ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/d5cc05075h

Received 2nd September 2025,
Accepted 21st October 2025

DOI: 10.1039/d5cc05075h

rsc.li/chemcomm

TMO_2 – a novel non-aqueous source of hydrogen peroxide

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Oxidation is a linchpin of the chemical industry, used in the manufacture of ~60% of all products and intermediates with an associated global value estimated at USD 20–40 billion. Hydrogen peroxide (H_2O_2) is the preferred green oxidant by virtue of outstanding atom economy and benign co-product (water), yet its routine delivery as dilute aqueous solutions imposes water-compatibility constraints, biphasic mass-transfer penalties, waste generation and costly separations. We report TMO_2, a non-aqueous, bench-stable source of H_2O_2 formed in the green, reusable solvent TMO, decoupling oxidant delivery from water. TMO_2 enables peroxide oxidations under homogeneous, organic conditions, obviating phase-transfer operations and reducing waste while avoiding hazardous peracids (Addible Ltd., TMO_2 International Patent Application No. PCT/EP2025/074472). Concept, preparation, and representative reactivity are described herein; full procedures and data are provided in the SI.

Oxidation reactions are arguably the most pervasive class of transformations in chemistry.[1] They are involved in the manufacture of ~60% of chemicals and intermediates, corresponding to a global commercial value in the order of USD 20–40 billion.[2] Beyond synthesis, oxidation supports numerous waste-treatment and valorisation systems. As such, a long-standing goal has been to couple the importance of oxidation with safer, cleaner reagents and operations. Hydrogen peroxide (H_2O_2) has emerged as the oxidant of choice for this purpose, offering exceptional atom efficiency relative to alternatives and producing only water as stoichiometric by-product.[3] Global H_2O_2 output exceeds 4 million tonnes per year sustaining applications from bleaching and sterilisation to high-volume syntheses (*e.g.*, caprolactam, propylene oxide).[4,5] Future important applications are likely to include oxidative upgrading of organic wastes, including polymers and end-of-life tyres where hydrogen peroxide would be preferred to more hazardous peracids.[6] However, the use of normal aqueous H_2O_2 is often problematic due to immiscibility or water sensitivity of substrates necessitating biphasic operations with halogenated solvents and phase-transfer catalysis, as well as transition-metal salts meaning multiple unit operations and waste-intensive downstream separations. Concentrated solutions can evolve O_2, heightening flammability risks in organic media, consequently, large excesses are routinely charged to offset decomposition.[7] These practicalities erode the intrinsic "greenness" of peroxide oxidation. Beyond the oxidant itself, the solvent environment is pivotal. In the drive towards greener chemistry, 2,2,5,5-tetramethyloxolane (TMO) has been identified as among the greenest and most sustainable solvents, outperforming widely used media such as tetrahydrofuran, 2-methyltetrahydrofuran, toluene, and dichloromethane.[8] Yet even in green solvents, many peroxide-based systems remain encumbered by complexity, for example, the classic Noyori biphasic oxidation of sulfides requires a multi-component mixture complicating scale-up and limiting adoption.[9] Solid adducts such as urea–hydrogen peroxide (UHP) avoid water but suffer reduced reactivity and atom economy while generating urea waste streams, limiting adoption in synthesis.[10] Organic peracids operate anhydrously yet are costly, produce stoichiometric carboxylates, and pose handling and transport hazards (*e.g.*, peracetic acid).[11] A non-aqueous, operationally simple, and safer peroxide source is therefore needed. Herein we introduce TMO_2 – hydrogen peroxide captured within TMO, a non-toxic, stable, and recyclable solvent – providing anhydrous delivery of H_2O_2 without peracids or phase-transfer scaffolding. TMO_2 is bench-stable and easy to dispense, enabling homogeneous peroxide oxidations in common organic media (Fig. 1). We have previously introduced 2,2,5,5-tetramethyloxolane (TMO) as a green, low-polarity, non-toxic ether solvent.[12]

A defining advantage of TMO over conventional ethers is its exceptional resistance to autoxidation, maintained even under forcing conditions. The α,α-disubstitution removes α-C–H bonds adjacent to oxygen and sterically shields the ring

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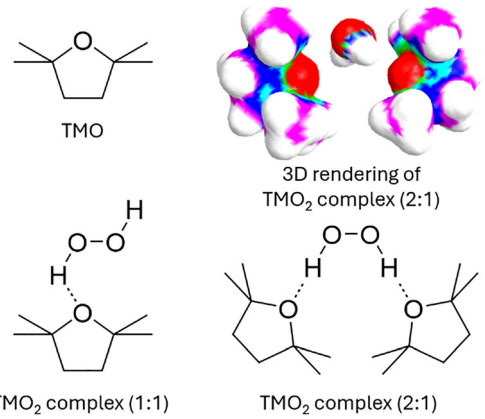


Fig. 1 Top left: TMO; bottom left and right TMO_2 complexes, top right 3D TMO_2 complex (see SI for calculation details).

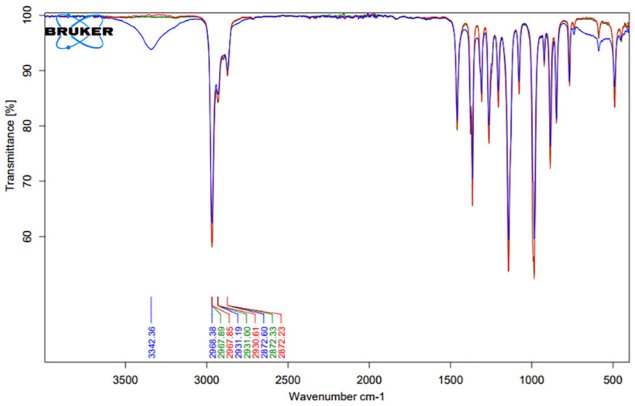


Fig. 2 FTIR spectra of neat TMO (red), TMO_2 after loading with H_2O_2 and drying with Na_2SO_4 (blue), showing the O–H stretch at ~3342 cm^{-1}, and TMO_2 after water washing/drying (green), in which the O–H band is absent. The cyclic ether C–H stretch at 2970 cm^{-1} remains constant and serves as an internal reference (see SI, Fig. S1–S3).

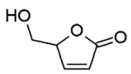
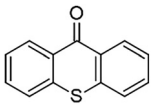
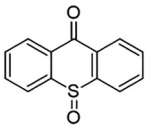
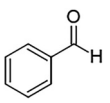
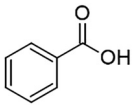
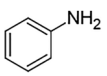
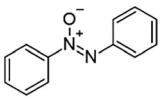
oxygen, suppressing radical initiation pathways. Although this steric encumbrance attenuates classical Lewis basicity, TMO retains strong hydrogen-bond acceptor character (high Kamlet–Taft β), enabling engagement in O···H–X interactions. Recognising that hydrogen peroxide functions as a hydrogen-bond donor (and weak Brønsted acid), we hypothesised that TMO could sequester H_2O_2 as a neutral, non-aqueous adduct (hereafter TMO_2), thereby delivering peroxide reactivity without exposing substrates or catalysts to bulk water while simultaneously avoiding solvent degradation. Simple partitioning experiments confirmed this design. Extraction from commercial 30 wt% aqueous H_2O_2 into TMO generated TMO_2 with typical molar concentrations of between 0.50 mol L^{-1} and 0.70 mol L^{-1} H_2O_2, (8–11 mol%, 0.8–0.9 mmol g^{-1}). Higher loadings can be achieved easily for example, by concentration of the produced TMO_2. The interaction is consistent with hydrogen bonding between the TMO oxygen and one or both O–H donors of H_2O_2; the extensive propensity of H_2O_2 to form hydrogen-bonds is well documented.[13] Notably, the observed peroxide loading exceeds that of water in TMO under comparable conditions. The resulting TMO_2 can be dried over Na_2SO_4 to low-ppm water without measurable loss of active oxygen, and the peroxide content is readily verified qualitatively (indicator strips) and quantified by standard titrimetric analysis (see SI for procedures and data). The incorporation of H_2O_2 into TMO was corroborated by FTIR spectroscopy (Fig. 2). Neat TMO exhibits only the expected ether and C–H absorptions, with no significant intensity in the O–H stretching region. In contrast, freshly prepared TMO_2 shows a strong broad band at ~3342 cm^{-1}, consistent with hydrogen-bonded O–H stretching from bound H_2O_2. Crucially, this feature is eliminated when the TMO_2 sample is washed with water and then dried under identical conditions used during preparation: the O–H band disappears, while the characteristic cyclic ether C–H absorption at 2970 cm^{-1} remains unchanged. The reversible appearance and removal of this band rules out adventitious water as its origin and confirms the signal derives from peroxide present in the TMO_2 phase (peroxide presence was confirmed by strips and permanganate titration SI). The stability of TMO_2 was evaluated under ambient and refrigerated conditions (Table 1). When a freshly prepared batch was stored in direct sunlight at room temperature, permanganate titration (performed in triplicate) revealed only a modest decline in peroxide content, from 2.7 to 2.3 wt% H_2O_2 even after 20 days. After 12 days, small water droplets were visible in the bulk liquid, consistent with partial decomposition of H_2O_2 to water, yet the active oxygen content remained >85% of its initial value as measured by titration. By contrast, TMO_2 stored at ~5 °C showed no detectable loss of peroxide over the same period. These results demonstrate that peroxide binding in TMO confers notable bench stability under ambient conditions, with near-quantitative stability when refrigerated. Importantly, TMO_2 can be readily regenerated from TMO by recharging with aqueous H_2O_2. When a sample of TMO_2 was maintained under reflux at 112 °C overnight (open condenser, no metals present), titrimetric analysis showed that some peroxide remained (1.2%, Table S3 SI). This persistence of active oxygen content under extended high-temperature exposure gave us confidence in its use in oxidation reactions.

Table 1 Stability of TMO_2 stored under direct light at room temperature, determined by permanganate titration (mean of triplicates)

Titration	Day	TMO_2 (grams)	$KMnO_4$ (5% w/w, grams)	w/w% H_2O_2
1	2	2.01	1.90	2.6
2	5	2.01	1.97	2.7
3	9	2.01	1.92	2.6
4	20	2.01	1.75	2.3

We next evaluated its performance in representative oxidations. Substrates were selected to span distinct mechanistic classes and highlight challenges faced by conventional peroxide systems. The Baeyer–Villiger oxidation of levoglucosenone (LGO) is typically performed in biphasic mixtures with halogenated solvents or with peracids, generating substantial waste. Comparable yields (71–75%) have been reported using bulk 30% aq. H_2O_2 with slow addition and long holds, albeit with significant exotherm risk and biphasic waste streams; by contrast, TMO_2 operates homogeneously, avoids peracids/

Table 2 Representative oxidations using TMO_2 as oxidant (reflux, 112 °C, overnight, 5 equiv. H_2O_2 in TMO_2; $B(OiPr)_3$). Isolated yields after flash column purification; full procedures in SI, Schemes S1–S4

	Substrate	Product	EF	RME (%)	AE (%)	Yield (%)
1			2.65	17.8	—	75
2			0.03	55.0	92.7	94
3			0.36	31.1	87.1	75
4			1.15	18.6	—	51

EF = E-factor, atom economy (AE) values are reported only for single oxygen-insertion reactions (entries 2 and 3). AE is not given for entry 1 (Baeyer–Villiger, skeletal rearrangement) or entry 4 (oxidative dimerisation). For full green metric calculations see SI, metrics section and Schemes S1–S4).

halogenated solvents, and minimizes aqueous effluent. Sulfide oxidation often requires peracids or chromate reagents, raising safety and toxicity concerns. Aldehyde oxidation to carboxylic acids with aqueous H_2O_2 is hindered by incomplete conversion and competing hydration. Lastly, aniline oxidation is classically non-selective, with nitrobenzene formation dominating under harsh or metal-catalysed conditions. Each transformation therefore represents a meaningful benchmark for assessing the utility of a non-aqueous peroxide system. Reactions were carried out at reflux in TMO_2 with catalytic or stoichiometric triisopropyl borate. We believe that the boron can form a HOO-B boron peroxo reaction intermediate as has been reported for other hydrogen peroxide reactions.[14] While this catalyst proved effective and convenient, we believe the catalyst aspects of our reaction can be improved and we are confident this will lead to improved product yields. The isolated yields of the corresponding oxidised products are summarised in Table 2. To benchmark the waste profile of TMO_2 oxidations, we report E-factor, reaction mass efficiency (RME) and atom economy (AE) alongside yield where a simple closed form applies (see SI, Schemes S1–S4, metrics section). Across all cases, water is the only stoichiometric by-product and is removed from the system quickly by evaporation (112 °C reaction temperature). At the end of the reaction TMO is recovered by evaporation, eliminating halogenated or biphasic aqueous waste streams typical of conventional peroxide protocols.

LGO was converted to hydroxymethyl-butenolide (75%) with complete peroxide consumption and no detectable side-products (entry 1, Table 2) consistent with a controlled, non-aqueous peroxide transfer. In this case, however, the reaction required stoichiometric triisopropyl borate due to the need to generate a sufficiently electrophilic peroxyborate intermediate to activate the relatively electron-poor LGO carbonyl, in the absence of strong Brønsted acids or metal catalysts. This contrasts with the lower borate loadings effective for more easily oxidised substrates (sulfides, aldehydes, amines, entries 2–4). From a metrics perspective, the stoichiometric borate depresses the RME (17.8%), while the E-factor (2.65) remains comfortably in the "good" fine-chemicals range. Both figures point to oxidant activation efficiency as the main bottleneck rather than wasteful by-products, since the only stoichiometric coproducts are water and recyclable solvent. Concentrating TMO_2, employing stronger catalytic borate or alternative Lewis acids, and staged oxidant addition represent clear optimisation strategies. Even under these unoptimized conditions, the 75% yield is comparable to the best reported solvent- and catalyst-free aqueous H_2O_2 protocols,[15] while offering the additional advantage of avoiding large aqueous volumes and energy-intensive separations.

Thioxanthone was oxidised selectively to the corresponding sulfoxide in 94% yield with no evidence of over-oxidation to the sulfone (entry 2). Under these conditions, TMO_2 delivers sufficient oxidising power for a single two-electron S-oxidation possibly due to heterolytic O-transfer from the proposed HOO-B intermediate. The low-polarity TMO_2 would provide less stabilisation for the formation of more polar sulfones, thereby disfavouring the second oxygen insertion (sulfoxide to sulfone) and enforcing clean mono-oxidation. The transformation has high atom economy (92.7%) with a strong RME (55.0%) and an exceptionally low E-factor (0.03). These values reflect both the intrinsic ease of TMO_2 S-oxidation and the efficient consumption of peroxide under catalytic borate loading (5 mol%). The ability to halt cleanly at the sulfoxide is significant for industrial targets such as esomeprazole, where over-oxidation to sulfone can be problematic.[16] Benzaldehyde to benzoic acid gave a strong atom economy (87.1%) and a low E-factor (0.36, excl. water), but the RME (31.1%) was modest due to residual oxidant at endpoint (entry 3). Benzoic acid was isolated in 75% yield, with no benzyl alcohol or other by-products, highlighting clean selectivity. Mechanistically, aldehyde oxidations with H_2O_2 often proceed *via* the gem-diol hydrate;[17] whereas in low-water TMO_2, suppressed hydration may have slowed turnover, leaving peroxide unconsumed. Importantly, some TMO_2 remained stable and detectable even after reflux, confirming that the oxidant is preserved rather than decomposed. Introducing small, controlled amounts of water or a protic co-solvent could enhance gem-diol formation and improve oxidant efficiency, but quantifying optimal water content lies outside the scope of this work and will be addressed in future studies.

Aniline to azoxybenzene gave an RME of 18.6% and an E-factor of 1.15, reflecting both the moderate yield (51%) and the presence of residual peroxide at endpoint (entry 4). Interestingly, only the azoxy product was detected with no nitrobenzene or azo by-products, indicating that the system progresses *via* a selective N–N coupling pathway. Mechanistically, this behaviour is consistent with stepwise oxidation to nitroso/phenylhydroxylamine, followed by condensation and dehydrogenation, rather than direct two-electron oxidation to nitro group. The anhydrous, low-polarity environment and mild

Lewis-acid activation appear to suppress formation of strongly electrophilic nitrating species, enforcing the unusual selectivity for azoxy. Conventional aqueous H_2O_2 or peracid oxidations of anilines typically deliver nitrobenzene or mixed azo/azoxy products, requiring additional purification.[18] By contrast, the TMO_2 system affords a single azoxy product under metal-free, recyclable conditions. Azoxybenzenes are valued intermediates in the dye and pigment industry and as mesogenic units in functional materials, and direct access under such simple conditions suggests an attractive synthetic shortcut. We emphasise that only four representative cases are presented here in line with the Chemical Communication format. A broader substrate scope, flow-operation studies, and optimisation of oxidant loading are ongoing and will be reported separately.

TMO_2 acts as a bench-stable, non-aqueous, recyclable carrier of H_2O_2, enabling clean, selective oxidations across diverse substrates under metal- and halogen-free conditions. Its low-polarity medium unlocks alternative selectivity manifolds, such as sulfoxide-only and azoxy-over-nitro, that are challenging in water. The only stoichiometric by-product is water, halogenated or aqueous waste is avoided. TMO is recovered simply by distillation, and TMO_2 can be regenerated indefinitely, limited only by solvent losses. The green chemistry metrics are very promising (see Table S4 in SI) and by looking more broadly using the "eco-scale" approach[19] we can see that apart from seeking better yields as discussed earlier, the only other "hot spot" is the current need for high reaction temperatures which are yet to be optimised. With further optimization of oxidant loading and activation, this platform could deliver truly low-waste, industrially relevant peroxide chemistry. Its stability and reloadability make it an ideal candidate for flow systems, scale-up, and solvent-integrated recycling, with promising applications across fine chemicals, pharma, and polymer or waste valorisation.

We thank Dr Vinnie Fagan, Gaia Ravetti and Lucas Roucou for their contributions to experimentation and Richard Porter for driving the lab build-out and capacity expansion that enabled this work. This work was self-funded by Addible Ltd.

Conflicts of interest

Addible Ltd has filed an international patent application relating to the TMO_2 system described in this Communication.

Data availability

All data supporting this study are provided in the electronic supplementary information (SI). Supplementary information: experimental procedures, metrics, and spectra. See DOI: https://doi.org/10.1039/d5cc05075h.

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