



Scheme 1 ortho Arylation of sulfoximine 1a with 2a.

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providing N-arylated sulfoximines 3 in the presence of metal catalysts.¹¹ To successfully carry out the ortho arylation reaction, the suppression of product 3 is highly important. Next, the reaction was tested with other oxidants and acetate sources such as AgOAc, NaOAc, K2CO3, CsOAc and Ag2O. Among them, silver salts such AgOAc and Ag₂O were active for the reaction and no N-arylated product 3a was observed. In AgOAc, product 4a in 5% and 5a in 12% vields were observed, respectively. In Ag₂O, product 4a in 8% and 5a in 40% yields were observed, respectively. Other acetate sources were not active for the reaction. Next, the coupling reaction was tested with an excess amount of phenylboronic acid 2a (3.0 equiv.). In the reaction also, a mixture of products 4a and 5a were observed in 3% and 45% yields, respectively. To increase the yield of 5a, the coupling reaction was performed in the presence of 10 mol% of catalyst and 40 mol% of AgSbF₆. Interestingly, in the reaction, only bis ortho arylated product 5a was observed in 68% isolated yield and no mono arylated product 4a was observed. For the detailed optimization studies, please see ESI.[†]

In addition to phenylboronic acid (2a), a wide range of aromatic boronic acids 2b-j also readily participates in the reaction with 1a. Table 1 summarizes the results of these reactions. Treatment of 4-phenyl substituted phenylboronic acid (2b) with 1a provided ortho bis arylated product 5ab in 72% yield (entry 1). Electron rich 4-methoxyphenyl boronic acid (2c) reacts smoothly with 1a, yielding the corresponding product 5ac in 66% yield (entry 2). Aromatic boronic acids having halogen groups I, Br, Cl and F 2d-g also undergo an ortho arylation reaction with 1a efficiently, giving products 5ad-ag in 65%, 62%, 64% and 60% yields, respectively (entries 3-6). However, 3-bromo phenylboronic acid (2h) yielded product 5ah only in 19% yield (entry 7). Benzo[d][1,3]dioxol-5-ylboronic acid (2i) and 2-naphthylboronic acid (2j) also efficiently participated in the reaction, affording coupling products 5ai and 5aj in 61% and 64% yields, respectively (entries 8 and 9).

The arylation reaction was examined with substituted aromatic sulfoximines **1b–g** (Scheme 2). Electron-rich, halogen and electrondeficient group substituted sulfoximines were compatible for the reaction. Methyl, Br and NO₂ substituted sulfoximines **1b–d** reacted with **2a**, providing products **5ba–da** in 65%, 63% and 54% yields, respectively. Similarly, Cl and F substituted aromatic sulfoximines **1e–f** reacted with **2c**, providing products **5ec–fc** in 60% and 63% yields, respectively. Likewise, (ethylsulfonimidoyl)-benzene (**1g**) afforded **5ga** in 71% yield.

Apart from bis arylation, mono arylation of phenyl sulfoximines was also disclosed (Scheme 3). Treatment of 2-methyl phenylsulfoximine (**1h**) with **2a** or **2f** gave mono arylated sulfoximine derivatives **5ha** and **5he** in 70% and 63% yields, respectively. However, 3-methyl phenylsulfoximine (**1i**) afforded regioisomeric mono arylated products **5ia** and **5ia'** in 62% and 7% yields, respectively.

Next, we tried to couple the N–H bond of sulfoximine with one of the C–H bond of phenyl groups of compound 5 *via* chelation-assisted remote C–H activation in order to prepare tricyclic dibenzothiazine derivatives. A $Pd(OAc)_2$ catalyst along with an oxidant is the suitable condition for this type of cyclization.^{7c,12} The intramolecular cyclization of compound 5aa

Table 1 Ruthenium-catalyzed ortho arylation of 1a with aromatic boronic acids $2b\!-\!j^a$



^{*a*} All reactions were carried out using **1a** (100 mg), aromatic boronic acids (**2b-j**) (3.0 equiv.), [{RuCl₂(*p*-cymene)}₂] (10 mol%), AgSbF₆ (40 mol%), Ag₂O (1.5 equiv.) in THF (3.0 mL) at 100 $^{\circ}$ C for 16 h. ^{*b*} Isolated yield.

proceeded smoothly in the presence of Pd(OAc)₂ (10 mol%) and PhI(OAc)₂ (2.0 equiv.) in toluene at 120 °C for 10 h giving a tricyclic dibenzothiazine derivative **6a** in 76% yield (Table 2, entry 1). The cyclization reaction also proceeded in the presence of PhI(OAc)₂ without a palladium catalyst. However, product **6a** was observed in a less amount of 25% yield. Under similar reaction conditions, products **5ab**, **5ac**, **5ad**, **5ae**, **5af** and **5ag** also efficiently participated in the reaction, providing cyclization products **6b–g** in good to excellent yields (entries 2–7). Similarly, products **5ba**, **5ca**, **5da**, **5ga** and **5ha** afforded dibenzothiazines **6h–l** in 80%, 84%, 79%, 83% and 41% yields, respectively (entries 8–12). The structure of compound **6f** was further confirmed by single crystal X-ray analysis (see ESI†).

This result prompted us to explore the possibility of synthesis of chiral tricyclic dibenzothiazines by using chiral phenyl



sulfoximines 7a-b (Scheme 4). Treatment of chiral (R)-(-)-Smethyl-S-phenylsulfoximine (7a) with substituted phenyl boronic acids 2a, 2d, 2f and 2g in the presence of $[{RuCl_2(p-cymene)}_2]$, AgSbF₆ and Ag₂O in THF at 100 °C for 16 h gave chiral ortho arylated phenyl sulfoximines 7aa-ag in 65%, 63%, 60% and 62% yields, respectively (Scheme 4). Interestingly, the enantiomeric excess (ee) of products 7aa-ag did not drop and in all cases >99% ee ratios were observed. Later, compounds 7aa-ag were cyclized into chiral dibenzothiazines 8a-d in excellent 74%, 73%, 75% and 79% yields, respectively, in the presence of a palladium catalyst. In all these reactions, >99% ee ratios were observed. Furthermore, (S)-(-)-S-methyl-S-phenylsulfoximine (7b) underwent ortho arylation with aromatic boronic acids 2a, 2b and 2e in the presence of a ruthenium catalyst, providing chiral ortho arylated phenyl sulfoximines 7ba-be in 67%, 65% and 61% yields, respectively, with >99% ee ratios. Furthermore, **7ba-be** were converted into chiral dibenzothiazines 8e-g in the presence of Pd(OAc)₂ in 72%, 82% and 83% yields, respectively.

A possible reaction mechanism is proposed to account for the present reaction in Scheme 5. Two different catalytic reactions were involved in the reaction. In the first catalytic cycle, $AgSbF_6$ likely removes all Cl^- ligands from the ruthenium complex providing a cationic ruthenium complex 9.¹³ Coordination of the nitrogen atom of sulfoximine 1 into catalyst 9 followed by *ortho*-metalation provides a ruthenacycle intermediate 10. Transmetallation of phenyl boronic acid 2 into intermediate 10 in the presence of Ag_2O affords intermediate 11. Subsequent reductive elimination of intermediate 11 in the presence of Ag^+ source provides product 5 and regenerates the

Table 2 Synthesis of dibenzothiazines^a



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^{*a*} All reactions were carried out using 5 (100 mg), Pd(OAc)₂ (10 mol%) and PhI(OAc)₂ (2.0 equiv.) in toluene at 120 °C for 10 h. ^{*b*} Isolated yield.



Scheme 4 Synthesis of chiral dibenzothiazines.



active ruthenium species **9** for the next catalytic cycle. Another *ortho* arylation also takes place in a similar fashion. In the second catalytic cycle, compound **5** reacts with $Pd(OAc)_2$ giving palladacycle **12**. Reductive elimination of intermediate **12** in the presence of $PhI(OAc)_2$ provides cyclic product **6** and regenerates the active $Pd(OAc)_2$ catalyst for the next catalytic cycle. The exact role of Ag_2O is not clear to us, it could be possible that the AgO^- anion acts as a base to accelerate the transmetallation of boronic acid **2** into intermediate **12** and the Ag^+ ion acts as an oxidant to oxidize Ru(0) to Ru(n).

In conclusion, we have described a two-step synthesis of dibenzothiazines *via* a ruthenium-catalyzed *ortho* arylation of phenyl sulfoximines with phenyl boronic acids followed by intramolecular cyclization in the presence of $Pd(OAc)_2$. Chiral dibenzothiazines were prepared efficiently by using chiral phenyl sulfoximine in a similar protocol.

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