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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Reductive Etherification via Anion-Binding Catalysis

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Supporting Information

ABSTRACT: Reductive condensations of alcohols with aldehydes/ketones to generate ethers are catalyzed by a readily accessible thiourea organocatalyst that operates in combination with HCl. 1,1,3,3-tetramethyldisiloxane serves as a convenient reducing reagent. This strategy is applicable to challenging substrate combinations and exhibits functional group tolerance. Competing reductive homocoupling of the carbonyl component is suppressed.

Reductive aminations are among the most reliable reactions for amine synthesis due to starting material availability, mild reaction conditions, and broad substrate scope (Figure 1).[1] In contrast, the corresponding reductive etherifications are less developed.[2] This is despite the availability of the prerequisite starting materials and the advantages such an approach would offer over classical methods such as the Williamson ether synthesis.[3] Significant efforts have been dedicated toward development of a general method for reductive etherification. Known strategies are based on transition metal catalysts,[4] Lewis acids,[5] and Brønsted acids.[6] Methods relying on silylated alcohols rather than unprotected alcohols have also emerged.[7−9] Despite these advances, a number of challenges have yet to be addressed to allow for a broader application of this process. Remaining limitations include first and foremost functional group compatibility, but also suppression of reductive homocoupling of the aldehyde or ketone component,[10] and applicability to challenging substrates such as aromatic ketones. Here we report a new concept for reductive etherification that is based on the cooperative action of a readily accessible organocatalyst, HCl, and a simple silane reductant.

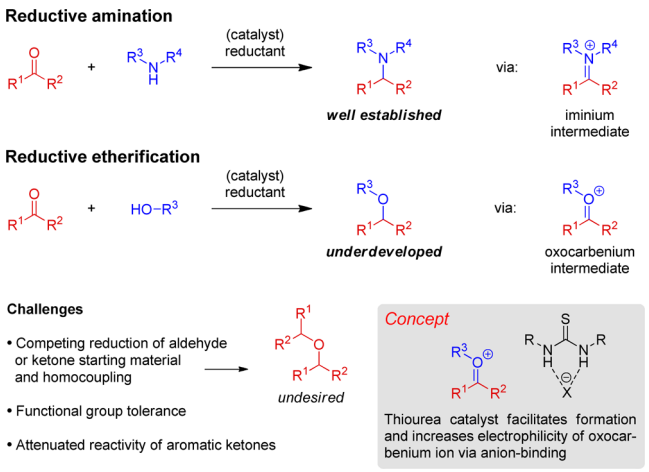
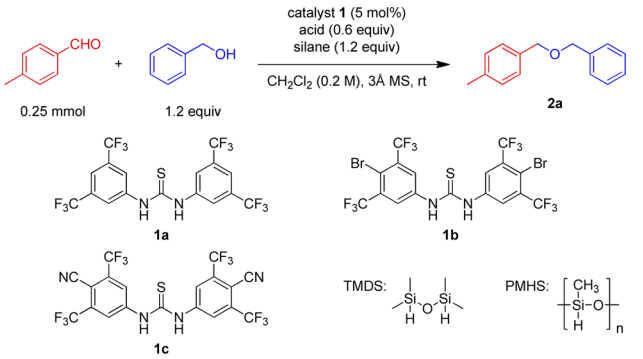


Figure 1. Reductive amination vs etherification and new concept.

Table 1. Evaluation of Reaction Conditions



entry	catalyst	acid	silane	time [h]	yield (%)[a]
1		TFA	Et_3SiH	24	6
2		HCl	Et_3SiH	24	44
3	**1a**	HCl	Et_3SiH	24	64
4	**1b**	HCl	Et_3SiH	24	74
5	**1b**	HCl	$PhSiH_3$	24	21
6	**1b**	HCl	Ph_2SiH_2	24	34
7	**1b**	HCl	Me_2PhSiH	24	95
8	**1b**	HCl	PMHS	24	12
9	**1b**	HCl	Ph_3SiH	24	46
10	**1b**	HCl	$MePhSiH_2$	24	66
11	**1b**	HCl	$(EtO)_2MeSiH$	24	trace
12	**1b**	HCl	TMDS	5	98
13	**1c**	HCl	TMDS	20 min	98 (94)
14	**1a**	HCl	TMDS	24	92
15		HCl	TMDS	24	70
16[b]	**1c**	HCl	TMDS	1	97
17[c]	**1c**	HCl	TMDS	24	91

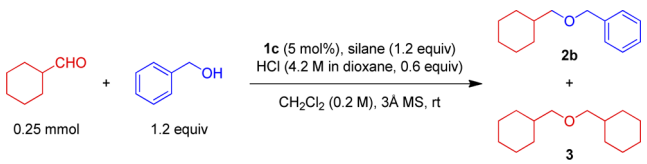
[a]NMR yields (1,3,5-trimethoxybenzene as internal standard), number in parentheses corresponds to isolated yield; HCl was used as 4.2 M solution in dioxane. [b]With 2 mol % of thiourea. [c]With 0.3 equiv of HCl.

Mirroring the requirements for reductive amination, a method for reductive etherification needs to facilitate condensation of an aldehyde/ketone with an alcohol to generate an oxocarbenium ion or related intermediate. The latter has to be reduced selectively over the aldehyde/ketone starting material. We envisioned the cooperative use of a simple Brønsted acid and a thiourea catalyst in the presence of an appropriate reducing agent

Received: June 6, 2017

DOI: 10.1021/jacs.7b05832
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 2. Optimization of Conditions for an Aliphatic Aldehyde



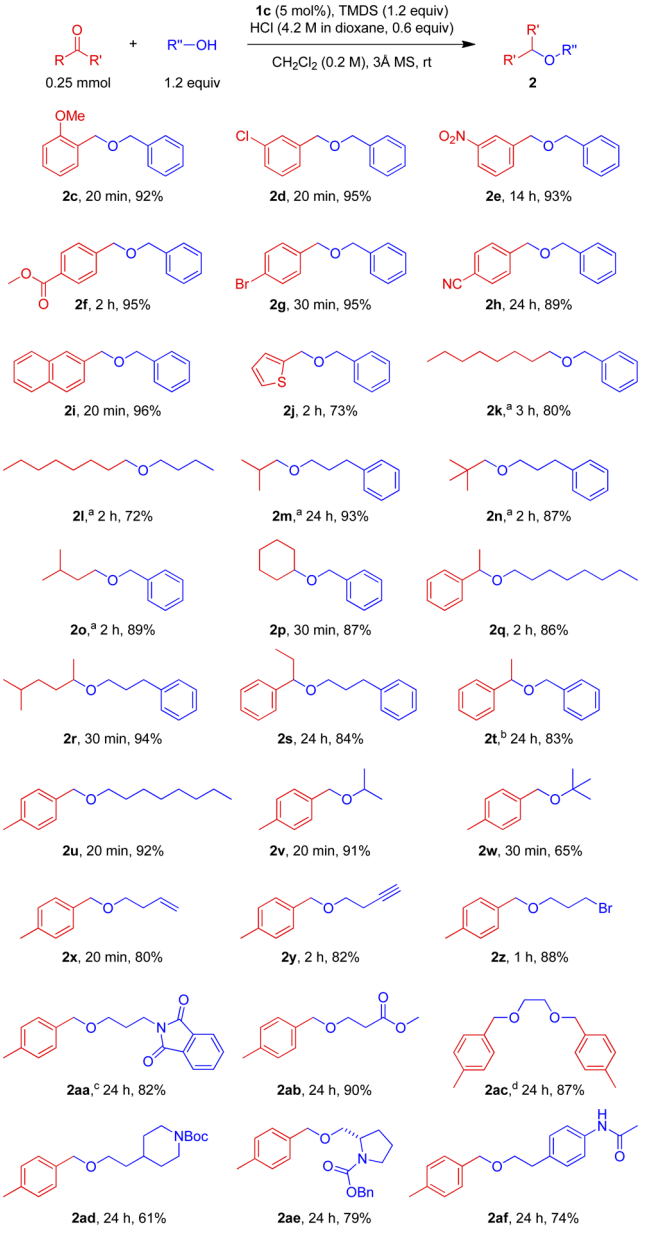
entry	silane	time	yield of **2b** (%)[a]	**2b**:**3**
1	TMDS	20 min	76	8:1
2	Et_3SiH	3 h	81	14:1
3	$PhSiH_3$	24 h	59	9:1
4	Ph_3SiH	24 h	66	14:1
5	Me_2PhSiH	30 min	78	15:1
6	$MePhSiH_2$	2 h	92 (87)	25:1

[a]NMR yields (1,3,5-trimethoxybenzene as internal standard), number in parentheses corresponds to isolated yield.

might allow for an efficient reductive etherification process (Figure 1).[11,12] Specifically, the thiourea catalyst is expected to facilitate the Brønsted acid promoted formation of the oxocarbenium ion intermediate and/or increase its equilibrium concentration. Interaction of the counteranion of the oxocarbenium cation with the thiourea catalyst via anion-binding should serve to increase the electrophilicity of the oxocarbenium cation.[13,14] In addition, the sulfur atom of the thiourea moiety may potentially serve as a Lewis base capable of interacting with the reducing reagent.[14r,15] The concept of anion-binding catalysis was first proposed by Schreiner and co-workers,[16] and is recognized as a general activation mode.[13]

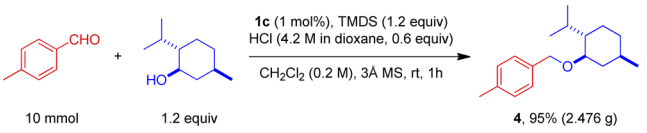
Para-tolualdehyde and benzyl alcohol were selected as model substrates to evaluate the proposed reductive etherification reaction (Table 1). In the absence of a thiourea catalyst with TFA as the Brønsted acid promoter and Et_3SiH as the reducing reagent, only trace amounts of product **2a** were observed after 24 h and starting materials remained mostly unaffected (entry 1). The use of HCl in an otherwise identical experiment provided **2a** with markedly increased yield (entry 2). As a proof of concept, addition of the well-known Schreiner thiourea catalyst (**1a**)[17] at a 5 mol % loading resulted in a further increase in yield (entry 3). Modified Schreiner catalyst **1b**, bearing bromine substituents between the trifluoromethyl groups, enabled further acceleration of the reductive etherification (entry 4). A number of different silanes were evaluated with catalyst **1b** (entries 5−12). Among the reducing reagents, 1,1,3,3-tetramethyldisiloxane (TMDS)[18] stood out as highly efficient. Although none of the reactions in entries 1−11 went to completion within 24 h, the corresponding reaction with TMDS led to complete consumption of aldehyde within 5 h and provided **2a** in excellent yield (entry 12). We rationalized further improvements in efficiency may be achieved by replacing the bromo substituents in **1b** for more electron-withdrawing cyano groups. The corresponding thiourea catalyst **1c** reduced the required reaction time to 20 min with no loss in efficiency (entry 13). The difference to catalyst **1a** is profound: under otherwise identical conditions, trace amounts of starting material were present after 24 h (entry 14). In the absence of any thiourea catalyst, the reaction slowed (entry 15). Use of catalyst **1c** at a loading of 2 mol % was equally efficient with regard to product yield but required a slightly prolonged reaction time (entry 16). However, a decrease in the amount of HCl led to a significant slowdown of the reaction (entry 17).[19]

Scheme 1. Substrate Scope



[a]$MePhSiH_2$ was used instead of TMDS; [b]With 1.2 equiv of HCl; [c]**1b** was used instead of **1c**; [d]With 2.4 equiv of *p*-tolualdehyde, 10 mol % of **1c**, 1.2 equiv of HCl, and 2.4 equiv of TMDS.

Scheme 2. Scale-Up Reaction at Lower Catalyst Loading

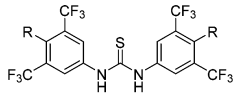


Under the optimized conditions of Table 1, reductive homocoupling of *p*-tolualdehyde was not observed. However, this undesired side reaction is known to occur in certain Brønsted acid catalyzed reductive etherification reactions.[6a,c] The competing reaction pathway not only compromises reaction yields but also complicates product purification. As we were exploring the substrate scope, such homocoupling side products were observed with aliphatic aldehydes, presumably due to an

DOI: 10.1021/jacs.7b05832
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 3. Binding Constants (K_a) of the Catalysts with TBACl[a]

catalyst	K_a (M^{-1})
1a	39.1 ± 0.49 (41)[b]
1b	41.7 ± 0.46
1c	81 ± 2.2



1a R = H
1b R = Br
1c R = CN

[a]Thiourea catalyst (0.01 M) in DMSO-d_6/0.5% H_2O was titrated with tetrabutylammonium chloride (TBACl); [b]K_a value in parentheses is from ref 21.

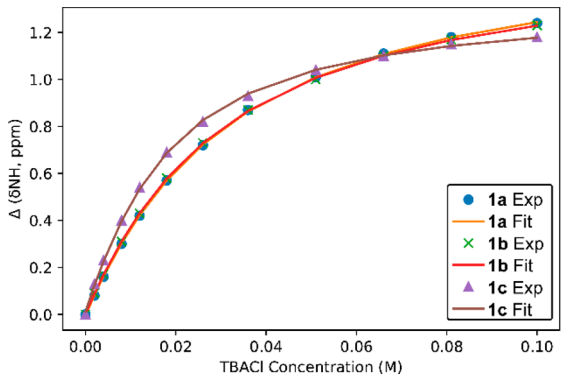


Figure 2. Titrations of thioureas (0.01 M) with TBACl in DMSO-d_6/0.5% H_2O. The chemical shifts refer to the thiourea N−H protons.

increased propensity of these substrates to undergo reduction. For instance, the reaction of cyclohexanecarboxaldehyde and benzyl alcohol provided an 8:1 mixture of desired product **2b** and undesired homocoupling product **3** (Table 2, entry 1). We speculated the product distribution may be shifted toward the desired product by utilizing a silane with attenuated reactivity. Upon evaluation of a number of silanes summarized in Table 2, methylphenylsilane was optimal in favoring product **2b** (Table 2, entry 6).

The scope of the reductive etherification is shown in Scheme 1. With regard to aromatic aldehydes, different substitution patterns and electronic properties were well tolerated. Linear, α-branched, and nonenolizable aliphatic aldehydes also performed well with methylphenylsilane as the reductant. Furthermore, cyclic and acyclic aliphatic ketones were viable substrates. Notably, in contrast to previous reports using Brønsted and Lewis acids, aromatic ketones demonstrated good reactivity. To our knowledge, the only direct reductive etherification method where aromatic ketones provide satisfactory yields calls for a ruthenium-hydride complex that requires handling in a glovebox.[4e] Various alcohols participated in reductive etherification. Ethylene glycol efficiently underwent double etherification. Importantly, the reaction was compatible with a range of functionalities including ether, alkyl and aryl halide, nitro, ester, nitrile, thienyl, amide, carbamate, alkenyl, and alkynyl groups. While the standard reaction conditions were seemingly incompatible with the presence of an imide due to partial reduction of this functional group, replacement of catalyst **1c** for **1b** allowed for the isolation of imide-containing product **2aa** in good yield. Notably, only trace amounts, if any, of reductive homocoupling products were observed in all but one case. In the formation of product **2w**, analysis of the crude reaction mixture indicated a 6.8:1 ratio of **2w** and reductive homocoupling product.[20]

To further demonstrate the practicality of the process, the reductive etherification of *p*-tolualdehyde and L-menthol was performed on a 10 mmol scale with 1 mol % of **1c** (Scheme 2). The reaction went to completion within 1 h and provided product **4** in 95% yield. In the absence of **1c** under otherwise identical conditions and reaction scale, the reaction remained incomplete after 24 h (66% conversion).

The dramatic differences in catalytic activity of the different thioureas are striking. In an attempt to correlate the reactivity differences of the catalysts with their chloride affinities, binding constants for chloride were determined via NMR titrations of the thiourea catalysts with tetrabutylammonium chloride in deuterated DMSO containing 0.5% water (Table 3, Figure 2).[21,22] Though perhaps not fully accounting for the substantially greater activity of **1c**, this catalyst showed a 2-fold binding affinity for chloride compared to **1a** and **1b**.

In summary, we have developed a method for direct reductive etherification where a readily accessible thiourea organocatalyst is used in combination with a simple Brønsted acid. Challenging substrates such as aromatic ketones and various functional groups were well tolerated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05832.

Binding constant studies, synthesis of catalysts, and preparation and characterization data of products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation under Grant No. CHE-1300382.

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DOI: 10.1021/jacs.7b05832
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(19) Dichloromethane was superior to other solvents such as ether and toluene. Reactions in which oxocarbenium ion intermediates are implicated frequently employ dichloromethane as solvent. See, for instance, refs 5a, c–e, 6b, 7a, b, d, e, 10c.
(20) With regard to scope, the combination of ketones and secondary alcohols remains challenging. For instance, under the standard conditions, a reaction between acetophenone and isopropyl alcohol remained incomplete after 24 h and provided the desired ether product in only 42% yield.
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(22) Because of solubility issues, the chloride binding study could not be performed in dichloromethane or chloroform. It should be noted that, under the reaction conditions, the catalyst becomes fully soluble upon addition of HCl.

DOI: 10.1021/jacs.7b05832
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX