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# Rhodium-catalyzed diastereoselective 1,2-addition of arylboronic acids to chiral trifluoroethyl imine

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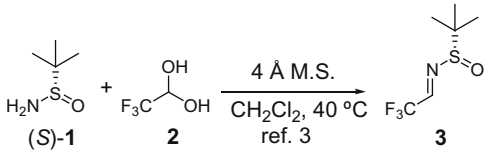
ABSTRACT

Rhodium-catalyzed 1,2-addition of arylboronic acids **4a–j** to chiral trifluoroethyl imine **3** afforded diastereomerically enriched sulfinamides **5a–j**. The chiral auxiliary of the sulfinamide products was readily removed under acidic methanolysis to provide the corresponding trifluoroethylamine analogs **6a–j**.



Trifluoroethylamine derivatives can be found in numerous pharmacologically active molecules due to their unique chemical and structural properties.[1] As such, the development for their asymmetric synthesis has gained considerable attention over the past years.[2] Despite recent advances, a more general and practical approach for the rapid synthesis of trifluoroethylamine analogs remains highly desirable. Along these lines, we had previously reported the synthesis of trifluoroethylamine derivatives via a key diastereoselective 1,2-addition of aryllithiums to chiral trifluoroethyl imine **3**.[3] We now disclose the rhodium-catalyzed diastereoselective 1,2-addition of arylboronic acids to imine **3**.

In the past, several groups had reported the rhodium-phosphine-catalyzed addition of arylboronic acids to *N*-sulfonyl aldimines.[4] More recently, Ellman's and Batey's groups have successfully demonstrated rhodium-catalyzed 1,2-addition of arylboronic acids to *N*-*tert*-butylsulfinyl aldimines to form the corresponding sulfinamides with high diastereoselectivities.[5] Notably, the conditions developed by Bolshan and Batey[5b] seem more practical by avoiding the use of external phosphine ligand and syringe pump for slow addition of the arylboronic acids. Accordingly, we envisioned adapting this procedure to examine the rhodium-catalyzed 1,2-addition of arylboronic acids to chiral trifluoroethyl imine **3** (Scheme 1). This imine can be prepared by condensation of *N*-*tert*-butylsulfinamide **1** with trifluoroacetaldehyde hydrate **2** in dichloromethane at 40 °C in the presence of 4 Å molecular sieves, and was further used without purification as previously reported.[3]

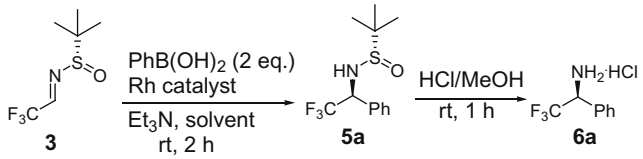



(*S*)-**1** **2** **3**

**Scheme 1.** Preparation of chiral trifluoroethyl imine **3**.

We began our investigation with phenylboronic acid as a model substrate to explore the rhodium-catalyzed diastereoselective 1,2-addition to imine **3** (Table 1). Using Batey's reaction conditions, only a trace amount of the desired sulfinamide **5a** was observed, possibly due to aminal formation, in the presence of water. In order to avoid the aminal formation, we then focused our effort on anhydrous conditions using dichloromethane as solvent since the imine formation proceeded in this solvent. A few rhodium catalysts were investigated in order to optimize high yields and diastereoselectivities of the desired sulfinamide **5a**. The diastereoselectivity of sulfinamide **5a** was determined by chiral HPLC of amine salt **6a**, which was obtained upon chiral ligand cleavage using HCl in

**Table 1**
Initial screening of rhodium for 1,2-addition of phenylboronic acid to imine **3**




**3** **5a** **6a**

| Entry | Catalyst | Solvent | Yield[a] (%) | de[b] |
|---|---|---|---|---|
| 1 | $[Rh(cod)(CH_3N)_2]BF_4$ | Dioxane/$H_2O$ | Trace | — |
| 2 | $[Rh(cod)(CH_3N)_2]BF_4$ | $CH_2Cl_2$ | 74 | 87 |
| 3 | $[Rh(cod)(OMe)]_2$ | $CH_2Cl_2$ | 80 | 81 |
| 4 | $[Rh(cod)(OH)]_2$ | $CH_2Cl_2$ | 80 | 87 |

[a] Isolated overall yield from *N*-*tert*-butylsulfinamide **1**.
[b] Diastereomeric excess (de) was determined by chiral HPLC of amine **6a**, *S* absolute configuration was determined by comparison with an authentic standard.[2a,d]

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0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
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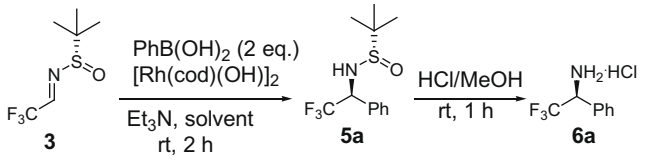
**Table 2**
Optimization of solvent for 1,2-addition of phenylboronic acid to imine **3**



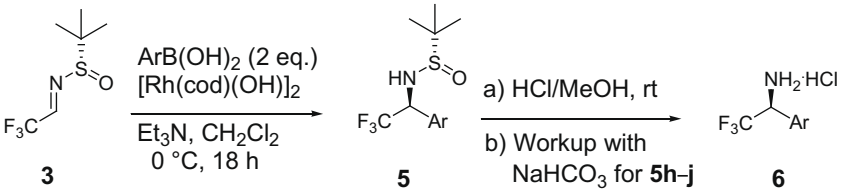

| Entry | Solvent | Yield[b] (%) | de[c] |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | 80 | 87 |
| 2 | $CHCl_3$ | 89 | 77 |
| 3 | $CH_2ClCH_2Cl$ | 79 | 87 |
| 4 | THF[a] | 59 | 83 |
| 5 | 2-Methyl-THF[a] | 24 | 90 |
| 6 | Dioxane[a] | 23 | 75 |
| 7 | Toluene | 75 | 76 |
| 8 | $CH_3CN$[a] | 25 | 91 |
| 9 | DMF[a] | 31 | 77 |

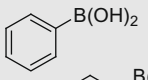
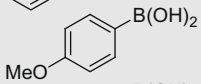
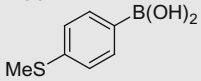
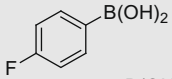
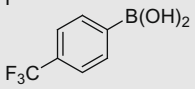
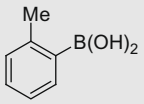
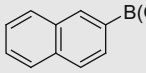
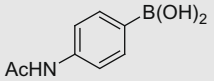
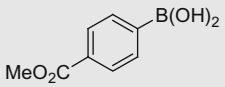
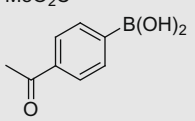
[a] $CH_2Cl_2$ was removed by distillation and replaced by the appropriate solvent.
[b] Isolated overall yield from *N-tert*-butylsulfinamide **1**.
[c] Diastereomeric excess determined by chiral HPLC of amine **6a**.

methanol.[3,5b,6] Both $[Rh(cod)OH]_2$ and $[Rh(cod)OMe]_2$ gave the highest yields of sulfinamide **5a**. Moreover, $[Rh(cod)OH]_2$ afforded the best diastereoselectivity of sulfinamide **5a** in the 1,2-addition. Therefore, $[Rh(cod)OH]_2$ was used in further reaction optimization. Besides catalyst screening, the effect of solvent was examined (Table 2). It was found that dichloromethane and chloroform afforded the highest yield (entries 1 and 2) when compared to 1,2-dichloroethane, THF, 2-methyl-THF, dioxane, acetonitrile, and DMF, which gave low to moderate yield of sulfinamide **5a** (entries 3–9). Interestingly, when 2-methyl-THF and acetonitrile were used as solvents, a slight improvement in diastereoselectivity was observed. Unfortunately, these solvents afforded lower yields. Thus, dichloromethane was found to be the optimal solvent for rhodium-catalyzed 1,2-addition of phenylboronic acid to imine **3** to provide sulfinamide **5a** in high yield and diastereoselectivity (entry 1).

Next, we investigated the effect of the base. Organic and inorganic bases were submitted to the reaction conditions. It was found that triethylamine remained the optimal choice in providing the best combination of high yield and diastereoselectivity.

**Table 3**
Rhodium-catalyzed diastereoselective 1,2-addition of various arylboronic acids to imine **3**




| Entry | $ArB(OH)_2$ (**4**) | Sulfinamide **5** | Yield of **5**[a] (%) | de[b] | Amine **6** | Yield of **6** (%) |
|---|---|---|---|---|---|---|
| 1 |  | **5a** | 72 | 90 | **6a** | 90 |
| 2 |  | **5b** | 73 | 81 | **6b** | 92 |
| 3 |  | **5c** | 55 | 93 | **6c** | 94 |
| 4 |  | **5d** | 75 | 93 | **6d** | 92 |
| 5 |  | **5e** | 58 | >99 | **6e** | 83 |
| 6 |  | **5f** | 72 | 91 | **6f** | 96 |
| 7 |  | **5g** | 62 | 91 | **6g** | 99 |
| 8 |  | **5h** | 47 | 94 | **6h** | 83 |
| 9 |  | **5i** | 49 | 94 | **6i** | 84 |
| 10 |  | **5j** | 66 | 85 | **6j** | 67 |

[a] Isolated overall yield from *N-tert*-butylsulfinamide **1**, calculated from average of two runs.
[b] Diastereomeric excess determined by chiral HPLC of amines **6**.

Finally, variation of the catalyst and phenylboronic acid loading, reaction concentration, and temperature of the reaction identified 5% of $[Rh(cod)OH]_2$ with 2 equiv of phenylboronic acid in dichloromethane (0.14 M of imine **3**) at 0 °C as the optimal reaction conditions for the preparation of sulfinamide **5a** from imine **3**. Using these optimized conditions, the rhodium-catalyzed 1,2-addition of phenylboronic acid to imine afforded sulfinamide **5a** in 72% overall yield from *N*-*tert*-butylsulfinamide **1** with an excellent diastereoselectivity (Table 3, entry 1).

Encouraged by the above results, we then examined the scope of this rhodium-catalyzed diastereoselective 1,2-addition to imine **3** using the optimized reaction conditions with various arylboronic acids.[7] The results are shown in Table 3. In general, a variety of substituted arylboronic acids with functional groups such as fluoro, methoxyl, methylthio, trifluoromethyl, acetamide, methylester, and ketone are compatible under the reaction conditions. The desired sulfinamides **5a–j** were generated in moderate to good yields and good to excellent diastereoselectivities. Sulfinamides **5a–j** were readily hydrolyzed to give the corresponding trifluoroethylamine analogs **6a–j**, which were analyzed by chiral HPLC for diastereomeric excess determination. So far, the scope of this 1,2-addition reaction to imine **3** has been limited to arylboronic acids. Only a trace amount of the corresponding sulfinamides was observed when attempted with propenylboronic acid and phenylvinylboronic acid. In addition, heterocyclic boronic acids such as pyridine, pyrimidine, thienyl, and furanyl boronic acids failed to participate in the 1,2-addition reaction. Presumably, the heteroatoms complexed with rhodium and impeded the catalytic process.

It has been proposed that in the rhodium-catalyzed 1,2-addition reaction, triethylamine acts as a buffer to prevent the protonation of the intermediate Ar-Rh(I) species.[5b] However, in our hands the protodeboration of arylboronic acids was identified as the major side reaction. For example, when 4-acetamidophenylboronic acid, 4-methoxycarbonylphenylboronic acid, and 4-acetylphenylboronic acid (**4h–j**) were employed, *N*-phenylacetamide, methyl benzoate, and acetophenone were obtained, respectively, in addition to the desired sulfinamides **5h–j**.

The addition of arylboronic acids to imine **3** appears to have proceeded via a non-chelated transition-state model, which is consistent with the literature for the addition of organolithium reagents[8] as well as boronic acids.[5b]

In summary, we have developed an efficient rhodium-catalyzed diastereoselective 1,2-addition of arylboronic acids **4a–j** to trifluoroethyl imine **3** to generate the corresponding sulfinamides **5a–j** in good yields and excellent diastereoselectivities. This protocol gives access to a variety of trifluoroethylamine analogs **6a–j**. The commercial availability of arylboronic acids as well as the mild reaction conditions make this methodology a very attractive alternative to this class of compounds.

## Acknowledgment

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7. *Typical experimental of rhodium-catalyzed addition reaction*: *Compound* **5a**: To a solution of *N*-*tert*-butylsulfinamide (*S*)-**1** (200 mg, 1.65 mmol) in dichloromethane (3.3 mL) in a sealed tube were added trifluoroacetaldehyde hydrate **2** (75% in aqueous solution, 200 μL, 1.82 mmol) and molecular sieves beads 4 Å (1 g) from Acros. The reaction mixture was stirred at 40 °C for 6 h under nitrogen to provide the crude imine **3**. The reaction mixture was cooled to 0 °C, 8.6 mL of dichloromethane was added followed by phenylboronic acid (402 mg, 3.3 mmol) and triethylamine (465 μL, 3.3 mmol). The reaction mixture was bubbled with nitrogen for 10 min, then $[Rh(cod)OH]_2$ (38 mg, 0.083 mmol) was added, bubbled again with nitrogen for 10 min. The reaction mixture was aged at 0 °C for 18 h. It was then filtered through Celite, the filtrate was quenched with a saturated sodium hydrogen carbonate solution. The aqueous layer was extracted three times with dichloromethane. The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using ethyl acetate–hexanes (10:90 to 30:70) to afford **5a** in 72% yield (332 mg).
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