Generally Applicable Organocatalytic Tetrahydropyranylation of Hydroxy Functionalities with Very Low Catalyst Loading

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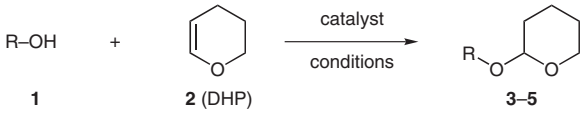
Abstract: This paper presents the first acid-free, organocatalytic tetrahydropyran and 2-methoxypropene protection of alcohols, phenols, and other ROH derivatives utilizing privileged *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea and a polystyrene-bound analogue. The reactions are broadly applicably (also on preparative scale), in particular, to acid-sensitive substrates such as aldol products, hydroxy esters, acetals, silyl-protected alcohols, and cyanohydrins. The catalytic efficiency is truly remarkably with turnover numbers of 100,000 and turnover frequencies of up to 5700 h^{-1} at catalyst loadings down to 0.001 mol%. The computationally supported mechanistic interpretation emphasizes the hydrogen bond assisted heterolysis of the alcohol and concomitant preferential stabilization of the oxyanion hole in the transition state.

Key words: acetals, alcohols, catalysis, protecting groups, supported catalysis

Introduction

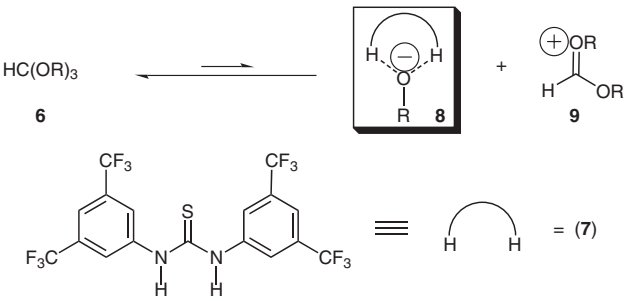
The acid-catalyzed reaction of alcohols and phenols **1** with 3,4-dihydro-2*H*-pyran (DHP, **2**) to give tetrahydropyranyl-substituted ethers **3** is a classic, and one of the most common, strategies for the protection of hydroxy functions (tetrahydropyranylation, Scheme 1).[1] The utility and popularity of this reaction lies in the ease of introducing and removing the tetrahydropyranyl (THP) group and the fact that pyrans of type **3** are remarkably stable under basic conditions.



Scheme 1 General tetrahydropyran protection (tetrahydropyranylation). The product numbering refers to different types of THP-protected alcohols, as depicted in Tables 1–3.

There are many ways to catalyze this important reaction. Various Brønsted acids, including acidic polymers and ionic liquids,[2] and also a large variety of Lewis acids, including zeolites,[3] acidic alumina,[4] and clays,[5] have been utilized. There have been a few attempts to find 'acid-free' variants of this reaction, e.g., with benzyltriphenylphosphonium tribromide or tetrabutylammonium tribromide salts,[6] but these generate HBr in situ;[7] cerium(III) chloride[8] also catalyzes this reaction but is ineffective for sterically hindered alcohols (e.g., adamantan-1-ol). There is no single catalyst that can be applied to the entire spectrum of alcohols, in particular, to sterically hindered tertiary alcohols (elimination is a major side reaction) and deactivated phenols. We do not know of any general approach to the THP protection of highly acid-labile substrates; such a method would, indeed, be highly desirable.

Based on our excellent experience on the catalysis of acetalization reactions[9] we contemplated that tetrahydropyranylations would also be feasible. The reasoning for this is based on the observation that in the acetalization reactions the thiourea catalyst (**7**, *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea) assists the heterolysis of the ortho ester **6** in the initial stages of the reaction by stabilizing the incipient alcoholate (**8**, Scheme 2). This rationalization is in line with well-established concepts in a multitude of enzymatic reactions that are characterized through 'oxyanion stabilization' through explicit hydrogen bonds to partially negatively charged oxygen atoms.[10]



Scheme 2 Initiation step in thiourea-catalyzed acetalizations and the structure of catalyst **7**.

A second clue was provided by the reactions of α,β-unsaturated carbonyl compounds **10** that underwent a domino Michael addition followed by acetalization to give highly oxygenated products **11** under the acetalization reactions conditions (Scheme 3).[9]

These mechanistic insights clearly mark the departure from the often-implied concept of carbonyl[11,12] (or imino[13,14]) group activation through hydrogen bonding with (thio)urea and other hydrogen-bonding catalysts. Hence, this mechanistic alternative suggests either the hydrogen bond assisted generation of the free nucleophile (e.g., RO^-, CN^-) or the stabilization of the active form of

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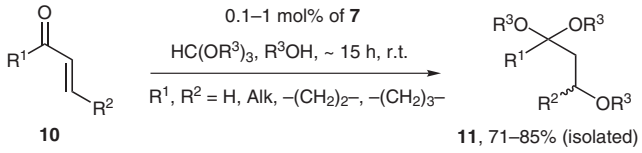

Scheme 3 Domino Michael addition of R^3OH to α,β-unsaturated carbonyl compounds followed by acetalization.

the nucleophile through hydrogen bonding and polar interactions to the respective precursor [ROH, $HC(OR)_3$, HCN, TMSCN, etc.].

We envisioned that the intrinsic reactivity (not necessarily acidity) of simple alcohols should be increased through hydrogen bonding so that the polar reactions with, e.g., enol ethers such as **2** should be significantly accelerated. As we will demonstrate in the following, this concept works extremely well for the tetrahydropyranylation of a wide variety of alcohols including phenols and sterically hindered alcohols. Furthermore, the generality of this method is demonstrated through the reactions of alcohols with 2-methoxypropene (MOP), the protection of oximes as well as aldols and several other highly acid-sensitive substrates. The application of polystyrene-bound thiourea catalysts and computations underscoring our mechanistic hypothesis are also included.

Results and Discussion

We used 3,4-dihydro-2*H*-pyran (DHP) as reactant and solvent and conducted most of our reactions using two equivalents of DHP; in cases where the alcohol was insoluble in DHP, a small amount of tetrahydrofuran was added as a co-solvent (see the experimental section for details). We conducted control experiments in parallel and found no conversion of the respective substrates in the given time required for full conversion of the starting materials in the catalyzed reactions. The catalyst loadings of **7** were 1 mol% or less. Organocatalysts incorporating a thiourea motif are generally highly effective and allow practically low catalyst loadings.[9] In combination with the 3,5-bis(trifluoromethyl)phenyl moiety, which was introduced by us,[11,15] these catalysts enjoy the status of being 'privileged'[16] because their success rate in a manifold of reactions[9,14,17,18] is exceptionally high. Our current results are summarized in Tables 1– 4 and emphasize the broad applicability of **7** in the THP protection of a very broad variety of alcohols and other hydroxy-functionalized compounds.

Primary and secondary alcohols can be THP protected at room temperature in excellent yields and reasonable reaction times (Table 1). Benzyl alcohol stands out as being

Biographical Sketches

Mike Kotke was born in Hanau, a city near Frankfurt/Main, Germany, in 1969. He joined the Degussa company (Hanau-Wolfgang, Germany) in 1989 on an apprenticeship as a chemical laboratory technicien. After two and a half years, Mike took his examination early in 1992 and continued working for six months as an assistant instructor in the training department of Degussa with responsibilities for the education of chemical laboratory workers. In October 1992 he began his chemistry studies at the Justus-Liebig University, Gießen, Germany, and he completed his coursework within eight semesters. After a period of working in various occupations, he returned to the university in 2001 to prepare his diploma thesis in organic chemistry in the group of Prof. R. Askani. Mike received his diploma degree on the 'Synthesis of potential precursors of a homoaromatic semibullvallene' in the spring of 2002 and then began his Ph.D. studies on thiourea-based organocatalysis under the supervision of Prof. Peter R. Schreiner.

Peter R. Schreiner is professor of organic chemistry at the Justus-Liebig-University Gießen. He studied chemistry in his native city at the University Erlangen-Nürnberg, Germany, where he received his Dr. rer. nat. (1994) in organic chemistry with P. v. R. Schleyer. Simultaneously, he received a Ph.D. (1995) with Henry F. Schaefer III in computational chemistry from the University of Georgia. He completed his Habilitation at the University of Göttingen (1999) in the group of A. de Meijere. Before becoming head of the Organic Institute in Gießen in 2002, he was associate professor of chemistry at the University of Georgia (1999–2002). P. R. Schreiner is the 2003 recipient of the Dirac Medal of the World Association of Theoretically Oriented Chemists. Amongst other awards, he also received the ADUC Prize for Habilitanden (assistant professors) in 1999, was a Liebig Fellow (1997–1999) of the Fonds der Chemischen Industrie, and held a Habilitandenstipendium of the Deutsche Forschungsgemeinschaft (1999). He currently serves as the assistant editor for the Journal of Computational Chemistry and as an international advisory board member of the European Journal of Organic Chemistry.

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the most reactive in this group. Its effective THP protection at very low catalyst loadings down to 0.001 mol% to give **3j** emphasizes the catalytic power of **7**. For the reaction with the lowest catalyst loading we calculate maximum turnover numbers (TONs) close to 100,000 and turnover frequencies (TOFs), a much more sensible measure of practicality, of around 2,000 h^{-1}.

While ethylene glycol is diprotected to give **3m**, the difference in the relative rates of reaction of primary vs. secondary hydroxy groups results in the formation of the di-THP-substituted glycerol **3n**. Our acid-free protocol also allows the protection of *tert*-butyldimethylsilyl-substituted substrates leading to orthogonal hydroxy protection as shown for **3k**. For the same reason, tertiary alcohols, which normally are difficult to protect as THP ethers owing to steric hindrance and elimination as a side reaction, can also be THP protected under our conditions (Table 2). Particularly striking is the tolerance of even the most sterically hindered adamantan-1-ol (**4k**),[8] diamantan-1-ol (**4l**), and triphenylmethanol (**4m**) that can not be THP protected by established methods (see above).

Phenol derivatives are also readily converted into their corresponding THP ethers (Table 2); only the reaction temperature must be raised to 50 °C in order to maintain comparable reaction times as for the substrates in Table 1. As shown for phenol, THP protection to **4a** can be achieved with catalyst loadings down to 0.001 mol%, resulting in a TOF of 5700 h^{-1}! This is in the range of excellent metal-catalyzed reactions and, to the best of our knowledge, the most efficient organocatalytic reaction to date.[9,19] Indeed, although we mostly report reactions run at 1 mol% catalyst loading used for our substrate screening, selected scale-up experiments show that a loadings of only 0.01–0.1 mol% are sufficient and practical for preparative THP protection; we routinely ran these reactions on a 50 mmol scale.

The phenol derivatives also provide the important clue that acidity is not a factor for the mechanistic interpretation of these reactions because (a) phenols are more acidic than alkanols and (b) electron-deficient phenols such as 4-chlorophenol, 4-(trifluoromethyl)phenol, and 4-hydroxybenzonitrile react more slowly than electron-rich 4-methylphenol or 4-methoxyphenol (products **4c**, **4e**, and **4f** vs. **4b** and **4d**, respectively).

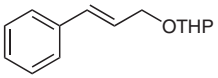
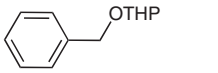
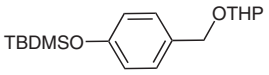
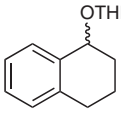
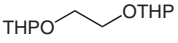
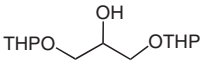
α-Hydroxy ketones can also be THP protected (Table 3, products **5a** and **5b**) at 50 °C in good yields. More remarkable is the possibility of protecting typical aldol products (**5c**, TOF = 2000 h^{-1}) as well as other highly acid-sensitive substrates (at r.t.) such as β-hydroxy ester **5d**, epoxide **5e**, and acetonides **5f** and **5g** without side reactions in excellent yields. Although there are methods for the THP protection of aldol products,[20] the present method is by far the most efficient and practical.

Cyanohydrins are also effectively THP protected at room temperature (**5h** and **5i**). As thiourea catalysts also affect the addition of HCN to carbonyl as well as imino functionalities,[18,21,22] this opens up possibilities for organocatalytic domino reactions.

Oximes can also be THP protected at longer reaction times in good preparative yields (**5j** and **5k**). Protected oximes are valuable building blocks in a variety of transformations.[23]

To improve the practicality of this reaction further, we attached the bis(trifluoromethyl)phenyl part of our catalytic motif to simple amino-terminated polystyrene beads (**P1** and **P3**, Scheme 4);[21] the coupling of the isothiocyanate **12** is highly efficient and generates polymers that can be handled easily. Commercially available, expensive com-

Table 1 THP Protection of Simple Primary and Secondary Substrates[a]

Product		Time (h)	Yield (%)
THP–O–THP (from H_2O)	**3a**[b]	19	94
EtOTHP	**3b**	24	98
PrOTHP	**3c**	24.5	98
BuOTHP	**3d**	23	96
i-PrOTHP	**3e**	24	96
CyOTHP	**3f**	28.5	98
	**3g**	19	97
	**3h**	16	96
	**3i**	15	98
	**3j**	9 9.5 10 48	98 98 (0.1 mol%)[c] 98 (0.01 mol%)[c] 98 (0.001 mol%)[c]
	**3k**	15.5	91
	**3l**[d,e]	31	93
	**3m**[d]	18	89
	**3n**[d]	24	63

[a] Preparative yields of products given from the respective alcohols (5 mmol scale). Catalyst loading = 1 mol%, unless noted otherwise; all reactions were carried out at r.t. No reactions occurred for reference experiments run in parallel even after one week.
[b] Reaction run as emulsion.
[c] Reaction scale increased (see experimental section).
[d] Run as emulsion with THF (0.1 mL) added as co-solvent.
[e] Reaction run at 50 °C, d.r. (GC) ~1:1.

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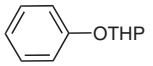
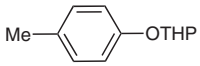
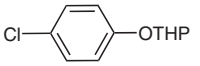
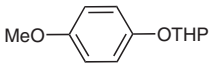
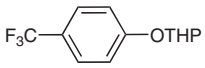
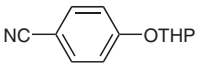
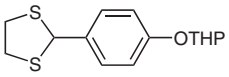
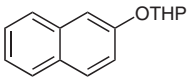
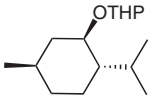
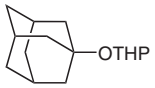
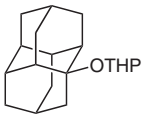
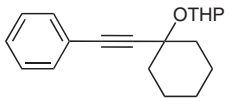
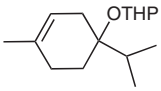
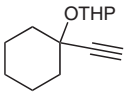
Table 2 THP Protection of Sterically Hindered and Phenolic Substrates[a]

Product		Time (h)	Yield (%)
	**4a**	10 10 11 17	97 97 (0.1 mol%)[b] 97 (0.01 mol%)[b] 97 (0.001 mol%)[b]
	**4b**	10	95
	**4c**	13	93
	**4d**	11	95
	**4e**	45	86
	**4f**	57	96
	**4g**[c]	61	84
	**4h**	48	83
	**4i**[c]	46	89
t-BuOTHP	**4j**	19 19 26 41	98 98 (0.1 mol%)[b] 98 (0.01 mol%)[b] 98 (0.001 mol%)[b]
	**4k**[d]	18.5	97
	**4l**[d,e]	40	83
Ph_3COTHP	**4m**	105	84
	**4n**[f]	18	98
	**4o**	51	92
	**4p**	16	98

[a] Scale: 5 mmol. Preparative yields of products given from the respective alcohols. Catalyst loading = 1 mol%, T = 50 °C. No reactions occurred for control experiments run in parallel, even after one week.
[b] Reaction scales increased (see experimental section).
[c] d.r. (GC) ~1:1.
[d] Carried out on a 2 mmol scale.
[e] DHP (1 mL) and THF (2 mL) were added as co-solvent.
[f] Run at r.t.

pound **12** can be prepared in a straightforward manner (see experimental section). We selected a variety of substrates for polymer-catalyzed THP protection and found these transformations generally to be quite effective (Table 4); this is in marked contrast to earlier attempts with some other simple polystyrene-bound thiourea derivatives.[24]

All reactions with polymer-bound catalysts were conducted on a 2 mmol scale with 50 mg of catalyst; the approximate thiourea concentration was 4 mmol per 1 g of polymer. The catalyst loading on the polymer was determined through determining the residual amounts of **12**. The change in the polymer texture is visually apparent; while the amino-terminated white polystyrene beads lump together and are difficult to handle, the thiourea-functionalized off-white beads are well defined and do not aggregate (Figure 1). The polymer-bound catalyst are handled and recovered easily (see below).

Figure 1 Untreated amino-terminated polystyrene beads (left) and polymer-bound thiourea **P2** (cf. Scheme 4).

The catalyst loading is calculated to be ca. 10 mol% in the reactions summarized in Table 4. Only **P2** proved to be effective in the THP protection of a selection of alcohols and phenols because the N/NH moieties present in **P4** apparently suppress the catalytic process. This is consistent with our finding that, in general, the presence of an NR_2 moiety is incompatible with the catalytic process presented here. As a consequence, amino alcohols cannot be THP protected with the current protocol.

The polymer-supported catalytic reactions essentially run to completion at the expense of longer reaction times (Table 4). It is encouraging to see that a large variety of different substrates can be protected with this very convenient method. The polymer catalyst can be readily separated by simple filtration, washed with dichloromethane and be reused several times without loss of activity; we checked this for the repeated preparation of **3j** (4 cycles).

Protection with Alternative Enol Ethers

Other enol ethers such as benzofuran, dihydrofuran, and 2-methoxypropene (MOP)[25] can also be used utilizing virtually the same experimental protocol (see below). MOP protection is particularly attractive because it does not

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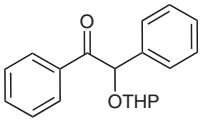
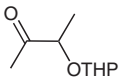
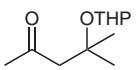
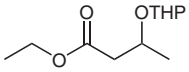
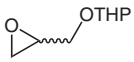
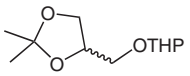
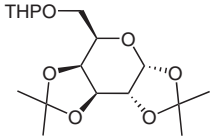
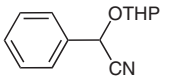
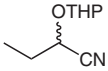
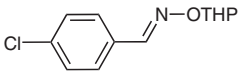
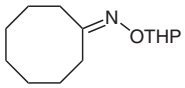
Table 3 THP Protection of Acid-Sensitive Substrates[a]

Product		Temp (°C)	Time (h)	Yield (%)
	**5a**[b,c]	50	26	59
	**5b**	50	19	87
	**5c**	r.t.	18 34 35 49	98 98 (0.1 mol%)[d] 98 (0.01 mol%)[d] 98 (0.001 mol%)[d]
	**5d**	50	30	98
	**5e**	r.t.	8	93
	**5f**	r.t.	20	96
	**5g**[c]	r.t.	14	91
	**5h**[c]	r.t.	36	89
	**5i**[c]	r.t.	34	88
	**5j**	r.t.	30	68
	**5k**	r.t.	31	94

[a] Preparative yields of products given from the respective alcohols (5 mmol scale). Catalyst loading = 1 mol%. No reactions occurred for reference experiments run in parallel even after one week.
[b] Reaction from suspension, THF (2 mL) and DHP (4.5 mL) added as co-solvents.
[c] d.r. (GC) ~1:1.
[d] Reaction scales increased (see experimental section).

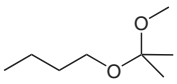
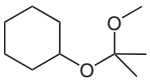
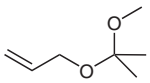
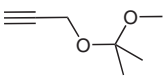
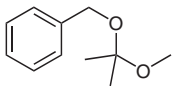
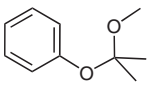
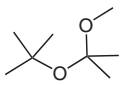
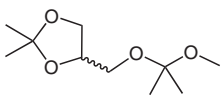
generate a stereogenic center that can sometimes unnecessarily clutter the NMR spectra of THP as well as other adducts. A second advantage is the low boiling point of MOP (34–36 °C) easing its removal after the reaction. As this normally limits the reaction temperature we were pleased to see that the catalyzed reactions run smoothly at room temperature for the examined subset of the substrates presented above (products **13**, Table 5). It must be noted, however, that MOP is so reactive that the uncatalyzed reaction also proceeds, albeit at lower rates.

Table 4 THP Protection of Selected Substrates Utilizing Polymer-Bound Thiourea **P2**[a]

Product	Time (h)	Yield (%)
4i	53	92
3j	21	97
4j	29	98
5c	36	95
5d	38	95
3g	21	97
4a	25	96

[a] Products given from the respective alcohols (suspension, 2 mmol scale). Catalyst loading approximately 10 mol%, T = 50 °C. Reference reactions without **P2** revealed no conversion under otherwise identical conditions.

Table 5 MOP Protection of Selected Substrates[a]

Product		Time (h)	Yield (%)
	**13a**	28	95
	**13b**	34	97
	**13c**	25	96
	**13d**	20	95
	**13e**	15	94
	**13f**	22	95
	**13g**	29	94
	**13h**	42	92

[a] Products given from the respective alcohols. Scale: 5 mmol; catalyst loading = 1 mol%, r.t.

Mechanism

From a mechanistic viewpoint, the addition of an alcohol **1** to the double bond of an enol **14** is formally a forbidden thermal [2+2] cycloaddition (Scheme 5). As a conse-

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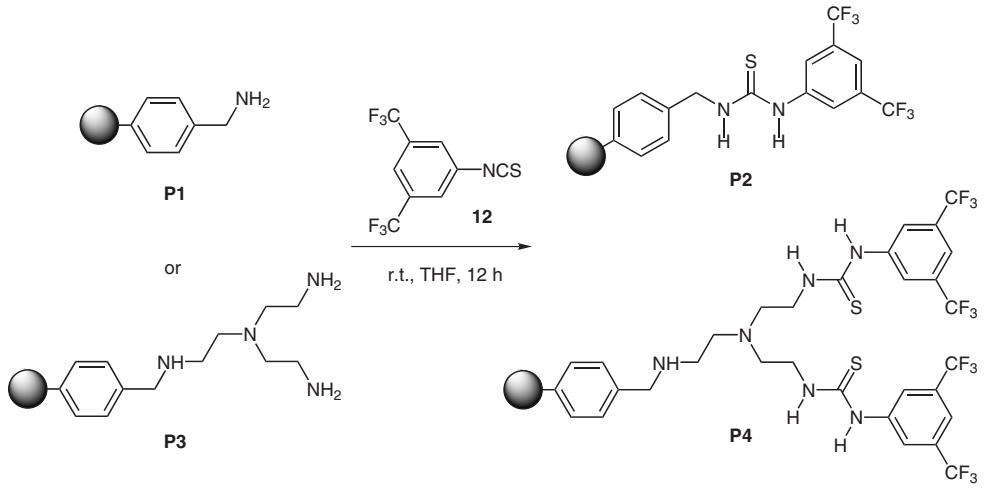
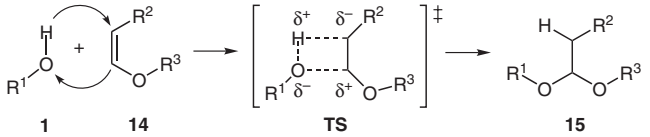


Scheme 4 Simple preparation of polymer-bound thiourea derivatives.



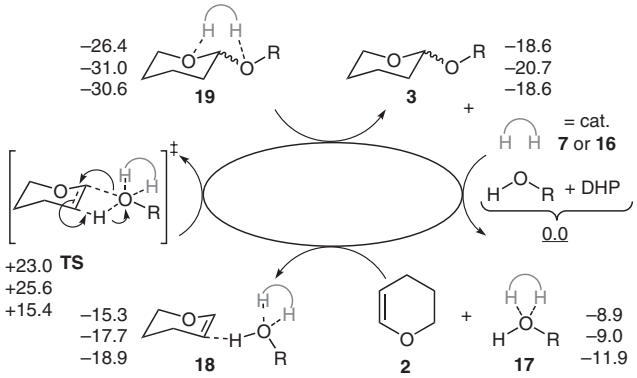
Scheme 5 Generalized mechanism for the uncatalyzed formally forbidden [2+2] cycloaddition of an alcohol to an enol ether, and importance of strong polarization in the transition structure.

quence, the transition structure (**TS**) must be highly polar and the overall addition highly asynchronous.

A reasonable mechanistic entry into this reaction may begin with the complexation of the thiourea catalyst **7**, or thiourea **16** itself, with the alcohol to give **17** (Scheme 6). This coordination increases the alcohol's acidity as well as polarizability and hence its ability to form a subsequent complex **18** with **2**; the catalyst remains attached during the polar addition through transition structure **TS** and in the product complex **19**. Dissociation delivers the free product **3** and returns the catalyst **7** or **16** for the next cycle.

In order to elucidate this mechanistic proposal we undertook density functional theory [DFT, B3LYP/6-31G(d,p)] and high-level coupled cluster computations (CCSD(T)/cc-pVDZ, see below for details); details are revealed in Figures 2 and 3 with energies given in Scheme 6. To the best of our knowledge, these are the first mechanistic computations on an addition reaction of ROH to enol derivatives and specifically for a tetrahydropyranylation.

A comparison of the DFT relative energies with the high level coupled cluster energy results (on the DFT optimized structures) in Scheme 6 reveals that although DFT methods do not include weak van der Waals interactions, the results are qualitatively rather similar for a model reaction of methanol with DHP catalyzed with thiourea **16**. In particular, the first complexation to give **17** is also quantitatively reproduced at the DFT level, which provides further evidence that this association and the steps



Scheme 6 Proposed thiourea-catalyzed tetrahydropyranylation cycle. First entry: ΔH_0 at B3LYP/6-31G(d,p) for MeOH and thiourea as models; second entry: ΔH_0 at CCSD(T)/cc-pVDZ//B3LYP/6-31G(d,p)+ZPVE for MeOH and thiourea **16** as models; third entry: ΔH_0 at B3LYP/6-31G(d,p) for MeOH and our thiourea catalyst **7** (all entries in kcal mol^{-1}).

thereafter are dominated by polar interactions (which are described well). The DFT approach is the only one feasible for our 'real' system utilizing **7** as the catalyst; these results are given as the third entries in Scheme 6.

The structural changes upon complexation of methanol with thiourea and **7** (Figure 2) are quite remarkable and much stronger for the latter. Generally, while the O–H bond of methanol is lengthened only very slightly, the C–O bond distance increases significantly (by 0.02 Å for **7**). This is the result of increased polarization of the alcohol because the increased negative charge on oxygen repels the C–H bonds of the methyl group. The interaction can also be analyzed based on the changes in the thiourea moiety in which the N–H and C=S bonds are significantly lengthened. The complexation energies are remarkably large (and would be significantly less in solution). Particularly striking is the fact that this complexation energy is even larger than that of thiourea with simple diketones (ca. 6.5 kcal mol^{-1}).[12]

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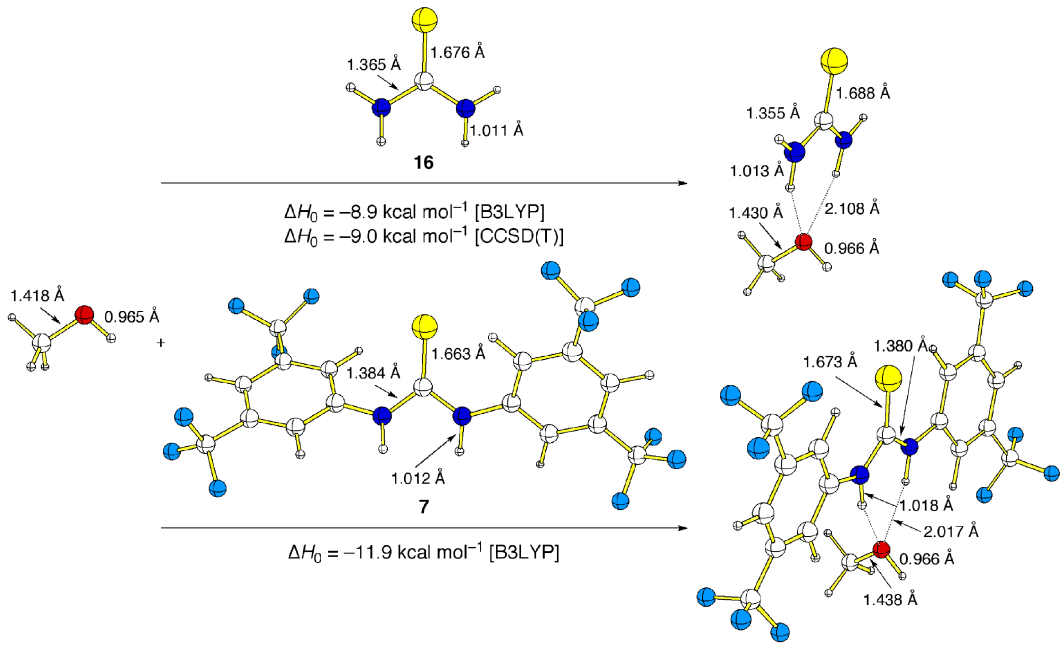

Figure 2 Computed structures [at B3LYP/6-31G(d,p) and CCSD(T)/-cc-pVDZ+ZPVE(B3LYP/6-31G(d,p)] and dissociation energies of the complexes of methanol as a model alcohol with thiourea **16** and our actual catalyst **7**.

The ternary complex **18** is stabilized relative to the complex without the catalyst or **7** by about 70% (Figure 3, top structures from left to right). The association is tightened upon complexation as evident from the geometrical features of the complexes. We also examined complexes to the oxygen atom of DHP but they were all considerably less favorably than those with the β-carbon atom that eventually accepts the proton. Hence, the catalyst helps pre-organize the reactants and the overall geometric changes in going from the complexes to the transition structures (**TS**s, Figure 3 bottom row) are small and evidently follow the least motion principle. The computed absolute barrier for the addition of methanol to DHP is prohibitively high (45.2 kcal mol^{-1} at CCSD(T)) and no reaction occurs, in agreement with experimentation. Complexation with thiourea **16** already lowers the absolute barrier by a remarkable 20 kcal mol^{-1}! Electron-deficient **7** maximizes this stabilization to yield a barrier of 'only' 17.7 kcal mol^{-1}. As a consequence, the catalytic effect is truly remarkable, as demonstrated by the experimental results discussed.

The transition structures follow all the expected geometrical parameters: the methanol O–H bond is lengthened (1.384 Å to 1.675 Å) and this is concomitant with H–C bond lengthening of the newly formed bond (1.251 Å to 1.161 Å); the other structural parameters follow this trend very closely. The only bond that is lengthened in going from the uncatalyzed to the reaction catalyzed with **7** is the newly forming C–O bond (2.187 Å to 2.578 Å), which perfectly agrees with the oxyanion stabilization concept that is particularly effective for **7**. A closer inspection of the transition structure with **7** reveals that the catalyst is placed sideways and points away from the R group on the alcohol. Hence, steric hindrance is not a critical factor, as found experimentally (Table 2).

A comparison of the differential stabilization energies of starting materials, transition structure, and product (Scheme 6) reveals that while the starting materials and product receive about 2–3 kcal mol^{-1} differential stabilization, the transition structure benefits by about 5–6 kcal mol^{-1} from complexation with the catalyst. Of course, this is a precondition in order to observe catalysis, but it is comforting to see that it is shown by the computations as well. Finally, the dissociation energies of the products associated with catalyst are in the same range (7.8, 10.3, and 12.0 kcal mol^{-1}, respectively, at the levels of theory given in Scheme 6) as those of the catalyst with the alcohol reactant (8.9, 9.0, and 11.9 kcal mol^{-1}). Within the expected level of accuracy of our qualitative computations, the comparable complexation energies suppress product inhibition and, as a consequence, this reaction displays very high turnover.

Conclusions and Outlook

Thiourea organocatalyst **7** allows the highly efficient THP protection of a large variety of hydroxy functionalities. While virtually all reported non-organocatalytic methods can protect either primary and secondary alcohols or tertiary as well as phenolic substrates, **7** operates effectively on all classes of hydroxy functionalities. This also includes acid-sensitive substrates such as α- and β-hydroxy carbonyl compounds (including aldol products), cyanohydrins, acetals, and oximes.

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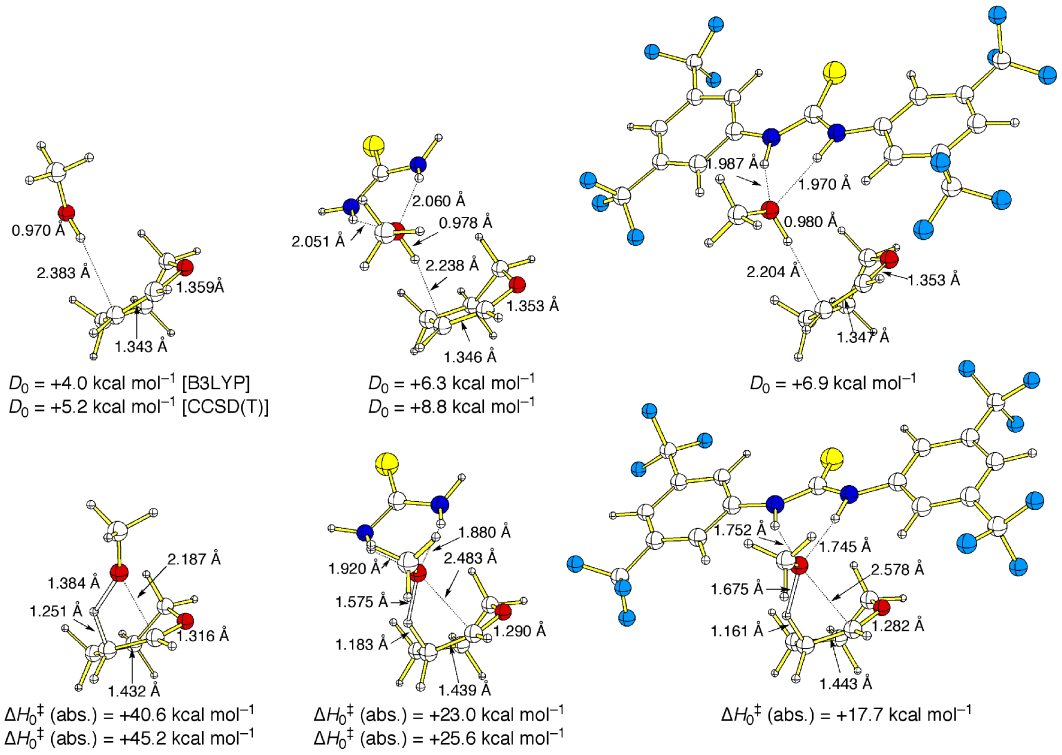

Figure 3 Optimized complexes (top) between methanol and DHP without and with thiourea **16** as well as catalyst **7**; transition structures (bottom) for the addition of methanol to DHP without and with thiourea as well as with **7** as catalyst. Level of theory for optimization: first entry = B3LYP/6-31G(d,p), energy evaluations: second entry = CCSD(T)/cc-pVDZ, including ZPVE corrections at B3LYP/6-31G(d,p).

The catalyst is remarkably active for THP protection reactions. Catalyst loadings can be as low as 0.001 mol%, giving a maximum turnover number of about 100,000 and turnover frequencies of up to 5700 h^{-1}. To the best of our knowledge, this is the most efficient organocatalytic reaction reported to date, and this emphasizes the power of noncovalent catalysis and the remarkable role the thiourea motif plays in organocatalysis.

From a mechanistic viewpoint, the reactions presented here also mark the deviation from carbonyl (and related functionalities) activation through double hydrogen bonding.[26] Instead, the catalyst preferentially stabilizes the developing oxyanion hole in the transition state through double hydrogen bonding. This conclusion was reached on the basis of a comparative computational analysis of the uncatalyzed vs. catalyzed reactions. The stabilizing effect of **7** on the key transition structures amounts to ca. 23 kcal mol^{-1}, which is in line with the experimentally found efficacy of **7**.

An analogue of **7** bound to polystyrene beads also effectively catalyzes THP protection reactions although the formal catalyst loading is significantly higher and the reaction times are longer.

All chemicals were purchased from Aldrich, Acros Organics, Alfa Aesar, Merck, and Lancaster in the highest purity available and were used without further purification unless otherwise noted. 3,4-Dihydro-2*H*-pyran (DHP) and 2-methoxypropene (MOP) (both 97% grade, Aldrich) were used as purchased; MOP was stored at –18 °C until required. Except for (–)-menthol and (–)-terpinen-4-ol all chiral substrates were used as racemates. Aminomethylated polystyrene **P1** (200–400 mesh, loading 2.00–3.00 mmol/g resin) and tris-(2-aminoethyl)amine polystyrene **P3** (200–400 mesh, loading 2.20 mmol/g resin) were ordered from Merck Novabiochem and were stored under an argon atmosphere at –18 °C. 4-*tert*-Butyldimethylsilyloxybenzyl alcohol was synthesized by reduction of TBDMS protected 4-hydroxybenzaldehyde with $NaBH_4$ following a literature protocol.[27] Hydroxy(phenyl)acetonitrile (technical grade) was distilled once over a 10 cm Vigreux column prior to use; all solvents used for extractions or filtrations were distilled once with a rotary evaporator. Drying followed established literature procedures: THF and Et_3N (both freshly distilled from Na/benzophenone ketyl); CH_2Cl_2 (P_2O_5, reflux, 3 h, then distilled once before storage); EtOH (Na/diethyl phthalate, reflux); PrOH, *i*-PrOH, BuOH, ethane-1,2-diol, and propane-1,3-diol (distilled once, 20 cm Vigreux column). All dry chemicals were stored under an argon atmosphere and over activated 3 Å molecular sieve (MS) (alcohols) and Na wire (Et_3N, THF), respectively: *t*-BuOH, allyl alcohol, BnOH, and propargyl alcohol were stored over MS 3 Å without prior distillation; $CDCl_3$ (99.8%, purchased from Deutero GmbH) was stored over MS 4 Å. Filtrations for product purification were performed on activated basic alumina (50–200 microns; Acros Organics). TLC was carried out on pre-coated Macherey-Nagel plastic sheets Polygram ALOX N/UV_{254} (40–80 mm) using UV light or molybdatophosphoric acid (5% in EtOH) for visualization. The progress of reactions was monitored by GC-MS analyses with a Quadrupol-MS HP MSD 5971(EI) and HP 5890A GC equipped with a J & W Scientific fused silica GC column (30 m × 0.250 mm, 0.25 micron DB–5MS stationary phase: 5% phenyl and 95% methyl silicone) using He (4.6 grade) as carrier gas; T-program standard 60–250 °C (15 °C/min heating rate), injector and transfer line 250 °C; ^1H and ^{13}C NMR spectra were recorded with Bruker spectrometer Avance II 200 MHz (AV 200) and Avance II 400 MHz

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WB (AV 400) using as the internal standard: TMS $\delta(^1H) = 0.00$, $\delta(^{13}C) = 0.0$; $CHCl_3$ [$\delta(^1H) = 7.26$], $CHCl_3$ [$\delta(^{13}C) = 77.0$]; ^{13}C signals were assigned with DEPT or APT (attached proton test) experiments. IR spectra were measured with Bruker IFS25 and IFS48 spectrophotometers [for **P2** and **P4** using attenuated total reflection (ATR)]; HRMS were recorded with a Sectorfield-MS: Finnigan MAT 95, CHN analyses were obtained with a Carlo Erba 1106 (balance: Mettler Toledo UMX-2) analyzer. To keep reaction temperatures constant a standard mercury contact thermometer controlled by an IKAMAG RET-GS hot plate-stirrer was used.

All analytical reaction mixtures were prepared in clean oven-dried one-necked 10 mL (2 and 5 mmol scale experiments) and 25 mL (50 and 100 mmol scale experiments) standard glass flasks (Schott DURAN) tightly sealed with a plastic plug. For experiments at 50 °C, reaction flasks were sealed with a clamped glass plug and were placed in a tempered oil bath (50 °C). For homogeneous catalysis organocatalyst **7** and solid hydroxy substrate **3**–**5** were directly weighed out into the reaction flasks, liquid substrates were added via syringe and were dissolved in DHP (2 equiv, 0.91 mL/5 mmol substrate, for larger scales the volume was adjusted proportionally) or MOP (2 equiv, 0.96 mol/5 mmol substrate), respectively. The quantity of catalyst refers to the substrate quantity that determines the scale of the experiment. To reveal catalyst efficiency various catalyst loadings (mol%) of **7** were employed: 1.0 [25 mg/5 mmol], 0.1 [12.5 mg/25 mmol], 0.01 [2.5 mg/50 mmol], and 0.001 mol% [1 mg/200 mmol scale]. If not otherwise noted all experiments utilizing **7** were run in homogeneous solns. In each experiment utilizing heterogeneous catalysis **P2** or **P4** (each 50 mg: ~10 mol% based on ~4 mmol thiourea motif per gram polymer) were weighed into the reaction flask, the respective hydroxy substrate **3**–**5** (2 mmol), and DHP (0.36 mL) was added. In general, all volumes for the preparation of analytical reactions were measured with new 1 mL plastic syringes using dry cannulas. The reaction time measurements started with stirring of the freshly prepared reaction mixture after addition of DHP or MOP, respectively, serving as reagent as well as solvent; in some cases THF was used as co-solvent (see Table footnotes). For stirring, standard Teflon-coated magnetic stirring bars (1 to 1.5 cm) were used. Reaction temperature (25 or 50 °C) for each substrate is given in Tables 1– 5. To determine the catalytic efficiency, all experiments were accompanied by a parallel control experiment under same conditions, but without catalyst. In the case of heterogeneous organocatalysis, reference experiments were performed with aminomethylated polystyrene resin **P1** or **P3**, respectively. Sample volumes (~0.5 μL) were taken directly from the stirred reaction mixture via 10 μL Hamilton syringe (in heterogeneous experiments given in Table 4 stirring was stopped prior to sampling to allow the catalyst to precipitate) and were injected immediately to record the GC-MS chromatogram. The course of each hydroxy-protection reaction was monitored by integrating the starting material and product signal; time-dependent conversion as a percentage was determined from the integral ratio of starting material and product signal. After completion of the reaction as confirmed by GC-MS, work-up followed according to the procedures described below. More details concerning the various substrates and potential exceptions to these general procedures are mentioned in the footnotes to Tables 1– 5.

All THP and MOP ethers were isolated and characterized by ^1H and ^{13}C NMR, IR, and MS; **3a**–**n**, **4a**–**k**, **4n**–**p**, **5a**–**i**, **13a**–**e**, and **13h** are known compounds and their spectral data were consistent with literature data.

1,3-Bis(trifluoromethyl)phenyl Isothiocyanate (12)

In an oven-dried, three-necked, 1 L flask equipped with argon-inlet, thermometer, septum, and magnetic stirring bar, a homogeneous mixture of 1,3-bis(trifluoromethyl)aniline (9.16 g, 40 mmol) and anhydrous Et_3N (16.9 mL) in anhydrous THF (400 mL) was prepared and subsequently cooled with an ice/salt bath at approx. –5 °C. Thiophosgene (7.85 mL, 100 mmol, 97% grade) was placed in a second oven-dried three-necked flask serving as reaction vessel, equipped with argon inlet, addition funnel with septum, thermometer, and magnetic stirring bar; it was cooled (–5 to –10 °C) with an ice/salt bath and vigorously stirred. The amine mixture was slowly added to the cooled thiophosgene through an addition funnel to initiate the exothermic reaction; to minimize warming of the amine mixture only small portions (20–30 mL) were transferred with a 50 mL plastic syringe into the addition funnel. The resulting orange mixture was stirred at –10 °C for 15 min and the mixture was allowed to warm to r.t. (~45 min) and stirred at r.t. for 12 h. The brown mixture was poured into demineralized H_2O (850 mL) in a separation funnel and NaCl was added to facilitate separation of layers. The aqueous layer was extracted with Et_2O (3 × 250 mL) and the organic layers were collected and dried (anhydrous Na_2SO_4/Na_2CO_3). The drying agent was separated by filtration and washed intensively with Et_2O (~300 mL) to reduce loss of product. Evaporation of the solvent from the combined organic layers afforded a red-brown oily residue. Fractionated distillation (10 cm Vigreux column) in vacuo gave analytically pure **12** as a yellowish transparent liquid that could be stored for several weeks under an argon atmosphere at 4 °C; yield: 8.03 g (74%); bp 103 °C/~20 mbar; n_{20}^D +1.4336.

IR (film): 2034 (NCS), 1992, 1620, 1465, 1378, 1279, 1235, 1181 1137, 1107, 1004, 892, 849, 785, 712, 698, 683 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 2 H), 7.78 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 118.5, 120.5, 123.9 ($^1J_{CF}$ = 273 Hz), 125.8, 133.3 ($^2J_{CF}$ = 32 Hz), 141.1.

HRMS: *m*/*z* calcd for $C_9H_3F_6NS$: 270.9890; found: 270.9891.

Anal. Calcd for $C_9H_3F_6NS$: C, 39.86; H, 1.12; N, 5.17. Found: C, 39.50; H, 1.08; N, 5.16.

Polystyrene-Bound Thiourea Organocatalysts P2 and P4

In an oven-dried, two-necked, 10 mL flask equipped with argon-inlet and septum, aminomethylated polystyrene **P1** (0.8 g) was suspended in anhydrous THF (5 mL) with low stirring with a magnetic stirring bar. Pure 1,3-bis(trifluoromethyl)phenyl isothiocyanate (**12**, 1.95 g, 7.2 mmol) was added over 5 min. The resulting mixture was stirred at r.t. under an argon atmosphere for 12 h, after which the resin was separated by suction filtration through a round filter paper. Excessive washing with anhydrous CH_2Cl_2 (5 × 10 mL) and subsequent removal of CH_2Cl_2 in vacuo furnished yellowish thiourea functionalized **P2**; this was stored until use in a Schlenk tube at –18 °C under argon. The unreacted excess of isothiocyanate **12** was recovered from the filtrate by evaporation of CH_2Cl_2. The catalyst loading (thiourea moiety per gram **P2**) was determined via consumption of isothiocyanate and amounted to about 4 mmol per 1 g polymer-bound organocatalyst.

P4 was synthesized analogously from tris(2-aminoethyl)amine polystyrene **P3** (0.8 g) suspended in anhydrous THF (5 mL) and isothiocyanate **12** (2.86 g, 10.56 mmol, 3 equiv per NH_2 group). Catalyst loading was identical to **P2**. Thiourea functionalization of **P2** and **P4**, respectively, was analytically detected via IR measurement revealing a strong thiocarbonyl band that is typical for thiourea derivatives; no residual isothiocyanate bands were detected.

P2

Yellowish, crystalline, free-floating particles.

IR (ATR): 3257, 2923, 1582 (C=S), 1470, 1381, 1274 (CF_3), 1170, 1125, 948, 883, 698, 680 cm^{-1}.

P4

Yellow, crystalline, free-floating particles.

IR (ATR): 3267, 3025, 2922, 1668 (C=S), 1376, 1331, 1274 (CF_3), 1170, 1126, 883, 846, 735, 697, 680 cm^{-1}.

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2-(Benzyloxy)tetrahydro-2*H*-pyran (3j); Typical Procedure for Homogeneous Organocatalysis Using Catalyst 7

Organocatalyst **7** (25 mg, 0.05 mmol, 1 mol% loading) was weighed into an oven-dried, one-necked, 10 mL flask equipped with a magnetic stirring bar (1.5 cm). After addition of BnOH (0.52 mL, 5 mmol) and DHP (0.91 mL, 10 mmol) via a 1 mL syringe, the reaction flask was sealed with a plastic plug and the mixture was vigorously stirred at r.t. until the reaction was complete (9 h, temperatures and times are given in Table 1). DHP was mostly evaporated in vacuo, the resulting yellowish crude product was dissolved in *n*-pentane (~ 8 mL) and slowly passed through a short column of basic alumina (2.5 × 4.5 cm). Evaporation of *n*-pentane and residual DHP with a rotary evaporator under reduced pressure (~30 mbar) at 50 °C bath temperature afforded analytically pure THP ether **3j**; yield: 0.94 g (98%); physical data were identical to those reported in literature.

2-(Phenoxy)tetrahydro-2*H*-pyran (4a); Typical Procedure on a Preparative Scale

In an oven-dried, one-necked, 25 mL flask, organocatalyst **7** (2.5 mg, 0.005 mmol, 0.01 mol% loading), phenol (4.71 g, 50 mmol), and DHP (9.1 mL, 100 mmol) were added and the mixture was magnetically stirred for 11 h (Table 2) at 50 °C. The scaled-up workup was performed according to the procedure for the 5 mmol experiment (alumina column, 2.5 × 8 cm) to give **4a**; yield: 8.64 g (97%); physical data were consistent with those reported in literature.

3-(1-Methoxy-1-methylethoxy)prop-1-ene (13c); Typical Procedure for Organocatalytic MOP Protection Using Catalyst 7

MOP protection of allyl alcohol (0.34 mL, 5 mmol) followed the procedure described for THP protection of benzyl alcohol with the modification that THP is replaced by MOP (0.96 mL, 10 mmol); excess MOP was evaporated without warming. Analytical grade MOP ether **13c** was obtained at r.t. in 25 h (Table 5); yield: 0.62 g (96%); physical data were consistent with those reported in literature.

2-(Phenoxy)tetrahydro-2*H*-pyran (4a); Typical Procedure for Heterogeneous Organocatalysis Using Polymer Catalyst P2

For heterogeneously catalyzed THP protection a suspension of phenol (0.19 g, 2 mmol), polystyrene-bound thiourea **P2** (50 mg, ~10 mol%), and DHP (0.36 mL, 4 mmol) was prepared in an oven-dried, one-necked, 10 mL flask sealed with a plastic plug. Under gentle stirring with a magnetic stirring bar (1 cm) at 50 °C the reaction was complete within 25 h (Table 4). The catalyst was removed from product by simple suction filtration, washed with CH_2Cl_2 (5 × 10 mL), and dried in vacuo to evaporate residual CH_2Cl_2. Recovered **P2** was directly reused for new THP protection reactions of phenol (4 use/recovery cycles were examined) only with minor weight loss (approx. 6% per recovery), but no detectable loss of catalytic activity. Evaporation of solvent with a rotary evaporator in vacuo (50 °C bath temperature/~30 mbar) afforded a yellowish crude THP ether that was diluted in *n*-pentane (5 mL) and slowly passed through a basic alumina column (2.5 × 3 cm) to give analytically pure **4a**; yield: 0.34 g (96%); spectroscopic data were consistent with those reported in literature.

2-(Diamantan-1-yloxy)tetrahydro-2*H*-pyran (4l)

Yellowish crude product, purification: basic alumina column (2.5 × 4.5 cm, *n*-pentane, ~6 mL, then Et_2O, ~10 mL); the solvent was evaporated in vacuo at 50 °C bath temperature.

Colorless oil, aromatic smell; yield: 83%.

IR (film): 2905, 2849, 1460, 1439, 1379, 1127, 1112, 1091, 1076, 1023, 982, 869 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.3–2.37 (m, 25 H), 3.48 (m, 1 H), 3.97 (m, 1 H), 4.82 (t, ^3J = 3.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 25.3, 25.9, 30.2, 32.3, 32.5, 32.6, 32.7, 32.9, 37.1, 37.4, 37.5, 38.2, 39.8, 42.2, 42.7, 63.4, 68.8, 92.2.

HRMS: *m*/*z* calcd for $C_{19}H_{28}O_2$: 288.2089; found: 288.2083.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 11.09. Found: C, 78.34; H, 10.10.

2-(Trityloxy)tetrahydro-2*H*-pyran (4m)

Yellowish crude product, purification: basic alumina column (2.5 × 8 cm, *n*-pentane, ~ 10 mL, then Et_2O ~15 mL); the solvent was evaporated in vacuo at 50 °C bath temperature.

Colorless solid; yield: 84%.

IR (film): 3061, 3033, 2942, 2851, 1959, 1665, 1598, 1490, 1445, 1331, 1277, 1203, 1180, 1156, 1077, 1032, 1010, 970, 891, 759, 698, 639, 584, 510, 449 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.54–1.89 (m, 6 H), 3.52–3.59 (m, 1 H), 3.85–3.92 (m, 1 H), 4.96 (t, ^3J = 3.3 Hz, 1 H), 7.19–7.78 (m, 15 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4, 25.4, 31.5, 64.2, 82.1, 102.1, 126.4, 128.6, 130.1.

HRMS: *m*/*z* calcd for $C_{24}H_{24}O_2$: 344.1776; found: 344.1761.

Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 84.01; H, 7.18.

4-Chlorobenzaldehyde *O*-(Tetrahydro-2*H*-pyran-2-yl)oxime (5j)

Yellowish crude product, purification: basic alumina column (2.5 × 3 cm, *n*-pentane, ~ 6 mL, then Et_2O, ~10 mL); the solvent was evaporated in vacuo without warming.

Colorless oil, aromatic smell; yield: 68%.

IR (film): 2944, 2870, 1648, 1596, 1492, 1203, 1113, 1090, 1079, 1041, 1015, 981, 948, 825, 514 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.62–1.93 (m, 6 H), 3.66–3.70 (m, 1 H), 3.89–3.95 (m, 1 H), 5.38 (t, ^3J = 3.3 Hz, 1 H), 7.42 (d, ^3J = 8.8 Hz, 2 H), 7.56 (d, ^3J = 8.8 Hz, 2 H), 8.16 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 23.8, 30.2, 62.9, 101.2, 128.2, 128.8, 128.9, 141.4, 149.2.

HRMS: *m*/*z* calcd for $C_{12}H_{14}ClNO_2$: 239.0713; found: 239.0705.

Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.00; H, 6.18; N, 5.67.

Cyclooctanone *O*-(Tetrahydro-2*H*-pyran-2-yl)oxime (5k)

Yellowish crude product, purification: basic alumina layer (2.5 × 4.5 cm, *n*-pentane, ~8 mL, then Et_2O, ~10 mL); the solvent was evaporated in vacuo at 50 °C bath temperature.

Colorless semi-solid; yield: 94%.

IR (film): 3102, 2926, 2855, 2688, 1659, 1466, 1445, 1424, 1449, 1340, 1277, 1228, 1103, 1025, 954, 923, 904, 856, 825, 767, 748, 738, 614, 575, 514 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.40–2.50 (m, 20 H), 3.48–3.51 (m, 1 H), 3.93–3.96 (m, 1 H), 4.68 (t, ^3J = 3.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 22.8, 24.3, 24.5, 24.6, 25.5, 25.7, 26.6, 27.2, 27.3, 65.8, 100.8, 164.2.

HRMS: *m*/*z* calcd for $C_{13}H_{23}NO_2$: 225.1728; found: 225.1782.

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.09; H, 9.93, N, 6.38.

(1-Methyl-1-methylethoxy)benzene (13f)

Yellowish crude product, purification: basic alumina column (2.5 × 5 cm, *n*-pentane, ~8 mL then Et_2O, ~15 mL); the solvent was evaporated in vacuo at 50 °C (bath temperature).

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Colorless oil, aromatic smell; yield: 95%.

IR (film): 2994, 2942, 2831, 1596, 1586, 1493, 1382, 1372, 1278, 1257, 1231, 1209, 1181, 1131, 1066, 1026, 946, 875, 803, 766, 730, 694, 630, 511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 6 H), 3.40 (s, 3 H), 7.05 (t, 1 H), 7.10 (d, 2 H), 7.27 (t, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 49.2, 103.5, 115.3, 120.81, 129.1, 155.2.

HRMS: *m/z* calcd for $C_{10}H_{14}O_2$: 166.0993; found: 166.0979.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.49; H, 8.73.

2-(1-Methoxy-1-methylethoxy)-2-methylpropane (13g)
Yellowish crude product, purification: basic alumina column (2.5 × 3 cm, *n*-pentane, ~8 mL, Et_2O, ~10 mL); the solvent was evaporated in vacuo (~200 mbar) and without warming.

Colorless oil, aromatic smell; yield: 94%.

IR (film): 2974, 1712, 1653, 1472, 1365, 1282, 1260, 1209, 1180, 1080, 1056, 994, 914, 827, 749 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9 H), 1.38 (s, 6 H), 3.19 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7, 30.6, 44.9, 54.6, 89.4.

HRMS: *m/z* calcd for $C_8H_{18}O_2$: 146.1306; found: 146.1328.

Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.82; H, 12.19.

Computations. Becke's gradient-corrected exchange functional[28] in conjunction with the Lee-Yang-Parr non-local correlation functional (B3LYP)[29] and a 6-31G(d,p) basis set as implemented in Gaussian03 were utilized for all optimizations.[30] The energies of the optimized structures were further refined at the coupled cluster level of theory including single, double, and perturbatively determined triple excitations [CCSD(T)][31] utilizing a cc-pVDZ basis set,[32] utilizing the frozen core (no deleted virtuals) approach. All optimized structures were characterized as stationary points by means of determining harmonic vibrational frequencies (with zero imaginary frequencies for minima and one imaginary frequency for transition structures). The xyz coordinates, structural drawings, and absolute energies as well as ZPVEs are available upon request from the authors.

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References

(1) (a) Baumeyer, G.; Dittus, G.; Muller, E. In *Houben-Weyl*, 4th ed., Vol. VI/4; Muller, G., Ed.; Georg Thieme Verlag: Stuttgart, **1963**, 368–374. (b) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772. (c) van Boom, J. H.; Herscheid, J. D. M.; Reese, C. B. *Synthesis* **1973**, 169.
(2) Branco, L. C.; Afonso, C. A. M. *Tetrahedron* **2001**, *57*, 4405.
(3) Kumar, P.; Dinesh, C. U.; Reddy, R. S.; Pandey, B. *Synthesis* **1993**, 1069.
(4) Campelo, J. M.; Garcia, A.; Lafont, F.; Luna, D.; Marinas, J. M. *Synth. Commun.* **1992**, *22*, 2335.
(5) Hoyer, S.; Laszlo, P.; Orlovic, M.; Polla, E. *Synthesis* **1986**, 655.
(6) Hajipour, A. R.; Pourmousavi, S. A.; Ruoho, A. E. *Synth. Commun.* **2005**, *35*, 2889.
(7) Shirini, F.; Zolfigolb, M. A.; Paktinat, M. *Synthesis* **2006**, 4252.
(8) Bartoli, G.; Giovannini, R.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Merchiorre, P.; Paoletti, M.; Sambri, L. *Eur. J. Org. Chem.* **2006**, 1476.
(9) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434.
(10) (a) Magnusson, A.; Hult, K.; Holmquist, M. *J. Am. Chem. Soc.* **2001**, *123*, 4354. (b) Tantillo, D. J.; Houk, K. N. *J. Comput. Chem.* **2002**, *23*, 84.
(11) (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (b) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407.
(12) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.
(13) (a) Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett* **2003**, 1919. (b) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.
(14) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.
(15) Wittkopp, A.; Schreiner, P. R. In *The Chemistry of Dienes and Polyenes*, Vol. 2; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, **2000**, 1029–1088.
(16) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.
(17) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817. (b) Gabriella, D.; Herrera, R. P.; Riccia, A. *Synlett* **2004**, 2374. (c) Hoashi, Y.; Yabuta, T.; Takemoto, Y. *Tetrahedron Lett.* **2004**, *45*, 9185. (d) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (e) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Muller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898. (f) Berkessel, A.; Cleemann, F.; Mukherjee, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 7466. (g) Dove, A. P.; Pratt, R. C.; Lohmeijer, B. G. G.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 13798. (h) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576. (i) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 4032. (j) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367. (k) Mosse, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361. (l) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (m) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643. (n) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6700. (o) Wang, J.; Li, H.; Duan, W. H.; Zu, L. S.; Wang, W. *Org. Lett.* **2005**, *7*, 4713. (p) Wang, J.; Li, H.; Yu, X. H.; Zu, L. S.; Wang, W. *Org. Lett.* **2005**, *7*, 4293. (q) Xu, X. N.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2005**, *12*, 466. (r) Ye, J. X.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (s) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466. (t) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (u) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375. (v) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (w) Dixon, D. J.; Richardson, R. D. *Synlett* **2006**, 81. (x) Hao, L.; Zu, L. S.; Wang, J.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 3145. (y) Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365. (z) Sohtome, Y.; Takemura, N.; Iguchi, T.; Hashimoto, Y.; Nagasawa, K. *Synlett* **2006**, 144. (aa) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894. (ab) Xu, X. N.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137. (ac) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826.

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(18) Tsogoeva, S. B.; Yalalov, D. A.; Hateley, M. J.; Weckbecker, C.; Huthmacher, K. *Eur. J. Org. Chem.* **2005**, 4995.
(19) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 6751.
(20) (a) Hoffman, C. H.; Wagner, A. F.; Wilson, A. N.; Walton, E.; Shunk, C. H.; Wolf, D. E.; Holly, F. W.; Folkers, K. *J. Am. Chem. Soc.* **1957**, *79*, 2316. (b) Pflieger, D.; Muckensturm, B. *Tetrahedron* **1989**, *45*, 2031. (c) Hassner, A.; Näumann, F. *Chem. Ber.* **1988**, *121*, 1823. (d) Hon, Y. S.; Lee, C. F.; Chen, R. J.; Szu, P. H. *Tetrahedron* **2001**, *57*, 5991. (e) Hamada, N.; Sato, T. *Synlett* **2004**, 1802.
(21) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279.
(22) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867.
(23) (a) Williams, D. R.; Benbow, J. D. *Tetrahedron Lett.* **1990**, *31*, 5881. (b) Kliegel, W.; Nanninga, D. *Monatsh. Chem.* **1983**, *114*, 465. (c) Tosco, P.; Bertinaria, M.; Di Stilo, A.; Cena, C.; Sorba, G.; Frutteroa, R.; Gascoa, A. *Bioorg. Med. Chem.* **2005**, *13*, 4750.
(24) Miyabe, H.; Tuchida, S.; Yamauchi, M.; Takemoto, Y. *Synthesis* **2006**, 3295.
(25) Kjolberg, O.; Neumann, K. *Acta Chem. Scand.* **1994**, *48*, 80.
(26) (a) Pihko, P. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2062. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.
(27) Weiss, K. L.; Alshafie, G.; Chapman, J. S.; Mershon, S. M.; Abou-Issa, H.; Clagett-Dame, M.; Robert, W.; Curley, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1583.
(28) Becke, A. D. *Phys. Rev. A: At., Mol., Opt. Phys.* **1988**, *38*, 3098.
(29) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B: Condens. Matter* **1988**, *37*, 785.
(30) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian version B.03*; Gaussian Inc.: Pittsburgh, **2003**.
(31) (a) Purvis, G. D.; Bartlett, R. J. *J. Chem. Phys.* **1981**, *75*, 1284. (b) Urban, M.; Noga, J.; Cole, S. J.; Bartlett, R. J. *J. Chem. Phys.* **1985**, *83*, 4041. (c) Bartlett, R. J.; Watts, J. D.; Kucharski, S. A.; Noga, J. *Chem. Phys. Lett.* **1990**, *165*, 513. (d) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. *Chem. Phys. Lett.* **1989**, *157*, 479.
(32) (a) Dunning, T. H. Jr.; Peterson, K. A.; Woon, D. E. In *The Encyclopedia of Computational Chemistry*, Vol. 1; Schleyer, P. v. R.; Allinger, N. L.; Clark, T.; Gasteiger, J.; Kollman, P. A.; Schaefer, H. F.; Schreiner, P. R., Eds.; John Wiley & Sons: Chichester, **1998**, 88–115. (b) Dunning, T. H. Jr. *J. Chem. Phys.* **1971**, *55*, 716. (c) Dunning, T. H. Jr. *J. Chem. Phys.* **1989**, *90*, 1007.

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