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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.

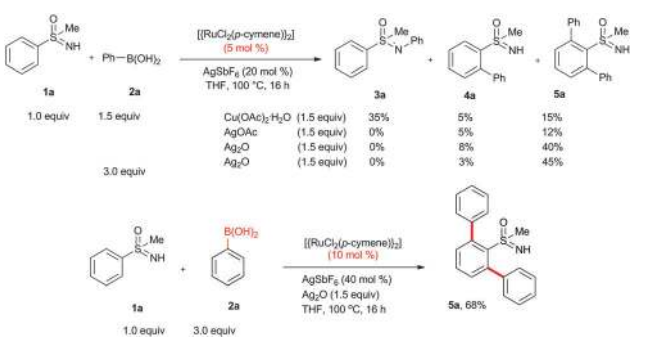
Sulfoximine is a pivotal structural motif which is present in various biologically active molecules, pharmaceuticals and agrochemicals (eqn (1)).[1] The sulfoximine derivatives are also successfully used as chiral auxiliaries and ligands in asymmetric synthesis of various chiral organic molecules.[2] 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]

(1)

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, $AlCl_3$-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.

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 [{$RuCl_2$-(*p*-cymene)}$_2$] (5 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (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 **4a** in 5% yield and bis *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, K_2CO_3, CsOAc and Ag_2O. Among them, silver salts such AgOAc and Ag_2O were active for the reaction and no *N*-arylated product **3a** was observed. In AgOAc, product **4a** in 5% and **5a** in 12% yields were observed, respectively. In Ag_2O, 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 $AgSbF_6$. 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.†

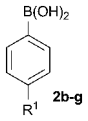
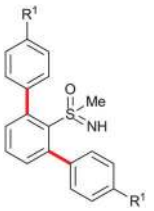
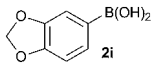
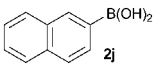
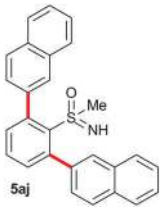
In addition to phenylboronic acid (**2a**), a wide range of aromatic boronic acids **2b–j** also readily participates in the reaction with **1a**. Table 1 summarizes the results of these reactions. Treatment of 4-phenyl substituted phenylboronic acid (**2b**) with **1a** provided *ortho* bis arylated 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 electron-deficient group substituted sulfoximines were compatible for the reaction. Methyl, Br and NO_2 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**

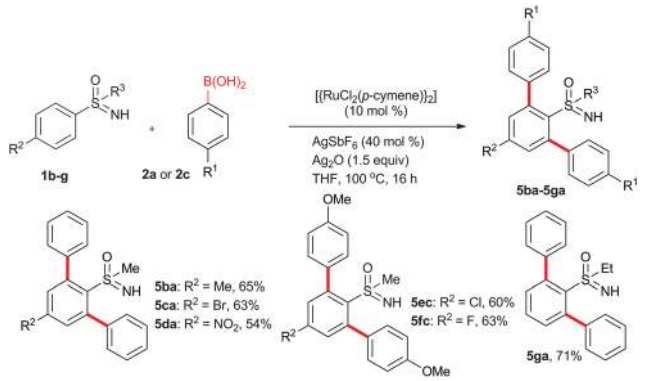
Table 1 Ruthenium-catalyzed *ortho* arylation of **1a** with aromatic boronic acids **2b–j**[a]

Entry	2b–j	Product 5	Yield[b] (%)
			
1	**2b:** R^1 = Ph	**5ab:** R^1 = Ph	72
2	**2c:** R^1 = OMe	**5ac:** R^1 = OMe	66
3	**2d:** R^1 = I	**5ad:** R^1 = I	65
4	**2e:** R^1 = Br	**5ae:** R^1 = Br	62
5	**2f:** R^1 = Cl	**5af:** R^1 = Cl	64
6	**2g:** R^1 = F	**5ag:** R^1 = F	60
7			19
8			61
9			64

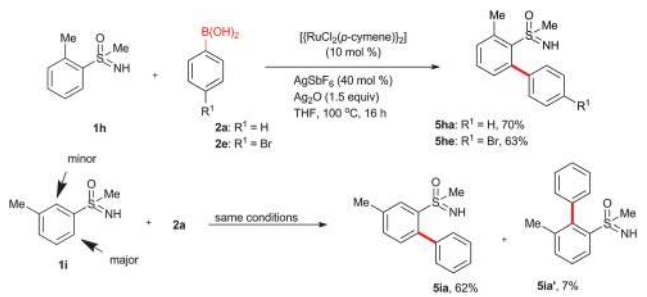
[a] All reactions were carried out using **1a** (100 mg), aromatic boronic acids (**2b–j**) (3.0 equiv.), [{$RuCl_2$(*p*-cymene)}$_2$] (10 mol%), $AgSbF_6$ (40 mol%), Ag_2O (1.5 equiv.) in THF (3.0 mL) at 100 °C for 16 h. [b] Isolated yield.

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



Scheme 2 Scope of aromatic sulfoximines.

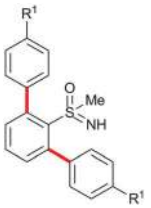
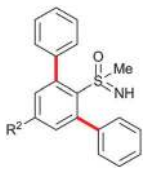
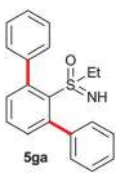
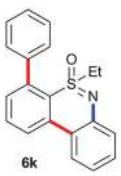
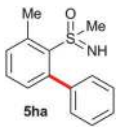


Scheme 3 Mono arylation of aromatic sulfoximines **1h–i**.

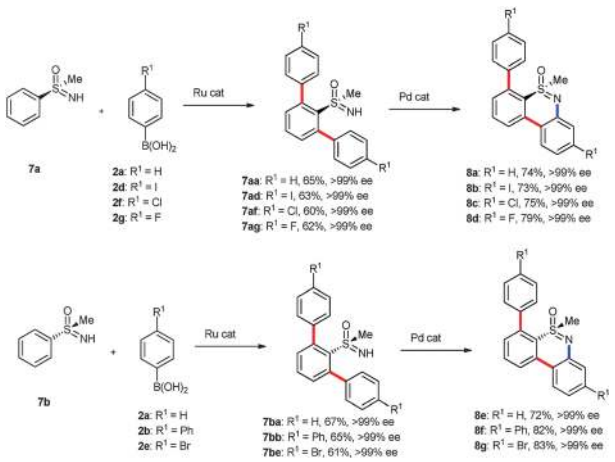
sulfoximines **7a–b** (Scheme 4). Treatment of chiral (*R*)-(−)-*S*-methyl-*S*-phenylsulfoximine (**7a**) with substituted phenyl boronic acids **2a**, **2d**, **2f** and **2g** in the presence of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and Ag_2O in THF at 100 °C for 16 h gave chiral *ortho* arylated 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

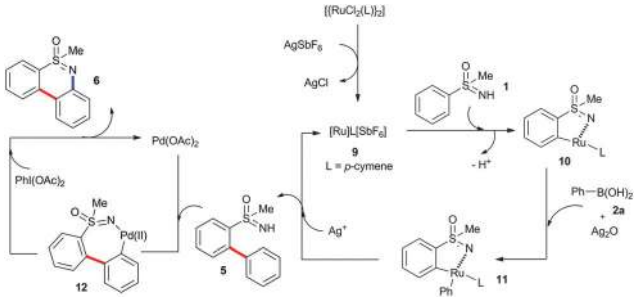
Table 2 Synthesis of dibenzothiazines[a]

Entry	5	Product 6	Yield[b] (%)
			 6f
1	**5aa:** R^1 = H	**6a:** R^1 = H	76
2	**5ab:** R^1 = Ph	**6b:** R^1 = Ph	85
3	**5ac:** R^1 = OMe	**6c:** R^1 = OMe	65
4	**5ad:** R^1 = I	**6d:** R^1 = I	77
5	**5ae:** R^1 = Br	**6e:** R^1 = Br	85
6	**5af:** R^1 = Cl	**6f:** R^1 = Cl	79
7	**5ag:** R^1 = F	**6g:** R^1 = F	81
			
8	**5ba:** R^2 = Me	**6h:** R^2 = Me	80
9	**5ca:** R^2 = Br	**6i:** R^2 = Br	84
10	**5da:** R^2 = NO_2	**6j:** R^2 = NO_2	79
11	 5ga	 6k	83
12	 5ha	 6l	41

[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.



Scheme 5 Proposed mechanism.

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(II).

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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