C–N Bond Formation

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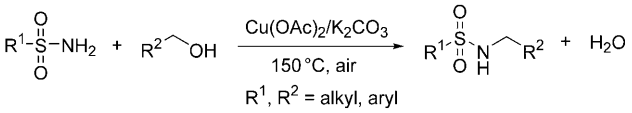
Copper-Catalyzed Alkylation of Sulfonamides with Alcohols**

Feng Shi, Man Kin Tse, Xinjiang Cui, Dirk Gördes, Dirk Michalik, Kerstin Thurow, Youquan Deng, and Matthias Beller**

The environmentally benign synthesis of carbon–nitrogen bonds is a central, but still challenging, area of organic synthesis.[1] In this context, salt-free alkylation reactions of amines through transhydrogenation processes have attracted significant attention in recent years.[2] The application of alcohols as alkylating agents has the advantages of high atom efficiency and the formation of water as the only side product. Unfortunately, to date only catalysts based on expensive precious metals—typically Ru or Ir—are known for these valuable transformations. On the other hand, the catalytic activity of readily available copper complexes in amination reactions, for example, coupling reactions of aryl halides, is well known.[3] A few copper complexes also display transhydrogenative activity in hydrostannation[4] and hydrosilylation reactions.[5] However, to the best of our knowledge, this potential has never been exploited in the alkylation of amines or amides.

On the basis of previous studies by others and us on the ruthenium-catalyzed alkylation of amines,[3,6] we became interested in environmentally benign alkylation reactions of amides and sulfonamides.[7,8] The resulting products are useful intermediates for the synthesis of pharmaceuticals and agrochemicals.[9] Herein, we describe the successful alkylation of sulfonamides with alcohols in the presence of copper catalysts (Scheme 1).



Scheme 1. Catalytic N-alkylation of sulfonamides with alcohols.

This novel reaction was observed during an investigation of the coupling of *p*-toluenesulfonamide and benzyl alcohol in the presence of various potential catalysts. When readily available $Cu(OAc)_2$ was used in the presence of K_2CO_3, significant conversion (ca. 50%) and high selectivity (99%) for the alkylated sulfonamide were observed. Notably, both high conversion (93%) and excellent selectivity (>99%) were observed when the reaction was performed in air (Table 1). Careful HRMS analysis revealed the formation of the bissulfonylated amidine **1** as a new reaction intermediate with the $Cu(OAc)_2/K_2CO_3$/air system; this intermediate was not formed when the reaction was carried out in the absence of K_2CO_3 under argon or in air, or with $Cu(OAc)_2$ and K_2CO_3 under argon (Figure 1; see also Figure S1 in the Supporting Information).

Table 1: Coupling of *p*-toluenesulfonamide and benzyl alcohol.[a]

Entry	Atmosphere	Conversion [%]	Selectivity [%]
1	Ar	48	>99
2	CO_2	51	>99
3	air	93	>99

[a] Reaction conditions: *p*-toluenesulfonamide (428 mg, 2.5 mmol), benzyl alcohol (1.08 g, 10 mmol), $Cu(OAc)_2$ (4.6 mg, 1 mol%), K_2CO_3 (69 mg, 10 mol%), 150°C, 12 h. Reactions were carried out in a 40 mL sealed pressure tube. Conversion and selectivity were determined directly from the GC-MS peak areas.

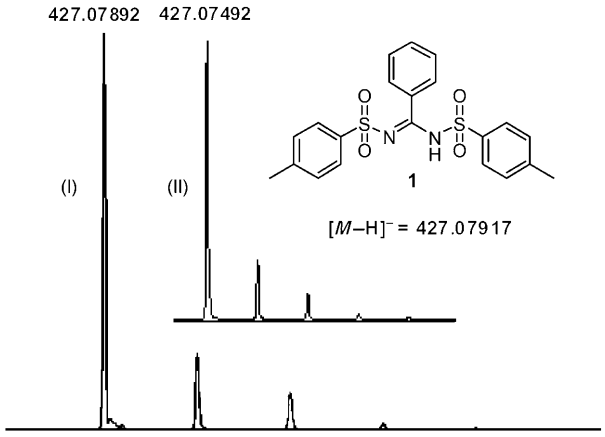


Figure 1. HRMS spectra of **1** formed during the coupling reaction (I) and synthesized **1** (II).

[*] Prof. Dr. F. Shi, X. Cui, Prof. Dr. Y. Deng
Lanzhou Institute of Chemical Physics
Chinese Academy of Sciences
No.18, Tianshui Middle Road, 730000 Lanzhou (China)
Fax: (+86) 931-496-8116
E-mail: fshi@lzb.ac.cn
Homepage: http://www.licp.ac.cn
Dr. D. Michalik, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse e.V. an der Universität Rostock
Albert-Einstein-Strasse 29a, 18059 Rostock (Germany)
Fax: (+49) 381-1281-5000
E-mail: matthias.beller@catalysis.de
Homepage: http://www.catalysis.de
Dr. M. K. Tse, Dr. D. Gördes, Prof. Dr. K. Thurow
Center for Life Science Automation (CELISCA)
Universität Rostock
Friedrich-Barnewitz-Strasse 8, 18119 Rostock (Germany)

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Apparently, **1** was formed by the oxidation of benzyl alcohol and condensation with *p*-toluenesulfonamide. We assumed that **1** acts as a stabilizing ligand to provide an active copper catalyst for dehydrogenation/hydrogenation reactions.[10] Thus, we synthesized **1** separately and added it to the original system to test its activity. Indeed, high catalyst activity and full conversion were observed in the presence of preformed compound **1** (Figure 2).

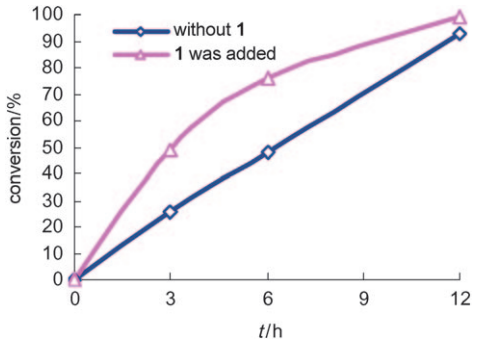
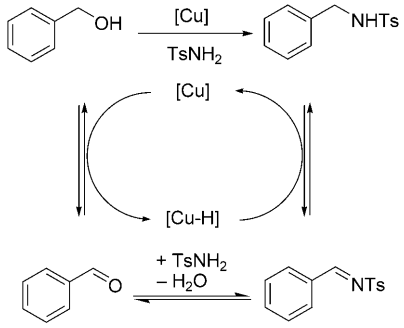


Figure 2. Coupling of *p*-toluenesulfonamide and benzyl alcohol with or without the addition of **1**.

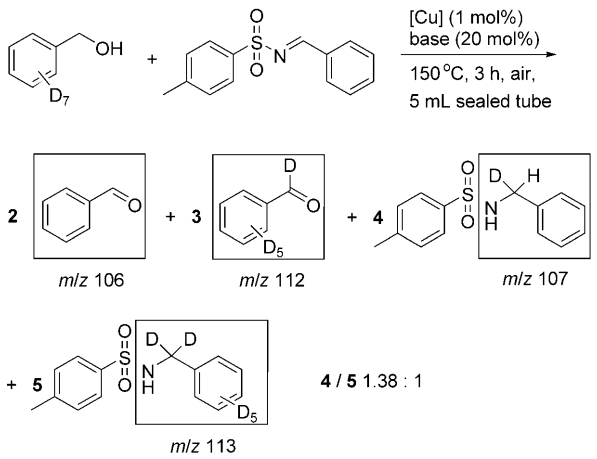
The activation of the hydroxy group by the active Cu species is an unexpected feature of the present reaction. In analogy to the ruthenium-catalyzed amination of alcohols, we propose that the reaction occurs through a hydrogen-borrowing mechanism (Scheme 2).



Scheme 2. Proposed mechanism. Ts = *p*-toluenesulfonyl.

In the overall process, the primary alcohol acts as the hydrogen donor. Hence, no additional hydrogen or hydrogen-transfer reagent is required. To understand the proposed mechanism, we investigated the coupling of [D_7]benzyl alcohol and *p*-toluenesulfonamide in more detail. ^{1}H NMR spectroscopic analysis of the resulting product (see Figure S2 in the Supporting Information) revealed that the dehydrogenation–imide formation–hydrogenation sequence is reversible.

The reaction of [D_7]benzyl alcohol with (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide was also used to test whether this domino process proceeds through a transhydrogenation mechanism (Scheme 3). If this hypothesis is right, **4** should be formed as a product. GC-MS analysis of the



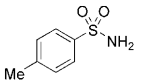
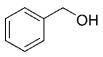
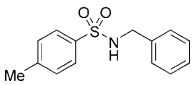
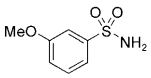
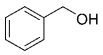
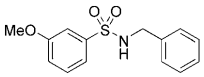
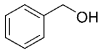
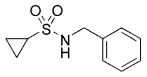
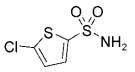
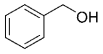
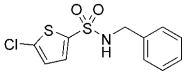
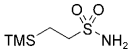
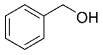
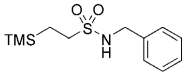
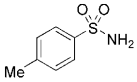
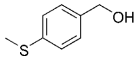
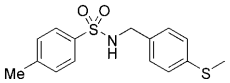
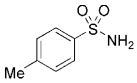
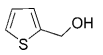
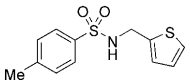
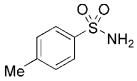
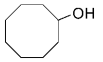
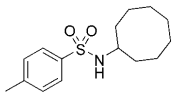
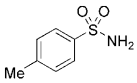
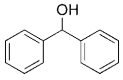
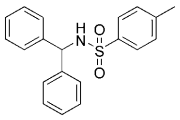
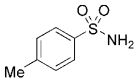
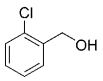
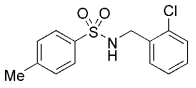
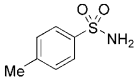
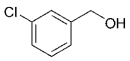
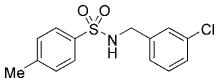
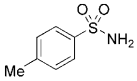
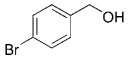
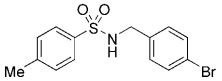
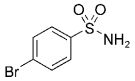
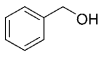
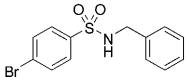
Scheme 3. Reaction of [D_7]benzyl alcohol and (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide.

reaction mixture confirmed the formation of products **2**–**5** (see Figures S3–S11 in the Supporting Information). (*E*)-*N*-Benzylidene-4-methylbenzenesulfonamide was fully consumed within 3 h. This result strongly supports our hypothesis. The observation of compounds **2**, **3**, and **5** suggests the reversibility of the whole process. According to ion-selective mass spectra, the ratio of **4** to **5** is 1.38:1 (area of peak at *m*/*z* 107/area of peak at *m*/*z* 113). This ratio is in perfect agreement with the results of ^{1}H NMR spectroscopic studies (see Figure S12 in the Supporting Information). Kinetic investigations of the coupling of benzyl alcohol and *p*-toluenesulfonamide demonstrated that benzaldehyde is formed at an early stage of the process, and that its concentration is then kept almost constant during the reaction. After a longer time (> 18 h), approximately 4% (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide is formed. All these results are in good agreement with the proposed reaction mechanism in Scheme 2.

Finally, the $Cu(OAc)_2/K_2CO_3$/air system was applied to the coupling of other alcohols and sulfonamides. To avoid contamination from minor degradation products of **1**, this ligand was only added in coupling reactions of benzyl alcohol and *p*-toluenesulfonamide. In all other cases, the respective ligand is formed in situ: an example of catalyst self-stabilization. The corresponding alkylated sulfonamides were obtained in good to excellent yields (71–99%; Table 2). Aromatic, heteroaromatic, and aliphatic substrates reacted well. Moreover, a range of functional groups, such as halo (Br, Cl), thiomethyl, and trialkylsilyl groups, were tolerated well. On the other hand, primary (nonbenzylic) aliphatic alcohols did not react under these conditions. Depending on the starting material, the concentration of K_2CO_3 had a significant influence on the yield. Notably, the coupling of secondary aliphatic and benzylic alcohols with *p*-toluenesulfonamide proceeded directly with $Cu(OTf)_2$ or $Cu(OAc)_2$ as the catalyst in the absence of a base (Table 2, entries 8 and 9).

In conclusion, we have demonstrated that the alkylation of sulfonamides with alcohols is possible with copper catalysts. The practical $Cu(OAc)_2/K_2CO_3$/air system enables the atom-efficient alkylation of sulfonamides in excellent

Table 2: Scope of the sulfonamide–alcohol coupling.[a]

Entry	Sulfonamide	Alcohol	Product	Yield [%][b]
1				96
2				91
3				97
4				89
5				94
6				95
7				93
8[c]				71
9[d]				99
10				89
11				94
12				92
13				96
14				95
15				95
16				91

[a] Reaction conditions: see Table 1; K_2CO_3 (0.2 equiv) for entries 1–3, 5, 10, 11, 13, 14, and 16; K_2CO_3 (0.3 equiv) for entries 6, 12, and 15; K_2CO_3 (0.4 equiv) for entries 4 and 7. [b] Yield of the isolated product. [c] No base was used; $Cu(OTf)_2$ (1 mol%) was used in place of $Cu(OAc)_2$. [d] No base was used. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

yield. In the presence of air, bissulfonylated amidines, such as **1**, are formed as novel ligands, which stabilize the catalyst in situ. It is likely that the described transformations proceed through a transhydrogenative mechanism.

Experimental Section

General procedure for coupling reactions: All reactions were carried out in a pressure tube (ca. 38 mL, Aldrich). *p*-Toluenesulfonamide (0.428 g, 2.5 mmol), benzyl alcohol (1.08 g, 10.0 mmol), $Cu(OAc)_2$ (4.6 mg, 1 mol% Cu), and K_2CO_3 (69.0 mg, 0.5 mmol) were placed in the pressure tube, the tube was sealed well, and the reaction mixture was stirred (250 rpm) at 150 °C (oil-bath temperature) under air for 12 h. The reaction mixture was then cooled to room temperature, acetone (ca. 20 mL) was added, and the mixture was filtered through Celite to remove the precipitated salts. The acetone and benzyl alcohol were removed under vacuum. The resulting yellow solid was washed with diethyl ether/hexane to remove residual benzyl alcohol and soluble impurities and then dried again under reduced pressure to give a white solid (625 mg, 96%). For quantitative analysis of the benzyl alcohol consumed in the reaction, dioxane (ca. 1.75 g, 20 mmol) was added, and the resulting solution was analyzed by GC/FID (FID = flame ionization detector; HP 6890) with an external standard. The amount of benzyl alcohol consumed in three reactions performed in parallel was 2.78, 2.52, and 2.65 mmol (2.65 ± 0.130 mmol).

Coupling reactions of [D_7]benzyl alcohol: *p*-Toluenesulfonamide (85.6 mg, 0.5 mmol) or *(E)*-*N*-benzylidene-4-methylbenzenesulfonamide (129.5 mg, 0.5 mmol), [D_7]benzyl alcohol (230.0 mg, 2.0 mmol), $Cu(OAc)_2$ (0.91 mg, 1 mol% Cu), and K_2CO_3 (13.9 mg, 0.1 mmol) were placed in a 5 mL pressure tube, which was then sealed and heated at 150 °C (oil-bath temperature) for 12 h (or 3 h). The reaction mixture was then cooled to room temperature, dissolved in acetone, and analyzed by GC-MS. The mixture was filtered through Celite, and the acetone and [D_7]benzyl alcohol were removed under vacuum. The resulting solid was washed with diethyl ether/hexane and then dried again under reduced pressure to give a white solid (ca. 85 mg from *p*-toluenesulfonamide; 130 mg, 99% from *(E)*-*N*-benzylidene-4-methylbenzenesulfonamide).

HRMS measurements: Two reactions were carried out in parallel (one under argon flow and the other in air). *p*-Toluenesulfonamide (0.855 g, 5.0 mmol), benzyl alcohol (2.16 g, 20.0 mmol), and $Cu(OAc)_2$ (9.1 mg, 1 mol% Cu) were placed in a glass vessel (ca. 50 mL), and the reaction mixture was stirred vigorously (500–750 rpm) at 150 °C for 3 h. A sample of the reaction mixture (ca. 100 mg) was shaken in methanol (ca. 1 mL) and then analyzed by HRMS. K_2CO_3 (138.0 mg, 1 mmol) was then added to the reaction mixture, which was analyzed again after 15 min.

HRMS experiments were performed with an Agilent series 1200 HPLC system and an Agilent 1969 A time-of-flight mass spectrometer. The TOF-MS conditions in negative ionization mode with a dual-sprayer API-ES source (API = atmospheric pressure ionization) were as follows: nebulizer and drying gas, nitrogen; nebulizer pressure, 35 psig; drying-gas flow, 10 L min^{-1}; drying-gas temperature, 300 °C; capillary voltage, 4 kV; fragmentor voltage, 215 V; skimmer voltage, 60 V; octopole voltage, 250 V; mass reference, *m*/*z* 112.98558 and 1033.98810. The sample was injected into a mobile phase of H_2O (0.1% HCOOH)/MeOH (1:9).

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