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

Yanagi, Tomoyuki; Nogi, Keisuke; Yorimitsu, Hideki


This is the peer reviewed version of the following article: T. Yanagi, K. Nogi, H. Yorimitsu, Chem. Eur. J. 2020, 26, 783., which has been published in final form at https://doi.org/10.1002/chem.201903570. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

This is not the published version. Please cite only the published version.
Ah 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 biaryls. Meanwhile, development of complementary metal-free strategies which provides rapid access to biaryls possessing catalyst poisonous and/or sterically demanding functionalities has been now attracting increasing attention.

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). Under acidic conditions, the protonated hydrazine undergoes [3,3] 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).

\[ \text{Ar}_1 \text{S} \text{Ar}_2 + \text{Ar}_1 \text{NHR} \rightarrow \text{Ar}_1 \text{NHR} \text{Ar}_2 \]

Supporting information for this article is given via a link at the end of the document.
As a model reaction, we chose the dehydrogenative coupling of 3,5-dimethoxypyridine 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 CH₂Cl₂. However, only trifluoroacetylation of 2a proceeded, resulting in recovery of 1a. Conversely, sulfoxide 1a could be selectively activated by means of Tf₂O as an activator. However, when TfOH was added to the reaction mixture before the basic workup, the desired biaryl 3aa was obtained (Scheme 2, bottom).\[^{[19]}\] To our delight, when TfOH was added to the reaction mixture before the basic workup, the desired biaryl 3aa was obtained (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 aryl sulfoxides (Scheme 3a). Employment of aryl sulfoxides having electron-donating groups at the ortho positions afforded 2-amino-2'-sulfanylbiphenyls 3aa–3af in a regioselective manner. A variety of functional groups including halogen, ester, nitro, and cyano groups was 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 biaryl sulfides 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-methoxypyridine 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-methoxypyridine sulfoxide 1e afforded a complex product mixture while the first S–N bond formation proceeded to form sulfinimine 4ea (Scheme 3c). Similarly, phenyl and 2-naphtyl 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 sulfinimine was not observed though 1h was fully consumed.

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 TfOH 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.
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 CDCl₃ 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 ($[\text{TfOH}]_0$). 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-d₃ with TfOH furnished biaryls 3aa and 3ab-d₃ exclusively through the intramolecular sigmatropic rearrangement without formation of the crossover products 3aa-d₃ 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).
A plausible reaction mechanism is shown in Scheme 6. The reaction would begin with the activation of 1a with Tf$_2$O, followed by S-N-forming interrupted Pummerer reaction with anilines 2 to provide sulfinium 3. Intermediate 5 would be reluctant to undergo [3,3] sigmatropic rearrangement, and the subsequent basic workup furnishes sulfimine 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 IV and IV' by the resonance effect, 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 sulfimine and sulfiminium, were successfully isolated. Mechanistic investigations with the intermediates revealed that the sigmatropic rearrangements proceed from dicaticionic 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

This work was supported by JSPS KAKENHI Grant Numbers JP16H04109, JP18H04254, JP18H04409, JP19H00895 and JP18K14124. T.Y. thanks JSPS Adoctoral Fellowship. H.Y. thanks The Mitsubishi Foundation for financial support.

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


COMMUNICATION


[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.


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

[22] Instead of TfOH, Tf2NH, HBF4•Et2O, and an excess amount of CF3CO2H also promoted the sigmatropic rearrangements of 4al. The rearrangements also proceeded in other solvents such as MeCN and HFIP. See Table S2 in Supporting Information for further details.

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'-sulfanyl-biphenyls. Mechanistic studies indicate that the C–C-bond forming sigmatropic rearrangement proceeds intramolecularly from dicationic S–N-tethered species.