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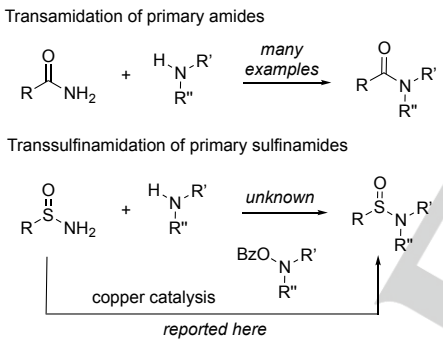
Copper-Catalyzed Transsulfinamidation of Sulfinamides as a Key Step in the Preparation of Sulfonamides and Sulfonimidamides

Hao Yu,[+] Zhen Li,[+] and Carsten Bolm*

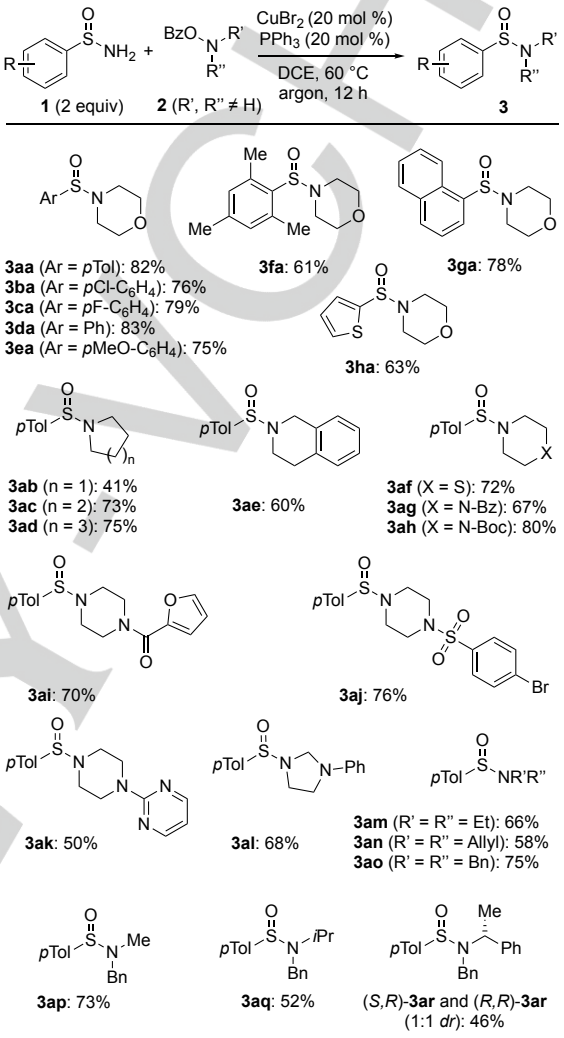
Abstract: Secondary or tertiary sulfinamides are prepared by copper-catalyzed transsulfinamidation of primary sulfinamides with O-benzoyl hydroxylamines. Subsequent oxidations of the resulting products lead to the corresponding sulfonamides. Treatment of N-aryl sulfinamides with O-benzoyl hydroxylamines under copper catalysis provides N-aryl sulfonimidamides.

Transamidations are synthetically highly valuable reactions for the preparation of amides.[1] Whereas significant progress has been made in transamidations of primary amides (Scheme 1),[2] analogous conversions of sulfinamides[3] have remained unknown. Considering the importance of such sulfur reagents as chiral auxiliaries,[4] ligands,[5] and intermediates in the preparation of sulfonamides,[6,7] this synthetic gap comes as a surprise. Here, we report on the development of trans-sulfinamidation reactions and the extension of those studies leading to the discovery of a novel approach towards N-arylated sulfonimidamides.



Scheme 1. Transamidations of primary amides (top) and analogous reactions starting from primary sulfinamides (bottom).

For the initial experiments, *para*-tolylsulfinamide (**1a**) was selected as representative starting material. Being guided by literature,[8] O-benzoyl hydroxylmorpholine (**2a**) was chosen as amino transfer agent.[9] After an extensive screening and optimization,[10] product **3aa** could be obtained in 82% yield. A combination of $CuBr_2$ (20 mol %) and PPh_3 (20 mol %) served as catalyst, which as applied in 1,2-dichloroethane (DCE) at 60 °C for 12 h under an argon atmosphere. The scope of this unprecedented reaction is depicted in Scheme 2.



Scheme 2. Substrate scope of transsulfinamidations with O-benzoyl hydroxylamines of secondary amines (on a 0.2 mmol scale).

First, the sulfinamide component was varied, and for products **3aa**-**3ha**, O-benzoyl hydroxylmorpholine (**2a**) served as amino source. In general, the transsulfinamidations worked well, and the products were obtained in yields ranging from 61-83%. While electronic factors appeared to be irrelevant for the reaction efficiency (as reflected by the results for variously para-substituted benzenesulfinamides **3aa**-**3ea**), steric crowding (as in **3fa**, 61% yield) and the presence of a heteroatom in the arene (as in **3ha**, 63% yield) seemed to hamper the reaction leading to lower product yields.

Subsequently, a range of O-benzoyl hydroxylamines **2** were examined in reactions with *para*-tolylsulfinamide (**1a**) as coupling partner (Scheme 2). Substrates derived from pyrrolidine, piperidine, azepane, tetrahydroisoquinoline and thiomorpholine provided the corresponding sulfinamides **3ab**-**3af** in yields of 41-75%. Various protected piperazine derivatives reacted well too, leading to products **3ag**-**3ak** in moderate to high yields (50-80%).

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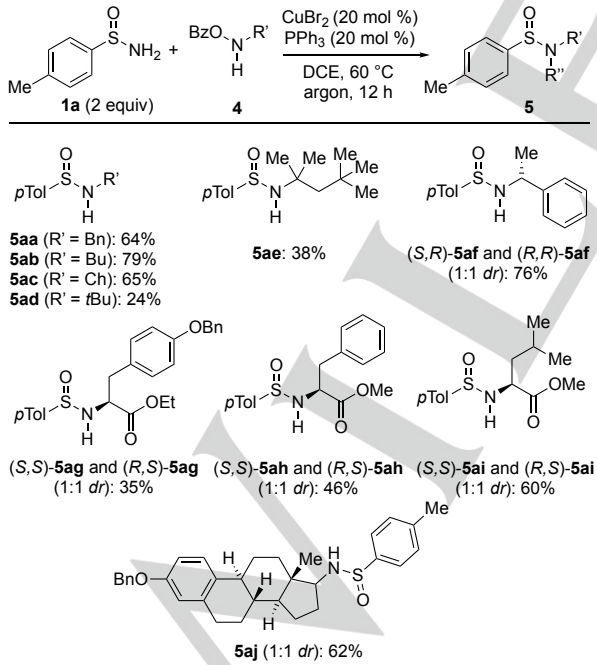
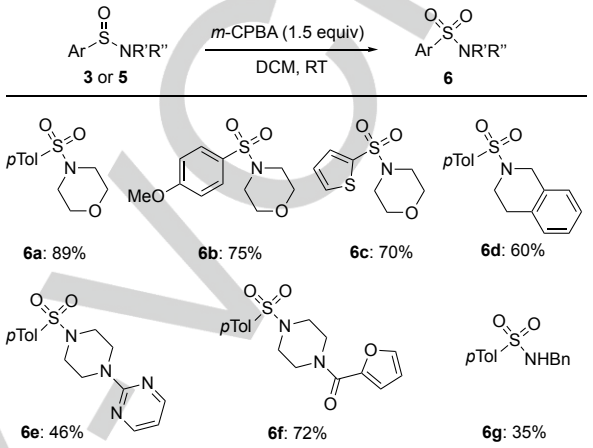
Product **3al** was obtained from O-benzoylhydroxyl N-phenyl-imidazolidine (**2l**) in 68% yield. Besides cyclic O-benzoylhydroxyl amines, acyclic derivatives could be applied, as shown by the formation of **3am**-**3ar**, which were isolated in 46−75% yield. In this series, the reaction with enantiopure (*R*)-N-benzyl-α-methylbenzylamine must be highlighted. It provided a 1:1 diasteremeric mixture of (*S,R*)-**3ar** and (*R,R*)-**3ar** in 46% yield, and to our delight, the diastereomers could be separated by column chromatography.

Until this stage, only O-benzoyl hydroxyl derivatives of secondary amines had been applied. With the goal to further extend the substrate scope, the preparation of secondary sulfinamides **5** from primary amine-based substrates **4**[9a, 11] was investigated. Again, *para*-tolylsulfinamide (**1a**) was used as coupling partner. Gratisfyingly, the aforedeveloped reaction conditions were also suitable here (Scheme 3), although in general, the yields of the resulting products **5aa**-**5aj** were only moderate to good (24–79%). Applying O-benzoyl hydroxyl amines with a low degree of branching led to the best results (products **5aa**-**5ac**). Increasing the steric bulk around the amino group had a negative effect on the reaction outcome as revealed by the yields of 24% and 38% in the formation of **5ad** and **5ae**, respectively. Using chiral O-benzoyl hydroxyl amine derivatives in reactions with *para*-tolylsulfinamide (**1a**) afforded **5af**-**5aj** as 1:1 mixtures of diastereomers. In this series, products **5ah** and **5ai** derived from the methyl esters of L-phenylalanine and L-leucine, respectively, are noteworthy because they could be separated by column chromatography affording single stereo-isomers. Also the conversion of estrone derivative **4j**, which gave a 62% yield of a 1:1 distereomeric mixture of sulfinamide **5aj**, shall be mentioned.



Scheme 3. Substrate scope of transsulfinamidations with O-benzoyl hydroxylamines of primary amines (on a 0.2 mmol scale).

Scheme 4 summarizes the results achieved in conversions of selected sulfinamides **3** and **5** into their corresponding sulfonamides **6** by treatment with 1.5 equiv of *m*-chloroperbenzoic acid (*m*-CPBA) in DCM at room temperature. For most substrates, the transformation proceeded well, providing the expected products in yields ranging from 46% to 89%. Only for **6g**, which stemmed from secondary sulfinamide **5aa**, the yields remained low (35%).



Scheme 4. Preparation of sulfonamides by oxidations of their corresponding sulfinamides with *m*-CPBA (on a 0.1 mmol scale).

Sulfonimidamides are mono-aza analogues of sulfonamides, which have recently attracted attention in both medicinal and agricultural chemistry.[12] Because of their interesting properties such as high chemical and metabolic stability, multiple hydrogen bond acceptor/donor functionalities, and structural diversity, sulfonimidamides can act as sulfonamide bioisosteres. Subsequently, medicinal chemists applied them, for example, as BACE and kinase inhibitors.[13,14] Until now, the utilization of sulfonimidamides has been restricted by a lack of commercial availability and limited synthetic accessibility.[15,16] Most often, they are prepared by nucleophilic substitution of sulfonimidoyl chlorides, which are obtained by electrophilic chlorination of sulfinamides followed by substitution with an amine. These protocols, however, suffer from the required multi-step reaction sequence and restrictions in substrate scope. Clearly, more convenient and efficient methods for the preparation of sulfonimidamides are desirable. In this context, we appreciated the finding that the aforementioned copper catalysis with O-benzoyl hydroxylamines as amino source could be adopted for the conversion of N-aryl sulfinamides into their corresponding sulfonimidamides (Scheme 5).[17]

Under the original reaction conditions with the catalyst based on $CuBr_2$/PPh_3, N-phenyl benzenesulfinamide (**7a**) reacted with **2a** providing sulfonimidamide **8aa** in 59% yield. After a series of experiments,[11] the optimal reaction conditions were identified to involve the use of CuBr (20 mol %) in acetonitrile at 80 °C under argon for 12 h. In this manner, **8aa** was obtained from **7a** and **2a** in 89% yield. Evaluating the substrate scope revealed a broad applicability of the method (Scheme 5).

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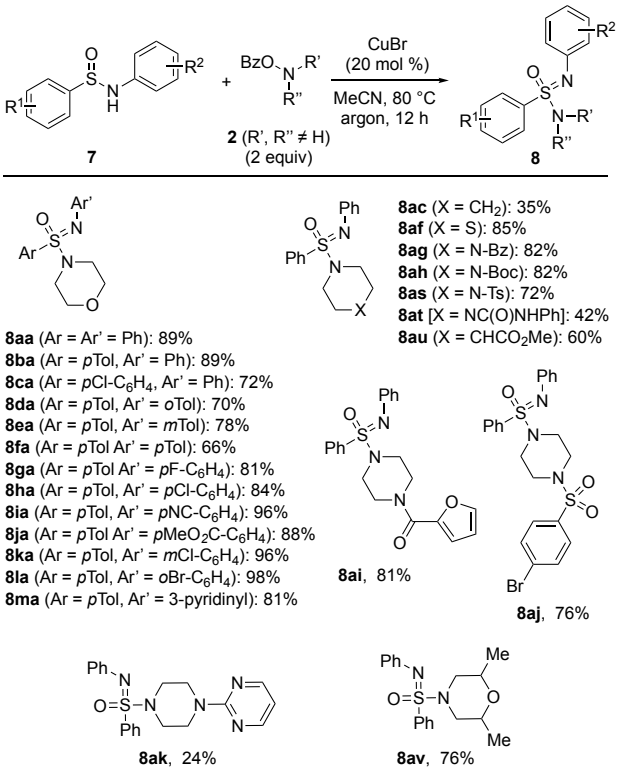
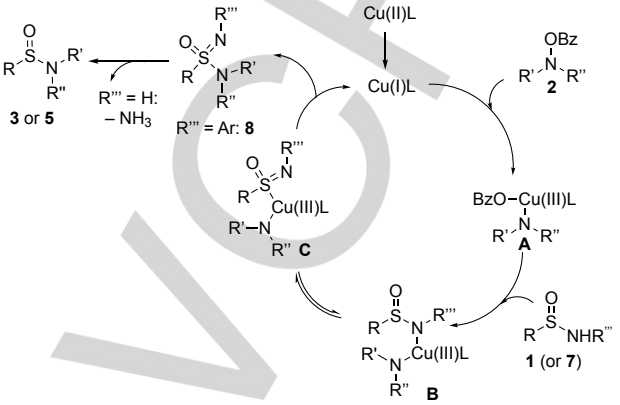


Scheme 5. Preparation of N-aryl sulfonimidamides (on a 0.2 mmol scale).

First, the sulfinamide structure was varied. In reactions with O-benzoyl hydroxylmorpholine (**2a**), all products (**8aa**-**8ma**) were obtained in high to excellent yields. Neither steric nor electronic factors had an apparent effect. A remarkable range of substituents including halo, cyano, carboxyl, and methoxy groups were tolerated well. Unexpectedly, the highest yield (98%) was observed in the formation of *ortho*-bromo aryl-containing product **8la**. Also **8na** bearing an N-3-pyridinyl substituent was obtained in high yield (81%).

To further explore the generality of the sulfonimidamide formation (Scheme 5), various O-benzoylhydroxyl amines **2** were tested in reactions with sulfinamide **7a**. Most educt combinations afforded the corresponding products in good to high yields. For example, sulfonimidamides **8af**, **8ag**, and **8ah** resulting from couplings of **7a** with thiomorpholine (**2f**), N-Bz piperazine (**2g**) and N-Boc piperazine (**2h**) were formed in yields of 85%, 82%, and 82%. Other N-protected piperazine derivatives worked too, but the yields were slightly lower (ranging from 24% for **8ak** to 81% for **8ai**). Reacting **7a** with piperidines **2c** and **2u** gave sulfonimidamides **8ac** and **8au** in yields of 35% and 60%. Finally, also disubstituted morpholine **2v** could be applied as illustrated by the formation of **8av**, which was obtained in 76% yield.

In the light of previous work,[2, 8, 9] the reaction pathway depicted in Scheme 6 is suggested: When starting from a Cu(II) salt, the process is initiated by metal reduction to provide a Cu(I) species. Oxidation by O-benzoylhydroxylamine **2** leads to Cu(III) intermediate **A**, which undergoes ligand exchange with sulfinamide **1** (or **7**) to give complex **B**. Subsequently, **B** converts to **C** by metal migration from nitrogen to sulfur. Reductive elimination of **C** regenerates the Cu(I) species needed for closing the catalytic cycle and provides a sulfonimidamide, which is stable if N-arylated (to give **8**) or labile if N-unsubstituted (leading to sulfinamides **3** or **5**).[18] The latter transformation appears to involve a loss of ammonia by reductive side reactions.[19]



Scheme 6. Proposed reaction pathway.

In conclusion, we discovered a copper-catalyzed trans-sulfinamidation of primary sulfinamides with O-benzoyl hydroxyl-amines providing secondary or tertiary sulfinamides. Simple oxidation reactions of the products lead to the corresponding sulfonamides. An analogous copper catalysis starting from N-aryl sulfinamides provides N-aryl sulfonimidamides.

Acknowledgements

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Keywords: Copper catalysis • sulfinamide • transsulfinamidation • sulfonamide • sulfonimidamide

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[17] Until now, only reactions with N-aryl sulfinamides have been studied. If other derivatives can be applied needs to be investigated and will be part of future work.

[18] This assumption was substantiated by the degradation of the NH-analog of **8ac** in the presence of **1a** or **2a**, which led to **3ac** in significant amounts under the standard catalysis conditions depicted in Scheme 5. For details, see the Supporting Information.

[19] The catalysis is not inhibited by the presence of 2 equiv of TEMPO, as shown by the coupling of **1a** and **2a**, which gave **3aa** in 67% yield under the standard catalysis conditions depicted in Scheme 2. For details, see the Supporting Information.

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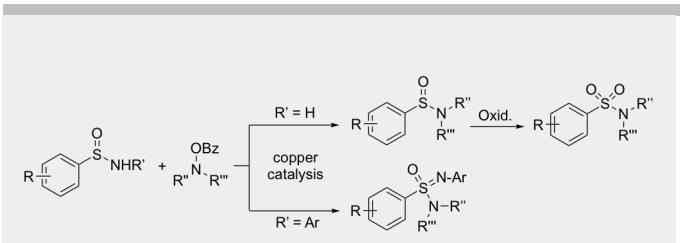

Copper-catalyzed transsulfinamidation of primary sulfinamides with O-benzoylhydroxylamines deliver secondary or tertiary sulfinamides. A simple oxidation reaction converts the products into sulfonamides. A related copper catalysis provides N-aryl sulfonimidamides from N-aryl sulfinamides.

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