Construction of Biaryls from Aryl Sulfoxides and Anilines by Means of Sigmatropic Rearrangement

Tomoyuki Yanagi,[a] Keisuke Nogi,[a] and Hideki Yorimitsu*[a]

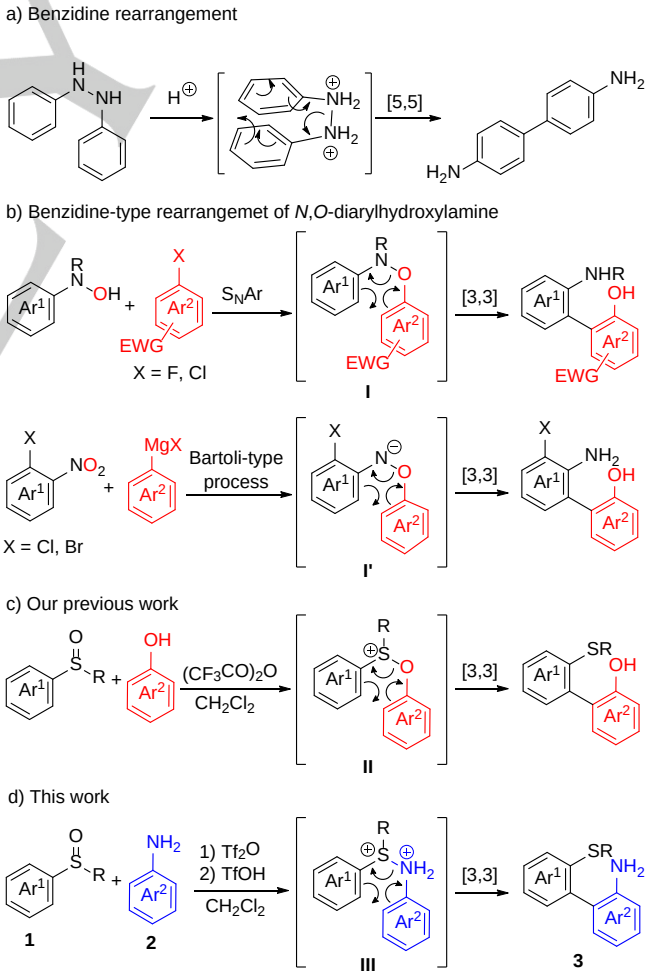
Dedication

Abstract: An unprecedented S–N variant of the benzidine rearrangement for construction of biaryls has been developed. Aryl sulfoxides underwent dehydrogenative coupling with anilines via successive treatment with trifluoromethanesulfonic anhydride and trifluoromethanesulfonic acid to provide the corresponding 2-amino-2'-sulfanyl- and/or 4-amino-4'-sulfanylbiphenyls. Mechanistic studies indicate that the C–C-bond forming sigmatropic rearrangement proceeds intramolecularly from dicationic S–N-tethered species.

Biaryl skeletons are important structural motifs in organic chemistry and its related fields including pharmaceuticals, agrochemicals, and functional materials. Therefore, a number of methodologies for the synthesis of biaryls have been actively investigated. Transition metal-catalyzed cross-coupling has been regarded as the most convenient and robust tool for the construction of biaryl skeletons.[1] Meanwhile, development of complementary metal-free strategies which provides rapid accesses to biaryls possessing catalyst poisonous and/or sterically demanding functionalities has been now attracting increasing attention.[2]

Among the metal-free strategies, C–C-bond forming sigmatropic rearrangement from heteroatom-tethered intermediates has been considered as a classical yet powerful method for connecting two aromatic rings. As a representative example, the benzidine rearrangement, whereby 1,2-diphenylhydrazine is converted into 4,4'-diaminobiphenyl (benzidine), has been well known (Scheme 1a).[3] Under acidic conditions, the protonated hydrazine undergoes [5,5] sigmatropic rearrangement, resulting in formation of the C–C bond.[4-7] Interestingly, an analogous N–O-tethered intermediate **I** also shows similar reactivity to participate in [3,3] and [5,5] sigmatropic rearrangements (Scheme 1b).[8] Generally, intermediate **I** is generated *in situ* from *N*-arylhydroxylamines and highly electrophilic aryl halides via S_NAr reaction.[9] As another approach, Kürti elegantly achieved the synthesis of biaryls from nitroarenes and arylmagnesiums via a Bartoli-type process[10] although the reaction accommodates only *ortho*-halogenated nitroarenes.

Recently, a cascade of interrupted Pummerer reaction/sigmatropic rearrangement[11] has emerged as a new strategy for dehydrogenative cross-coupling of aryl sulfoxides with phenols. (Scheme 1c).[12-14] The reaction is initiated by interrupted Pummerer reaction to form S–O-tethered intermediate **II**. Subsequent charge-accelerated [3,3] sigmatropic rearrangement[15,16] constructs the C–C bond to end up with the formation of biaryls. We envisioned that the reaction with anilines instead of phenols would offer an unprecedented S–N variant of the benzidine rearrangement.[17] Herein, we report the construction of biaryls from aryl sulfoxides **1** and anilines **2** via the cascade of interrupted Pummerer reaction/sigmatropic rearrangement to afford 2-amino-2'-sulfanylbiaryls **3** (Scheme 1d). Mechanistic experiments have revealed that the sigmatropic rearrangement takes place from S–N-tethered dicationic species **III** generated from **1** and **2** via sequential additions of trifluoromethanesulfonic anhydride (Tf_2O) and trifluoromethanesulfonic acid (TfOH).



Scheme 1. Construction of biaryls through sigmatropic rearrangement from heteroatom-tethered intermediates

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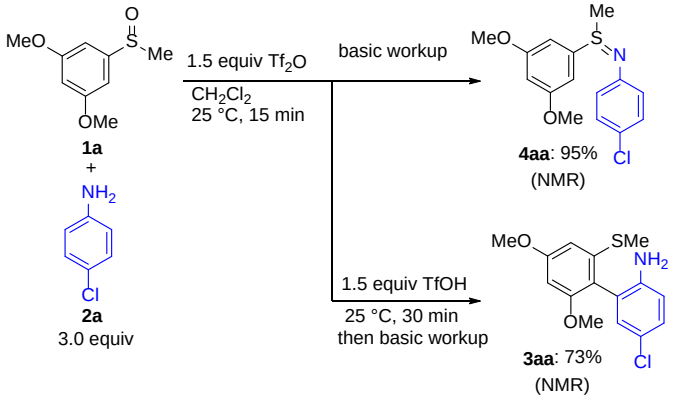
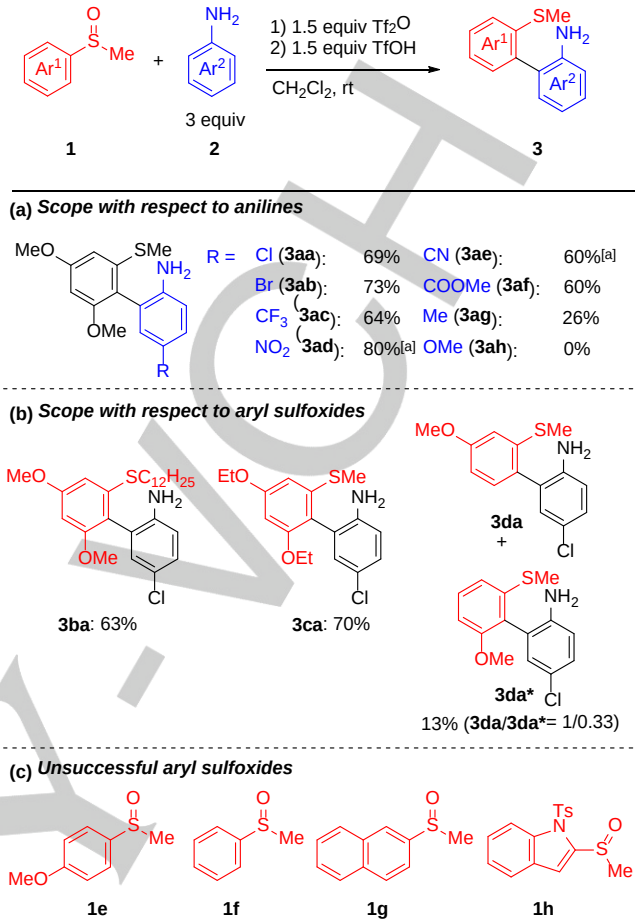
As a model reaction, we chose the dehydrogenative coupling of 3,5-dimethoxyphenyl sulfoxide **1a** with *p*-chloroaniline (**2a**). According to our previous reactions with phenols, [12a] a mixture of **1a** and **2a** was treated with trifluoroacetic anhydride in CH_2Cl_2. However, only trifluoroacetylation of **2a** proceeded, resulting in recovery of **1a**. Conversely, sulfoxide **1a** could be selectively activated by means of Tf_2O as an activator. However, the target biaryl **3aa** was not observed. Instead, a 95% yield of sulfilimine **4aa** was obtained after basic workup of the reaction (Scheme 2, top).[18] To our delight, when TfOH was added to the reaction mixture before the basic workup, the desired biaryl **3aa** was obtained in 73% yield (Scheme 2, bottom).[19]



Scheme 2. Initial attempts for dehydrogenative coupling of **1a** with **2a**

With this reaction system, we then investigated the reaction scope with respect to anilines (Scheme 3a). Employment of anilines having electron-withdrawing groups at the *para* positions afforded 2-amino-2'-sulfanylbiphenyls **3aa**–**3af** in a regioselective manner. A variety of functional groups including halogen, ester, nitro, and cyano groups were well tolerated. The reactions with highly electron-deficient anilines **2d** and **2e** required the addition of 3 equivalents of TfOH probably due to the low basicity of the corresponding sulfilimine-type intermediates (*vide infra*). Unfortunately, electron-rich anilines such as *p*-toluidine (**2g**) and *p*-anisidine (**2f**) were unsuitable as the coupling partners. In these cases, undesired *N*-sulfonylation of the anilines proceeded, resulting in recovery of sulfoxide **1a**.

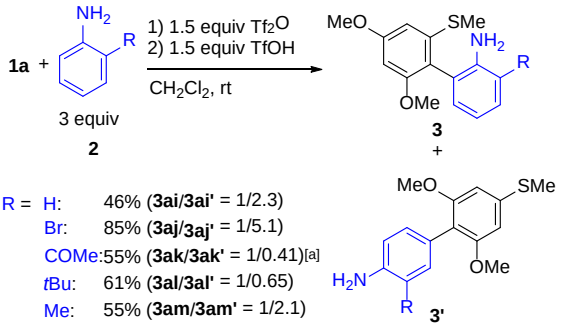
We then explored the reaction scope with respect to aryl sulfoxides (Scheme 3b). Electron-donating groups at the *meta*-positions of aryl sulfoxides play an important role. Aryl sulfoxides having 3,5-dialkoxyphenyl groups afforded the corresponding biaryls **3aa**–**3ca** in good yields. However, removal of one of the methoxy groups from **1a** resulted in a significant drop of the yield; the reaction with 3-methoxyphenyl sulfoxide **1d** afforded only a 13% yield of the product as a mixture of regioisomers **3da** and **3da***. Electron-donating groups should be attached to the *meta* positions; the reaction of 4-methoxyphenyl sulfoxide **1e** afforded a complex product mixture while the first S–N bond formation proceeded to form sulfilimine **4ea** (Scheme 3c). Similarly, phenyl and 2-naphthyl sulfoxides **1f** and **1g** went through the S–N bond formation, whereas the subsequent addition of TfOH gave complex product mixtures. When indolyl sulfoxide **1h** was used, the corresponding sulfilimine was not observed though **1h** was fully consumed.



[a] 3.0 equiv of TfOH was added.

Scheme 3. Scope of the reaction

When simple aniline (**2i**) was used as the coupling partner, [5,5] sigmatropic rearrangement from intermediate **III** competed with the [3,3] sigmatropic rearrangement, and a mixture of biaryls **3ai** and **3ai'** was obtained in 46% yield (Scheme 4). Competition of [3,3] vs [5,5] sigmatropic rearrangements was also observed in our previous dehydrogenative coupling of aryl sulfoxides with phenols.[12a, 20] Anilines **2j** and **2k** having bromo and acetyl groups, respectively, at the *ortho* position also underwent [3,3] and [5,5] sigmatropic rearrangements to afford the corresponding biaryls as mixtures of the isomers. Interestingly, electron-rich anilines **2l** and **2m** having alkyl groups at the *ortho* positions successfully participated in the reaction, whereas *p*-toluidine (**2g**) preferentially undergo the *N*-sulfonylation (Scheme 3a). The *ortho* substituents would hamper the *N*-sulfonylation of anilines **2l** and **2m**, which leads to the selective reaction of Tf_2O with sulfoxide **1a**. The regioselectivity would depend on the substituents of anilines and the reaction conditions (See Table S3 in Supporting Information) while the origin of the selectivity remains still unclear.



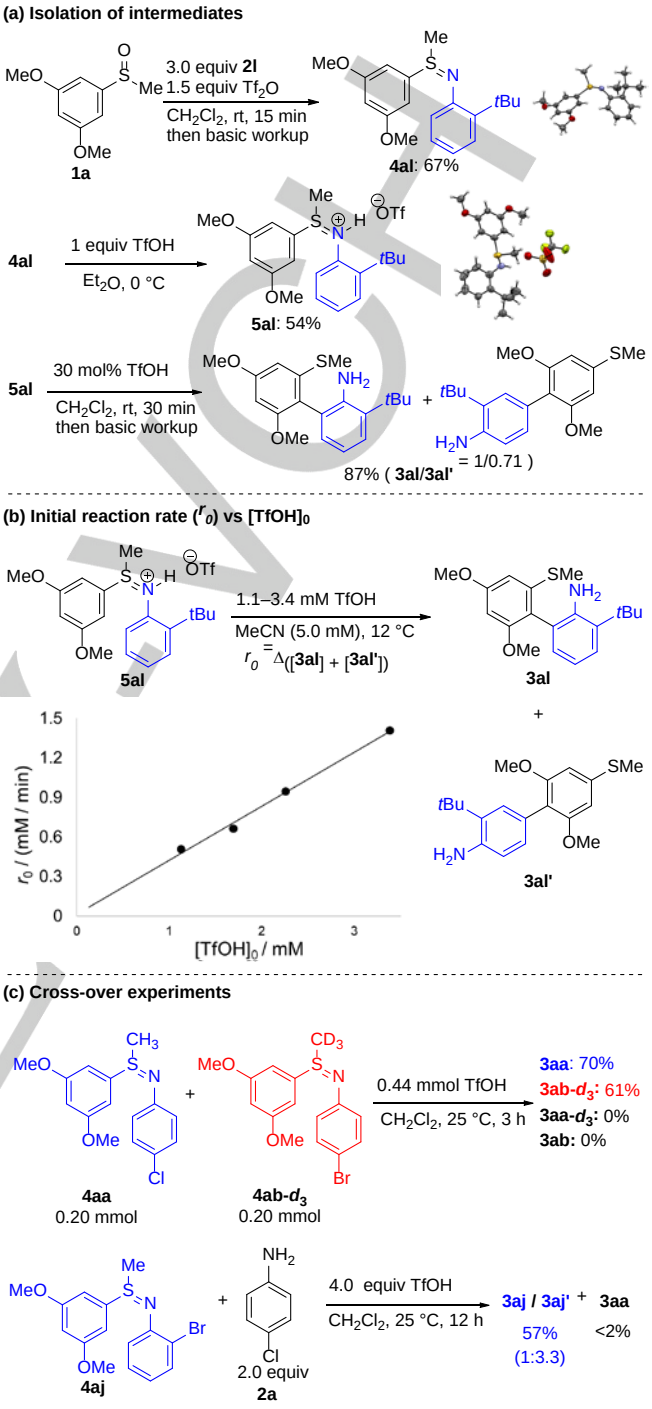
[a]3.0 equiv of TfOH was added.

Scheme 4. Competition between [3,3] and [5,5] sigmatropic rearrangements

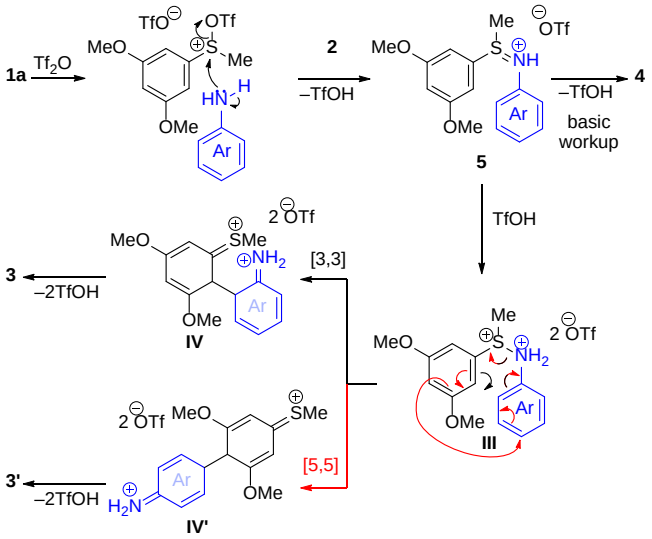
To gain insight into the reaction mechanism, we attempted to isolate the reaction intermediates by employing **1a** and **2l** (Scheme 5a). The reaction of **1a** with **2l** followed by basic workup afforded sulfilimine **4al** in 67% yield. As expected, the corresponding trifluoromethanesulfonate salt **5al** was obtained as a stable solid by protonation of **4al** with 1 equivalent of TfOH. The structures of **4al** and **5al** were confirmed by X-ray crystallographic analysis.[21] Although neither decomposition nor rearrangement of **5al** in $CDCl_3$ was observed for more than a week at room temperature, once a catalytic amount of TfOH was added, **5al** smoothly underwent [3,3] and [5,5] sigmatropic rearrangements to provide **3al** and **3al'**.[22] These results clearly indicate that dicationic species **III** in Scheme 1d would participate in the sigmatropic rearrangements as is the case with the benzidine rearrangement.

To further evaluate the effect of TfOH, we plotted the initial reaction rate (r_0) for the acid-catalyzed sigmatropic rearrangement of **5al** against the initial concentration of TfOH ($[TfOH]_0$). As shown in Scheme 5b, the plotting shows positive dependence, and the reaction was estimated to be approximately first-order in $[TfOH]_0$ (See Figure S4 in Supporting Information for details). This result implies that the protonation of monocationic **5al** to form dicationic **III** would be the rate-determining step.

The intramolecular nature of the [3,3] and [5,5] sigmatropic rearrangements was supported by crossover experiments. Treatment of a mixture of sulfilimines **4aa** and **4ab**-d_3 with TfOH furnished biaryls **3aa** and **3ab**-d_3 exclusively through the intramolecular sigmatropic rearrangement without formation of the crossover products **3aa**-d_3 and **3ab** (Scheme 5c, top). Even in the presence of external aniline **2a**, sulfilimine **4aj** was selectively converted to **3aj** and **3aj'** accompanied with a trace amount of **3ab** (Scheme 5c, bottom).



Scheme 5. Mechanistic studies



Scheme 6. Plausible reaction mechanism

A plausible reaction mechanism is shown in Scheme 6. The reaction would begin with the activation of **1a** with Tf_2O, followed by S–N-forming interrupted Pummerer reaction with aniline **2** to provide sulfiliminium **5**. Intermediate **5** would be reluctant to undergo [3,3] sigmatropic rearrangement, and the subsequent basic workup furnishes sulfilimine **4** unless external TfOH is added. The addition of TfOH to the reaction mixture containing **5** would lead to the formation of dicationic species **III** which finally undergoes [3,3] and [5,5] sigmatropic rearrangement to afford **IV** and **IV'**, respectively. The *meta*-alkoxy groups of **1** stabilize **IV** and **IV'** by the resonance effect, [23] the sigmatropic rearrangements from **III** to **IV** and **IV'** would be thus promoted. Finally, double rearomatization of **IV** and **IV'** via deprotonation would provide biaryls **3** and **3'**, respectively.

In conclusion, we have developed dehydrogenative coupling of aryl sulfoxides with anilines via a cascade of interrupted Pummerer reaction/sigmatropic rearrangement. Reaction intermediates, S–N-tethered sulfilimine and sulfiliminium, were successfully isolated. Mechanistic investigations with the intermediates revealed that the sigmatropic rearrangements proceed from dicationic species like the benzidine rearrangement. Expansion of the reaction scope with respect to aryl sulfoxides as well as improvement of regioselectivity are now in progress.

Acknowledgements

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Keywords: biaryl • dehydrogenative coupling • aryl sulfoxide • sigmatropic rearrangement • aniline

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[19] Although one equivalent of TfOH would be generated via the S–N bond formation, generated TfOH would be instantly neutralized by aniline in the reaction mixture. Therefore, the addition of external TfOH is required for the acid-promoted [3,3] sigmatropic rearrangement.

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[21] For XRD analyses, see the Supporting Information (CCDC 1943978 and 1945506)

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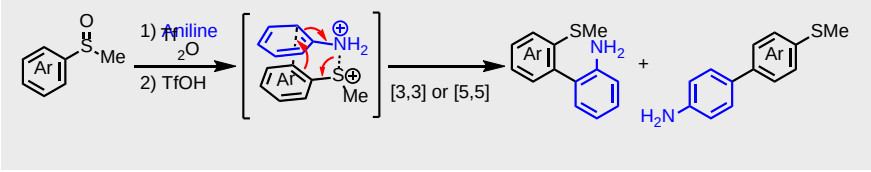

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