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Copper-Catalyzed *N*-Alkylation of Sulfonamides with Benzylic Alcohols: Catalysis and Mechanistic Studies

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Abstract: The *N*-alkylation of sulfonamides with alcohols is efficiently performed in the presence of easily available copper catalysts *via* hydrogen borrowing methodology. Applying a copper acetate/potassium carbonate system the reaction of sulfonamides and alcohols gave the corresponding secondary amines in excellent yield. *In situ* HR-MS analysis indicated that bissulfonylated amines are formed under air atmosphere, which act as self-stabilizing ligands for the catalytic system. UV-visible measurements suggest the interaction between the copper centre and the bissulfonylated amine. Reactions of benzyl alcohol-d_7 with *p*-toluenesulfonamide, *N*-benzyl-*p*-toluenesulfonamide or *N*-benzylidenetoluenesulfonamide revealed that the reaction proceeds *via* a transfer hydrogenation mechanism and the whole process is micro-reversible. Competitive reactions of benzyl alcohol and benzyl alcohol-d_7 with *p*-toluenesulfonamide revealed a kinetic isotope effect (kH/kD) of 3.287 (0.192) for the dehydrogenation of benzyl alcohol and 0.611 (0.033) for the hydrogenation of the *N*-benzylidene-*p*-toluenesulfonamide intermediate, which suggests that dehydrogenation of the alcohol is the rate-determining step.

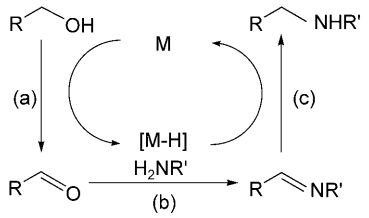
Keywords: alcohols; alkylation; C–N bond formation; copper catalysts; sulfonamides

Introduction

Nitrogen-containing compounds are of significant importance as building blocks for pharmaceuticals and novel bio-active compounds.[1] In the past decades, versatile catalytic procedures for carbon-nitrogen (C–N) bond formation, for instance, amination of aryl halides,[2] hydroaminations[3] and hydroaminomethylations[4] have been developed. Nevertheless, further improvements are still possible.

With respect to alkylated amides, *N*-alkylated sulfonamides constitute an important class of compounds because the sulfonamide moiety is found in a large number of agrochemicals and pharmaceuticals.[5] In addition, sulfonamides have also been used as protecting groups, which can be readily removed.[6] Thus, *N*-alkylated sulfonamides are easily converted to give primary amines. Unfortunately, the preparation of alkylated sulfonamides is carried out mainly *via* condensation of amines with sulfonyl chlorides.[7] Although this protocol is efficient and various *N*-alkylated products can be obtained, the usage of sulfonyl chlorides results in storage and handling problems.[8] Other known methods, such as reductive amination of sulfonamides and nucleophilic substitutions with alkyl halides have also been employed.[9] But all these methods suffer from the generation of unwanted inorganic salts.

Recently, significant attention has been focused on the *N*-alkylation of amines with alcohols as the alkylation reagents. Clearly, alcohols are readily available, non-expensive, and non-toxic. However, the direct use of alcohols as alkylation reagents is limited due to the poor electrophilicity of most alcohols. Based on the hydrogen borrowing methodology,[10] this drawback can be overcome due to the *in situ* generation of



Scheme 1. Transfer-hydrogenative alkylation of amines with alcohols.

a much more reactive aldehyde (Scheme 1, a). Until today, many transition metal catalysts, based on ruthenium,[11] rhodium,[12] platinum[13], and iridium[14] complexes have been employed for alkylations of amines with alcohols since the first homogeneous catalysts for such transformations were introduced by Grigg[15] and Watanabe.[16] Interestingly, *N*-alkylations of sulfonamides and carboxamides have also been realized successfully *via* a carbocation mechanism using benzylic and allylic alcohols as *N*-alkylating reagents.[17] In addition, only two reports on the catalytic *N*-alkylation of sulfonamides with alcohols in the presence of ruthenium catalysts are known till now.[18] Obviously, the use of such noble metal catalysts is limited due to their high price and the indispensable need of stabilizing ligands.[19] Thus, it is of significant importance to find more economic catalyst systems for transfer hydrogenative alkylations. In this respect copper is an interesting option, which has been employed as a heterogeneous catalyst using alcohols as alkylating reagent.[20]

Recently, we demonstrated for the first time that the alkylation of sulfonamides with alcohol proceeds in the presence of copper acetate *via* hydrogen borrowing methodology.[11a] Herein, we report a full account of this study. The coupling reaction of various sulfonamides and alcohols takes place using various copper catalysts. Detailed studies of the mechanism are also presented.

Results and Discussion

Initially, the reaction of *p*-toluenesulfonamide with benzyl alcohol was studied as model reaction to investigate the activity of different copper catalysts. In general, the amination reaction was carried out under base-free condition at 150 °C for 12 h in the presence of 1 mol% copper salt. In order to promote the formation of the desired product, an excess amount of benzyl alcohol with respect to amine was used (4:1). As shown in Table 1 all copper salts tested showed some activity for the conversion of *p*-toluenesulfonamide. For example, 20–30% conversion was obtained when CuCl, $CuCl_2$, CuBr, $CuCO_3{\cdot}Cu(OH)_2$ or $CuBr_2$ were used as catalysts (Table 1, entries 1–5). Much higher conversion, that is, ~50%, was observed if $CuSO_4$, $Cu(NO_3)_2$ or $Cu(OAc)_2$ were applied (Table 1, entries 6–8). Unfortunately, large amounts of side-products such as dibenzyl ether and benzyl benzoate derived from benzyl alcohol were observed (Table 1, entries 6 and 7). Clearly, these side-products cause severe problems in product purification and benzyl alcohol recycling. Notably, the side-reactions from benzyl alcohol were less pronounced when $Cu(OAc)_2$ was employed as catalyst (Table 1, entry 8). Therefore, $Cu(OAc)_2$ was used for the further optimization of the reaction conditions.

Table 1. *N*-Alkylation of *p*-toluenesulfonamide with benzyl alcohol using different copper catalysts.[a]

Entry	Catalyst	Conv. [%][b]	Sel. [%][c]	**3:4:5:6:7**[d]
1	CuCl	27	56	3:45:38:6:8
2	$CuCl_2$	27	85	5:33:45:6:11
3	CuBr	21	24	1:68:22:5:4
4	$CuCO_3{\cdot}Cu(OH)_2$	21	33	2:66:25:5:2
5	$CuBr_2$	30	63	4:37:47:4 :12
6	$CuSO_4$	46	93	3:20:49:7 :21
7	$Cu(NO_3)_2$	54	94	11:12:55:7:15
8	$Cu(OAc)_2$	44	68	8:63:21:6:2

[a] *Reaction conditions:* 2.5 mmol (428 mg) *p*-toluenesulfonamide, 10 mmol (1080 mg) benzyl alcohol, 1 mol% copper, 150 °C, 12 h, air, 40-mL sealed pressure tube.

[b] The conversion was directly measured from the peak area of GC-MS.

[c] The selectivity was measured from the peak area of GC-MS. Beside *N*-benzyl-*p*-toluenesulfonamide **1**, the only by-product from *p*-toluenesulfonamide was *N*-benzylidene-*p*-toluenesulfonamide **2**.

[d] The distribution of products from benzyl alcohol. The ratio was obtained from the peak area of GC-MS. **3** = benzaldehyde; **4** = benzyl alcohol; **5** = dibenzyl ether; **6** = benzyl benzoate; **7** = unknown.

Recently, it has been shown that the presence of base promotes the transfer hydrogenative coupling of sulfonamides with alcohols.[18] Thus, different bases were used as additive to improve the conversion of the copper-catalyzed alkylation reaction (Table 2). As a typical base in hydrogen borrowing reactions,[21] KO-*t*-Bu was tested first (Table 2, entry 1). Similar activity was obtained in comparison with the base-free system with increased selectivity to *N*-benzyl-*p*-toluene sulfonamide. Clearly, this result suggests that the addition of base promotes the hydrogenation of the imine intermediate.

If common strong bases such as KOH and NaOH were used as co-catalyst, the reaction is facilitated. The conversions were 54% and 67% with 88% and 95% selectivity, respectively (Table 2, entries 2 and 3). To our delight, almost 100% conversion and >90% selectivity are achieved in the presence of K_2CO_3 or

Table 2. $Cu(OAc)_2$/base-catalyzed alkylation of *p*-toluenesulfonamide with benzyl alcohol.[a]

Entry	Cu catalyst	Conv. [%]	Sel. [%]	**3:4:5**
1	KO-*t*-Bu	39	84	9:86:4
2	NaOH	54	88	11:83:6
3	KOH	67	95	10:84:6
4	Na_2CO_3	>99	90	11:85:5
5	K_2CO_3	>93	99	12:84:4
6	$K_3PO_4 \cdot 3H_2O$	46	58	5:89:6
7[b]	K_2CO_3	>99	>99	11:89:0

[a] *Reaction conditions:* see Table 1. 10 mol% base were added in each case.
[b] 20 mol% K_2CO_3 were used.

Na_2CO_3 (Table 2, entries 4 and 5). Furthermore, only a moderate result was obtained when K_3PO_4 was applied (Table 2, entry 6). Finally, it was found that *p*-toluenesulfonamide was quantitatively converted into the alkylated product with the addition of 20 mol% K_2CO_3 (Table 2, entry 7). It is worth mentioning that the side-products originated from benzyl alcohol are effectively inhibited when a catalytic amount of base was added in all cases. Normally, the by-products are benzaldehyde and dibenzyl ether. In the presence of 20 mol% K_2CO_3, the only detectable by-product on GC-MS analysis was benzaldehyde. Quantitative analysis revealed selectivities to *N*-benzyl *p*-toluenesulfonamide and benzaldehyde of 94% and 6%, respectively, based on the consumed benzyl alcohol.

Next, the catalyst activities of different copper salts in the presence of K_2CO_3 were tested as shown in Table 3.

Under these conditions copper salts, that is, CuCl and CuBr, exhibited low activity. The conversion of *p*-toluenesulfonamide was ~30% and large amounts of the corresponding imine intermediate remained at the end (Table 3, entries 1 and 2). When using $CuSO_4$ as catalyst, the conversion of *p*-toluenesulfonamide was quite low but large amounts of undesirable ether and ester derived from benzyl alcohol were produced (Table 3, entry 3). Here, the selectivity based on benzyl alcohol was lower than 50%. Similar activity as $Cu(OAc)_2$ was exhibited by using $CuCl_2$ and $CuBr_2$ as catalysts (Table 3, entries 4 and 5). With these catalysts conversion of *p*-toluenesulfonamide and selectivity towards *N*-benzyl-*p*-toluenesulfonamide were around 90% and >90% selectivity was also achieved based on consumed benzyl alcohol. However, still ~5% of the imine intermediate remained. Thus, the optimal choice for the alkylation of sulfonamides is the $Cu(OAc)_2/K_2CO_3$ system.

Table 3. Alkylation of *p*-toluenesulfonamide in the presence of copper-K_2CO_3 catalysts.[a]

Entry	Catalyst	Conv. [%]	Sel. [%]
1	CuCl	31	87
2	CuBr	36	25
3	$CuSO_4$	21	86
4	$CuCl_2$	89	93
5	$CuBr_2$	90	95
6	$Cu(OAc)_2$	93	>99

[a] *Reaction conditions:* see Table 1. 10 mol% K_2CO_3.

Typically, hydrogen borrowing reactions are performed under an inert atmosphere. Hence, the best reaction was performed under argon to check its effect on the catalytic activity, too. However, only moderate conversion was detected (Table 4, entry 1). Apparently, the presence of a catalytic amount of air/oxygen promotes the reaction. In the presence of 7 mol% oxygen, the conversion of *p*-toluenesulfonamide was increased from 48% to 84% (Table 4, entry 2). More than 90% conversion and >99% selectivity was obtained with 14 mol% oxygen. However, if the amount of oxygen was further increased to 70 mol%, the conversion of *p*-toluenesulfonamide and the selectivity to *N*-benzyl-*p*-toluenesulfonamide dropped to 82% and 36%, respectively (Table 4, entries 4 and 5). It is likely that the presence of too much oxygen inhibits the transfer hydrogenation step.

In order to elucidate the effect of oxygen on the catalyst systems, *in situ* HR-MS analysis of the model reaction in the presence of $Cu(OAc)_2/K_2CO_3$/air and $Cu(OAc)_2/K_2CO_3$/Ar was performed. To our delight, HR-MS analysis revealed that compound **8** was formed in the $Cu(OAc)_2/K_2CO_3$/air system compared with the $Cu(OAc)_2/K_2CO_3$/Ar (Scheme 2).

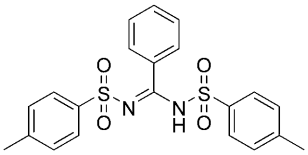
Apparently, this compound is formed *via* oxidation of benzyl alcohol and condensation with *p*-toluenesulfonamide. It is likely that the formation of this compound is the reason for the remarkably higher catalytic activity under air.

Therefore, **8** was separately synthesized and added to the reaction of *p*-toluenesulfonamide and benzyl

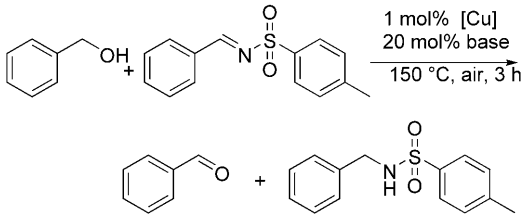
Table 4. Alkylation of *p*-toluenesulfonamide in the presence of air/oxygen.[a]

Entry	Atmosphere/O_2:*p*-toluenesulfonamide[b]	Conv. [%]	Sel. [%]
1	Ar/0%	48	>99
2	Air/7%	84	95
3	Air/14%	93	>99
4	O_2/35%	81	82
5	O_2/70%	82	36

[a] *Reaction conditions:* see Table 1.
[b] By tuning the volume of the reaction tube and reaction environment (air or pure oxygen), reaction systems with different oxygen:*p*-toluenesulfonamide mol ratio were obtained. The mol ratio was estimated according to $PV = nRT$.



Scheme 2. Compound **8** observed in $Cu(OAc)_2/K_2CO_3$/air system by HR-MS.

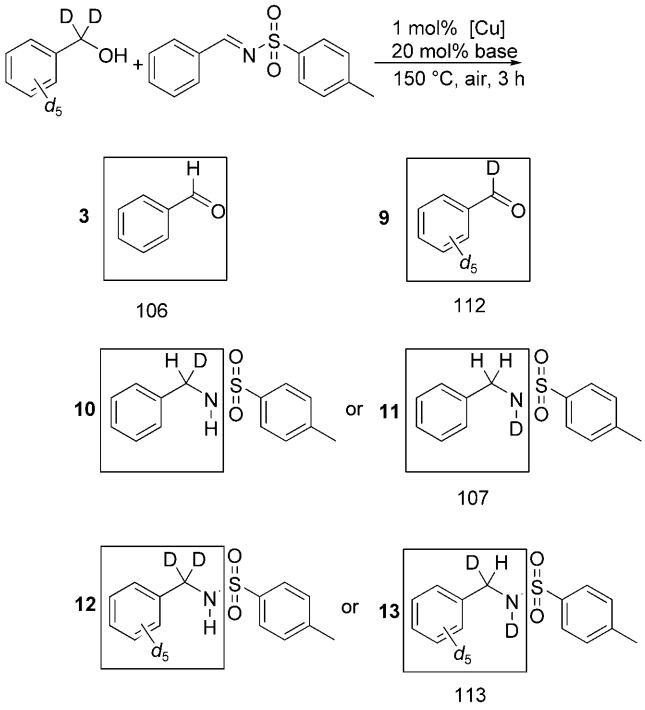


Scheme 3. Reaction of *N*-benzylidenetoluenesulfonamide with benzyl alcohol.

Table 5. Reaction of *p*-toluenesulfonamide and benzyl alcohol in the presence of **8.**[a]

Time [h]	0	3	6	12
without (**1**)[b]	0	26	48	93
(**1**)[b]	0	49	76	99

[a] *Reaction conditions:* see Table 1.
[b] Conversion of *p*-toluenesulfonamide. The data were obtained by GC-MS.



Scheme 4. Reaction of *N*-benzylidene-*p*-toluenesulfonamide with benzyl alcohol-d_7.

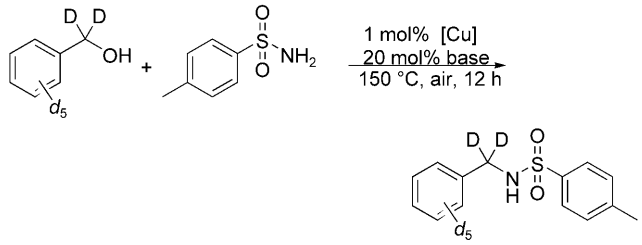
alcohol in the presence of 10 mol% K_2CO_3. Indeed, nearly full conversion and excellent selectivity were obtained with the addition of 2 mol% of compound **8**, while 93% conversion was attained in the absence of **8** (Table 5). These results give strong evidence that the bissulfonylated amine **8** acts as a stabilizing ligand to the copper catalyst in the *N*-alkylation reaction of *p*-toluenesulfonamide. A low amount of oxygen disfavours the formation of such ligands, at the same time, the transfer hydrogenation step is restrained with an excess of oxygen resulting in large amounts of imine. Thus, 14 mol% of oxygen give the best results for the overall reaction.

Further GC-MS investigations of the model reaction revealed that *N*-benzylidene-*p*-toluenesulfonamide is formed as the major product at the initial stage of the reaction. Subsequent hydrogenation led to >99% *N*-benzyl-*p*-toluenesulfonamide in the end. Simultaneously, benzaldehyde is also detected at the early stage of the reaction. These results indicate that *N*-benzylidene-*p*-toluenesulfonamide is the main intermediate, which is formed *via* condensation of benzaldehyde and sulfonamide. The following hydrogenation is the rate-determining step in this process.

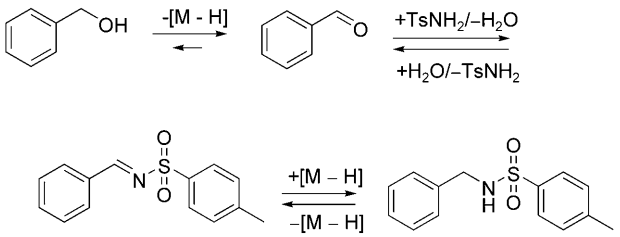
To confirm that $Cu(OAc)_2/K_2CO_3$ is active in transfer hydrogenations a competition experiment between *N*-benzylidene-*p*-toluenesulfonamide and benzyl alcohol was performed (Scheme 3). As expected, *N*-benzylidenetoluenesulfonamide was fully converted into *N*-benzyl-*p*-toluenesulfonamide in the end with concomitant formation of benzaldehyde.

Isotopic tracing is an ideal method for mechanistic investigations. Therefore, the reaction of *N*-benzylidene-*p*-toluenesulfonamide with benzyl alcohol-d_7 was further studied (Scheme 4). GC-MS analysis of this experiment showed the formation of the expected *N*-benzyl-*p*-toluenesulfonamide-d_1 and also benzaldehyde-d_6, which supports the proposed hydrogen borrowing mechanism. Meanwhile, compounds **3** and **11** were also produced, which suggests that the reaction is reversible. Noteworthy, based on ^{1}H NMR measurements, the ratio of products **10** and **11** is 1.38:1, which is consistent with the result found in the GC-MS analysis, that is, 1.38:1.

Then, the reaction of *p*-toluenesulfonamide and benzyl alcohol-d_7 was conducted to clarify the position of deuterium in compounds **10/11** and **12/13** (Scheme 5). This reaction provided evidence of the hydride transfer. According to ^{1}H NMR and GC-MS analyses, the major product (>95%) was *N*-benzyl-*p*-toluenesulfonamide-d_7. There were no deuterated NH or OH groups observed in the final product. Moreover, deuterium was not incorporated into the ring of



Scheme 5. Alkylation of *p*-toluenesulfonamide with benzyl alcohol-d_7.

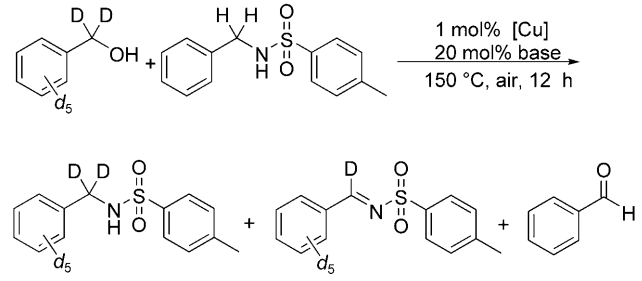


Scheme 7. The reversible pathway of the reaction between benzyl alcohol and *N*-benzyl-*p*-toluenesulfonamide.

p-toluenesulfonamide. Clearly, the deuterium atoms eliminated from benzyl alcohol were added to the *in situ* generated methylene group rather than other positions. The results outlined above provide experimental evidence that the reaction is micro-reversible. This is also in good accordance with the reported results.[18a,23]

However, the reversibility of the whole reaction route is unclear in spite of the hydrogen borrowing mechanism. Hence, we reacted benzyl alcohol-d_7, *N*-benzyl-*p*-toluenesulfonamide and $Cu(OAc)_2/K_2CO_3$ together. Based on the GC-MS analysis, *N*-benzyl-*p*-toluenesulfonamide-d_7 and *N*-benzylidene-*p*-toluenesulfonamide-d_6 were detected (Scheme 6). At the same time, a small amount of non-deuterated benzaldehyde was formed. However, no benzyl alcohol ($C_6H_5CH_2OH$) was observed. This means that the imine formed from the condensation of the aldehyde and amine is more easily hydrogenated to the corresponding secondary amine than the aldehyde, which has been proven by a DFT study.[22] These results indicate also the reversibility of the whole reaction.

On the basis of the studies above, the alkylation of *p*-toluenesulfonamide and benzyl alcohol proceeds *via* a domino dehydrogenation-condensation-hydrogenation sequence. First, the hydride is removed temporarily from alcohol and a more reactive carbonyl compound is produced. Then, nucleophilic condensation takes place between the corresponding aldehyde and the sulfonamide, generating the imine intermediate. Finally, this imine is reduced to form the desired product (Scheme 7). The presence of excess benzyl alcohol is important in order to achieve high yield of the alkylated sulfonamide due to the reversibility of the reaction.



Scheme 6. Reaction of benzyl alcohol-d_7 with *N*-benzyl-*p*-toluenesulfonamide.

Isotope competitive reactions are a convenient method to determine whether the hydride elimination is the rate-determining step.[12] In the current work, the competitive reaction was carried out with *p*-toluenesulfonamide and deuterated benzyl alcohol-d_7/benzyl alcohol. According to GC-MS analysis, the reaction took place with high conversion (>99%) and selectivity (>99%). Due to the micro-reversibility of the process four different products were obtained. As it was shown in Scheme 8, **1** and **10** were derived from benzyl alcohol and **12** and **14** were products from deuterated benzyl alcohol. After ion selective mass spectra calibration, their characteristic m/z^+ numbers are 106, 107, 112 and 113, respectively. Based on the corresponding peak area, the mol ratio of compounds **1**, **10**, **12** and **14** was as follows: Peak area$_{106:107:112:113}$ = 7.409(0.503):3.695(0.236):2.377(0.027):1.

The proton ratio of the methyl group to the methylene group and aromatic group to methylene group were calibrated from the ratio of compounds **1**, **10**, **12** and **14**.

$$\text{Proton}_{\text{-CH}_3}/\text{Proton}_{\text{-CH}_2\text{-}} = [(\mathbf{1})+(\mathbf{10})+(\mathbf{14})+(\mathbf{12})]\times 3/[(\mathbf{1})\times 2+(\mathbf{10})\times 1+(\mathbf{14})\times 1] = 2.080\ (0.016):1$$

$$\text{Proton}_{\text{aromatic}}/\text{Proton}_{\text{-CH}_2\text{-}} = [(\mathbf{1})\times 9+(\mathbf{10})\times 9+(\mathbf{14})\times 4+(\mathbf{12})\times 4]/[(\mathbf{1})\times 2+(\mathbf{10})\times 1+(\mathbf{14})\times 1] = 5.956\ (0.449):1$$

To our delight, these ratios confirm exactly the data from ^{1}H NMR measurements:

$$\text{Proton}_{\text{-CH}_3}/\text{Proton}_{\text{-CH}_2\text{-}} = 2.094(0.033):1$$

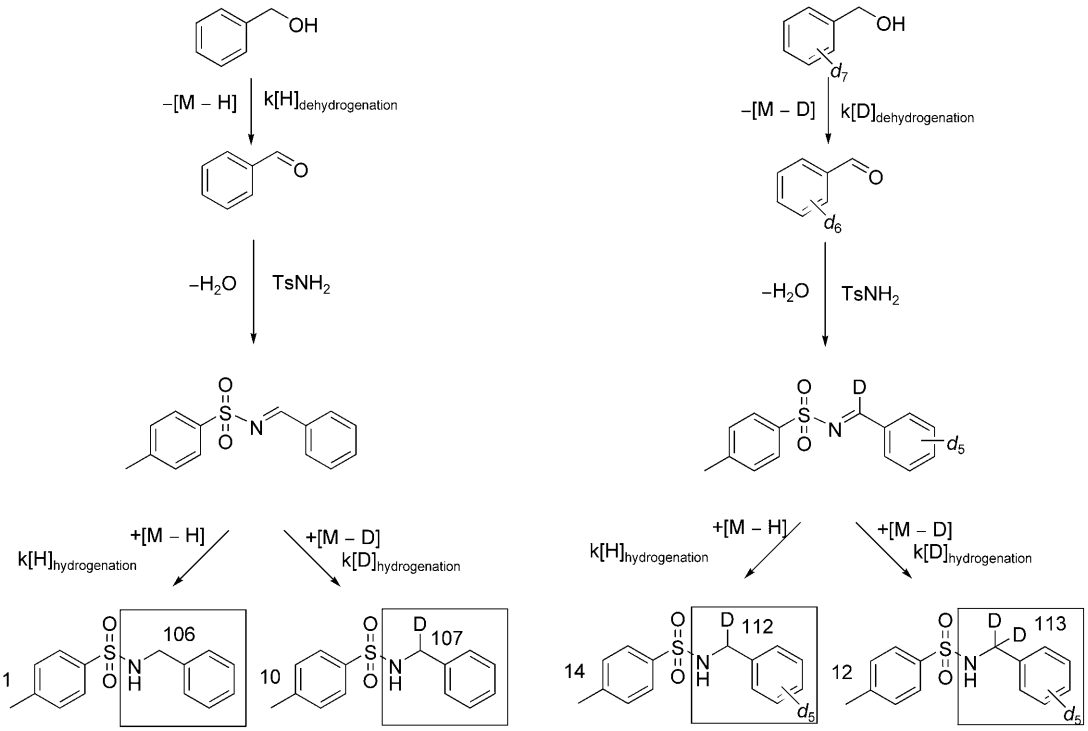
$$\text{Proton}_{\text{aromatic}}/\text{Proton}_{\text{-CH}_2\text{-}} = 5.433(0.007):1$$

Thus, the ratio of **1**, **10**, **12**, and **14** is reliable for a kinetic study. The numbers of KIE_1 and KIE_2 were calibrated as follows:

$$KIE_1 = k[H]/k[D]_{\text{dehydrogenation}} = \text{product}(\mathbf{1})+\text{product}(\mathbf{10})]/[\text{product}(\mathbf{14})+\text{product}(\mathbf{12})] = 3.287\ (0.192):1$$

$$KIE_2 = k[H]/k[D]_{\text{hydrogenation}} = [\text{product}(\mathbf{1})/\text{product}(\mathbf{10})]/(k[H]/k[D]_{\text{dehydrogenation}}) = 0.611\ (0.033):1$$

The observation of a primary kinetic isotope effect (KIE_1) of 3.287 (0.192) in the *N*-alkylating reaction of *p*-toluene sulfonamide provided strong evidence for



Scheme 8. An illustration of the kinetic studies by isotope competitive reactions.

C–H cleavage as rate-determining step. A similar result has been reported by DFT studies and transfer hydrogenation of imines with the Ru-based Shvo catalyst,[23] but far smaller compared to hydrogen atom abstraction by other metal-oxo-complexes.[23] This result is also in consistent with the GC-MS analysis. Benzaldehyde is formed at the early stage of the reaction but its concentration remains constant during the reaction. The secondary kinetic isotope effect of 0.611 (0.033) is obtained for the hydrogenation step.

To study the interaction of reactants and catalyst UV-visible measurements were performed. The spectra of different mixtures were given in Figure 1. Clearly, there was no absorbance in the UV-visible area for benzyl alcohol, *p*-toluenesulfonamide, ligand **8** or their mixtures (Figure 1, I–III; 400–1000 nm). However, strong absorbing peaks were observed at 698 nm after $Cu(OAc)_2$ was added (Figure 1, IV–VI). The absorbing strength decreased in the presence of *p*-toluenesulfonamide or ligand in comparison with benzyl alcohol. This indicates that the interaction between Cu^{2+} and *p*-toluenesulfonamide or ligand **8** occurred although no new adsorbing peak is observed. After the addition of potassium carbonate, all the adsorbing peaks disappeared. Precipitation of copper ions might be the reason for this but it is still not clear at this stage.

Finally, based on the optimized reaction conditions, the generality of the $Cu(OAc)_2/K_2CO_3$ catalyst for the alkylation of sulfonamides with alcohols was tested. As shown in Table 6, benzyl alcohols with different functional groups are well tolerated. More specifically, benzyl alcohols substituted with electron-donating

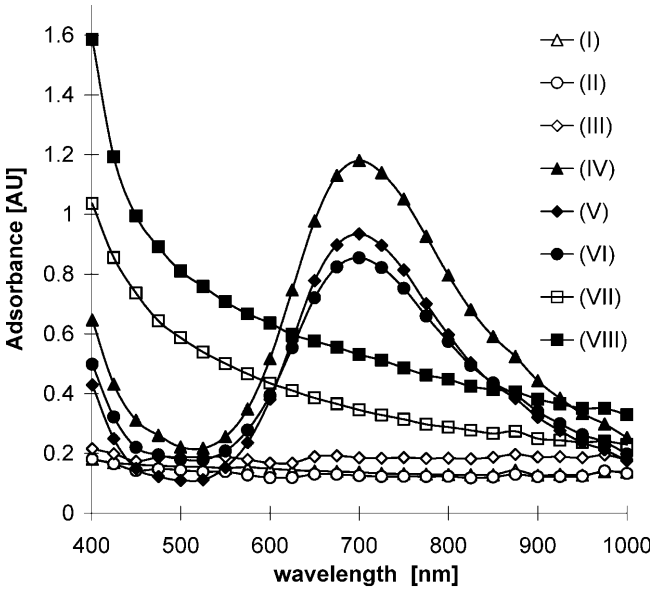
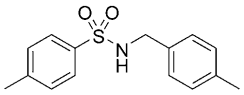
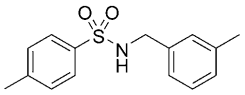
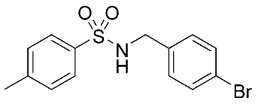
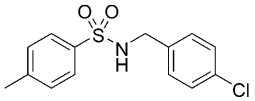
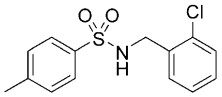
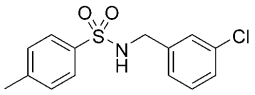
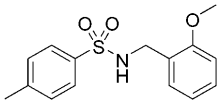
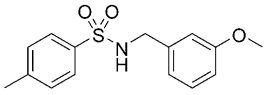
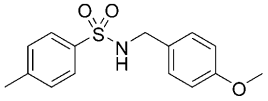
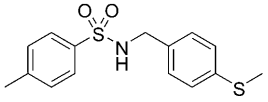
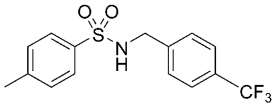
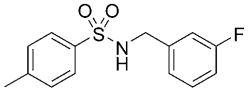
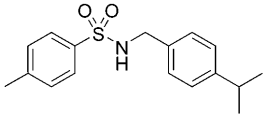
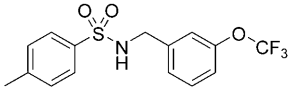
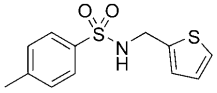
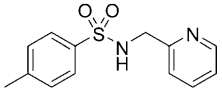
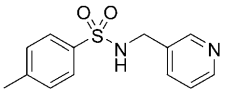
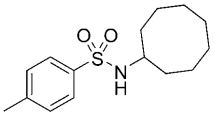
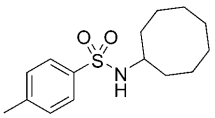
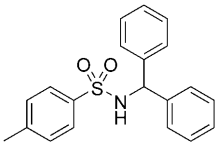
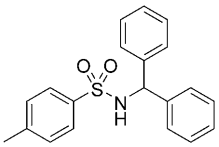
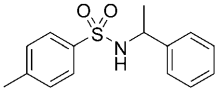


Figure 1. UV-visible spectra of (I) $PhCH_2OH$, (II) $PhCH_2OH + TsNH_2$, (III) $PhCH_2OH + TsNH_2 +$ ligand **8**, (IV) $PhCH_2OH + Cu(OAc)_2$, (V) $PhCH_2OH + TsNH_2 + Cu(OAc)_2$, (VI) $PhCH_2OH + TsNH_2 +$ ligand **8** $+ Cu(OAc)_2$, (VII) $PhCH_2OH + TsNH_2 + Cu(OAc)_2 + K_2CO_3$ and (VIII) $PhCH_2OH + TsNH_2 +$ ligand **8** $+ Cu(OAc)_2 + K_2CO_3$.

Table 6. Catalytic *N*-alkylation of *p*-toluenesulfonamide with different benzylic alcohols.[a]

Entry	Product	Yield [%][b]
1		94[c]
2		93
3		92[c]
4		91[c]
5		89[c]
6		94
7		90
8		91
9		93
10		92
11		89
12		92
13		95
14		89
15		93
16[c]		93[d]
17[c]		87[d]
18		0
19[e]		71
20		0
21[f]		99
22[f]		99

[a] *Reaction conditions:* see Table 1. 20 mol% K_2CO_3.
[b] Isolated yield.
[c] 30 mo% K_2CO_3.
[d] Selectivity based on GC-MS. The by-product is imine. Conversion is 100%.
[e] 1 mol% $Cu(OTf)_2$.
[f] 1 mol% $Cu(OAc)_2$.

as well as electron-withdrawing groups in *ortho*-, *meta*-and *para*-position of the aryl ring afforded the expected products in excellent yields. All additional functional groups, that is, F, Cl, Br, CH_3, CF_3, OCH_3, SCH_3, $(CH_3)_2CH$ and OCF_3, were stable (Table 6, entries 1–14). In comparison with the *ortho*-, *meta*- substituted groups, the *para*-position of the aromatic ring is less active. However, with an increasing amount of base, excellent yields are also achieved.

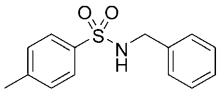
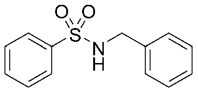
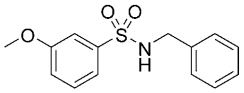
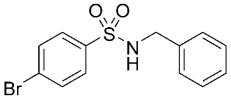
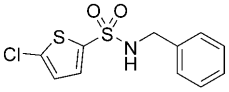
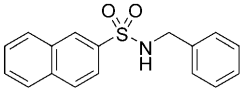
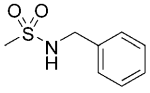
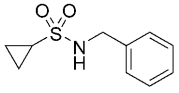
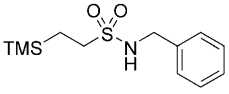
Interestingly, not only simple benzyl alcohols gave the desired products in excellent yield, but also thiophen-2-ol led to the corresponding sulfonamide in 93% yield (Table 6, entry 15). In case of pyridine derivatives it was difficult to isolate the imine from the sulfonamide although high conversion and selectivity are observed (Table 6, entries 16 and 17). Unfortunately, primary (non-benzylic) aliphatic or secondary alcohols did not react under these conditions (Table 6, entries 18 and 20). On the other hand, the coupling of aliphatic alcohols and secondary benzylic alcohols with *p*-toluenesulfonamide proceeded directly using

$Cu(OTf)_2$ or $Cu(OAc)_2$ as catalyst (Table 6, entries 19, 21 and 22). In this way, it should pass through a carbocation mechanism.[17]

Furthermore, reactions of benzyl alcohol with various sulfonamides bearing different functional groups were tested. As shown in Table 7, substituted groups on the aromatic ring had no negative influence on the alkylation reactions and the corresponding secondary sulfonamides were produced in 91–97% isolated yields (Table 7, entries 1–4). By comparing the *N*-alkylation reactions of *p*-toluenesulfonamide, 3-methoxybenzenesulfonamide and 4-bromobenzenesulfonamide, it is clear that electron-rich as well as electron-poor groups were well tolerated. For the alkylation of other aromatic sulfonamides such as 5-chlorothiophene-2-sulfonamide and naphthalene-2-sulfonamide, 89% and 91% isolated yields were also obtained (Table 7, entries 5 and 6).

The developed catalyst system works also with aliphatic sulfonamides. The reaction of methanesulfonamide with benzyl alcohol provided full conversion and >98% selectivity (Table 7, entry 7). The isolated yield of *N*-benzylmethanesulfonamide was 95%. There was no decomposition of starting material observed with cyclopropanesulfonamide or 2-(trimethylsilyl)ethanesulfonamide as starting material. Here, the isolated yields were 97% and 94%, respectively (Table 7, entries 8 and 9).

Table 7. Alkylation of different sulfonamides with benzyl alcohol.[a]

Entry	Product	Yield [%][b]
1		95
2		97
3		91
4		96
5		89[c]
6		91
7		95
8		97
9		94

[a] *Reaction conditions:* see Table 1. 20 mol% K_2CO_3.
[b] Isolated yield.
[c] 40 mol% K_2CO_3.

Conclusions

In summary, we have reported the *N*-alkylation of sulfonamide by a practical copper catalyst *via* a hydrogen borrowing mechanism. The simple $Cu(OAc)_2$/K_2CO_3 system allows for a benign alkylation of sulfonamides with alcohols in good to excellent yields. Mechanistic studies proved the transfer hydrogenation mechanism and C–H cleavage as the rate-determining step.

Experimental Section

General Procedure for Alkylation Reactions

All reactions were carried out in pressure tubes (~38 mL, Aldrich). Typically, 2.5 mmol *p*-toluenesulfonamide (428 mg), 10.0 mmol benzyl alcohol (1080 mg), 1 mol% $Cu(OAc)_2$ (4.6 mg) catalyst and 0.5 mmol K_2CO_3 (69.0 mg) were added, respectively. Then, the pressure tube was sealed and the reaction mixture was stirred at 150 °C (oil bath temperature) for 12 h. Then it was cooled to room temperature. ~20 mL acetone were added to dissolve the reaction mixture which was filtered through celite. The acetone and benzyl alcohol were removed under vacuum and a yellow solid was obtained. It was further washed with diethyl ether/hexane to remove benzyl alcohol residue and soluble impurities. After it was further dried under reduced pressure, a white solid were obtained; yield: 625 mg (96%). All the products were analyzed by ^1H NMR, ^{13}C NMR and MS.

General Procedure for the Reaction of Benzyl Alcohol-d_7 and *p*-Toluenesulfonamide

0.5 mmol (85.6 mg) *p*-toluenesulfonamide, 2.0 mmol (230.0 mg) benzyl alcohol-d_7, 0.91 mg $Cu(OAc)_2$ (1 mol% Cu) catalyst and 0.1 mmol (13.9 mg) K_2CO_3 were added into a 5-mL reaction tube, respectively. Then, it was sealed and reacted at 150 °C (oil bath temperature) for 12 h. After it had been cooled to room temperature, the reaction mixture was dissolved in acetone and analyzed by GC-MS. Then, it was filtrated through celite. The acetone and benzyl alcohol-d_7 were removed under vacuum and a yellow solid was obtained. It was further washed with diethyl ether/hexane to remove benzyl alcohol-d_7 residues and soluble impurities. After it was further dried under reduced pressure tio afford a white solid; yield: ~85 mg.

General Procedure for the Reaction of Benzyl Alcohol or Benzyl Alcohol-d_7 and *(E)*-*N*-Benzylidene-4-methylbenzenesulfonamide

0.5 mmol (129.5 mg) *(E)*-*N*-benzylidene-4-methylbenzenesulfonamide, 2.0 mmol (230.0 mg) benzyl alcohol, 0.91 mg $Cu(OAc)_2$ (1 mol% Cu) catalyst and 0.1 mmol (13.9 mg) K_2CO_3 were added into a 5-mL reaction tube, respectively. Then, it was sealed and reacted at 150 °C (oil bath temperature) for 3 h. After it had been cooled to room temperature, the reaction mixture was dissolved in acetone and analyzed by GC-MS. Then, it was filtered through celite. The acetone and benzyl alcohol-d_7 were removed by evaporation. The mixture was further washed with diethyl ether/hexane and a white solid were obtained after drying under reduced pressure; yield: 130 mg.

General Procedure for High-Resolution Mass Spectrometry (HR-MS) Measurement

2 reactions were done in parallel (one under argon flow and the other one under air). 5.0 mmol *p*-toluenesulfonamide (855 mg), 20.0 mmol benzyl alcohol (2160 mg), and 1 mol% Cu [$Cu(OAc)_2$ (9.1 mg)] were added into a 50-mL reaction tube, respectively. Then, the reaction mixture was stirred at 150 °C. After it was reacted for 3 h, a ~100 mg sample was dropped into ~1 mL methanol for HR-MS analysis. Then, 1 mmol (138.0 mg) K_2CO_3 was added to the reaction mixture and analyzed again after 15 min. HR-MS experiments were performed with an Agilent Series 1200 HPLC system and an Agilent 1969 A time-of-flight mass spectrometer (Waldbronn, Germany) The TOF-MS conditions in negative ionization mode with a dual sprayer API-ES source 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 10% H_2O (0.1% HCOOH): 90% MeOH.

General Procedure for the Reaction of Benzyl Alcohol-d_7 and *N*-Benzyl-*p*-toluenesulfonamide

0.2 mmol (52.4 mg) *N*-benzyl-*p*-toluenesulfonamide, 2.0 mmol (230.0 mg) benzyl alcohol-d_7, 0.025 mmol (4.6 mg) $Cu(OAc)_2$ and 0.5 mmol (69.0 mg) K_2CO_3 were added into a 5-mL reaction tube respectively. Then, it was sealed and reacted at 150 °C (oil bath temperature) for 12 h. After it was cooled to room temperature, the reaction mixture was dissolved in acetone and analyzed by GC-MS.

General Procedure for Isotope Effect Studies (3 Reactions were run in Parallel)

0.5 mmol (85.6 mg) *p*-toluenesulfonamide, 2.0 mmol benzyl alcohol (230.0 mg), 20 mol% K_2CO_3 (13.6 mg), 1 mol% $Cu(OAc)_2$ (0.9 mg) were successively added into a 5-mL reaction tube. Then the tube was sealed and stirred at 150 °C (oil bath temperature) for 12 h. After it had been cooled to room temperature, ~5 mL acetone were added to dissolve the mixture. The reaction mixture was filtrated through celite. Acetone and benzyl alcohol were removed by evaporation under reduced pressure and the mixture was washed with hexane to remove the impurities. All samples were analyzed by GC-MS and ^{1}H NMR.

General Procedure for the Synthesis of Compound 8

a): $TsNH_2$ (3.42 g, 0.02 mol) and K_2CO_3 (6.9 g, 0.05 mol) were dissolved in 200 mL THF and stirred for 20 min at room temperature, then cooled to 0 °C with an ice-bath. Benzoyl chloride (36 g, 0.026 mol) in 100 mL THF was dropped into the reaction mixture. After stirring for 48 h, a white precipitate formed, and the reaction mixture was then refluxed for 12 h. The reaction was quenched by 50% H_2SO_4 and was extracted with 100 mL ethyl acetate twice. After recrystallization from diethyl ether and drying under vacuum, white crystals of *N*-tosylbenzamide were obtained; yield: 90%.

b): A mixture of *N*-tosylbenzamide (2.40 g, 8.7 mmol) and PCl_5 (1.90 g, 8.8 mmol) was dissolved in benzene (30 mL) at room temperature, and stirred at this temperature for 0.5 h. Then the reaction mixture was refluxed overnight and traced by TLC. The solvent was removed under vacuum, and the crude product was recrystallized from diethyl ether to afford the *N*-sulfonylketimine as a white solid; yield: 65%.

c): To the suspension of dried sodium salt of 4-methylbenzenesulfonamide (0.97 g, 5 mmol) in benzene (30 mL), an equimolar amount of the *N*-sulfonylketimine (1.46 g, 5 mL) was added. Then the mixture was refluxed for 14 h and traced by TLC analysis. The product was purified by chromatography (Et_2O); yield: 70%.

General Procedure for UV-Visible Measurements

Eight samples including (I) benzyl alcohol, (II) benzyl alcohol/*p*-toluenesulfonamide, (III) benzyl alcohol/*p*-toluenesulfonamide/ligand **8**, (IV) benzyl alcohol/$Cu(OAc)_2$, (V) benzyl alcohol/*p*-toluenesulfonamide/$Cu(OAc)_2$, (VI) benzyl alcohol/*p*-toluenesulfonamide/ligand **8**/$Cu(OAc)_2$, (VII) benzyl alcohol/*p*-toluenesulfonamide/$Cu(OAc)_2$/K_2CO_3 and (VIII) benzyl alcohol/*p*-toluenesulfonamide/ligand **8**/$Cu(OAc)_2$/K_2CO_3 with the same composition as the real reaction system were prepared and measured with UV-visible spectroscopy (Agilent 8453). All the samples were prepared under ultrasonic conditions and allowed to settle overnight to get a limpid solution. Then the solution was measured directly at 25.0 °C.

Acknowledgements

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