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Triflic Acid Catalyzed Reductive Coupling Reactions of Carbonyl Compounds with O-, S-, and N-Nucleophiles

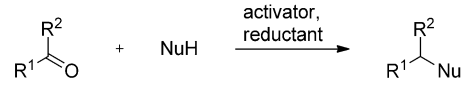
Beate A. Gellert, Nils Kahlcke, Markus Feurer, and Stefanie Roth*[a]

Abstract: Highly efficient metal-free reductive coupling reactions of aldehydes and ketones with a range of nucleophiles in the presence of triflic acid (1–5 mol%) as the catalyst are presented. The reactions can be performed at ambient temperature without exclusion of moisture or air. A range of symmetrical and unsymmetrical ethers were obtained by this method in high yields and short reaction times. For the first time, the influence of additional functionalization has been studied. Furthermore, the formation of thioethers from ketones (by addition of unmodified thiols) and of sulfonamides from either aldehydes or ketones has been achieved under catalytic conditions.

Keywords: Brønsted acids · reductive etherification · silanes · sulfonamides · thioethers

Introduction

The reduction of carbonyl compounds with organosilanes usually leads directly to the corresponding alcohols or silyl ethers.[1] However, the combination of reduction and subsequent coupling with a nucleophile allows for the synthesis of a variety of functionalized compounds directly from carbonyl compounds in a one-step procedure (Scheme 1).[2]



Scheme 1. General scheme for reductive couplings of carbonyl compounds with nucleophiles.

The most prominent example of direct carbonyl compound transformations of this kind is reductive etherification, but this has found only limited applications in, for example, the synthesis of natural products.[3]

This methodology circumvents major problems of classical etherification methods such as the Williamson ether synthesis (the formation of side products through elimination and high amounts of waste, for example). Furthermore, the introduction of a leaving group after the reduction step is rendered unnecessary. Additionally, the major byproducts of reductive etherifications with organosilanes are nontoxic and environmentally friendly disiloxanes or silanols.

[a] Dipl.-Chem. B. A. Gellert, Dipl.-Chem. N. Kahlcke, Dipl.-Chem. M. Feurer, Dr. S. Roth
Organisch-Chemisches Institut
Ruprecht-Karls-Universität Heidelberg
Im Neuenheimer Feld 270; 69120 Heidelberg (Germany)
Fax: (+49) 6221-544205
E-mail: stefanie.roth@oci.uni-heidelberg.de

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Most of the procedures developed for the reductive coupling of carbonyl compounds, dating back to the 1970s, furnish symmetrical ethers. Originally, Doyle and co-workers reported that reductive coupling requires large excesses of strong Brønsted acids such as trifluoroacetic acid.[4] In 1987 Olah reported on the first catalytic procedure to employ TMSOTf or TMSI as the catalyst.[5] Later reports showed that a wide range of metal salts—such as $BiBr_3$[5] or metal triflates[7]—were also able to activate silanes in a catalytic fashion.[8] Recently, Yadav and co-workers improved Olah's procedure by substitution of the catalyst by molecular iodine, which presumably forms the catalytically active species in situ.[9]

The synthesis of unsymmetrical ethers from carbonyl compounds and silyl ethers has also been achieved in the presence of a variety of Lewis acid catalysts.[10] However, the more direct approach for the synthesis of unsymmetrical ethers from carbonyl compounds and unprotected alcohols with the aid of catalytic methods has been only little investigated and has so far only been achieved by employment either of large amounts of $BiCl_3$[11] (>20 mol%) or of catalytic amounts of $FeCl_3$.[12] None of the described methods has included study of the impact of additional functionalization of the alcohol coupling partner[13] or attempts to introduce nucleophiles based on different heteroatoms. However, there have been a limited number of reports on the use of stoichiometric reagents for reductive amidation[14] or for thioether[15] formation.

It is noteworthy that the practicabilities of the described methods are often hampered by the requirement for anhydrous conditions, mainly due to the sensitivity of the catalytically active species (formed in situ) towards hydrolysis.

Here we wish to report on a general metal-free method for the direct reductive synthesis of symmetrical ethers, unsymmetrical ethers, thioethers and amides from carbonyl compounds through the use of organosilanes, each performed under one set of reaction conditions with triflic acid

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(1–5 mol%) as the catalyst and capable of being carried out in an open flask without any exclusion of moisture or air.

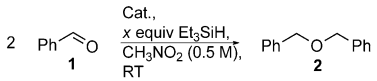
Results and Discussion

Initial experiments and optimization studies: We began our investigations with the development of a robust and moisture-tolerant catalytic system for the reductive homocoupling of carbonyl compounds. We chose benzaldehyde (**1**, Table 1) as substrate and triethylsilane as a reducing agent. Initially we studied the potential for application of cerium-based Lewis acids. We assumed that the unique oxophilicities and moisture stabilities of these lanthanide salts would make them suitable catalysts for the desired transformations.[16] To promote the reactivities of the cerium salts further, we chose nitromethane as solvent.[17]

Out of a range of different cerium(III) salts, cerium(III) perchlorate hexahydrate[18] (5 mol%) catalysed the reductive etherification of benzaldehyde (**1**) to dibenzyl ether (**2**) with triethylsilane in short reaction times and high yields (Table 1, entry 4). Interestingly, cerium(III) triflate[19] was less efficient (Table 1, entry 2), whereas $CeCl_3$[20] showed only very low activity (Table 1, entry 3). To our surprise, use of the same amounts of triflic acid or perchloric acid even shortened the reaction time (Table 1, entries 6, 7).[21,22] In acetonitrile in place of nitromethane, conversion was incomplete and reduction to the alcohol dominated over ether formation (Table 1, entry 12). The reactions also proceeded in halogenated solvents, albeit with lower selectivities than in nitromethane (Table 1, entry 13). As expected, there was hardly any conversion with phosphoric acid (Table 1, entry 5) and no conversion in the absence of catalyst (Table 1, entry 1).

Because of its easier and safer handling we chose triflic acid as catalyst and focused on further optimizations of the reaction conditions. Lowering the catalyst loading to 1 mol% had no effect on reaction time or yield (Table 1, entry 8). It was even possible to use as little as 0.1 mol% triflic acid to achieve complete consumption of benzaldehyde (**1**) in reasonable reaction times (Table 1, entry 9), but a further reduction to 0.01 mol% led to incomplete conversion even after a 36 h reaction time (Table 1, entry 10). The amount of triethylsilane could be decreased to 1.1 equiv with 1 mol% of triflic acid at an optimal concentration of 1 M (Table 1, entry 11).

Table 1. Optimization studies of reaction conditions.



	Catalyst ([mol%])	Equiv Et_3SiH	Reaction time	Yield [%][a]
1	no catalyst	2	16 h	–[b]
2	$Ce(OTf)_3$ (5)	2	90 min	99
3	$CeCl_3$ (10)	2	>24 h	–[c]
4	$Ce(ClO_4)_3 \cdot 6H_2O$ (5)	2	15 min	99
5	H_3PO_4 (5)	2	>72 h	3
6	$HClO_4$ (5)	2	2 min	99
7	TfOH (5)	2	2 min	99
8	TfOH (1)	2	3 min	99
9	TfOH (0.1)	2	3.5 h	99
10	TfOH (0.01)	2	>36 h	–[d]
11	TfOH (1)	1.1	>1 min	99[e]
12	TfOH (5)	2	3 h	17 (83)[f]
13	TfOH (5)	2	2 min	84 (16)[g]

[a] Isolated yields after column chromatography; yields in parentheses refer to benzyl alcohol. [b] No conversion according to ^1H NMR spectroscopy. [c] $CeCl_3$ was dried in vacuo at 140°C prior to use. The reaction was performed at 45°C and was incomplete. The yield was not determined. [d] Incomplete conversion; yield not determined. [e] The reaction was performed at a 1 M concentration. [f] The reaction was performed in acetonitrile and was stopped after 80% conversion; yields were determined by ^1H NMR spectroscopy. [g] The reaction was performed in dichloromethane; yields were determined by ^1H NMR spectroscopy.

Synthesis of symmetrical ethers: With the optimized set of conditions to hand, we next turned our attention to the substrate scope of the reaction.

Firstly, we studied different aldehydes (Table 2). Like benzaldehyde (**1**), electron-deficient aromatic aldehydes could be transformed into their corresponding ethers in high yields (Table 2, entries 1–3). We noted that along with nitro-substituted ethers the corresponding alcohols were formed as side products (Table 2, entry 1). Aliphatic aldehydes could be applied successfully, leading to the ethers **10** and **12** in high yields (Table 2, entries 4 and 5).[23]

We also investigated the reactivities of different ketones (Table 2, entries 6–12). Surprisingly, electron-rich aromatic ketones such as acetophenone (**13**) showed almost no reactivity under the optimized reaction conditions (Table 2, entry 6).[24] Electron-deficient aromatic ketones, however, could be successfully transformed into the corresponding ethers, accompanied by alcohol byproducts as previously observed for electron-deficient aromatic aldehydes (Table 2, entries 7 and 8). The diastereomeric ratios of the formed symmetrical ethers strongly depend on the positions of the substituents on their aromatic rings, with the highest ratio of 4:1 being obtained with an *ortho*-substituted acetophenone (Table 2, entry 8). A range of aliphatic ketones underwent selective reductive etherification to furnish the corresponding ethers in high yields without the formation of any side products (Table 2, entries 9–12). Interestingly, the reductive etherification of octan-3-one (**20**) led to the corresponding ether **21** with a high diastereoselectivity of 10:1. We assume that this might be due to a hydrophobic effect of the lipophilic starting material in nitromethane, leading to an increase in the steric bulk of the aliphatic side chains caused by back-folding.

Alcohols as nucleophiles: After having established a general procedure for the direct reductive synthesis of symmetrical ethers from carbonyl compounds, we turned our attention to the synthesis of unsymmetrical ethers from carbonyl compounds and alcohols.

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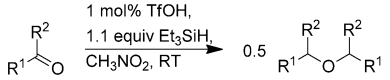
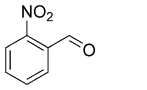
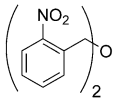
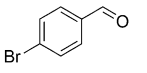
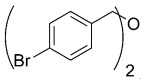
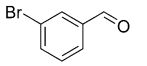
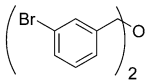
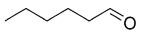
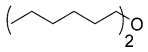
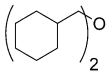
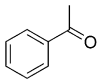
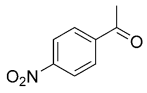
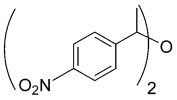
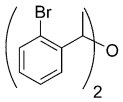
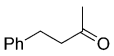
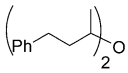
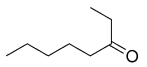
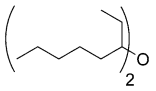
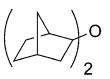
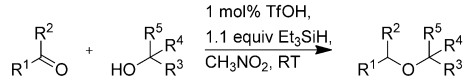
Table 2. Reductive etherification of aldehydes and ketones.

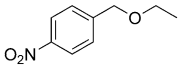
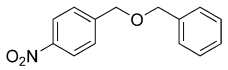
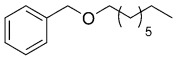
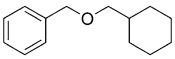
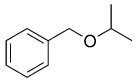
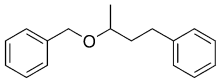
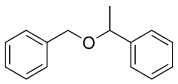
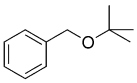
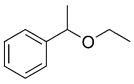
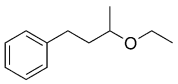
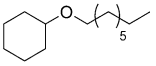
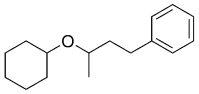


	Substrate		Product		Reaction time	Yield [%][a]
1		**3**		**4**	2 min	78 (22)
2		**5**		**6**	2 min	99
3		**7**		**8**	2 min	85
4		**9**		**10**	3 h	77
5		**11**		**12**	<1 min.	99
6		**13**	–		>24 h	–
7		**14**		**15**	20 min	70 (13)[b]
8		**16**		**17**	4 h	77 (10)[c]
9		**18**		**19**	90 min	90[d]
10		**20**		**21**	15 min	77[e]
11		**22**		**23**	25 min	83
12		**24**		**25**	5 min	94[b]

[a] Isolated yields after column chromatography; yields in parentheses refer to the corresponding alcohols. [b] Mixture (1:1) of diastereoisomers. [c] Mixture (4:1) of diastereoisomers. [d] Mixture (2:1) of diastereoisomers. [e] Mixture (10:1) of diastereoisomers.

Table 3. Reductive etherification of aldehydes and ketones with alcohols.[a]

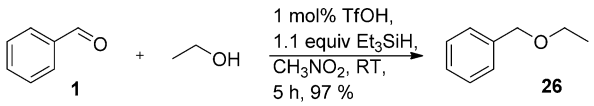


	Substrate	Product		Reaction time [h]	Yield [%][b]
1	**27**		**28**	16	55
2	**27**		**29**	16	63 (37)
3	**1**		**30**	3.5	73
4	**1**		**31**	16	84
5	**1**		**32**	18	73
6	**1**		**33**	15	80
7	**1**		**34**	15	72
8	**1**		**35**	72	68
9	**13**[c]		**36**	7	12
10	**18**[c]		**37**	48	58
11	**38**[c]		**39**	7	43
12	**38**[c]		**40**	2	15[d]

[a] 1.3 equiv of the alcohols were used. [b] Isolated yields after column chromatography; yield in parentheses refers to the corresponding alcohol. [c] TfOH (3 mol%) was used. [d] Obtained as an inseparable mixture with dicyclohexyl ether.

In an initial experiment we were able to show that the addition of a simple aliphatic alcohol such as ethanol (1.3 equiv) to the reaction medium led to almost exclusive formation of the unsymmetrical ether **26** (Scheme 2) without any need for further changes in the reaction conditions.

Although the reaction time was around two orders of magnitude longer than for the formation of dibenzyl ether (**2**) under the same reaction conditions, the predominant reaction product was the unsymmetrical ether **26**, with only traces of dibenzyl ether (**2**) being formed. The reason for the prolonged reaction time remains unclear. The benzaldehyde (**1**) was only completely consumed after 5 h, however, with only small traces of homoether being formed during the whole course of the reaction, so it seems unlikely that **26** is formed by transetherification of **2** with ethanol.



Scheme 2. Synthesis of the unsymmetrical ether **26**.

We examined the reductive couplings of a variety of carbonyl compounds with a range of alcohols (Table 3). Couplings of primary aliphatic alcohols and aldehydes generally led to the corresponding ethers with high selectivities and good yields (Table 3, entries 1–4). Use of the less nucleophilic benzyl alcohol led to the formation of considerable

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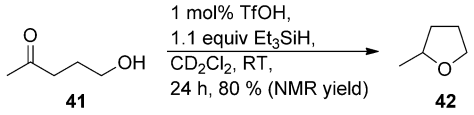
amounts of side products such as alcohols or homocoupling products, but the unsymmetrical ether **29** remained the major product (Table 3, entry 2). Secondary alcohols gave the unsymmetrical ethers as the sole products (Table 3, entries 5–7), even when benzylic alcohols were employed (Table 3, entry 7). Much to our delight, even *tert*-butanol could be applied as a nucleophile, giving the benzylic ether **35** in 68% yield with a prolonged reaction time (Table 3, entry 8). Ketones generally required longer reaction times than aldehydes, together with higher catalyst loadings (3 mol%, Table 3, entries 9-12). However, even acetophenone (**13**) could now be used as a substrate for the first time, leading to the corresponding ethyl ether **36**, albeit in a low yield of 12% (Table 3, entry 9).

Primary aliphatic alcohols and ketones generally furnished the corresponding ethers in moderate to good yields (Table 3, entries 9–11). When secondary alcohols were applied, however, the reactions were dominated by homocoupling and the unsymmetrical ethers were only obtained as side products in low yields (Table 3, entry 12).

We also studied the application of the reaction conditions to the intramolecular reaction of a hydroxy ketone (**41**, Scheme 3). Similar, but stoichiometric, approaches had previously been used by Nicolaou in the total synthesis of brevetoxin B[3a] and by Carren~o in the total syntheses of (+)-isolaurepan[3b] or (−)-centrolobin.[3c]

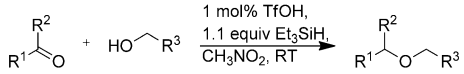


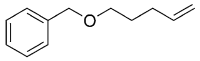
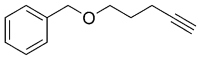
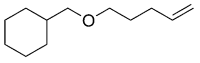
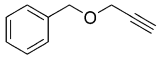
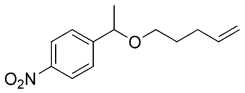
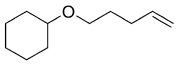
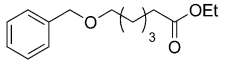
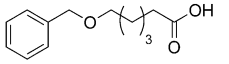
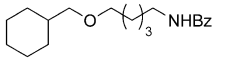
Scheme 3. Intramolecular reductive etherification of 5-hydroxypentan-2-one (**41**).

Pleasingly, 2-methyltetrahydrofuran (**42**) could be obtained in 80% yield (NMR) from 5-hydroxypentan-2-one (**41**), even in deuterated dichloromethane as reaction medium. Subsequent studies revealed that the reaction in nitromethane proceeded in much shorter reaction times of less than five minutes. Further investigations into intramolecular applications of the developed method are currently underway.

We next investigated the influence of additional functionalization of the alcohols (Table 4). Double or triple bonds were not tolerated in cases of reductive homocoupling of carbonyl compounds because they gave rise to Prins-like reaction products. Pleasingly, distal double or triple bonds in the corresponding alcohols gave the corresponding unsymmetrical ethers in good yields (Table 4, entries 1–3). Even propargyl alcohol could be employed, although due to its lower nucleophilicity a larger excess had to be used and an equal amount of homocoupling product was obtained (Table 4, entry 4). Use of allylic alcohols, however, did not lead to product formation in any case. We assume that the allylic ethers are formed initially, but are too sensitive towards the reaction conditions to withstand further transformations (data not shown).

Table 4. Reductive etherification of carbonyl compounds with functionalized alcohols.[a]



	Substrate	Product		Reaction time [h]	Yield [%][b]
1	**1**		**43**	24	88
2	**1**		**44**	26	75
3	**11**		**45**	3	64
4	**1**		**46**	26	22 (23)
5	**14**		**47**	93	34
6	**38**		**48**	24	51
7	**1**		**49**	6	84
8	**1**		**50**	16	88
9	**11**		**51**	22	24

[a] 1.3 equiv of the alcohols were used. [b] Isolated yields after column chromatography; yield in parentheses refers to the corresponding homocoupling product.

Other functional groups, including esters or carboxylic acids, were tolerated without exception (Table 4, entries 7 and 8). The selective formation of **49** (Table 4, entry 7) is noteworthy, because esters are prone to reduction under hydrosilylation conditions.[2] The benzamide **51** (Table 4, entry 9), however, was only obtained in a low yield, even after a prolonged reaction time. Later we were able to show that tosyl-protected amides were tolerated much better under the given reaction conditions (vide infra).

Further investigations into the tolerance of functional groups under the optimized reaction conditions are currently in progress.

Reactions with thiols and amides: We next turned our attention to nucleophiles based on sulfur (Table 5). This has previously only been studied with employment of stoichiometric procedures,[15a] such as for the synthesis of dithioethers.[15b]

When ethanethiol was added to a reaction mixture containing benzaldehyde (**1**), considerable amounts of the corresponding thioacetal were formed (Table 5, entry 1). The thioacetal formation could not be suppressed through any changes in reaction conditions, such as increased catalyst

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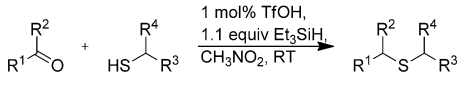
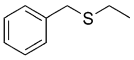
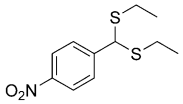
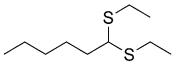
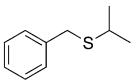
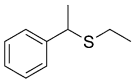
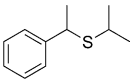
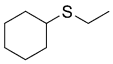
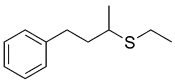
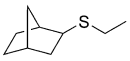
Table 5. Reductive coupling of aldehydes and ketones with thiols.



	Substrate	Product		Reaction time	Yield [%][a]
1	**1**		**52**	30 min	74 (13)
2	**27**		**53**	30 min	93
3	**4**		**54**	30 min	99
4	**1**		**55**	1 h	22 (23)
5	**13**		**56**	4 h	64
6	**13**		**57**	30 min	87
7	**38**		**58**	1 h	74
8	**18**		**59**	3 h	63
9	**24**		**60**	36 h	67[b]

[a] Isolated yields after column chromatography, yields in parentheses refer to the corresponding thioacetals. [b] d.r. > 95:5, determined by ^{1}H NMR spectroscopy.

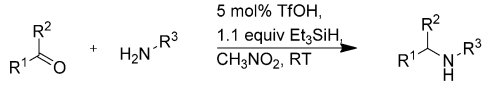
loading, decreased concentration or increased amount of triethylsilane. The thioacetals were also the sole products when other aldehydes were used (Table 5, entries 2 and 3). With 2-thiopropane a similar result was achieved (Table 5, entry 4).

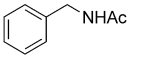
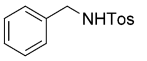
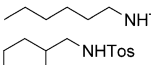
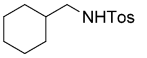
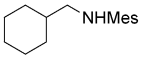
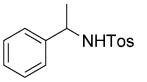
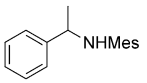
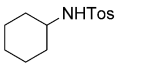
Pleasingly, ketones were selectively transformed into the corresponding thioethers (Table 5, entries 5–9). Notably, the reductive coupling of acetophenone (**13**) and 2-thiopropane led to the tetrasubstituted thioether **57** in a high yield of 87% (Table 5, entry 6). With norbornan-2-one (**24**) as the substrate the reaction was slower than with other ketones but the thioether **60** was obtained as a single diastereoisomer in 67% yield as confirmed by ^{1}H NMR spectroscopy (Table 5, entry 9).

In a next step, we investigated the application of nitrogen-based nucleophiles (Table 6).[14]

We started this investigation with a range of different amides as nucleophiles, because they display high enough nucleophilicities but low enough basicities not to interfere with the acidic reaction conditions. Whereas acetamide inhibited any reaction with benzaldehyde (**1**) under standard conditions (Table 6, entry 1), the use of a slight excess of tosylamide led to the corresponding sulfonamide **62** in 80% yield (Table 6, entry 2). Based on this initial result, a range

Table 6. Reductive amidation of aldehydes and ketones.[a]



	Substrate	Product		Reaction time	Yield [%][b]
1	**1**		**61**	24 h	–
2	**1**		**62**	30 min	80
3	**4**		**63**	15 min[c]	51
4	**11**		**64**	30 min	76
5[d]	**11**		**65**	30 min	55
6	**13**		**66**	16 h	87
7[d]	**13**		**67**	72 h	83
8	**38**		**68**	< 5 min[c]	24

[a] 1.5 equiv of *p*-toluenesulfonamide were used. [b] Isolated yields after column chromatography. [c] Extensively dried *p*-toluenesulfonamide was used. [d] 2 equiv of methanesulfonamide were used.

of aldehydes could be transformed into the corresponding sulfonamides in good yields by application of the same reaction conditions (Table 6, entries 3 and 4). Methanesulfonamide could also be employed as a nucleophile, albeit with slightly lower yields than in the reactions with tosylamide (Table 6, entry 5). Ketones also reacted with the sulfonamides to afford the corresponding amides in good yields (Table 6, entries 6–8). Acetophenone (**13**) could be reductively coupled successfully, giving the corresponding tosylamide **66** in a yield of 87% (Table 6, entry 6) and the methanesulfonamide **67** in a yield of 81% after a prolonged reaction time (Table 6, entry 7).

In all cases, small amounts of symmetrical ethers or alcohols were formed as side-products (1–10%). However, these could easily be removed by column chromatography, giving the desired sulfonamides in their analytically pure states (Table 6, entries 2–8). When commercially available *p*-toluenesulfonamide was thoroughly dried in vacuum prior to use, reaction times were significantly shortened and yields were higher (Table 6, entries 3 and 8). When **4** was treated with moist sulfonamide, for example, the reaction time was doubled and **63** was obtained only in a low yield of 31%.

Mechanistic proposal: On the basis of mechanistic proposals by Doyle[4] and Olah,[5] we believe that in an initial step TESOTf is formed as the active catalyst from triflic acid, triethylsilane and the carbonyl substrate (Scheme 4).

The catalyst generated in situ then activates the carbonyl compound for a nucleophilic attack. Proton transfer and reduction gives the coupled product and silanol byproduct.

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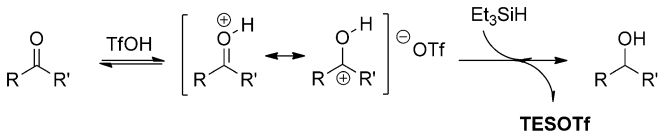
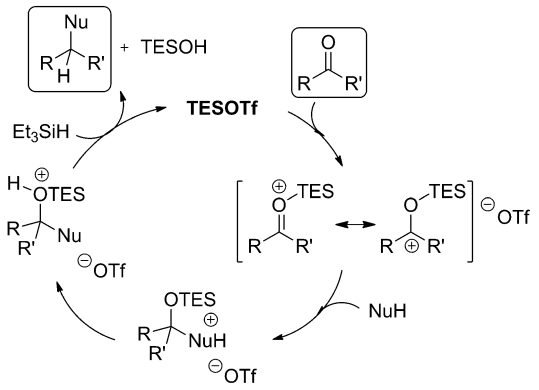


Scheme 4. Proposed generation of the active catalyst.

The catalyst is regenerated and the catalytic cycle is closed. A proposed catalytic cycle of a general reductive coupling reaction is given in Scheme 5. Detailed investigations into the mechanism are currently in progress.



Scheme 5. Proposed simplified catalytic cycle based on TESOTf as active catalyst.

Conclusion

Reductive coupling of carbonyl compounds with nucleophiles has the potential to be a powerful tool for the synthesis of a range of functionalized compounds directly from aldehydes or ketones. We have been able to demonstrate here that a simple Brønsted acid such as triflic acid could be used as a general efficient catalyst for reductive couplings of carbonyl compounds with oxygen-, sulfur- and nitrogen-based nucleophiles under the same set of reaction conditions. The reaction can be performed in open air and at ambient temperature.

For the first time, a wide range of alcohols as coupling partners both for aldehydes and for ketones has been studied. The corresponding ethers were formed in good to excellent yields when aldehydes were treated variously with primary, secondary or even tertiary alcohols, such as *tert*-butyl alcohol. Ketones could be successfully coupled with primary alcohols, but when secondary alcohols were employed the yields were considerably lower. The influence of additional functionalization of the alcohols was also studied, revealing that the reaction conditions are compatible with the presence of distal double and triple bonds, as well as of carboxylic acids, esters and amides.

When thiols were applied as nucleophiles, it could be shown that aldehydes predominantly formed stable thioacetals. Ketones, however, formed the desired thioethers in high yields with either primary or secondary thiols. For the first time, an efficient catalytic system for successful reductive couplings of ketones with thiols to yield substituted thioethers in good yields has been established.

Subsequently, nitrogen-based nucleophiles were also studied. It was demonstrated that sulfonamides could be successfully introduced as coupling partners for aldehydes and ketones without major changes in reaction conditions to give the corresponding substituted sulfonamides in good yields.

Overall, a general, efficient metal-free method for reductive couplings of aldehydes and ketones with a wide range of nucleophiles, based on triflic acid (1–5 mol%) together with triethylsilane as reducing agent to form a widely applicable reductive coupling procedure, has been developed. The reaction only produces either nontoxic hexaethyldisiloxane or triethylsilanol as byproducts and does not require any form of activation, neither of the carbonyl compound nor of the nucleophile prior to reaction. This, in our opinion, emphasizes the usefulness of the reaction by minimizing synthetic effort and producing significantly reduced amounts of environmentally hazardous waste.

Experimental Section

Only representative procedures and products are shown below. Full analytical data for all new compounds can be found in the Supporting Information.

Representative procedure for the reductive coupling of aldehydes and ketones to afford symmetrical ethers

Dibenzyl ether (2): Triethylsilane (0.55 mmol, 1.1 equiv, 50 μL) and trifluoromethanesulfonic acid (1 mol%, 5 μmol, 5 μL, as a 1 M stock solution in nitromethane) were added at ambient temperature to a solution of benzaldehyde (**1**, 0.50 mmol, 1.0 equiv, 50 μL) in nitromethane (0.5 mL) or dichloromethane. The reaction mixture was stirred for 1 min and directly transferred to a column of silica gel (containing a small layer of silica-supported sodium hydrogen carbonate to remove traces of acid). The crude product was purified by column chromatography with a mixture of petroleum ether and ethyl acetate (100:1 to 3:2) as eluent to give **2** (49 mg, 99%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.61$ (s, 4H; CH_2), 7.31–7.45 ppm (m, 10H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 72.1$ (CH_2), 127.6, 127.7, 128.4, 138.3 ppm (Ar).[25]

Representative procedure for the reductive coupling of aldehydes and ketones with alcohols

(Ethoxymethyl)benzene (26): Ethanol (0.325 mmol, 1.3 equiv, 19 μL), triethylsilane (0.275 mmol, 1.1 equiv, 44 μL) and trifluoromethanesulfonic acid (1 mol%, 2.5 μmol, 5 μL, as a 0.5 M stock solution in nitromethane) were added at ambient temperature to a solution of benzaldehyde (**1**, 0.250 mmol, 1.0 equiv, 25 μL) in nitromethane (0.5 mL). The reaction mixture was stirred for 16 h and directly transferred to a column of silica gel (containing a small layer of silica-supported sodium hydrogen carbonate to remove traces of acid). The crude product was purified by column chromatography with a mixture of petroleum ether and ethyl acetate (100:0 to 5:1) as eluent to give **26** (32 mg, 97%) as a colourless oil. ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 1.23$ (t, $^3J = 7.0$ Hz, 3H; CH_3), 3.45 (q, $^3J = 7.0$ Hz, 2H; CH_2CH_3), 4.49 (s, 2H; CH_2Ph), 7.23–7.41 ppm (m, 5H; Ar); ^{13}C NMR (75 MHz, CD_2Cl_2): $\delta = 15.0$ (CH_3), 66.1 (CH_2CH_3), 72.9 (CH_2Ph), 127.7, 128.0, 128.6, 139.4 ppm (Ar).[8e]

Representative procedure for the reductive coupling of ketones with thiols

Ethyl(1-phenylethyl)sulfane (56): Ethanethiol (1.3 mmol, 1.3 equiv, 96 μL), triethylsilane (1.1 mmol, 1.1 equiv, 176 μL) and trifluoromethanesulfonic acid (1 mol%, 10 μmol, 10 μL, as a 1 M stock solution in nitrome-

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thane) were added at ambient temperature to a solution of acetophenone (**13**, 1.0 mmol, 1.0 equiv, 117 μL) in nitromethane (1 mL). The reaction mixture was stirred for 4 h and directly transferred to a column of silica gel (containing a small layer of silica-supported sodium hydrogen carbonate to remove traces of acid). The crude product was purified by column chromatography with a mixture of petroleum ether and ethyl acetate (100:0 to 10:1) as eluent to give **56** (97 mg, 59%) as a volatile, colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.20$ (t, $^3J = 7.4$ Hz, 3H; SCH_2CH_3), 1.61 (d, $^3J = 7.1$ Hz, 3H; $PhCH(SEt)CH_3$), 2.37 (q, $^3J = 7.4$ Hz, 2H; SCH_2CH_3), 4.01 (q, $^3J = 7.1$ Hz, 1H; $PhCH(SEt)CH_3$), 7.21–7.41 ppm (m, 5H; Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.4$ (SCH_2CH_3), 22.5 ($PhCH(SEt)CH_3$), 25.2 (SCH_2CH_3), 43.7 ($PhCH(SEt)CH_3$), 126.9, 127.2, 128.4, 144.1 ppm (Ar).[26]

Representative procedure for the reductive coupling of aldehydes and ketones with sulfonamides

***N*-Benzyl-4-methylbenzenesulfonamide (62)**: *p*-Toluenesulfonamide (1.5 mmol, 1.5 equiv, 257 mg), triethylsilane (1.1 mmol, 1.1 equiv, 176 μL) and trifluoromethanesulfonic acid (5 mol%, 50 μmol, 50 μL, as a 1 M stock solution in nitromethane) were added at ambient temperature to a solution of benzaldehyde (**1**, 1.0 mmol, 1.0 equiv, 101 μL) in nitromethane (1 mL). The reaction mixture was stirred for 30 min and directly transferred to a column of silica gel (containing a small layer of silica-supported sodium hydrogen carbonate to remove traces of acid). The crude product was purified by column chromatography with a mixture of petroleum ether and ethyl acetate (100:0 to 5:1) as eluent to give **62** (209 mg, 80%) as a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.45$ (s, 3H; CH_3), 4.12 (d, $^3J = 6.2$ Hz, 2H; CH_2), 4.87 (br m, 1H; NH), 7.15–7.32 (m, 7H; Ph, SO_2PhMe), 7.77 ppm (d, $^3J = 8.1$ Hz, 2H; SO_2PhMe); ^{13}C NMR (75 MHz): $\delta = 21.5$ (CH_3), 47.2 (CH_2), 127.1, 127.8, 127.8, 128.6, 129.7, 136.3, 136.9, 143.5 ppm (Ar).[27]

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[1] For reviews on asymmetric hydrosilylation of ketones, see: a) S. Díez-González, S. P. Nolan, *Acc. Chem. Res.* **2008**, *41*, 349–358; b) O. Riant, N. Mostefaï, J. Courmarcel, *Synthesis* **2004**, 2943–2958.

[2] G. L. Larson, J. L. Fry, *Ionic and Organometallic-Catalyzed Organosilane Reductions*, Wiley, New York, **2010**.

[3] a) K. C. Nicolaou, C.-K. Hwang, M. E. Duggan, D. A. Nugiel, Y. Abe, K. Bal Reddy, S. A. DeFrees, D. R. Reddy, R. A. Awartani, S. R. Conley, F. P. J. T. Rutjes, E. A. Theodorakis, *J. Am. Chem. Soc.* **1995**, *117*, 10227–10238; b) M. C. Carreño, R. Des Mazery, A. Urbano, F. Colobert, G. Solladié, *Org. Lett.* **2004**, *6*, 297–299; c) F. Colobert, R. Des Mazery, G. Solladié, M. C. Carreño, *Org. Lett.* **2002**, *4*, 1723–1725.

[4] For selected references, see: a) M. P. Doyle, D. J. DeBruyn, D. A. Kooistra, *J. Am. Chem. Soc.* **1972**, *94*, 3659–3661; b) C. T. West, S. Donelly, D. A. Kooistra, M. P. Doyle, *J. Org. Chem.* **1973**, *38*, 2675–2681; c) M. P. Doyle, C. T. West, *J. Org. Chem.* **1975**, *40*, 3835–3838.

[5] a) M. B. Sassaman, K. D. Kotian, G. K. S. Prakash, G. A. Olah, *J. Org. Chem.* **1987**, *52*, 4314–4319; b) M. B. Sassamann, G. K. S. Prakash, G. A. Olah, *Tetrahedron* **1988**, *44*, 3771–3780.

[6] See for example: N. Komatsu, J.-y. Ishida, H. Suzuki, *Tetrahedron Lett.* **1997**, *38*, 7219–7222.

[7] P. Bach, A. Albright, K. K. Laali, *Eur. J. Org. Chem.* **2009**, 1961–1966.

[8] For selected examples, see: a) Y. Kikugawa, *Chem. Lett.* **1979**, 415–418; b) J.-i. Kato, N. Iwasawa, T. Mukaiyama, *Chem. Lett.* **1985**, 743–746; c) J. M. Aizpurua, B. Lecea, C. Palomo, *Can. J. Chem.* **1986**, *64*, 2342–2347; d) S. Chandrasekhar, G. Chandrasekhar, B. N. Babu, K. Vijeender, K. V. Reddy, *Tetrahedron Lett.* **2004**, *45*, 5497–5499.

[9] J. S. Yadav, B. V. S. Reddy, K. S. Shankar, T. Swamy, *Tetrahedron Lett.* **2010**, *51*, 46–48.

[10] For selected examples, see: a) S. Hatakeyama, H. Mori, K. Kitano, H. Yamada, M. Nishizawa, *Tetrahedron Lett.* **1994**, *35*, 4367–4370; b) N. Komatsu, J.-y. Ishida, H. Suzuki, *Tetrahedron Lett.* **1997**, *38*, 7219–7222; c) X. Jiang, J. S. Bajwa, J. Slade, K. Prasad, O. Repic, T. J. Blacklock, *Tetrahedron Lett.* **2002**, *43*, 9225–9227; d) W.-C. Yang, X.-A. Lu, S. S. Kulkarnia, S.-C. Hung, *Tetrahedron Lett.* **2003**, *44*, 7837–7840; e) K. Iwanami, H. Seo, Y. Tobita, T. Oriyama, *Synthesis* **2005**, 183–186.

[11] M. Wada, S. Nagayama, K. Mizutani, R. Hiroi, N. Miyoshi, *Chem. Lett.* **2002**, 248–249.

[12] K. Iwanami, K. Yano, T. Oriyama, *Chem. Lett.* **2007**, *36*, 38–39.

[13] Wada and co-workers have employed a hydroxyl carboxylic acid as sole example for an additional functionalization, see reference [11].

[14] a) M. D. Alexander, R. E. Anderson, J. Sisko, S. M. Weinreb, *J. Org. Chem.* **1990**, *55*, 2563–2564; b) D. D. Dubé, A. A. Scholte, *Tetrahedron Lett.* **1999**, *40*, 2295–2298.

[15] a) G. A. Olah, Q. Wang, N. J. Trivedi, G. K. S. Prakash, *Synthesis* **1992**, 465–466; b) Q. Wang, X.-y. Li, G. K. S. Prakash, G. A. Olah, *ARKIVOC* **2001**, *viii*, 116–128.

[16] For examples of cerium(III) salts in organic synthesis, see: a) T. Imamoto, *Pure Appl. Chem.* **1990**, *62*, 747–752; b) G. Bartoli, E. Marcantoni, M. Marcolini, L. Sambri, *Chem. Rev.* **2010**, *110*, 6104–6143.

[17] It is known, that nitromethane enhances the reactivity of cerium(III) triflate in a range of reactions, see: G. Bartoli, A. De Nino, R. Dalpozzo, L. Maiuolo, M. Nardi, A. Procopio, A. Tagerelli, *Lett. Org. Chem.* **2005**, *2*, 51–53.

[18] For an example of a cerium(III) perchlorate catalyzedreaction, see: W.-S. Kim, S. Hosono, H. Sasai, M. Shibasaki, *Tetrahedron Lett.* **1995**, *36*, 4443–4446.

[19] For a review on rare earth metal triflates in organic synthesis, see: S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, *Chem. Rev.* **2002**, *102*, 2227–2302.

[20] Cerium(III) chloride heptahydrate was also applied but was equally less efficient as the dried salt as compared to other cerium(III) salts applied.

[21] It is noteworthy, that stoichiometric amounts of triflic acid together with triethylsilane have been used for the reduction of carbonyl compounds to hydrocarbons, see: G. A. Olah, M. Arvanaghi, L. Ohannessian, *Synthesis* **1986**, 770–772.

[22] It has been shown before, that triflic acid can initiate reactions in a similar manner to metal triflates, see for example: D. C. Rosenfeld, S. Shekhar, A. Takemiya, M. Utsunomiya, J. F. Hartwig, *Org. Lett.* **2006**, *8*, 4179–4182.

[23] Conversions of aliphatic aldehydes were generally 100%, lower yields can be contributed to the high volatility of the ether products, e.g. **10**.

[24] This has previously been observed by Wada and co-workers using $BiCl_3$ as the catalyst, see reference [11].

[25] G. A. Molander, B. Canturk, *Org. Lett.* **2008**, *10*, 2135–2138.

[26] W. E. Bacon, W. M. LeSuer, *J. Am. Chem. Soc.* **1954**, *76*, 670–676.

[27] A. Shaabani, E. Soleimani, A. H. Rezayan, *Tetrahedron Lett.* **2007**, *48*, 2185–2188.

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