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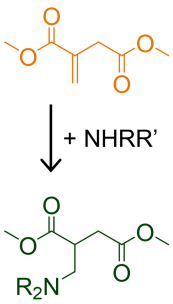
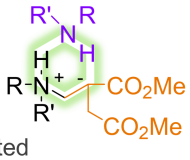
**Aza-Michael addition:** New mechanistic insights

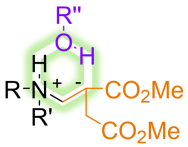



- Aprotic solvent = Amine (reactant) assisted





- Low concentration = Self-assisted
- Protic solvent = Alcohol (solvent) assisted



# An experimental investigation into the kinetics and mechanism of the aza-Michael additions of dimethyl itaconate

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## Abstract

The aza-Michael addition is a versatile reaction for the modification of α,β-unsaturated carbonyl compounds with amines. The reactivity of dimethyl itaconate as a bio-based Michael acceptor is explored in this work. Through its reactions with piperidine and dibutylamine, it was found that the order of reaction can be changed by the choice of catalyst, solvent, or the concentration of the amine reactant. The effectiveness of catalysts was proportional to their Lewis acidity. Competitive isomerisation of dimethyl itaconate into unreactive regioisomers can be suppressed using low-polarity solvents and lower temperatures. This investigation of the aza-Michael additions of dimethyl itaconate has clarified the possible reaction mechanisms and optimised the protocol, supporting further use of this reaction in small molecule synthesis and modification of polymers.

## Keywords

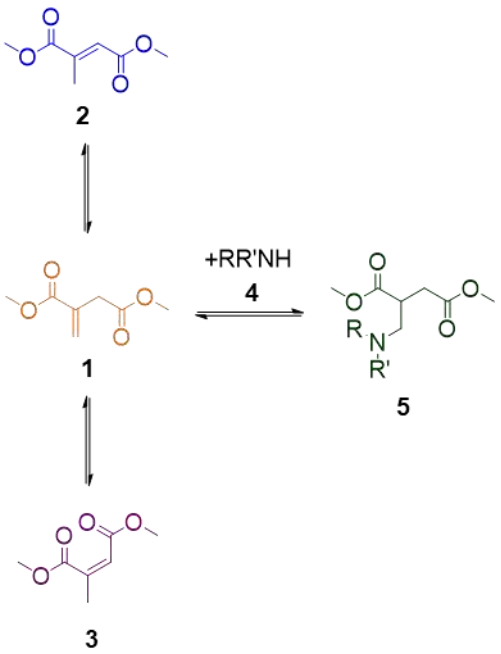
Michael addition; Kinetics; Catalysis; Solvent effect

## 1. Introduction

Itaconic acid is an unsaturated dicarboxylic acid and a valuable bio-based chemical intermediate. Itaconic acid is produced from carbohydrates by microbial fungi fermentation.[1] The production of bio-based polymers from itaconic acid is of major interest,[2] as is the synthesis of small multifunctional molecules.[3] The modification of itaconate polyesters by addition reactions has recently been explored as a means of modifying material properties.[4,5,6,7,8] The conventional Michael addition undertaken by a nucleophilic carbanion (Michael donor) onto an α,β-unsaturated carbonyl compound (Michael acceptor) is well studied. As summarised by Mather,[9] the Michael addition is base-catalysed with a rate limiting bimolecular 1,4-addition step.

Michael-type additions, such as those between an amine and a Michael acceptor (hereafter described as an aza-Michael addition) are commonplace in organic synthesis (Scheme 1). It is suggested from the calculated reaction intermediates (via a Density Functional Theory model) that the aza-Michael addition onto acrylates occurs via a third order reaction. A second amine molecule stabilises proton transfer in a 1,2-addition.[10,11] Experimental evidence of a trimolecular, entropy-controlled reaction of nitroethylenes with amines has also been reported.[12] Thus the Michael addition and aza-Michael addition have fundamental differences. A base

catalyst is not required for aza-Michael additions, and instead Lewis acids are commonly used as catalysts.[13] Iodine is particularly interesting as an effective catalyst, owing to its ability to form halogen bonds.[14,15,16,17] Furthermore, iodine can be supported on alumina or silica to aid recyclability.[18]




Scheme 1. The reaction of dimethyl itaconate (**1**) to form its isomers dimethyl mesaconate (**2**) and dimethyl citraconate (**3**) and reaction with an amine (**4**) to give a dimethyl 2-(dialkylamino)methyl butanedioate (**5**).

Alcohols are commonly used as solvents for aza-Michael additions, having previously been shown to provide rate enhancements.[19,20,21] Solvents that do not interact as strongly with the reactants, e.g. hydrocarbons and hydrochlorocarbons, are preferred in asymmetric syntheses to preserve high stereoselectivity, sometimes at the expense of yields.[22,23,24] It is not known if the assumed third order mechanism of aza-Michael addition applies to itaconates, or under what conditions the mechanism may change to accommodate catalysts or (hydrogen bonding) solvents.

In this work, the aza-Michael addition of dimethyl itaconate (**1**) has been studied to clarify its specific reaction pathways and inform future studies. Itaconic acid and its esters may be subject to isomerisation under certain conditions. **1** can form dimethyl mesaconate (**2**) and dimethyl citraconate (**3**), which have previously been shown to be unreactive towards amines (**4**).[25] Therefore, it was of interest to understand the equilibria between isomers **1**-**3**. Regarding the aza-Michael addition itself, the influence of **4** on the rate of reaction has been evaluated, as has the role of catalysts, solvents, and reaction temperature on the formation of the aza-Michael adduct (**5**). This fundamental mechanistic information has been used to develop an understanding of the mechanism and permit reaction optimisation on a challenging (i.e., sterically hindered) substrate.

# 2. Results and Discussion

## 2.1 Isomerisation of dimethyl itaconate

Dimethyl itaconate (**1**) has 2 common regioisomers: dimethyl mesaconate (**2**) and dimethyl citraconate (**3**). The regioisomerisation is not spontaneous and no isomers of **1** were present in the start material. However, amines catalyse the isomerisation of **1**, and so by performing an aza-Michael addition, isomers of **1** are likely to be formed.[25] Fortunately, the aza-Michael addition was observed only to occur on the itaconate isomer under the conditions used in this work. A methyl group sterically blocks addition reactions onto **2** or **3**. By contrast, fumarates do undergo Michael additions.[25]

The isomerisation of **1** in the presence of non-nucleophilic amines and Lewis acids was observed by $^{1}$H NMR spectroscopy after 24 hours at 30 °C without an auxiliary solvent (Table 1 and Figure S1). Lewis acids do not catalyse the isomerisation of **1** without the addition of an amine (Table 1 entries 1-3). The weak base pyridine also did not cause the isomerisation of **1** (Table 1 entry 4). A 2.5 mol% loading of triethylamine (TEA) resulted in 7% conversion from **1** to **2**, increasing to 25% conversion with 1 equivalent of triethylamine present (Table 1 entries 5-6). Cooperative catalysis by a Lewis acid in the presence of triethylamine (1 equivalent) modestly increased the proportion of **2** (Table 1 entries 7-9). The stronger base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was more effective, and able to convert 67% of **1** into **2** within 24 hours, and additionally 3% conversion to **3** was observed (Table 1 entry 10). Reactions with 1 equivalent of DBU caused the decomposition of **1** and were not pursued further. When DBU (2.5 mol%) was used in conjunction with a Lewis acid, the proportion of **2** present was reduced (Table 1 entries 11-13), the opposite of what occurred with triethylamine. This is likely to be caused by an acid-base interaction between DBU and the Lewis acid, reducing the basicity of DBU and preventing the desired coordination between the Lewis acid and **1**.

Table 1. Catalysed isomerisation of dimethyl itaconate (**1**) to dimethyl mesaconate (**2**). Visualised data is provided as ESI, Figure S1.

| Entry | Lewis acid (2.5 mol%) | Base (mol%) | Molar ratio | | |
|---|---|---|---|---|---|
| | | | **1** | **2** | **3** |
| 1 | Iodine | None | 100% | 0% | 0% |
| 2 | Scandium triflate | None | 100% | 0% | 0% |
| 3 | Zinc chloride | None | 100% | 0% | 0% |
| 4 | None | Pyridine (2.5%) | 100% | 0% | 0% |
| 5 | None | TEA (2.5%) | 93% | 7% | 0% |
| 6 | None | TEA (100%) | 75% | 25% | 0% |
| 7 | Iodine | TEA (100%) | 67% | 33% | 0% |
| 8 | Scandium triflate | TEA (100%) | 54% | 45% | 2% |
| 9 | Zinc chloride | TEA (100%) | 70% | 30% | 0% |
| 10 | None | DBU (2.5%) | 30% | 67% | 3% |
| 11 | Iodine | DBU (2.5%) | 78% | 22% | 1% |
| 12 | Scandium triflate | DBU (2.5%) | 72% | 27% | 1% |
| 13 | Zinc chloride | DBU (2.5%) | 90% | 10% | 0% |

In the absence of solvent, 77% conversion to **2** can be achieved in the presence of TEA (but only after 1 month). The internal alkene of **2** is therefore more stable than the terminal alkene of **1** but the isomerisation has a high activation barrier that requires a catalyst to overcome. Anticipating that most transformations of itaconates will require a solvent, the influence of the solvent on the equilibria between **1**, **2**, and **3** was

explored (Figure 1 and Figure S2). A linear solvation energy relationship (LSER) describes the effect of solvent polarity on chemical phenomena, typically rate constants (k) and equilibrium constants (K). Solvent polarity is usually described for this purpose using the Kamlet-Abboud-Taft solvatochromic parameters. A combination of hydrogen bond donating ability (α), hydrogen bond accepting ability (β) and dipolarity (π*) can be used to quantify solvent effects.[26] Solutions of **1** in the presence of triethylamine (1 eq.) were stirred at 30 °C for 2 weeks. At this time, the equilibrium was reached or was approaching equilibrium based on analysis at earlier intervals. The proportion of **3** was small across this study of ten solvents, so as an approximation, a simple equilibrium between **1** and **2** was presumed to construct the LSER. In eight solvents, ln(K) was proportional to π*: methanol (MeOH), ethanol (EtOH), isopropanol (IPA), tetrahydrofuran (THF), *N*,*N*-dimethyl formamide (DMF), acetonitrile (MeCN), polyethylene glycol-400 (PEG), and chloroform-*d* ($CDCl_3$) (Figure 1). The most effective solvent (PEG) resulted in 64% conversion, and conversely only 43% conversion to **2** was achieved in $CDCl_3$. This solvent effect (i.e., proportionality with π*) is also observed in keto-enol tautomerisation. It was previously found that keto tautomers are more stable in dipolar solvents, and the equilibrium begins to favour the enol tautomer in less polar solvents (with a low π* value).[27] If the base catalysed isomerisation of **1** into **2** occurs via an enol or enolate, low polarity solvents will stabilise the enol tautomer of **1** and reduce the equilibrium constant.

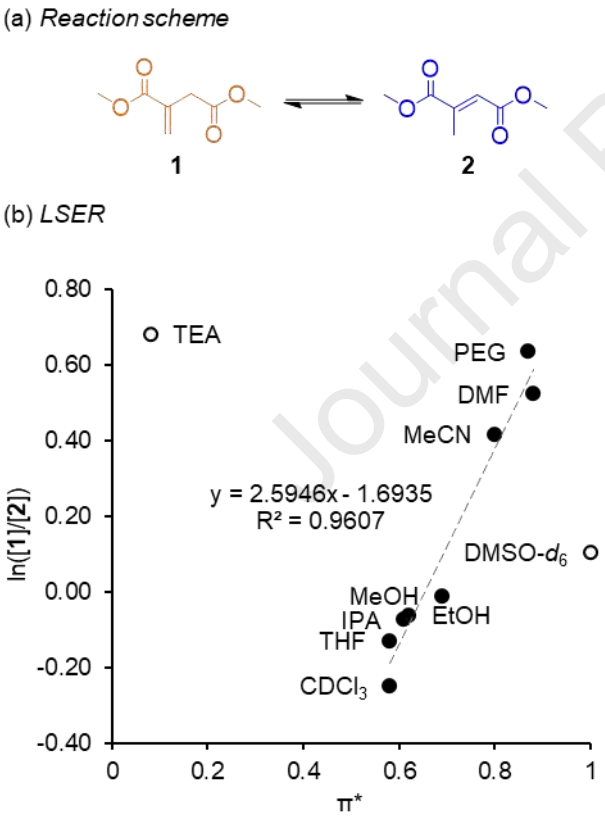


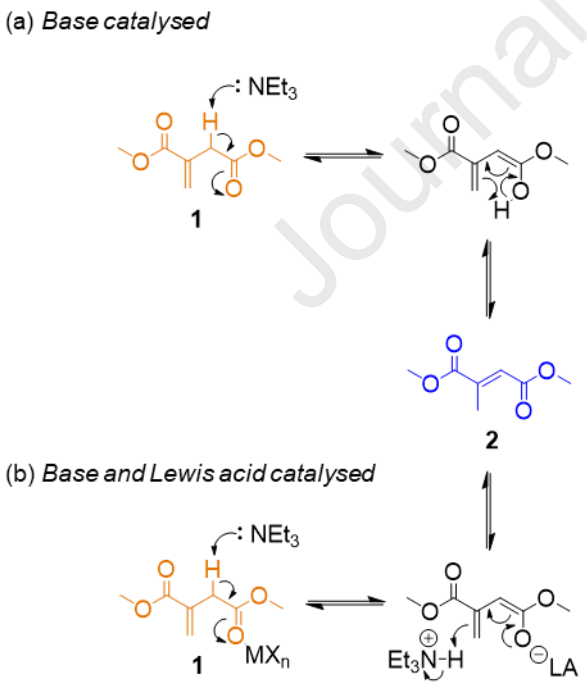

Figure 1. The relationship between the isomerisation of dimethyl itaconate (**1**) to dimethyl mesaconate (**2**) and solvent dipolarity. (a) Reaction scheme. (b) Linear solvation energy relationship (LSER).

There were two exceptions to the correlation in Figure 1. Excess TEA in the role of the solvent produced a high concentration of **2** (66% conversion) relative to its dipolarity. This cannot be directly attributed to the catalytic nature of TEA, but the excess base may create an environment conducive to an alternative mechanism. By contrast, deuterated dimethyl sulphoxide (DMSO-$d_6$) produced a lower equilibrium constant

than predicted from its dipolarity. The solution turned a dark purple colour, which is indicative of side reactions.

Previous reports of fumarate-maleate isomerisation in the presence of amines show the reaction is third order, catalysed by nucleophilic primary and secondary amines but not tertiary amines.[28,29,30] Isomerisation of itaconate esters must occur by a different mechanism in which tertiary amines can participate. The greater rate of isomerisation of **1** caused by DBU compared to triethylamine, and no reaction in the presence of pyridine, implies base catalysis. Additional kinetic experiments were conducted with triethylamine in either isopropanol (IPA) or tetrahydrofuran (THF) applying the Variable Time Normalisation Analysis of Burés (Figure S3).[31] At 50 °C the observed reaction is consistent with a bimolecular mechanism, first order with respect to **1** and first order with respect to catalyst (triethylamine), in either solvent. By contrast, fumarate isomerisation is second order with respect to amine concentration, with one equivalent of amine acting as a nucleophile and the second equivalent of amine transferring a proton. The reaction has a greater rate constant in IPA than THF, although both were slow to progress. Conversely, further reactions in ethanol and DMSO-$d_6$ progressed rapidly, quickly reaching the presumed equilibrium and thus unsuitable for accurate kinetic studies under equivalent conditions to the reactions already performed in IPA and THF.

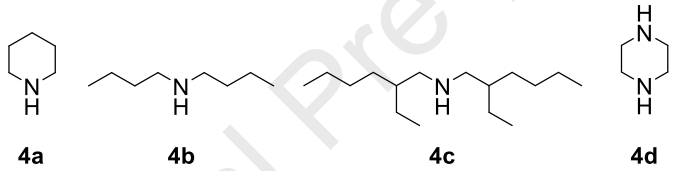
As represented in Scheme 2, the kinetic analysis suggests deprotonation of **1** by a base will result in an enol that undergoes rearrangement. A low energy cyclic transition state favours the formation of **2**. The formation of **3** was limited, when observed at all. The ability of a Lewis acid to modify the observed quantity of **2** after 24 hours (see Table 1) implies an interaction with a Lewis acid may also have a role, potentially stabilising an enolate intermediate.




Scheme 2. Isomerisation of dimethyl itaconate (**1**) to dimethyl mesaconate (**2**) catalysed by (a) triethylamine and (b) co-catalysed by triethylamine and a Lewis acid represented as LA.

## 2.2 Michael donors

The reactions of dimethyl itaconate (**1**) with piperidine (**4a**), dibutylamine (**4b**), and *bis*(2-ethylhexyl)amine (**4c**) (Scheme 3) were performed neat at 30 °C and 50 °C to ascertain the relative reactivity of the three secondary amines in aza-Michael additions. Primary amines were excluded to avoid secondary reactions.[32,33,34] Reactions were once again monitored by $^{1}$H NMR spectroscopy. Increasing the temperature had a minor effect on conversions to the intended product **5** but did enhance isomerisation (Table 2 and Figure S4). Piperidine (**4a**) reacted rapidly with **1** at 30 °C, resulting in 85% conversion to dimethyl 2-(1-piperidinylmethyl)butanedioate (**5a**) in 90 minutes, and 4% conversion to **2** (Table 2 entry 1). An increase in temperature to 50 °C only slightly improves the conversion to **5a**, reaching 91% after 24 hours (Table 2 entry 4). Dibutylamine (**4b**) is less reactive than **4a**, which can be attributed to steric hindrance (Table 2 entries 5-8). The conversion is only 3% after 90 minutes regardless of the temperature, improving marginally after 24 hours. The addition of 10 equivalents of **4b** was more effective at promoting the aza-Michael addition at 30 °C than an increase in temperature to 50 °C, but still only 23% conversion to dimethyl 2-(dibutylamino)methyl butanedioate (**5b**) was observed (Table 2 entry 9). Ultimately we concluded that 30 °C is an appropriate reaction temperature, for the formation of isomerisation products **2** and **3** is suppressed and conversion to the intended product is similar to that achieved in reactions at the higher temperature of 50 °C.




Scheme 3. Amine reactants used in this study.

Table 2. The reactivity of amines (**4**) with dimethyl itaconate (**1**) in solvent-free equimolar reactions (unless otherwise stated). The complete set of visualised data is provided as ESI, Figure S4.

| Entry | Duration /hours | Temp. /°C | Amine | Molar ratio | | | |
|---|---|---|---|---|---|---|---|
| | | | | **1** | **2** | **3** | **5** |
| 1 | 1.5 | 30 | **4a** | 11% | 4% | 0% | 85% |
| 2 | 24 | 30 | **4a** | 1% | 4% | 0% | 95% |
| 3 | 1.5 | 50 | **4a** | 7% | 8% | 0% | 86% |
| 4 | 24 | 50 | **4a** | 1% | 8% | 0% | 91% |
| 5 | 1.5 | 30 | **4b** | 86% | 10% | 0% | 3% |
| 6 | 24 | 30 | **4b** | 45% | 45% | 2% | 8% |
| 7 | 1.5 | 50 | **4b** | 74% | 24% | 0% | 3% |
| 8 | 24 | 50 | **4b** | 27% | 61% | 2% | 11% |
| 9 | 24 | 30 | **4b** [a] | 35% | 40% | 1% | 23% |
| 10 | 24 | 30 | **4d** [b] | 1% | 4% | 0% | 94% |

a. Ten equivalents of **4b**.
b. 0.5 equivalents of **4d**.

The reactions of **4c** were unsuccessful, with a slow rate of isomerisation to **2** but no aza-Michael addition observed (Figure S4). The reaction of **1** with 0.5 equivalents of piperazine (**4d**) progressed rapidly at 30 °C

despite poor mixing of the solid reactants (Table 2 entry 10). A white crystalline solid was isolated (*N*,*N*'-*bis*(dimethyl 2-methylene butanedioate) piperazine, **5d**) which was characterised and consistent with the double aza-Michael addition of diamine **4d**.

## 2.3 Solvent effects

Given that the aza-Michael addition between **1** with **4a** is fast, this reaction was chosen for the study of solvent effects. The time scale of the uncatalysed reaction becomes suitable for kinetic analysis at low concentrations of the reactants. The formation of **5a** was conducted in the same ten solvents used to study the isomerisation of **1** (Section 2.1). Benzyl benzoate was added as an internal standard to calculate the concentration of the reaction components by $^{1}$H NMR spectroscopy. Formation of **5a** was most rapid in the primary alcohols and dipolar aprotic solvents DMF and DMSO-$d_6$, although conversions were ultimately higher in methanol and ethanol (Figure S5). The remaining solvents performed similarly with the exception of $CDCl_3$, in which the reaction is considerably slower (Figure 2). It was expected that TEA would accelerate the reaction,[12] but no benefit over non-basic solvents was found. Although TEA catalyses the isomerisation of **1** to **2**, the aza-Michael addition is presumably not base catalysed (unlike the conventional Michael addition), and the possibility of an amine assisted mechanism must operate by other means. The competing isomerisation to **2** was significant in DMSO-$d_6$ but negligible in methanol, ethanol, and $CDCl_3$ in particular. Isomerisation in DMSO-$d_6$ and $CDCl_3$ followed the trend with π* established in Figure 1. Although isomerisation can be significant in alcohols (~50% of **2** was observed in previous experiments) the rapid aza-Michael addition consumes the majority of **1** so that it cannot be converted into **2** or **3**.

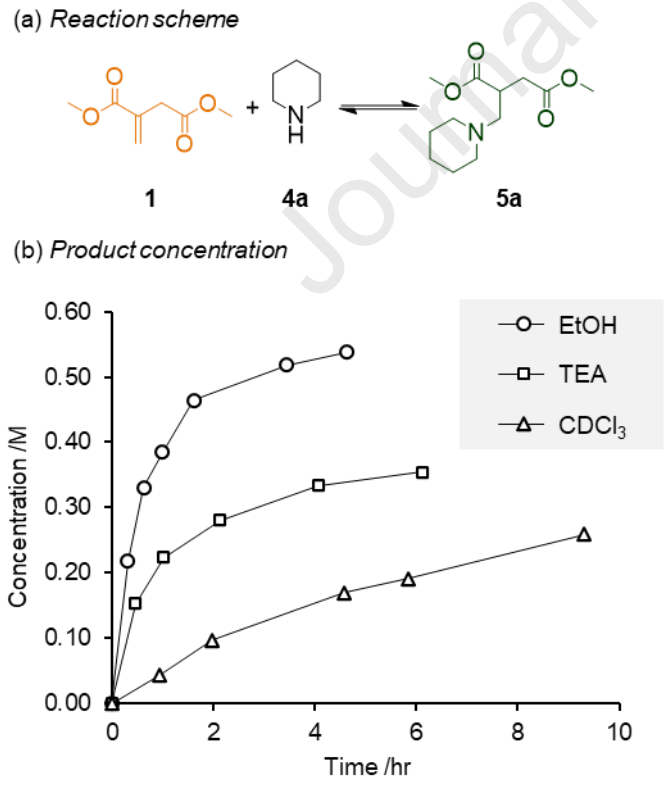
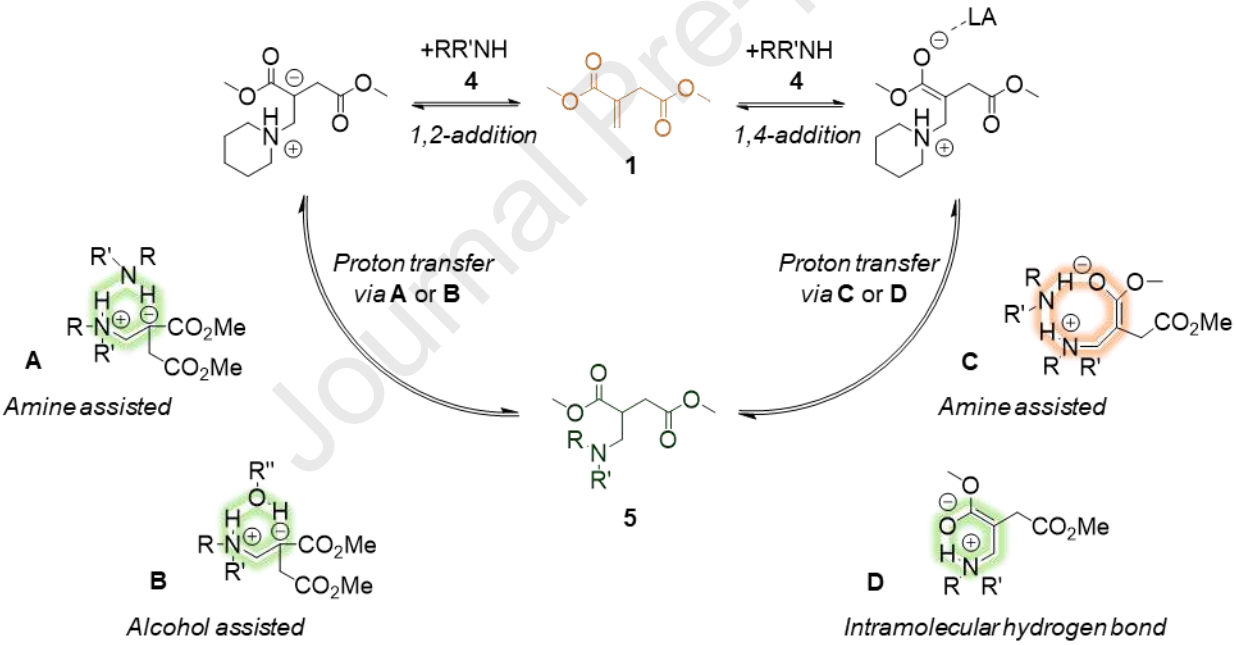



Figure 2. Production of aza-Michael adduct **5a** in selected solvents from an initial concentration of dimethyl itaconate (**1**) of 0.6 M. (a) Reaction scheme. (b) Rate of **5a** formation. Additional data is presented in Figure S5.

The performance of the reaction in secondary alcohol IPA and diol PEG was noticeably different to methanol and ethanol. These alcohols can be differentiated by their hydrogen bond donating ability (α), with methanol and ethanol superior in this respect compared to IPA and PEG. Previous work has shown a relationship between the rate of aza-Michael additions and the $pK_a$ of alcohol solvents.[Error! Bookmark not defined.] The present experiments indicate a correlation between the rate of **5a** formation and hydrogen bond donating ability (α) in alcohol solvents. This supports the hypothesis that proton transfer is rate determining and assisted by protic solvents.[Error! Bookmark not defined.] However, in this case the reaction may no longer proceed via a third order reaction (Scheme 4, species **A**) if a solvent molecule performs the proton transfer in place of an amine (Scheme 4, species **B**). Furthermore, the relationship between α and reaction rate does not explain the differences observed between aprotic solvents. To investigate further, the order of reaction was ascertained in ethanol, IPA, DMSO-$d_6$, THF, and $CDCl_3$, again using Variable Time Normalisation Analysis (Figure S6).[31] The order of reaction with respect to **1** was always found to be 1 (Table 3). In the aprotic solvents DMSO-$d_6$ and THF, the reaction was second order with respect to **4a** and therefore third order overall. As suspected, in ethanol the reaction was found to be bimolecular (first order with respect to **4a**). This finding suggests a 1,2-addition is preferred because the stabilisation offered to the 1,4-addition mechanism by a non-reactive equivalent of amine or alcohol can be expected to be weaker due to the 8-membered ring that is formed (Scheme 4, species **C**) instead of the more stable 6-membered ring.




Scheme 4. The reaction of dimethyl itaconate (**1**) with an amine (**4**) to give a dimethyl 2-(dialkylamino)methyl butanedioate (**5**) annotated with intermediates. Cycles are highlighted in green (6-membered ring) or orange (8-membered ring). There is the possibility of a Lewis acid (LA) interacting with the reaction components.

Table 3. Reaction rate parameters for the reaction between dimethyl itaconate (**1**) and piperidine (**4a**). Visualised data is provided as ESI, Figure S6-7. Error ranges correspond to 1 standard deviation.

| Solvent | Reaction order | | Activation parameters | | $10^4 \cdot k_{obs}$ at 30 °C |
|---|---|---|---|---|---|
| | **1** | **4a** | $\Delta H^{\ddagger}$ /kJ·mol$^{-1}$ | $\Delta S^{\ddagger}$ /J·mol$^{-1}$·K$^{-1}$ | |
| EtOH | 1 | 1 | 30.9±1.0 | -203±3 | 7.25±0.18 dm$^3$·mol$^{-1}$·s$^{-1}$ |
| IPA | 1 | 1.6 | 26.0±0.6 | -226±2 | 3.48±0.08 dm$^{4.8}$·mol$^{-1.6}$·s$^{-1}$ |
| THF | 1 | 2 | 13.5±0.2 | -268±1 | 2.90±0.06 dm$^6$·mol$^{-2}$·s$^{-1}$ |
| DMSO-$d_6$ | 1 | 2 | n.d. [a] | n.d. [a] | 23.9±0.89 dm$^6$·mol$^{-2}$·s$^{-1}$ |
| $CDCl_3$ [b] | 1 | 2 | n.d. [a] | n.d. [a] | 0.88±0.03 dm$^6$·mol$^{-2}$·s$^{-1}$ |
| $CDCl_3$ [c] | 1 | 1 | n.d. [a] | n.d. [a] | 0.30±0.01 dm$^3$·mol$^{-1}$·s$^{-1}$ |

a. Not determined.
b. At concentrations of **4a** of 0.5 M and greater.
c. At concentrations of **4a** less than 0.5 M.

The reaction in IPA did not fit the profile of an overall second or third order rate equation. A non-integer reaction order of 1.6 with respect to **4a** produced the best data fit (Table 3 and Figure S6). In this example, the competing bimolecular and trimolecular mechanisms must have a similar rate constant. This will occur if IPA (bimolecular mechanism, via species **B** of Scheme 4) and **4a** (trimolecular mechanism, via species **A** of Scheme 4) offer comparable proton transfer stabilisation. The reaction temperature was then varied and reactions repeated in ethanol, IPA, and THF to obtain the enthalpy and entropy of activation from the Eyring equation. Both terms decrease as the order of reaction with respect to **4a** increases from 1 to 2 (Figure S7). In THF, the trimolecular reaction has an enthalpy of activation ($\Delta H^{\ddagger}$) of 13.5 kJ·mol$^{-1}$ and an entropy of activation ($\Delta S^{\ddagger}$) of -268 J·mol$^{-1}$·K$^{-1}$ (Table 3). In ethanol, the enthalpy of activation increases to 30.9 kJ·mol$^{-1}$ (despite the greater rate constant magnitude), higher than expected for a proton transfer. This may be explained by the lower basicity of ethanol compared to **4a** which is replaced in the activated complex (species **B** rather than species **A**, Scheme 4). The reason it is favourable to replace **4a** with the (relatively) poor proton transfer agent ethanol (or IPA) within the activated complex is the relative increase in the entropy term to -203 J·mol$^{-1}$·K$^{-1}$ (in ethanol, see Table 3). As expected, the bimolecular reaction undergoes a lesser reduction in entropy ($\Delta S^{\ddagger}$) compared to the trimolecular reaction. The activation parameters in IPA are intermediate of ethanol and THF. The non-integer reaction order of 1.6 in IPA did not change at higher temperatures (Figure S6).

Both bimolecular and trimolecular reaction mechanisms are required to explain the reaction kinetics in $CDCl_3$. Unlike IPA, in which both mechanisms are simultaneously in operation, a preference for one mechanism prevails in $CDCl_3$ depending on the concentration of the reactants. At higher concentrations of **4a**, a trimolecular reaction, second order with respect to **4a**, accounts for the observed reaction kinetics (Figure S6). Unexpectedly, even though $CDCl_3$ will not stabilise proton transfer as an alcohol solvent might, the kinetic study was consistent with a bimolecular reaction at low initial reactant concentrations. The rate constant is about a third of the magnitude of the trimolecular reaction in $CDCl_3$. The bimolecular mechanism is observed when low reactant concentrations result in a greater rate of reaction than the trimolecular mechanism (i.e., the derivative of **5a** concentration as a function of time, d[**5a**]/dt, Figure S8). This observation is consistent with a change of mechanism rather than a change of rate determining step. If the latter were true, the order of reaction with the slower rate of reaction would be observed. Instead, we can deduce the entropy-controlled trimolecular reaction becomes unfavourable at low reactant concentrations. The reaction may now proceed via a bimolecular 1,4-addition so that an intramolecular hydrogen bond is formed to assist proton transfer (Scheme 4, species **D**). Previously published computational studies suggest that the 1,2-addition mechanism is often the most energetically favourable, but a 1,4-addition is competitive

depending on the nature of the reactants.[10,35] The concentration of the reactants was not previously identified as a cause of a change in mechanism.

A LSER is needed for each mechanism to accurately describe the solvent effect in the reaction between **1** and **4a**. Six solvents promote the trimolecular reaction proceeding via species **A** in Scheme 4 (including $CDCl_3$ but excluding IPA, see Figure S9). The Kamlet-Abboud-Taft parameters were correlated to rate constants in the form ln(k) (Figure 3). Both β and π* were statistically significant in describing the trimolecular reaction, both being beneficial to the rate of reaction (see inset equation in Figure 3). This quantifies the observation that dipolar aprotic solvents accelerate the reaction. Polar solvents (with high π* values) may stabilise the pericyclic activated complex, analogous to a Diels-Alder reaction.[36] Hydrogen bond accepting solvents (with high β values) may additionally stabilise the amine hydrogen atoms during proton transfer.

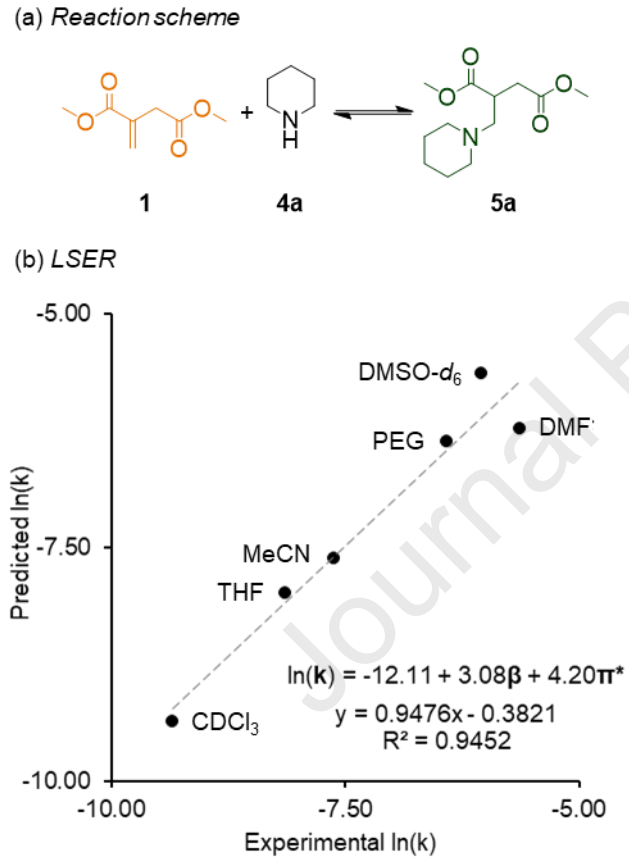
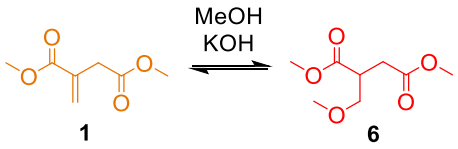



Figure 3. Predicted rate constants for trimolecular reactions between dimethyl itaconate (**1**) and piperidine (**4a**). (a) Reaction scheme. (b) Linear solvation energy relationship (LSER). The complete set of visualised data is provided as ESI, Figure S9.

Only four solvents produced bimolecular reactions (methanol, ethanol, low concentration reactants in $CDCl_3$, and TEA) and so a LSER was unreliable. However, α was statistically significant, reflecting the rate acceleration provided by alcohol solvents (Figure S9). The strength of the intermolecular interaction between an alcohol solvent's –OH hydrogen atom and the carbanion formed upon 1,2-addition onto **1** (Scheme 4, species **B**) would appear to be important in dictating the rate of reaction. For this reason, hexafluoroisopropanol was applied as the solvent. With an α value of 1.96,[26] about double that of typical alcohols, a high rate of reaction was anticipated. In practice, the intended reaction did not occur. The

exothermic addition of **4a** to the solvent suggested the nucleophilicity of the amine reactant is nullified by the acidity of the solvent. This is not true of every aza-Michael addition, for fluoroalcohols are effective solvents for the reaction of less basic anilines.[Error! Bookmark not defined.,37,38] The significant health hazards possessed by fluoroalcohols should also be considered before being used as solvents.

The valuable rate-enhancing effect of alcohol solvents can only be exploited if the competitive oxa-Michael addition with the solvent or transesterification of **1** does not occur. The reaction in methanol did not produce any significant isomerisation of **1** or other observable by-products. The oxa-Michael addition of methanol onto **1** to give dimethyl 2-(methoxy)methyl butanedioate (**6**) can be achieved by the use of 50 mol% potassium hydroxide as base and this method was used to provide a reference spectrum (Figure S10) and material for further study (Scheme 5). Replacing KOH with TEA produced a low conversion to **6** (~5%) after 24 hours at 50 °C. This suggests that in the presence of amines, alcohols can form the oxa-Michael addition product with **1**, but in the case of the synthesis of **5a**, the intended aza-Michael reaction is sufficiently faster than the competing oxa-Michael addition to preserve essentially 100% reaction selectivity. In a complementary experiment, **4a** was found to be unreactive in the presence of **6**, indicating the latter is not an unstable (and hence unobservable) intermediate during the formation of **5a** should methanol be used as the solvent. Additionally, transesterification of the methyl esters **1** and **5a** was not observed in ethanol or IPA under the standard reaction conditions used in this work (30 °C, <10 hours).




Scheme 5. The oxa-Michael addition between dimethyl itaconate (**1**) and methanol.

## 2.4 Catalysis

It was possible to conduct the reaction between **1** and a less reactive amine, dibutylamine (**4b**), in the absence of a solvent or catalyst, but the conversion to dimethyl 2-(dibutylamino)methyl butanedioate (**5b**) was slow (Table 2 and Figure S4). Following previous work employing iodine as a catalyst,[18] the conversion to **5b** was much improved with the addition of 2.5 mol% iodine, reaching 75% in 24 hours. It was pertinent to determine the order of reaction and understand the role of the catalyst before a wider catalyst screening. In ethanol, IPA, and THF the reaction is first order with respect to each of **1**, **4b**, and the catalyst iodine (Table 4 and Figure S11). With the addition of the catalyst, the reaction is no longer trimolecular in THF, and if a proton transfer agent is no longer required in THF, the same could be true of the reaction in alcohol solvents. The reaction is faster in IPA than it is in THF, as was the case in the reactions of **4a**, but now the rate of reaction in ethanol is suppressed, with a rate constant between that of IPA and THF. This is further evidence of a change in mechanism, the catalyst providing a lower energy reaction pathway than a proton transferring amine or solvent molecule. The rate constants are proportional to the hydrogen bond accepting ability (β) of the solvent (Figure S11), which implies the solvent stabilises the proton transfer through solvation but not necessarily as a direct participant.

Table 4. Reaction rate parameters for the reaction between dimethyl itaconate (**1**) and dibutylamine (**4b**) catalysed by iodine. Visualised data is provided as ESI, Figure S11.

| Solvent | Reaction order | | | $10^4 \cdot k_{obs}$ at 30 °C |
|---|---|---|---|---|
| | **1** | **4b** | Iodine | |
| EtOH | 1 | 1 | 1 | 2.97±0.06 $dm^3 \cdot mol^{-1} \cdot s^{-1}$ |
| IPA | 1 | 1 | 1 | 5.22±0.20 $dm^3 \cdot mol^{-1} \cdot s^{-1}$ |
| THF | 1 | 1 | 1 | 2.40±0.07 $dm^3 \cdot mol^{-1} \cdot s^{-1}$ |

The Lewis acid catalysed aza-Michael addition between **1** and **4b** is likely to be a 1,4-addition of the type preferred in $CDCl_3$ at low concentrations (Scheme 4, species **D**). A change in the rate determining step (i.e., to the initial addition reaction) is again ruled out on the basis that the presence of a Lewis acid catalyst would only accelerate this step. What is unclear is whether it is the catalyst or the extra steric hindrance of **4b** compared to **4a** that prevents a second amine molecule from participating in the activated complex. Computational studies indicate a 1,4-addition is energetically preferable to a bimolecular 1,2-addition in the case of sterically hindered amines.[10] However, this is not the only way in which a 1,4-addition might be favoured. Lewis acid catalysts will interact preferentially with the carbonyl oxygen of an enolate intermediate, drawing electron density away from the alkene moiety of **1** as in a 1,4-addition (Scheme 4, species **D**).[39,40,41]

Additional catalysts (2.5 mol% loading) were studied without an auxiliary solvent and stirring at 30 °C to attempt to maximise the rate of product formation. Conversions to **5b** were calculated after 90 minutes, 24 hours, and 4 days using $^1$H NMR spectroscopy (Table 5 and Figure S12). Non-nucleophilic amines had a modest effect on the reaction (Table 5 entries 2 and 3). Metal triflates were all effective, generally providing a greater rate of reaction compared to iodine (Table 5 entry 4) initially and a slight improvement to the final conversion after 4 days (Table 5 entries 5-10). The differences in the Lewis acidity of the metal triflates do not correlate with the perceived rate of reaction,[42,43] although the reaction was relatively rapid regardless of the metal triflate present. Scandium triflate ultimately provided the highest conversion of 88%. The concentration of **3** was negligible across this study.

Table 5. Conversion of dimethyl itaconate (**1**) after four days reacting with dibutylamine (**4b**) in the presence of 2.5 mol% catalyst.

| Entry | Catalyst | Molar ratio | | |
|---|---|---|---|---|
| | | **1** | **2** | **5b** |
| 1 | No catalyst | 23% | 61% | 17% |
| 2 | TEA | 20% | 60% | 20% |
| 3 | DBU | 25% | 38% | 37% |
| 4 | Iodine | 5% | 18% | 77% |
| 5 | Copper triflate | 8% | 10% | 83% |
| 6 | Magnesium triflate | 2% | 15% | 83% |
| 7 | Indium triflate | 5% | 10% | 85% |
| 8 | Bismuth triflate | 2% | 10% | 87% |
| 9 | Scandium triflate | 5% | 8% | 88% |
| 10 | Zinc triflate | 6% | 9% | 84% |
| 11 | Zinc tosylate | 11% | 38% | 51% |
| 12 | Zinc acetate | 15% | 50% | 35% |
| 13 | Zinc sulphate | 20% | 51% | 30% |
| 14 | Zinc chloride | 1% | 17% | 82% |
| 15 | Zinc bromide | 3% | 17% | 80% |
| 16 | Zinc iodide | 2% | 13% | 85% |

An extended investigation of zinc complexes was undertaken to optimise the reaction with a catalyst based on an inexpensive, low supply risk metal.[44] The zinc halides performed similarly to the triflate salts (Table 5 entries 14-16). The conversion to **5b** that was achieved generally followed the order established by the $pK_a$ of the acid form of the zinc salt, the notable exception being the poor performance of zinc sulphate (Table 5 entry 13). This may be due to the use of the heptahydrate $ZnSO_4 \cdot 7H_2O$, thus introducing water into the reaction.

Further studies were performed with scandium triflate (as the best performing catalyst), zinc chloride (a simpler and more sustainable metal complex) and the molecular catalyst iodine. It was found that the scandium triflate or (to a lesser extent) iodine loading can be reduced significantly with minimal loss of product conversion (Figure S13). Changing the scandium triflate catalyst loading from 2.5 mol% to 0.25 mol% reduced conversion to **5b** from 88% to 81% (in the 4 day reaction). The reaction is more dependent on zinc chloride concentration, falling to 50% when using 0.25 mol% of catalyst.

It may be that the limited solubility or poor mixing of some catalysts in the neat reactants makes higher catalyst loadings irrelevant. To overcome any such limitations, solvents were introduced to the reaction between **1** and **4b**, both uncatalysed and catalysed by scandium triflate. Interestingly, methanol and DMSO-$d_6$ improved conversions to **5b** in the absence of a catalyst compared to the neat reaction (Figure S14). Reactions were performed as equimolar 2.4 M solutions, with methanol producing a satisfactory conversion to **5b** of 79%, albeit after 1 week. The addition of a solvent can increase the observed rate of reaction, despite considerably reducing the concentration of the reactants, due to the alleviation of mass transfer limitations. The solvent effect is also important, as the reaction in IPA was virtually identical to that without an auxiliary solvent. The relative performance of the solvents is analogous to the uncatalysed reaction between **1** and **4a**, but now the formation of **3** was measurable (up to 3%) and transesterification was observed in IPA. Minor signals in the $^1$H NMR spectrum of the reaction mixture in IPA after 1 week correspond to the isopropyl esters of **1** and **2** (Figure S15). An isopropyl ester equivalent of aza-Michael product **5b** was not identified, but the slow rate of reaction and low concentration of transesterified

substrates meant this by-product was not expected to be observed in significant quantities. Transesterification by IPA was not observed in the catalysed reactions of **4b** (which were performed on a shorter time scale).

The introduction of a solvent also had a small but beneficial effect on the conversion to **5b** when in the presence of scandium triflate (Figure S16). This enhancement only occurred with small quantities of solvent. More than a few equivalents of solvent slowed the reaction significantly (due to dilution). The choice between methanol, IPA and DMSO-$d_6$ was not significant, all were capable of >80% conversion to **5b** after 24 hours (slightly higher than the 76% conversion without solvent). Although this is likely to be a matter of improved mixing and mass transfer, it is surprising that only 0.44 equivalents of methanol resulted in the optimum conversion (88%). This mass of methanol is similar to the mass of catalyst used.

At this point, the reaction of **4c** with **1** was revisited. Previously no aza-Michael addition was observed to occur (without a solvent or catalyst). Now with an understanding of solvent, catalyst and temperature effects, the reaction was repeated in the presence of 2.5 mol% scandium triflate and 0.44 equivalents of methanol at 50 °C. The reaction was slow but after 4 days 64% conversion to dimethyl 2-(di(2-ethylhexyl)amino)methyl butanedioate (**5c**) was observed (Figure S19). Thus, conditions were found to transform a previously assumed unreactive amine into the intended aza-Michael adduct.

## 3. Conclusions

It was found that the aza-Michael additions of dimethyl itaconate are very susceptible to changes in conditions and can access different mechanisms. By controlling the observed reaction pathway, conversion and selectivity can be maximised. The hypothesis of an amine assisted proton transfer step was previously accepted, but superior rates of reaction are achieved by an alternative bimolecular reaction, be it via an alcohol or other catalyst. This work has clarified the acceleration of reaction rates by alcohol solvents and revealed other phenomena such as the effect of concentration on the preferred reaction mechanism. These findings can be used to optimise the synthesis of other aza-Michael additions including the synthesis of pharmaceuticals and post-polymerisation modification of polymers.

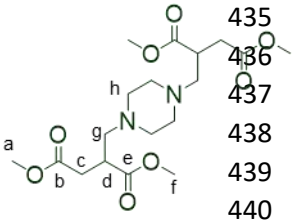
## 4. Experimental

All reactions were performed under air in sealed vials. Solutions of dimethyl itaconate (**1**) were preheated (typically to 30 °C) prior to addition of amine (**4**) and catalyst. Reactions were typically conducted on a 2 mL scale and monitored by $^1$H NMR spectroscopy using 300 MHz and 400 MHz spectrometers. Aliquots of the reaction mixture were studied as solutions in $CDCl_3$ or DMSO-$d_6$. The concentration of compounds was calculated from the known concentration of internal standard benzyl benzoate ($CH_2$ signal) and compared to the integrals of characteristic signals belonging to the reaction components **1**-**5**. Representative spectra are provided as Figure S17-S20.

Kinetic analysis was performed using Variable Time Normalisation Analysis. The literature method was followed,[31] from which orders of reaction and rate constants were derived. This technique requires the visual interpretation of several overlaid datasets, which must be adjusted to consider the potential orders of reaction. To avoid producing a large number of similar charts, the data is provided in an interactive format as a supplementary spreadsheet (ESI) which can be manipulated freely.

Solvent effects were determined using linear solvation energy relationships (LSER). Correlations were found using the regression function of Microsoft Excel. Variables were excluded if p-values were above 0.1. In all cases, molar volume was not determined as significant.

Dimethyl 2-(1-piperidinylmethyl)butanedioate (**5a**), dimethyl 2-(dibutylamino)methyl butanedioate (**5b**), and dimethyl 2-(di(2-ethylhexyl)amino)methyl butanedioate (**5c**) were not isolated, but representative $^{1}$H NMR spectra of the crude products are provided in Figures S17-S19 for reference. *N*,*N*'-*bis*(Dimethyl 2-methylene butanedioate) piperazine (**5d)** was isolated (method below). $^{1}$H NMR and $^{13}$C NMR spectra are provided in Figure S20.




**5d**

*N*,*N*'-*bis*(Dimethyl 2-methylene butanedioate) piperazine (**5d**). To 0.949 g (6.0 mmol) of dimethyl itaconate (**1**) was added 0.258 g (3.0 mmol) of piperazine (**4d**) and stirred for 24 hours at 30 °C. The resultant solid was washed with cold acetone, filtered and dried to give a white crystalline solid (*ca*. 1 g, 94% conversion). $^{1}$H NMR 300 MHz ($CDCl_3$). 3.69 (6H, s, $H_a$), 3.67 (6H, s, $H_f$), 3.07 (2H, m, $H_d$), 2.71-2.55 (6H, m, $H_c$ and $H_g$), 2.43-2.36 (10H, m, $H_c$ and $H_h$). $^{13}$C NMR 75 MHz ($CDCl_3$). 174.5 ($C_e$), 172.5 ($C_b$), 59.3 ($C_c$), 53.1 ($C_h$), 51.9 ($C_a$), 51.7 ($C_f$), 39.7 ($C_d$), 34.3 ($C_g$). HRMS (ESI). Calculated 403.2075, observed 403.2077 (MH+).

Dimethyl 2-(methoxymethyl)butanedioate (**6**). To 0.237 g (1.5 mmol) of dimethyl itaconate (**1**) was added methanol (*ca*. 1 g, 20 equivalents) and 0.042 g of ground potassium hydroxide (0.75 mmol),[45] and stirred for 24 hours at 30 °C. The reaction mixture was then concentrated, to which was added water (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic phase was dried with magnesium sulphate, filtered and concentrated. The crude product also contains **1** and its isomers. This was used directly in subsequent reactions. Characterisation was consistent with an earlier synthesis.[46] An annotated $^{1}$H NMR spectrum is provided as Figure S10.

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- The mechanism of the aza-Michael addition is solvent-dependent.
- Lewis acid catalysts also change the mechanism.
- Optimised conditions allow the reaction of very sterically hindered amines.

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: