Catalyst-Free Transfer Hydrogenation of Activated Alkenes Exploiting Isopropanol as the Sole and Traceless Reductant

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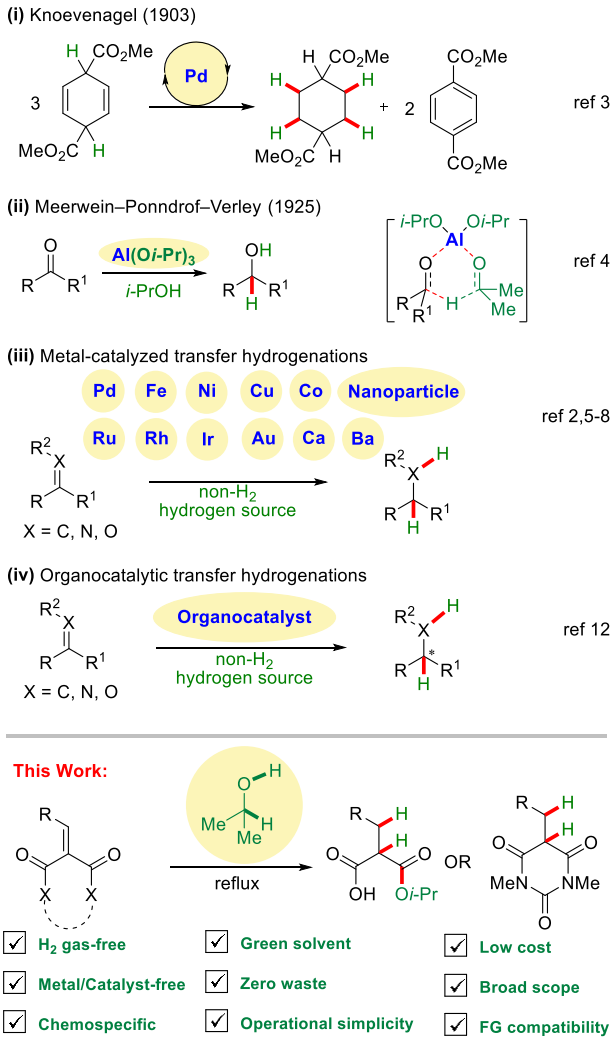
ABSTRACT: Both metal-catalyzed and organocatalytic transfer hydrogenation reactions are widely employed for the reduction of C=C, C=O and C=N bonds. Described herein is an unconventional catalyst-free transfer hydrogenation reaction of activated alkenes using isopropanol as an eco-friendly reductant and solvent. The reaction gives convenient synthetic access to a wide range of substituted malonic acid half oxyesters (SMAHOs) in moderate to good yields. Mechanistic investigations point towards an unprecedented hydrogen bond-assisted transfer hydrogenation process.

The catalytic hydrogenation of unsaturated bonds is one of the most valuable and often the key transformation used in the production of fine chemicals, active pharmaceutical ingredients (APIs) and agrochemicals. Both homogeneous and heterogenous catalyst systems, with molecular H_2 as the hydrogen source, have been widely studied and used for traditional hydrogenation reactions.[1] Transfer hydrogenation (TH) has emerged as a practical and greener alternative to traditional hydrogenation methods since it avoids the use of flammable gases and complicated experimental set-ups. Specifically, the serious safety hazards associated with the use of high-pressure hydrogenation reactors are eliminated by employing readily available, inexpensive and environmentally friendly alternative hydrogen sources in TH methods.[2] The first TH reaction was reported nearly 120 years ago by Knoevenagel and coworkers. They described the simultaneous hydrogenation/dehydrogenation of 1,4-cyclohexadiene derivatives (Scheme 1, eq.(i)).[3] The Meerwein–Ponndorf–Verley reduction of ketones using a main-group metal compound (e.g., aluminum isopropoxide) as a mediator is another classic example of TH developed in the early 20th century (Scheme 1, eq.(ii)).[4] In search for greener and more economical alternatives, dozens of new and catalytic TH reactions have been developed during the past few decades. Transition metal complexes, main group metals, alkaline earth metals and nano-materials have been successfully employed as catalysts to reduce carbonyls, imines and both alkene and alkynes, leading to the "Golden age of TH reactions". Parallel to the refinement of the metal-based catalytic systems, significant advancement has been observed in the choice of green hydrogen sources that range from primary and secondary alcohols to various unconventional hydrogen donors (e.g.; Hantzsch esters, 1,4-cyclohexadiene, formic acid and even water) (Scheme 1, eq. (iii)).[2,5-8]

As a metal-free alternative, Frustrated Lewis Pair (FLP)-catalyzed TH methods were developed for the hydrogenation of activated C=C bonds or polar C=X bonds. However, these methods still require the use of both molecular H_2 and high pressure reactors.[9] As a significant advancement in this direction, nearly a dozen organocatalytic TH reactions have been developed using non-H_2 hydrogen sources.[10] The MacMillan and List groups independently reported an ammonium salt-catalyzed transfer hydrogenation of α,β–unsaturated aldehydes using Hantzsch esters as biomimetic hydrogen sources.[11] Subsequently, the Rupeing and List groups contemporaneously extended this concept further to include the chiral Brønsted acid-catalyzed asymmetric TH of imines using Hantzsch esters as hydrogen sources (Scheme 1, eq. (iv)).[12] The only catalyst-free chemoselective reduction of conjugated alkenes using Hantzsch esters was reported by the Wang group in 2014.[13]

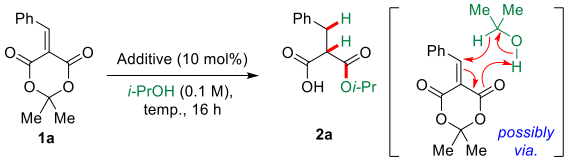


Scheme 1: The evolution of transfer hydrogenation reactions.

Despite all the advancements outlined above, a chemoselective, green and cost effective TH method for alkenes remains highly desirable. Nearly all known TH strategies require a catalyst, therefore, a catalyst-free TH reaction of alkenes using a readily available and inexpensive hydrogen source would contribute significantly to the evolution of TH reactions. Herein, we report the catalyst-free

transfer hydrogenation reaction of activated alkenes exploiting isopropanol as the sole and traceless reductant.

The present study was initiated after a serendipitous observation: the C=C double bond in benzylidene Meldrum's acid **1a** was unexpectedly reduced when heated in isopropanol under reflux conditions. The overall transformation gave rise to the benzyl-substituted malonic acid half oxyester **2a** in 66% isolated yield (Table 1, entry 1). It is noteworthy that the substituted malonic acid half oxyesters (SMAHOs) are an important class of molecules well known as pronucleophiles or enolate surrogates for a range of olefination and addition reactions in the modern synthetic organic chemistry.[14] To our surprise, the reduction of the C=C bond (i.e., a formal hydrogenation) did not require the presence of any catalyst and occurred readily in boiling isopropanol which, apparently functioned as both the solvent and the sole reductant. To the best of our knowledge, this is the first example of a catalyst/metal-free transfer hydrogenation reaction of electron-deficient alkenes using isopropanol as the sole hydrogen source. Realizing the potential of this catalyst-free TH reaction as a greener and more economical alternative to the currently known catalytic TH reactions, we decided to investigate further and explore the scope and limitations of this unprecedented TH reaction. Initially, we carried out a few control experiments to understand the impact of changing some of the key reaction parameters on the feasibility of the overall transformation. Using primary or tertiary alcohols as solvents (e.g., methanol, ethanol or *tert*-butanol) at reflux temperature, the starting material **1a** remained unchanged and neither reduced nor ring-opened products were detected. A quick temperature screen revealed that the TH reaction does not proceed at room temperature (25 °C) in isopropanol solvent (Table 1, entry 3), however, heating the reaction mixture for 16 h at 60 °C afforded product **2a** in 32% yield (Table 1, entry 2). Based on these initial experiments, our working hypothesis was that the reduction of the C=C bond proceeds via a hydrogen bond-assisted hydride-transfer (*see* header of Table 1).[15] We anticipated that the use of either Brønsted or Lewis acids would further activate the ester carbonyls of the Meldrum's acid moiety to make the C=C more electrophilic and thus would facilitate the hydride-transfer process.[16] Therefore, we studied how employing 10 mol% of various Brønsted and Lewis acid additives (Table 1, entries 4-16) affected the efficiency of the transformation. Hydrochloric acid in ethereal solution markedly improved yield of **2a** from 66 to 82% (entry 4), while other Brønsted acids (e.g., HBr, AcOH, Amberlyst and CSA) produced similar or lower yields of the product **2a** (entries 5-8). Next, we screened electronically different aryl boronic acid derivatives as additives, as they are expected to activate the substrates either as Brønsted or Lewis acids (entries 11–16).[17] Electron-deficient boronic acids furnished higher yields of **2a** (entries 14–16) in contrast to electron rich boronic acids (entries 12–13). Among the screened additives, 3,5-*bis*(trifluoromethyl)phenyl boronic acid was found to be the most efficient, furnishing **2a** in 83% isolated yield (90% NMR yield) (entry 16). Reactions carried out at lower temperatures (60, 40 and 25 °C) in presence of 3,5-*bis*(trifluoromethyl)phenyl boronic acid showed drastic drop in the yield of **2a** (entries 17–19). The increase of the reaction concentration (e.g., 0.5 M & 0.2 M versus 0.1 M) resulted in a substantial decrease in the yield (entries 20 & 21).

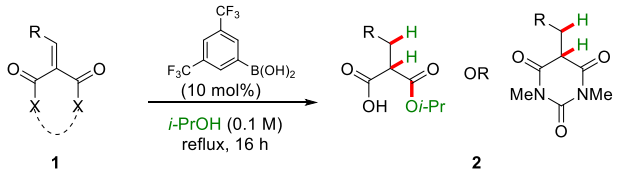


entry[a]	additive	temp	yield (%) of **2a**
1	none	reflux	66[b]
2	none	60 °C	32
3	none	25 °C	<5
4	HCl (in ether)	reflux	82
5	HBr (33% in H_2O)	reflux	40
6	AcOH (glacial)	reflux	60
7	Amberlyst	reflux	70
8	CSA	reflux	64
9	$Sc(OTf)_3$	reflux	41
10	$B(OH)_3$ [Boric Acid]	reflux	70
11	Ph-$B(OH)_2$	reflux	58
12	4-MeO-Ph-$B(OH)_2$	reflux	67
13	4-NMe_2-Ph-$B(OH)_2$	reflux	59
14	4-NO_2-Ph-$B(OH)_2$	reflux	83
15	3,5-*di*-F-Ph-$B(OH)_2$	reflux	73
16	3,5-*bis*-CF_3-Ph-$B(OH)_2$	reflux	83[b]
17	3,5-*bis*-CF_3-Ph-$B(OH)_2$	25 °C	<5
18	3,5-*bis*-CF_3-Ph-$B(OH)_2$	40 °C	10
19	3,5-*bis*-CF_3-Ph-$B(OH)_2$	60 °C	32
20	3,5-*bis*-CF_3-Ph-$B(OH)_2$	reflux	60[c]
21	3,5-*bis*-CF_3-Ph-$B(OH)_2$	reflux	16[d]

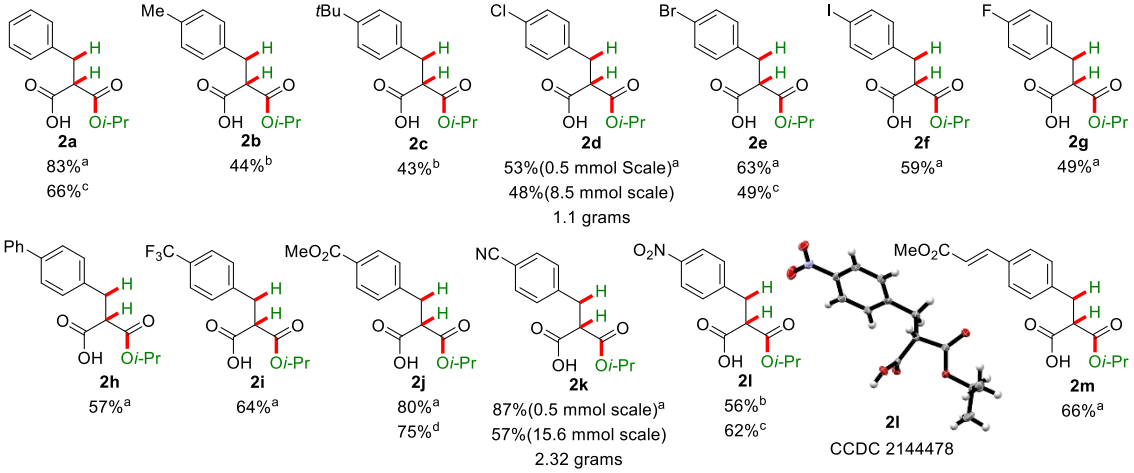
[a] Reactions were conducted on a 0.5 mmol scale. **1a** (0.5 mmol) and additive (10 mol%) were suspended in *i*-PrOH (0.1 M) and then heated to the given temperature. The reaction was stirred for 16 h. All given yields are NMR yields using 1,3,5-trimethoxybenene as standard. [b] Isolated yields. [c] Concentration: 0.2 M. [d] Concentration: 0.5 M.

Table 1: Optimization of the TH reaction conditions.

With the optimized reaction conditions in hand, we were ready to explore the scope and limitations of this unprecedented transfer hydrogenation reaction (Scheme 2). A series of electronically dissimilar alkylidene Meldrum's acids was prepared by the condensation of Meldrum's acid and substituted aldehydes (see SI, page S-5). The substituted malonic acid half oxyester products (**2a–2z**) were isolated in moderate to good yields using the optimized reaction conditions. Alkylidene Meldrum's acids with electron-donating substituents at the *para* position (Scheme 2B, **1n–1o**) reacted slower than those with electron-neutral and electron-withdrawing substituents (Scheme 2A, **1a–1m**) to furnish the corresponding malonic acid half oxyesters (**2a–2o)** in moderate to good yields (43% to 87%).

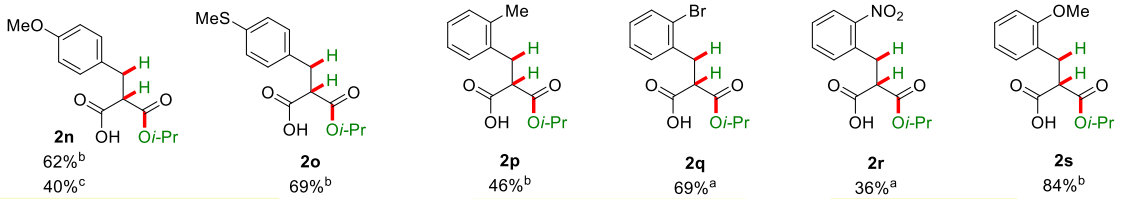


A. Electron-Neutral and Electron-Deficient *p*-Substituted Arenes



B. Electron-Rich *p*-Substituted Arenes

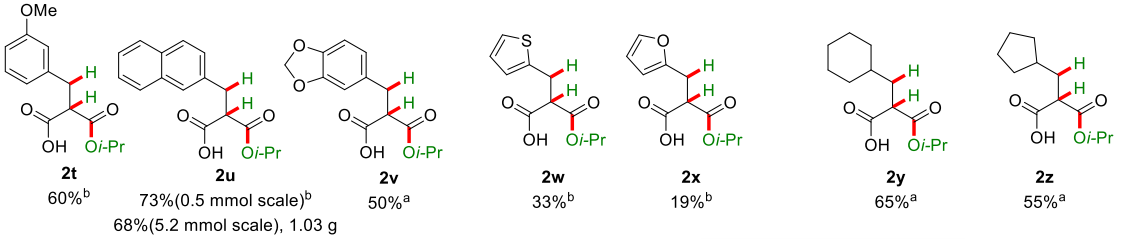
C. *o*-Substituted Arenes



D. *m*-Substituted and Fused Arenes

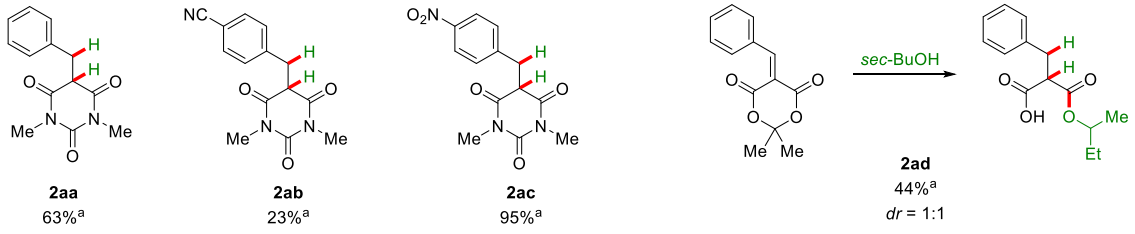
E. Heteroaromatic Substituents

F. Alkyl Substituents

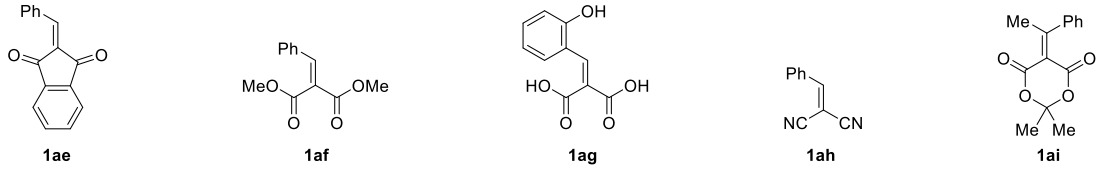


G. Barbituric Acid Derivatives

H. Other Secondary Alcohols



I. Unsuccessful substrates

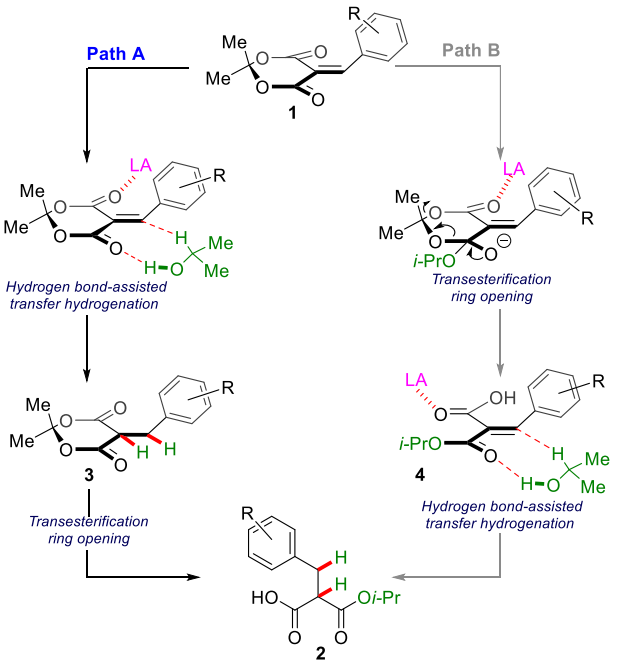


[a] Unless noted otherwise, all hydrogenation reactions are carried out in *i*-PrOH (at 0.1 M concentration) with 0.5 mmol of the substrate **1**, 0.05 mmol of 3,5-*bis*-CF_3-Ph-$B(OH)_2$ under reflux condition for 16 hours. See Supporting Information for detailed procedures. The yields shown are isolated yields of the half oxyester products **2** after flash column chromatography. [b] Reaction carried out for 40 hours. [c] Reaction carried out without 3,5-*bis*-CF_3-Ph-$B(OH)_2$. [d] Reaction carried out at 60 °C instead of reflux.

Scheme 2: Scope of substrates for the TH reaction.

Interestingly, the TH/transesterification reaction showed chemospecificity for the C=C double bond of the alkylidene Meldrum's acid moiety over the C=C bond of a simple α,β–unsaturated ester (**2m**). Alkylidene Meldrum's acid substrates featuring *ortho*- and *meta*-monosubstituted as well as fused arenes (**1p**–**1v**) were well-tolerated under the reaction conditions, furnishing the expected products (Scheme 2C & 2D, **2p**–**2v**) in moderate to good yields (36% to 84%). Next, we investigated the reactivity of heteroarene-bearing alkylidene Meldrum's acids (Scheme 2E, **1w** & **1x**) and found that the more electron-rich heteroarene rings resulted in a decrease of isolated yield (**2w**–**2x**; 33% to 19% and alkylidene Meldrum's acid derived from pyrrole-2-carboxaldehyde did not reduce under this condition). Replacing the aromatic rings with cyclic alkyl substituents on the alkylidene Meldrum's acid were also successfully reduced and transesterified (**2y**-**2z,** Scheme 2F). Overall, we found the TH reaction to be readily scalable; the larger scale (5 to 15 mmol) reactions afforded gram quantities of the products **2d**, **2k** and **2u** (1.10 grams, 2.32 grams and 1.03 grams, respectively).

We then shifted our attention to varying the structure of the cyclic 1,3-dicarbonyl moiety. Thus, alkylidene barbituric acids underwent smooth TH under identical reaction conditions, however, unlike alkylidene Meldrum's acids, the barbituric acid ring remained intact (Scheme 2G, **2aa**–**2ac**). Interestingly, when the Meldrum's acid moiety was replaced with 1,3-indandione and acyclic malonic ester/acid or malononitrile (**1ae**–**1ah**), the TH reaction was not successful. Moreover, the acetophenone-derived alkylidene Meldrum's acid **1ai** also did not undergo transfer hydrogenation. Finally, we were curious to see if other secondary alcohols besides isopropanol would serve as viable reducing agents - the use of *sec*-butanol as solvent afforded the corresponding malonic acid half oxyester compound **2ad** in 44% yield as an 1:1 inseparable mixture of diastereomers (Scheme 2H). This observation indicates that a rigid, six-membered cyclic ester or an amide is a key requirement for the transfer hydrogenation reaction.



Scheme 3: Proposed possible reaction pathways leading to the product **2**.

We propose that there are two possible distinct mechanistic pathways (Scheme 3, **Path A** or **B**) that could lead to the formation of the observed products **2**: a TH followed by transesterification (i.e., ring-opening) or a transesterification followed by transfer hydrogenation. Specifically, in **Path A**, alkylidene Meldrum's acid derivative **1** first undergoes a concerted hydrogen bond-assisted hydride-transfer from *i*-PrOH to generate alkyl-substituted Meldrum's acid **3**. We surmise that the hydride-transfer step is the key step as it likely requires a hydrogen bonding network to create a cyclic transition state similar to the MPV reduction[4] in order to facilitate the hydride-transfer process. The Lewis acid additive [3,5-bis(trifluoromethyl)phenyl boronic acid] further activates the alkylidene Meldrum's acid moiety as a hydride acceptor, potentially through additional hydrogen bonding network. Finally, the alkyl-substituted Meldrum's acid **3** undergoes a transesterification reaction with *i*-PrOH to furnish compound **2**. On the other hand, **Path B** would first undergo a ring-opening transesterification to generate the corresponding alkylidene malonic acid half oxyester intermediate **4**, which then would undergo a concerted hydride-transfer process to furnish the observed product **2**.

To experimentally differentiate between these two possible mechanistic event sequences (i.e., **Path A** or **Path B**), we aimed to detect the intermediates **3** and **4** (Scheme 3) using ^{1}H-NMR. Towards this end, alkylidiene Meldrum's acid **1e** was heated at reflux in *i*-PrOH only for 1 h. The ^{1}H-NMR of the resulting crude reaction mixture was compared with the spectra of pure alkyl-substituted Meldrum's acid **3e** and pure alkylidene malonic acid half oxyester **4e,** synthesized independently (See SI Page S-10). This experiment clearly showed the presence of intermediate **3e** along with the product **2e** in a 1:5 ratio (Figure 1) (See SI, Page S-12). Surprisingly, presumed intermediate **4e** was not observed in the crude reaction mixture. Moreover, complete conversion to product **2e** occurred when intermediate **3e** was heated in *i*-PrOH for 16 hours at reflux (Scheme 4, eq. (i)). On the other hand, the proposed intermediate **4e**, from the alternative **Path B**, remained unreacted under identical conditions (Scheme 4, eq. (ii)). Taken together, these observations support Path A over Path B, that is, that a transfer hydrogenation occurs first, followed by a transesterification reaction (Scheme 3).

We further investigated whether the *i*-PrOH would still be viable as a reducing agent in the presence of a co-solvent. Using toluene as the main solvent in the presence of 5 equivalents of *i*-PrOH, the reduction of alkylidene Meldrum's acid **1a** did not occur based on the fact that product **2a** was not detected. However, when equal volumes (1:1) of toluene and *i*-PrOH were used as the reaction medium, product **2a** was isolated in 36% yield; in contrast, 83% of **2a** was isolated when pure *i*-PrOH was used as the solvent. These results strongly suggest the critical importance of a hydrogen-bonding network to making this TH reaction possible. We also studied the TH reaction in pure hexafluoroisopropanol (HFIP) and also using an HFIP-IPA (1:1 mixture). Interestingly, the TH did not take place in pure HFIP medium, however, in the presence of HFIP-IPA mixture (1:1) the expected reduced malonic acid half oxyester **2a** product was isolated in 40% yield along with the non-reduced ring opened half oxyester **4a** in 24% yield. (Scheme 4, eq. (iii)).

Finally, a set of deuterium-labelling experiments were carried out to study the deuterium incorporation during the reduction. Reduction of **1ac** with *i*-PrOD resulted in the formation of the reduced product **2ac** with 68% D-incorporation at the enolizable C2 position (Scheme 4, eq. (iv)). Furthermore, when the reduction was carried out in the presence of *i*-PrOH-2-D resulted the reduced product **2ac** with 84% D-incorporation at the benzylic position (Scheme 4, eq. (v)) (See SI Page S-9).

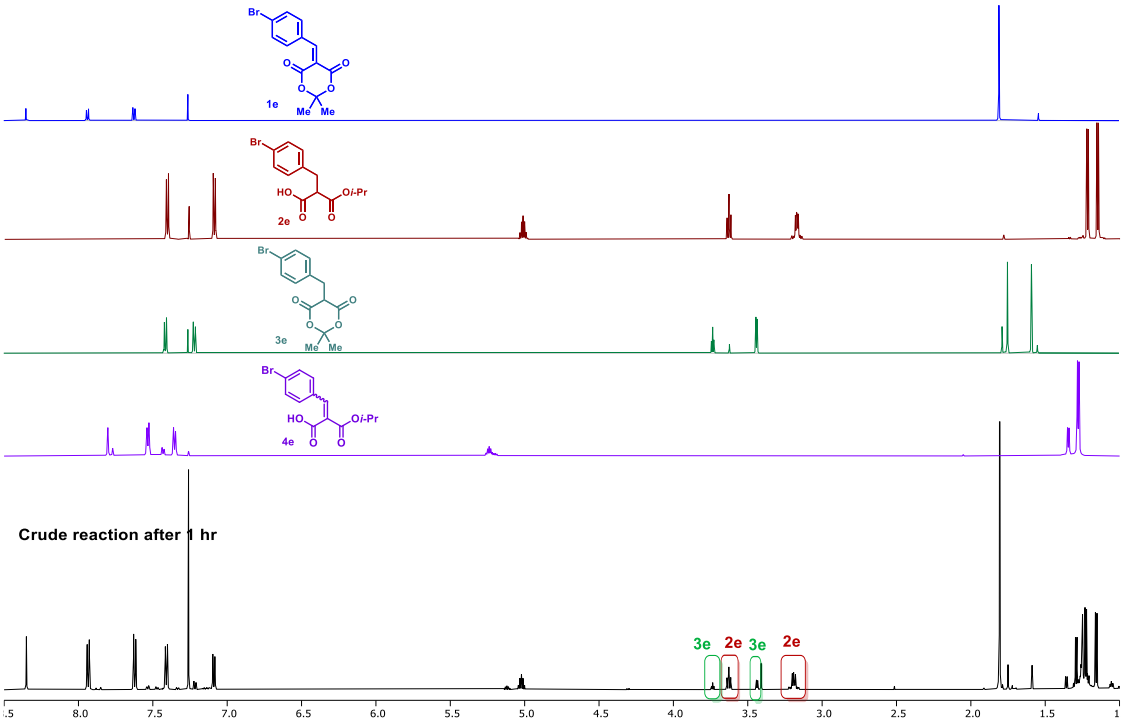
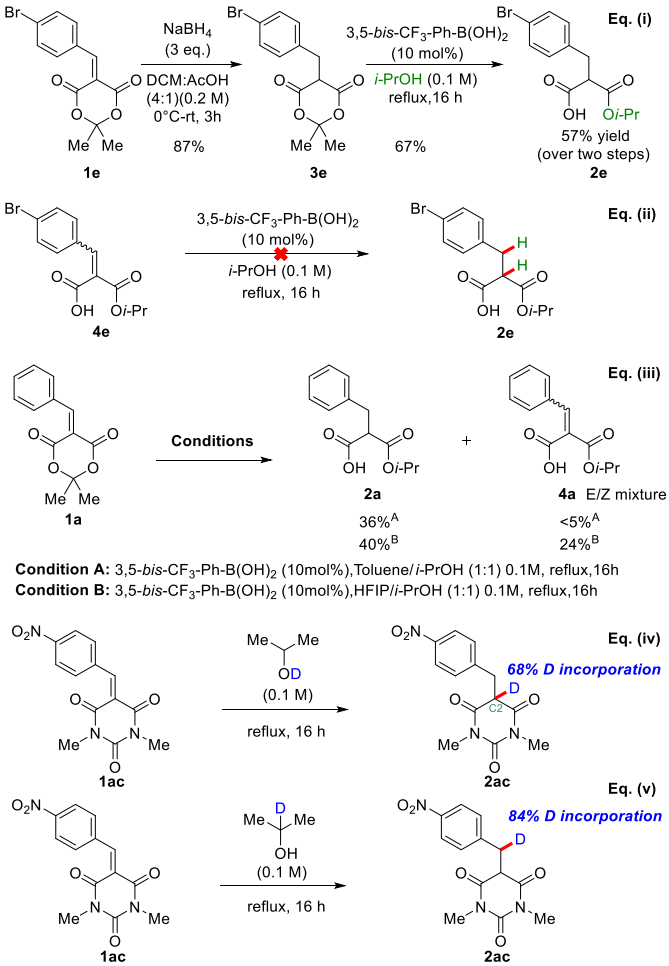


Figure 1: Mechanistic studies for the identification of reaction intermediates.



Scheme 4: Mechanistic control experiments.

Finally, to better understand the hydrogen-transfer process itself, we employed computational studies at B97D3/def2TZVP/CPCM(*i*-PrOH) level using a model of **1a** reacting with a single molecule of isopropanol using orca 5.0.2.[18] This simplified model arrives to the key transition state, which is expected to be further modulated by an external hydrogen bonding network. Carrying out a full conformational search of **1a** and isopropanol using CREST/gfn2 followed by DFT refinement identified a highly bound precomplex, where the isopropanol is bound in a pocket of **1a** through a C=O···H hydrogen bond (Figure 2A).[19] The lowest energy pathway from this hydrogen-bonded precomplex towards the reduction is a concerted transfer hydrogenation event, with a calculated barrier of ΔG_{TS} = 17.7 kcal/mol, fitting well with the needed elevated temperature. The identified lowest energy path proceeds *via* an 8-membered concerted hydride-proton exchange transition state (Figure 2A).

In order to understand the experimentally observed requirement for a cyclic 1,3-dicarbonyl system, we also computed the pathway for a model compound where the distal C=O of **1a** was replaced with a methylene unit (**1aj**, Figure 2A). This electronic change, while maintaining the cyclic backbone, resulted in an almost twice as high of a reduction barrier at ΔG_{TS} = 27.1 kcal/mol compared to **1a**, suggesting that the cyclic backbone is needed for conformational locking to achieve full planarization of the 1,3-dicarbonly motif (Figure 2B). The coplanarity of both C=O groups with the C=C system results in full conjugation over the system and a significant increase of electrophilicity through π^*-lowering. This planarization can be seen in the minimum energy conformer of **1a** where the O=C-C=O dihedral angle 8.0 ° (planarization observed in scXRD structure of **1a**, see SI, page S-8). Comparing this against the computed minimum energy conformer for acyclic dimethyl ester **1af**, the non-planarity is highly pronounced: O=C-C=O dihedral angle for computed minimum energy geometry of **1af** is 107.6 °, and one of the carbonyl systems lies near-orthogonal to the C=C π-

system (Figure 2C). Such C=C conjugation to only one of the C=O systems results in higher reduction barrier, as observed for **1aj**. Based on the twisted nature of **1a**, it is likely the reduction also enjoys some contribution from strain-release effects. The observed higher yields with hydrogen bonding to solvent, and both protic and Lewis-acidic activation can also be rationalized with this model, as all of these can bind to the distal carbonyl group and provide further π*-lowering.

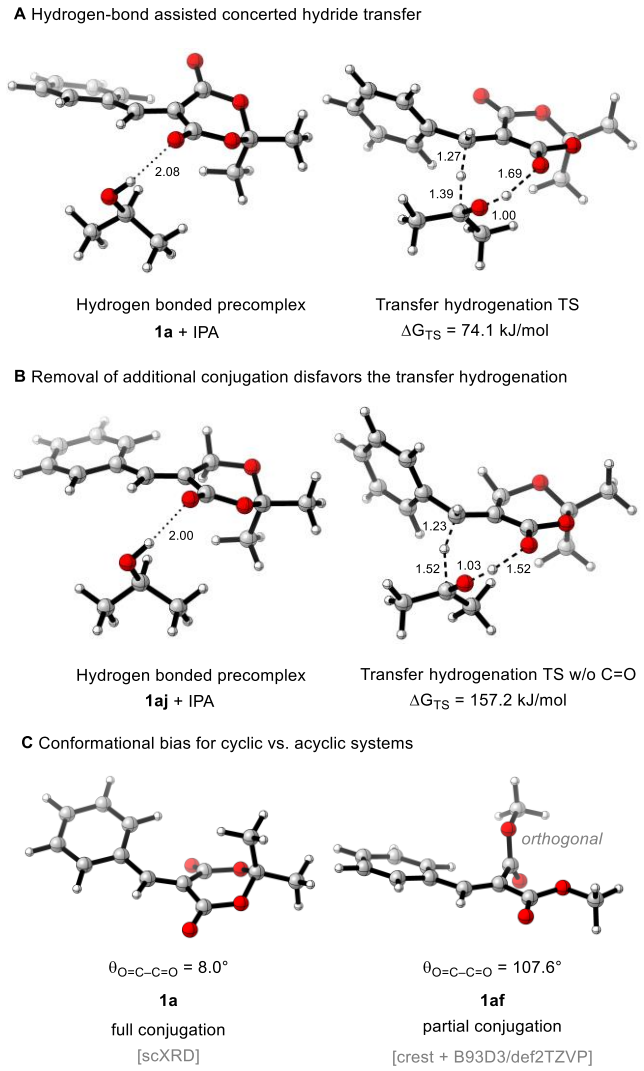
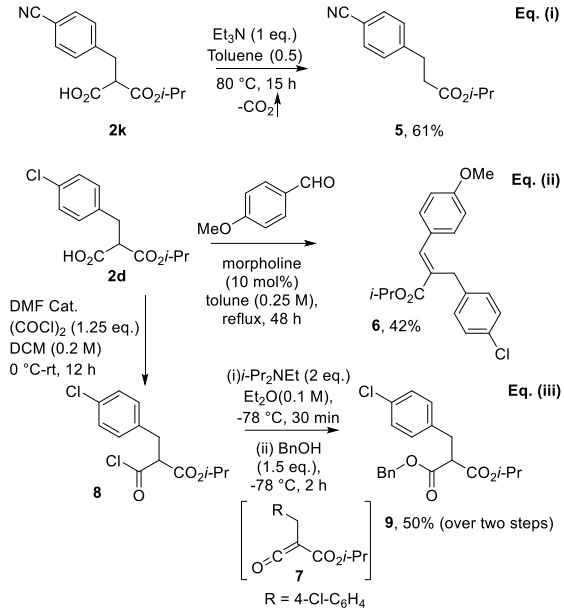


Figure 2: Reduction barriers for the hydrogen bond-assisted transfer hydrogenation process.

This transfer hydrogenation/transesterification method allows straightforward synthetic access to a wide variety of substituted malonic acid half oxyesters (SMAHOs).[14] The method offers improved overall yields and operational simplicity when compared to the previously reported methods to access various half oxyester derivatives from malonate esters or Meldrum's acids.[21] The resulting SMAHOs are valuable compounds for the generation of versatile reactive intermediates, such as enolates, isocyanates and ketenes.[14] Towards this end, we carried out a few representative transformations (Scheme 5). In the first reaction, compound **2k** underwent smooth decarboxylation when heated at 80 °C in the presence of triethylamine to furnish dihydrocinnamate ester **5** (Scheme 5, Eq. i). Next, a Galat reaction was carried out using compound **2d** in presence of 4-methoxybenzaldehyde which led to the formation of a substituted phenylacrylic acid derivative (**6**, exclusively the *E*–isomer; Scheme 5, Eq. ii). Finally, we were able to prepare mixed malonate ester **9** from **2d** via the corresponding ketene intermediate **7**.



Scheme 5: Synthetic utility of SMAHOs.

In conclusion, we have discovered a previously unknown catalyst-free transfer hydrogenation reaction of alkylidene Meldrum's acids and -barbituric acids. Our detailed experimental/computational mechanistic studies point toward an unprecedented hydrogen-bond assisted transfer hydrogenation process. Overall, this newly developed TH method allows the convenient synthesis of a wide range of synthetically useful substituted malonic acid half oxyesters (SMAHOs) which, in turn, can be utilized as versatile building blocks for the preparation of structurally complex organic molecules.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, computational details, spectroscopic data of compounds, NMR spectra of compounds and crystal structure data. (PDF)

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All authors have given approval to the final version of the manuscript. SMR and MY analyzed the crystal structures. SI and JHS carried out the computational analysis.

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Notes

The authors declare no competing financial interests.

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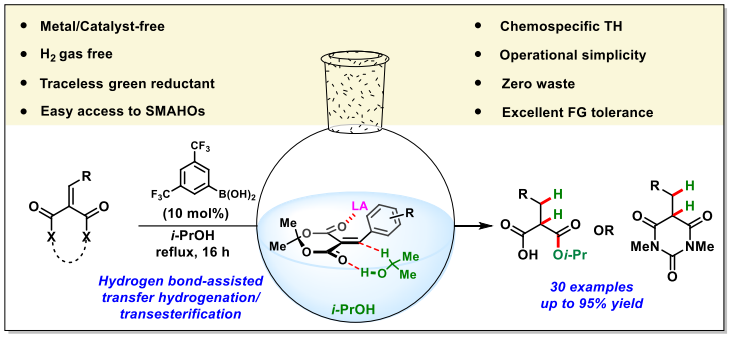
Metal/Catalyst-free
H2 gas free
Traceless green reductant
Easy access to SMAHOs
Chemospecific TH
Operational simplicity
Zero waste
Excellent FG tolerance
(10 mol%)
i-PrOH
reflux, 16 h
Hydrogen bond-assisted transfer hydrogenation/ transesterification
LA
i-PrOH
OR
30 examples
up to 95% yield