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DABCO/Amberlyst® 15-Cocatalysed One-Pot Three-Component Aza-Morita–Baylis–Hillman Reaction Under Green Conditions

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Abstract: The one-pot multicomponent aza-Morita–Baylis–Hillman (MBH) reaction was performed under green conditions using 1,4-diazabicyclo[2.2.2]octane (DABCO) and Amberlyst® 15 as a co-catalyst, at ambient temperature and under negligible amounts of non-hazardous solvent. A number of α-methylene-β-amino acid derivatives were produced in good to excellent yields from different arylaldehydes, *p*-toluenesulfonamide and α,β-unsaturated carbonyl compounds. The environmental benignity of the process is accounted by the low E-factor (0.7) and high atom economy (95%) values obtained.

Keywords: α-methylene-β-amino acid; multicomponent reaction; heterogeneous catalysis; one pot; aza-Morita–Baylis–Hillman reaction; DABCO; Amberlyst® 15

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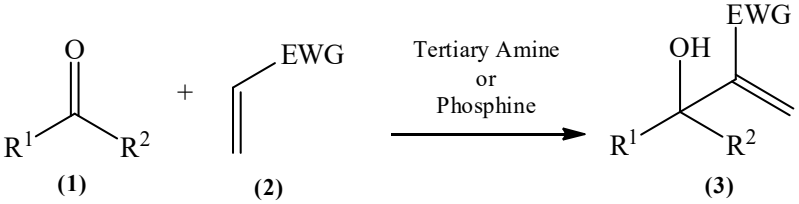
1. Introduction

Carbon–carbon (C-C) bond formation is the foundation for the biogenesis of nature's essential molecules. A vast number of C-C bond-forming reactions have been developed and their applications have been studied extensively during the last decades. Present-day research in this field is changing. The incorporation of green chemistry criteria, prioritising atom economy, environmental benignity and minimisation of waste, sets new targets in the endeavour of identifying new C-C bond-forming reactions [1].

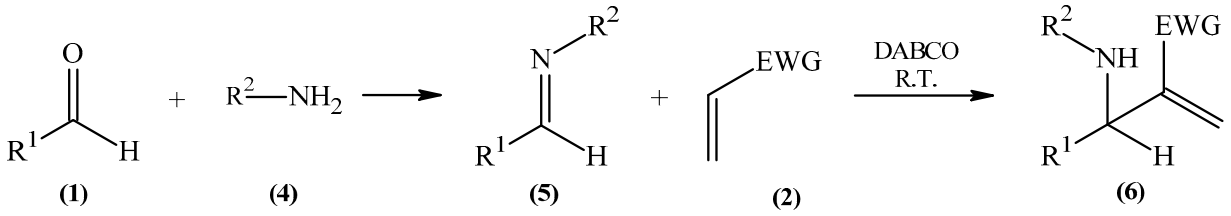
The Morita–Baylis–Hillman (MBH) reaction has established itself as a powerful atom-economic method for C-C single bond formation involving the coupling of aldehydes with electron-deficient alkenes to form highly functionalised carbonyl compounds [2]. The origin of this reaction dates back to 1968 when Morita reported the reaction between various aldehydes and acrylates (or acrylonitrile) catalysed by tertiary phosphine to yield α-methylene-β-hydroxy alkanoates (or alkanenitriles) [3]. Subsequently, in 1972, Baylis and Hillman published a similar reaction, catalysed using tertiary amine [4]. The combination of the two protocols broadly defined the overall reaction as a condensation between an electrophilic carbonyl compound (**1**) and an electron-deficient alkene (**2**), in the presence of a nucleophilic catalyst, generally a tertiary amine or phosphine, to yield an α-hydroxylated product (**3**), as shown in Scheme 1.



R^1 = aryl, alkyl, heteroaryl; R^2 = H, COOR, alkyl; EWG = COR, CHO, CN, COOR, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh

Scheme 1. General MBH reaction [4].

The product of the related aza-version of the MBH reaction is an α-methylene-β-amino carbonyl, usually obtained via amine substitution of the alcohol functionality in the Baylis–Hillman adduct [5]. One major disadvantage of this method is that the product is obtained over a two-step reaction, increasing the possibility of forming regioisomers as side products, via S_N2-substitution or Michael addition reactions [6]. A few publications propose an alternative route towards the formation of α-methylene-β-amino derivatives (**6**), in which the electrophilic aldehyde is replaced with an imine (**5**), as shown in Scheme 2 [7]. In this way, the reaction product is usually formed over a one-step reaction, though the imine is usually freshly prepared and isolated before being added into the reaction pot.



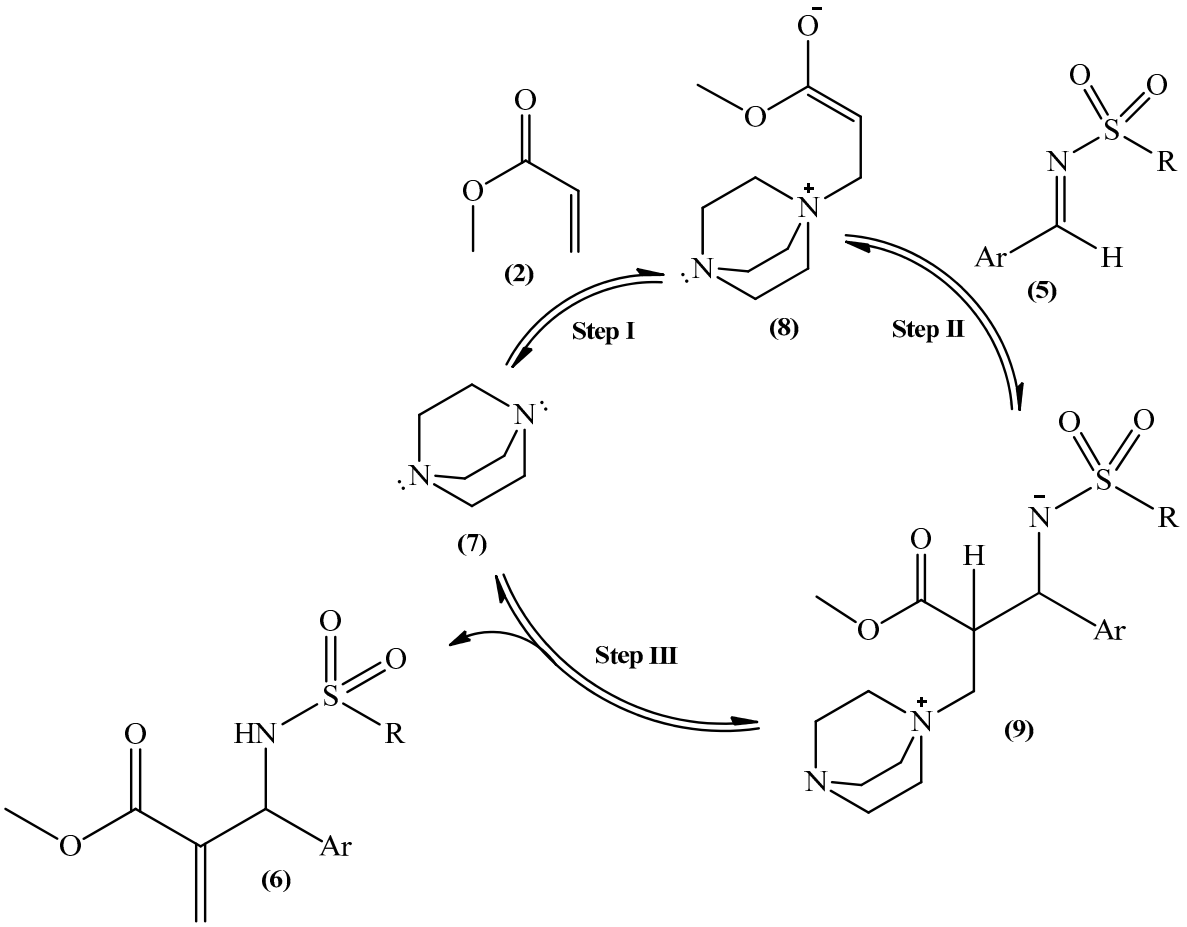
Scheme 2. aza-MBH reaction to form α-methylene-β-amino derivatives [7].

These derivatives can be converted into a range of biologically important molecules, in particular, β-amino esters [8]. The reputation of this reaction is attributed to its advantages including high atom economy nature, its operational simplicity, mild reaction conditions, possibility to generate densely functionalised compounds, commercial availability of starting materials, suitability of reaction for scaling-up and use of purely organic catalysts [2,9].

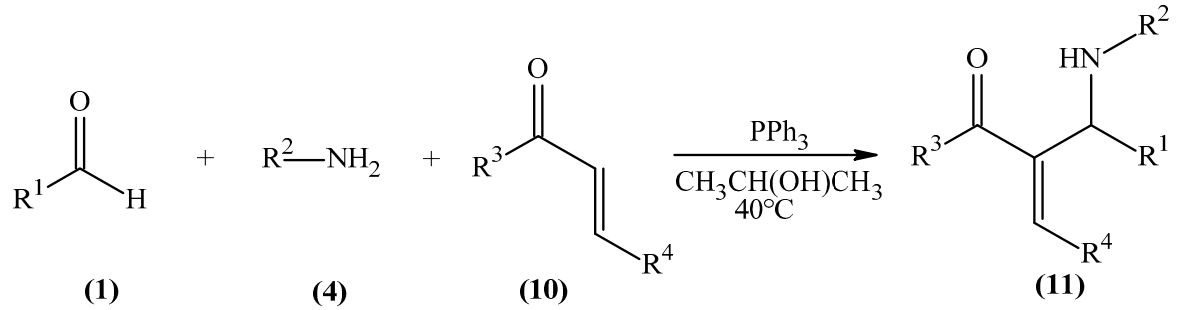
The mechanism of the aza-MBH reaction follows the same steps of the mechanism originally proposed by Morita for the MBH reaction, except for using an aldimine (**5**) instead of an aldehyde (Scheme 3) [10,11]. The catalytic cycle is initiated by a Michael-type 1,4-nucleophilic addition of a Lewis base catalyst (**7**) transferring its electron density to the terminal alkene carbon of an α,β-unsaturated carbonyl compound **2** (step I). As a result, a zwitterionic enolate intermediate **8** with an enhanced nucleophilic character at C2 is formed. This species then undergoes a nucleophilic attack onto the imine (**5**) electrophilic carbon to form a second zwitterionic intermediate **9** (step II). To conclude the cycle, a proton shifts from the α-carbon atom to the β-alkoxide (or amine), followed by a β-elimination to yield the aza-MBH adduct **6** and regenerate the catalyst (step III).

The first three-component aza-MBH reaction was published by Bertenshaw and Kahn in 1989 [12]. The method provided a facile synthesis of α-methylidene-β-aminopropanoates (**11**), utilising triphenylphosphine as base catalyst at 40 °C, as shown in Scheme 4. The three-component strategy revealed several interesting features. The optimal reaction conditions required the use of amines (**4**) possessing an electron-withdrawing group, such as the *p*-toluenesulfonamide (tosyl) group. Furthermore, like in the classical MBH reaction, no product formation was observed when utilising β-substituted activated alkenes (**10**, $R_4 = CH_3$).

The enolate (**10a**), formed by the Michael addition reaction of DABCO catalyst on the alkene (**10**), can attack the in situ formed imine (**5**) to form the product (**11**) or the aldehyde (**1**) to form the side product (**12**) (Scheme 5). In the one-pot reaction, the imine can readily react with the enolate, reducing the possibility of side-product formation while in the multi-step approach, the side product is more likely to form due to the higher aldehyde concentration in the first equilibrium reaction step [6].



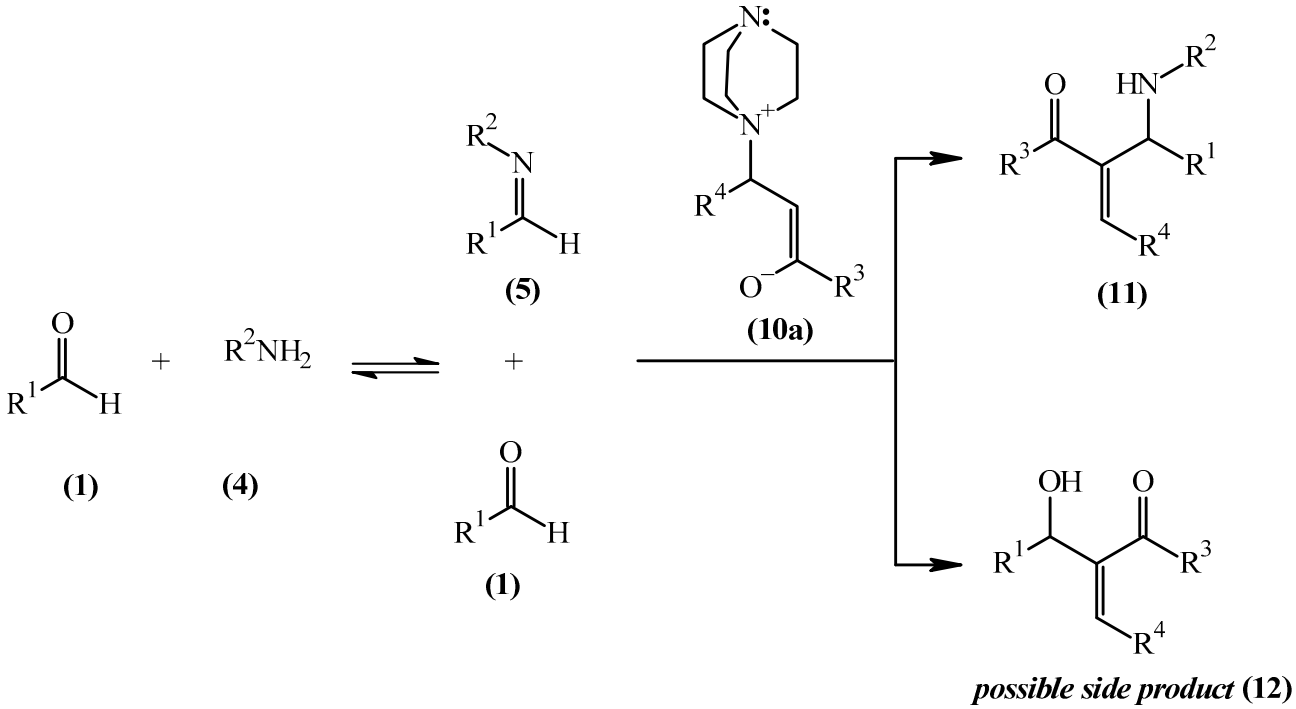
Scheme 3. Postulated catalytic cycle for the aza-MBH reaction employing DABCO as an amine catalyst [10,11].



Scheme 4. The first three-component aza-MBH as published by Bertenshaw et al. [12].

The three-component aza-MBH synthesis was also reported to be catalysed using bifunctional catalysis with metal-based Lewis acids such as $Sc(SO_3CF_3)_3$, $(CF_3SO_3)_3Yb$ and $Ti[OCH(CH_3)_2]$, in the presence of 3-hydroxyquinuclidine (3-HQD) or 1,4-diazabicyclo[2.2.2] octane (DABCO) as a Lewis base [6]. The reaction was carried out at ambient temperature and pressure using propan-2-ol and molecular sieves. The methodology shows varying degrees of success as well as limitations: despite the mild reaction conditions employed, one also has to factor in the use of the expensive, hazardous, metallic-based homogeneous catalyst, long reaction times employed (11 h) and low chemoselectivity. Recent studies mainly focus on the applications and further transformations of α-methylene-β-amino compounds relying solely on this method or previously published two-component methods [13]. Following our systematic study towards the design of efficient, safe and environmentally benign methods for organic transformations [14,15], in this study, we describe a more

sustainable protocol, employing cheaper, non-hazardous catalysts for the three-component aza-MBH synthesis.



Scheme 5. Possible side-product formation (**12**) in the multi-step synthesis of the aza-MBH product (**11**) [6].

2. Results

2.1. Catalyst Screening and Condition Optimisation

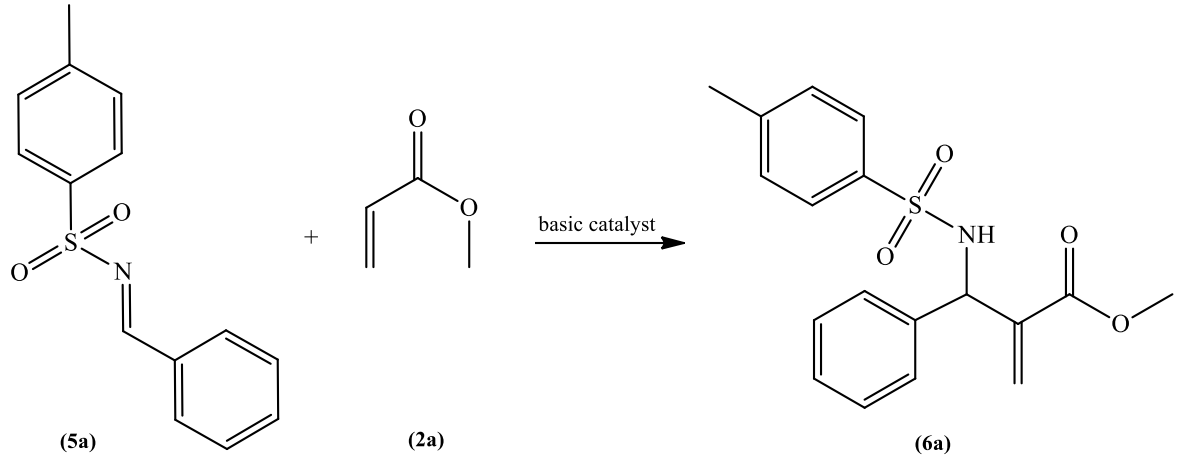
According to the literature, the reaction has been shown to work most efficiently when using a Lewis base and a Lewis acid catalyst mixture. A number of catalysts were tested for the model aza-MBH reaction between benzaldehyde (**1a**), *p*-toluenesulfonamide (**4a**) and methyl acrylate (**2a**), the same reaction model employed in previous publications on this topic [6,12]. The imine intermediate, formed from the reaction between the aldehyde and the amide, requires a Lewis base catalyst in order to undergo a coupling reaction with the Michael acceptor (methyl acrylate), as shown in the catalytic cycle in Scheme 3 [10,11]. The first studies were therefore focused on the activation of the Michael acceptor towards nucleophilic attack onto the imine. A number of two-component reaction trials were carried out between the freshly prepared and purified imine (**5a**) and methyl acrylate (**2a**), as shown in Table 1 All trials were performed at a scale of 1.5 mmol and in a 1:1.1 ratio of reactants (*p*-tosyl imine and methyl acrylate, respectively), in the presence of 15 mol% of catalyst and 0.250 µL of propan-2-ol. All reactions were given a time limit of 48 h.

As a choice of base catalysts, a number of Lewis organic bases varying in the nucleophilicity were selected. These included the following: triethylamine, 4-dimethylaminopyridine (DMAP), 1,8-diazabiciclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO) and 3-quinuclidinol (3-HQD), in increasing order of nucleophilicity measured on Csp^2 centres by previous studies [16]. The yields generated ranged from low to good yields, with the best yields obtained when using DABCO and 3-HQD as catalysts. The difference in yield is related to the degree of nucleophilicity of the base catalysts employed. The least nucleophilic bases triethylamine and DMAP result in the lowest yields, while DABCO and 3-HQD, displaying a higher nucleophilicity, resulted in higher yields of product. Both DABCO and 3-HQD are quinuclidine-based amines and tend to have a higher nucleophilicity than the rest of the catalysts employed as a result of the restricted carbon bonds, keeping the amine active sites open to reaction. In addition to these amine-based

catalysts

bases, the phosphine-based catalyst was also tested, giving a significantly lower yield (only 14%). To address the challenge of green chemistry, our efforts were focused on implementing a heterogeneous catalyst, using organic functional ion-exchange resins, such as the macroporous macroreticular resins Amberlyst-21 and Amberlyst-26 and the gel-type microreticular resin Amberlite IRA-400. Amberlyst-21 bears a dimethylamino functional group while Amberlyst-26 and Amberlite IRA-400 bear a quaternary ammonium salt, therefore presenting variations in the basicity and reactivity towards the reaction. The use of the three different solid catalysts was however unsuccessful with no product being produced.

Table 1. Two-component aza-MBH reaction trials between *p*-tosyl imine (**5a**) and methyl acrylate (**2a**) with various Lewis base catalysts.



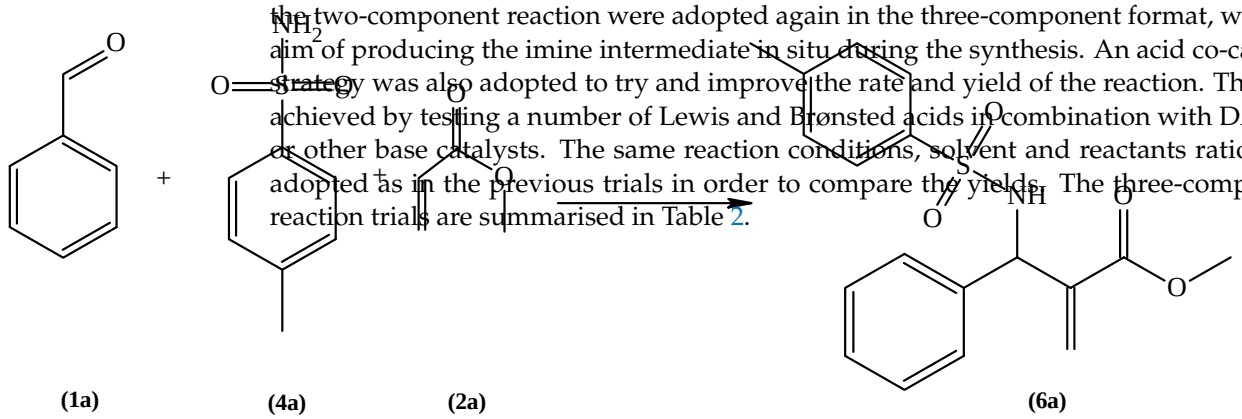
(5a) **(2a)** **(6a)**

Entry	Catalyst	Yield (%) [a]
1	Triethylamine	0
2	DMAP	18
3	DBU	28
4	DABCO	79
5	3-HQD	85
6	PPh_3	14
7	Amberlyst-21	0
8	Amberlyst-26 hydroxide	0
9	Amberlite IRA-400 chloride	0

[a] Isolated yield.

After having synthesised and characterised the model product using the two-component version, we moved on to study the three-component reaction. Most of the catalysts tested in the two-component reaction were adopted again in the three-component format, with the aim of producing the imine intermediate in situ during the synthesis. An acid co-catalyst strategy was also adopted to try and improve the rate and yield of the reaction. This was achieved by testing a number of Lewis and Brønsted acids in combination with DABCO or other base catalysts. The same reaction conditions, solvent and reactants ratio were adopted as in the previous trials in order to compare the yields. The three-component reaction trials are summarised in Table 2.

Table 2. Catalyst screening for the one-pot, multicomponent model reaction between benzaldehyde (**1a**), *p*-toluenesulfonamide (**4a**) and methyl acrylate (**2a**).



(1a) **(4a)** **(2a)** **(6a)**

Entry	Acid Catalyst (Quantity)	Base Catalyst (Quantity)	Temperature (°C)	Yield [a] (%)
1	-	-	R.T.	/ [b]
		PPh_3		

6	PPh_3	14
7	Amberlyst-21	0
8	Amberlyst-26 hydroxide	0
9	Amberlite IRA-400 chloride	0

[a] Isolated yield.

Table 2. Catalyst screening for the one-pot, multicomponent model reaction between benzaldehyde (**1a**), *p*-toluenesulfonamide (**4a**) and methyl acrylate (**2a**).

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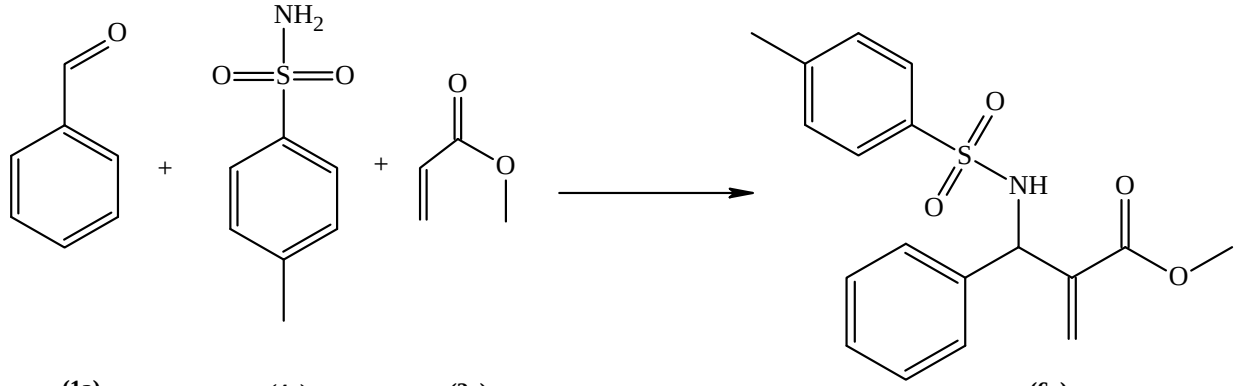


(1a) **(4a)** **(2a)** **(6a)**

Entry	Acid Catalyst (Quantity)	Base Catalyst (Quantity)	Temperature (°C)	Yield [a] (%)
1	-	-	R.T.	/ [b]
2	-	PPh_3 (15 mol%)	40	/
3	-	DIPEA (15 mol%)	R.T.	/
4	-	DMAP (15 mol%)	R.T.	/
5	-	DBU (15 mol%)	R.T.	/
6	-	DABCO (15 mol%)	R.T.	48
7	-	DABCO (15 mol%)	100	/
8	-	DABCO (30 mol%)	R.T.	52
9	-	3-HQD (15 mol%)	R.T.	35
10	-	Amberlyst-21 (15 mol%)	R.T.	/
11	Neutral alumina (5 mol%)	DABCO (30 mol%)	R.T.	57
12	Acidic alumina (5 mol%)	DABCO (30 mol%)	R.T.	63
13	Montmorillonite K10 (5 mol%)	DABCO (30 mol%)	R.T.	66
14	Montmorillonite K30 (5 mol%)	DABCO (30 mol%)	R.T.	66
15	Amberlyst® 15 (5 mol%)	DABCO (30 mol%)	R.T.	77
16	Nafion® NR50 (5 mol%)	DABCO (30 mol%)	R.T.	56

Table 2. *Cont.*

Entry	Acid Catalyst (Quantity)	Base Catalyst (Quantity)	Temperature (°C)	Yield [a] (%)
17	Amberlyst® 15 (5 mol%)	3-HQD (30 mol%)	R.T.	53
18	Amberlyst® 15 (5 mol%)	PPh_3 (30 mol%)	R.T.	9
19	Amberlyst® 15 (5 mol%)	DBU (30 mol%)	R.T.	28

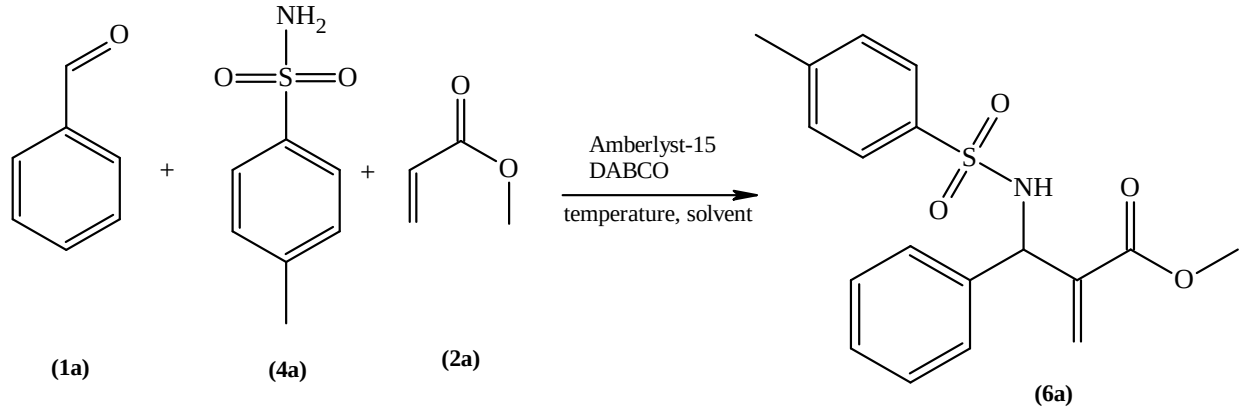
[a] Isolated yield. Reaction conditions: benzaldehyde, *p*-toluenesulfonamide and methyl acrylate in a 1:1:1.1 ratio, respectively, and at a 1.5 mmol scale, 0.3 g of 4 Å molecular sieves (200 mg/mmol), 200 µL of propan-2-ol solvent, 48 h; [b] "/" meaning no product formed.

Like in the previous trials, both DABCO and 3-HQD performed well; however, the in situ presence of the imine intermediate had a substantial effect on the reaction yields of product. The same effect was also noticeable with the other bases including PPh_3, DBU, DMAP and *N*,*N*-diisopropylethylamine (DIPEA), which was tested instead of triethylamine. The drop in the synthetic yield observed in the three-component format is due to the formation of various side products, including the classical MBH α-methylene-β-hydroxy product (**3**), shown in Scheme 1. This indicates that while DABCO and 3-HQD catalysts were suitable for the nucleophilic addition between the zwitterionic intermediate and the imine, they were not suitable for activation of aldehydes towards the N-sulfonyl imine formation. A rapid in situ formation of *N*-sulfonyl imine is necessary for a better selectivity of the overall reaction. A catalytic acid is believed to enhance the three-component reaction by protonating the carbonyl oxygen of the aldehyde in order to have a better leaving group and accelerate the dehydration reaction towards the formation of the imine intermediate. It also aids in the proton transfer step of the mechanism, therefore accelerating the β-elimination of the nucleophilic base catalyst. Only heterogeneous acid catalysts were tested in the reaction. Both acidic and neutral alumina were tested as co-catalysts. When compared to the control reaction (entry 8, Table 2) a slight improvement in the yield is observed. The other inorganic oxide tested in these reaction trails was the zeolite Montmorillonite clay. It is an aluminosilicate clay which contains polarisable Al^{+3} cations in the interlamellar spaces. Similar to silica surface molecules, the Brønsted acidity is a result of the terminal silanol groups, located at the external surface of aluminosilicate layers [17,18]. These clays are commercially found in a series of varying acidity depending on the method of acid activation. Montmorillonite K10 and K30, the variations tested in this reaction, gave an increase in yield compared to the trials with alumina (entries 13, 14). The increase in yield can be explained as a result of the higher surface area in the Montmorillonite clay catalysts compared to Alumina. However, the highest yield (77%) of isolated aza-MBH product was obtained using Amberlyst® 15 as an acid co-catalyst with DABCO (entry 15). Amberlyst® 15 is a commercially available catalyst, in the form of beads, consisting of a macroreticular polystyrene-based ion-exchange resin with sulfonic acid moieties and was reported in our previous publication as an efficient catalyst for simple imine formation [19]. The trial with Nafion® NR 50 gave a significantly lower yield than that with Amberlyst-15, probably due to the increased acidity, brought by the perfluorinated acidic terminal $-CF_2CF_2SO_3H$, which can decrease the available DABCO [20]. Another reason can be related to the differences in surface area; in fact, Nafion has a very low surface area when compared to Amberlyst® 15, and for optimum acid site accessibility, it requires the use of swelling solvents [20]. For further testing, Amberlyst-15 was also used with other bases, giving unsatisfactorily low yields of product (entries 17–19).

The best catalyst mixture is clearly DABCO (30 mol%) with Amberlyst® 15 (5 mol%), giving a 77% yield of product. The optimisation of the process was then carried out on the model reaction with benzaldehyde, *p*-toluenesulfonamide and methyl acrylate, on a

1.5 mmol scale, using DABCO and Amberlyst-15 in different quantities, as reported in Table 3. The reaction was tested under different temperatures and solvents. Trials 1–4 were solely focused on the ratio of DABCO and Amberlyst® 15 catalysts used. Decreasing the amount of DABCO from 30 mol% to 20 mol% and 10 mol% did not result in a significant decrease in yield. Opting for the most efficient and green conditions, we decided to adopt the ratio of 5 mol% Amberlyst-15 and 10 mol% DABCO (entry 4). As indicated by entries 6–7, the yield decreased with higher temperatures due to a substantial increase in side reactions, possibly including polymerisation of the acrylate and aza-Michael reaction, amongst other possible reactions. A selection of different solvents varying in polarity were tested in the reaction. The solvents employed were all carefully selected based on the Pfizer selection table of green solvents [21,22]. They are listed with decreasing polarity from methanol to 2-methyltetrahydrofuran. Overall, a general decrease in the yield was observed with decreasing polarity, with propan-2-ol being selected as the best overall solvent. The ideal conditions for the three-component aza-MBH reaction for *p*-toluenesulfonamide, benzaldehyde and methyl acrylate were found to be: 1:1:1.1 ratio of reactants, 10 mol% of DABCO, 5 mol% Amberlyst® 15, room temperature, 250 µL of propan-2-ol solvent and 0.3 g 4 Å molecular sieves.

Table 3. Condition optimisation using DABCO and Amberlyst® 15 as co-catalysts.



(1a) **(4a)** **(2a)** **(6a)**

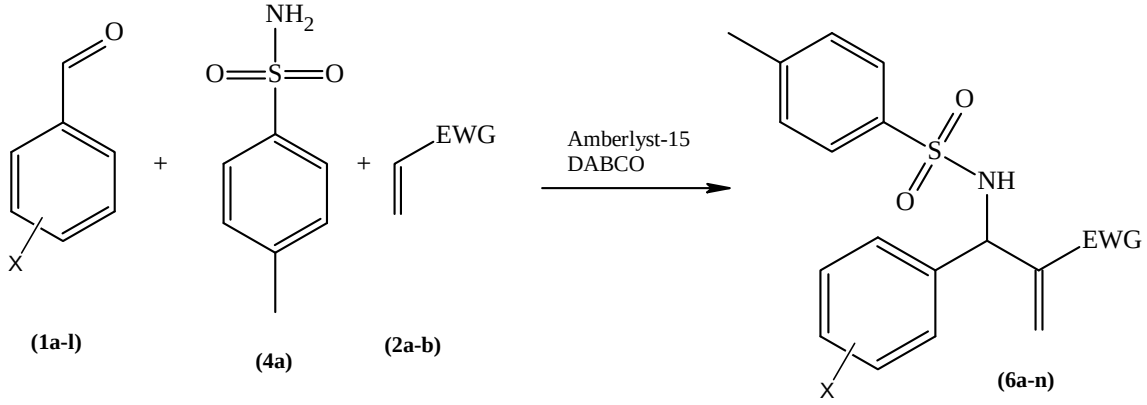
Entry	Acid Catalyst Amberlyst® 15 (Quantity)	Base Catalyst DABCO (Quantity)	Temperature (°C)	Solvent (200 µL)	Yield [a] (%)
1	(50 mol%)	(30 mol%)	R.T.	Propan-2-ol	8
2	(30 mol%)	(30 mol%)	R.T.	Propan-2-ol	24
3	(5 mol%)	(20 mol%)	R.T.	Propan-2-ol	75
4	(5 mol%)	(10 mol%)	R.T.	Propan-2-ol	75
5 [b]	(5 mol%)	(10 mol%)	R.T.	Propan-2-ol	71
6	(5 mol%)	(10 mol%)	40	Propan-2-ol	64
7	(5 mol%)	(10 mol%)	60	Propan-2-ol	46
8	(5 mol%)	(10 mol%)	Reflux	Propan-2-ol	/ [c]
9	(5 mol%)	(10 mol%)	R.T.	Solventless	58
10	(5 mol%)	(10 mol%)	R.T.	Methanol	61
11	(5 mol%)	(10 mol%)	R.T.	Acetonitrile	55
12	(5 mol%)	(10 mol%)	R.T.	Tetrahydrofuran	55
13	(5 mol%)	(10 mol%)	R.T.	2-Methyltetrahydrofuran	74

[a] Isolated yield. Reaction conditions: benzaldehyde, *p*-toluenesulfonamide and methyl acrylate in a 1:1:1.1 ratio, respectively, and at a 1.5 mmol scale, 0.3 g of 4 Å molecular sieves (200 mg/mmol), 200 µL of solvent, 48 h; [b] run for 24 h; [c] "/" meaning no product formed.

2.2. Substrate Screening

A substrate scope analysis to test the flexibility of the reaction was then performed. The aim was to understand how the reactivity varies with molecules possessing different substituents at secondary positions and to observe trends in steric and electronic influences. This screening also allowed the development of a library of α-methylene-β-amino compounds that can be further studied for applications, including bioactivity. Various aromatic aldehydes and activated alkenes were used, giving similar results with minimal time and yield deviations from the model reaction, as shown in Table 4.

Table 4. Yields and reaction times for the aza-MBH reaction involving aldehydes (**1a**–**l**), *p*-toluenesulfonamide (**4a**) and activated alkenes (**2a**–**b**).



(1a-l) **(4a)** **(2a-b)** **(6a-n)**

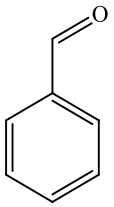
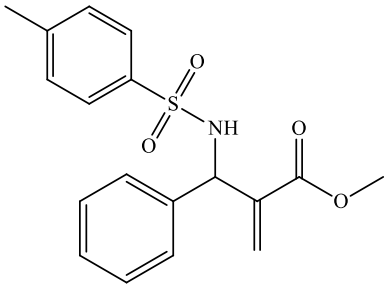
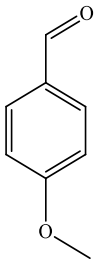
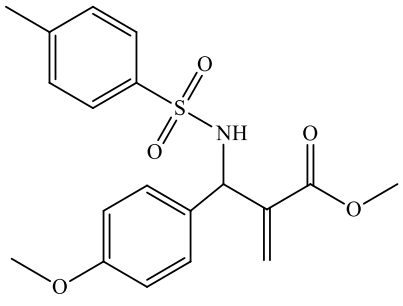
Entry [a]	Aldehyde	Product	Yield (%) [b]
1	 (**1a**)	 (**6a**)	75
2	 (**1b**)	 (**6b**)	75

Table 4. *Cont*.

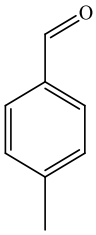
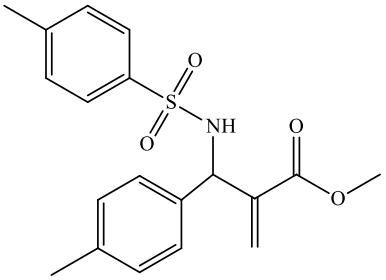
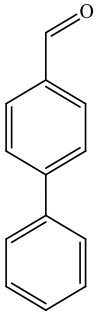
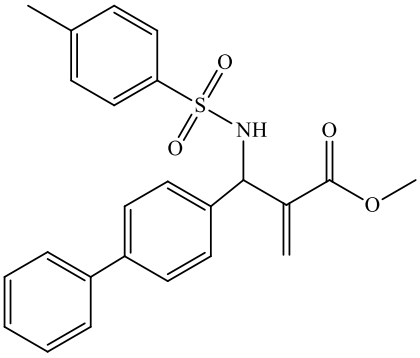
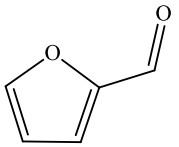
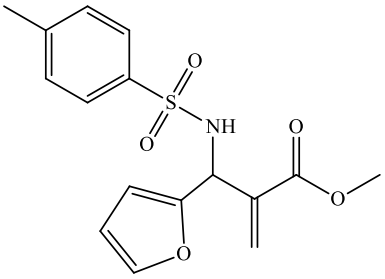
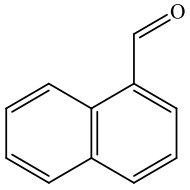
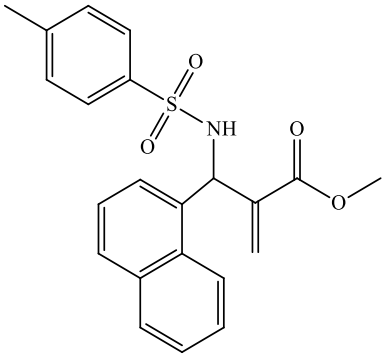
Entry [a]	Aldehyde	Product	Yield (%) [b]
3	 (**1c**)	 (**6c**)	81
4	 (**1d**)	 (**6d**)	81
5	 (**1e**)	 (**6e**)	74
6	 (**1f**)	 (**6f**)	62

Table 4. *Cont*.

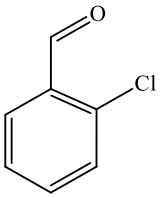
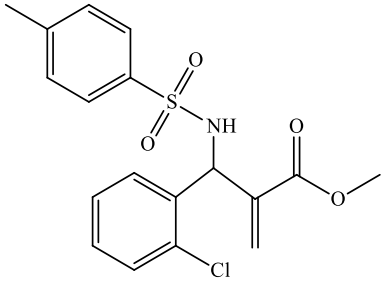
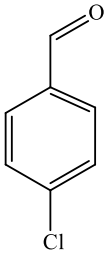
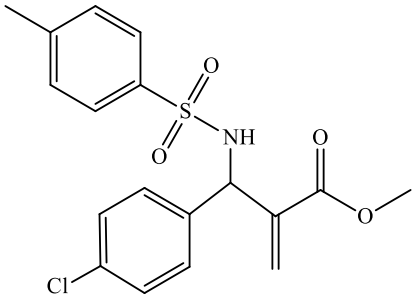
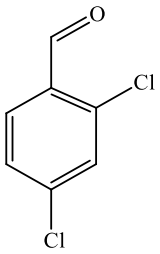
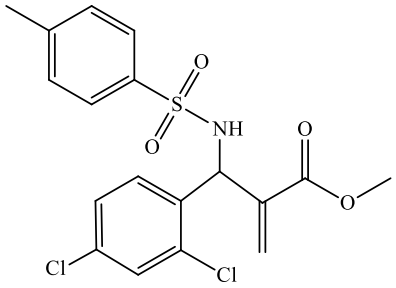
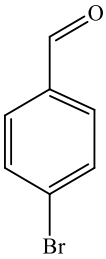
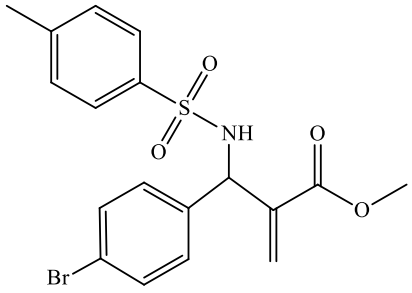
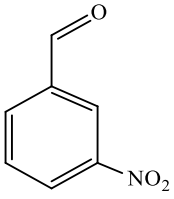
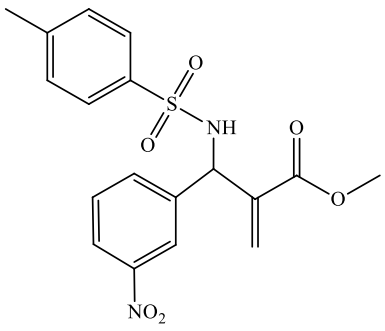
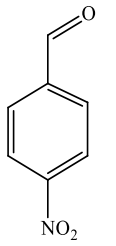
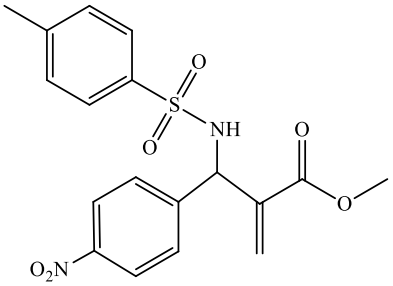
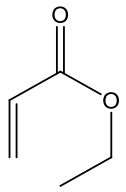
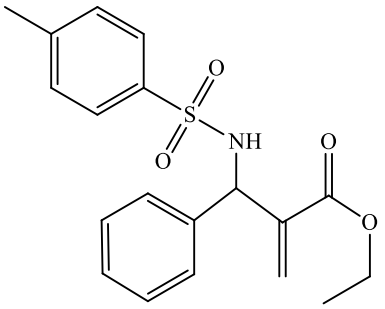
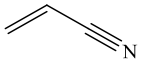
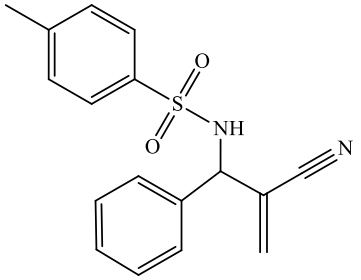
Entry [a]	Aldehyde	Product	Yield (%) [b]
7	 (**1g**)	 (**6g**)	60
8	 (**1h**)	 (**6h**)	60
9	 (**1i**)	 (**6i**)	52
10	 (**1j**)	 (**6j**)	57
11	 (**1k**)	 (**6k**)	42

Table 4. *Cont.*

Entry [a]	Aldehyde	Product	Yield (%) [b]
12	 (**1l**)	 (**6l**)	53
	Alkene		
13	 (**2a**)	 (**6m**)	83
14	 (**2b**)	 (**6n**)	69

[a] Aldehydes (**1a**–**l**), *p*-toluenesulfonamide (**4a**) and activated alkenes (**2a**–**b**) present in a ratio of 1:1:1.1 on a 2.5 mmol scale. All reactions were carried out at room temperature for 48 h, using 5 mol% of dried Amberlyst-15 and 10 mol% of DABCO, with 0.3 g of dried 4 Å molecular sieves and 250 µL of propan-2-ol as a solvent; [b] yield of pure product, purified by column chromatography (hexane/acetone).

The first component of the aza-MBH reaction to be replaced was the aldehyde. Various aromatic aldehydes (**1a**–**l**) were reacted with *p*-toluenesulfonamide (**4a**) and methyl acrylate (**2a**). The best yields were obtained when using moderate electron-donating groups such as methoxy and methyl groups in the para-position to the aldehyde carbonyl (entries 2–3). Similar results were obtained with halogen-substituted aldehydes, furfuraldehyde and naphthalene-1-carbaldehyde (entries 5–10). On the other hand, when using strong electron-withdrawing groups such the nitro group (entries 11–12), a decrease in the yield of product was observed. This decrease in the % yield was not expected with electron-withdrawing groups since they can pull electrons from the delocalised aromatic ring, therefore reducing the electron density of the carbonyl carbon in the aldehyde or azomethine (C=N) carbon atom in the intermediate aldimine, making them more susceptible towards nucleophilic attack. Thus, electron-withdrawing groups were expected to improve the reactivity of the aldehyde or imine intermediate towards nucleophilic attack. However, increasing the electrophilicity of the carbonyl carbon not only increases the chance of imine formation,

but also activates the aldehyde for the classical MBH reaction to take place and form the alcohol adduct as a side product.

The second component of the aza-MBH reaction to be varied was the electron-deficient alkene. The activated alkenes (**2a**, **2b**) were reacted with benzaldehyde (**1a**) and *p*-toluenesulfonamide (**4a**), obtaining respectable yields of product (entries 13–14). Ethyl acrylate (entry 13) furnished the highest yield. It is possible that the positive inductive effect from the ethyl group slightly counteracts the electron-withdrawing effect of the ester functionality, thus stabilising the zwitterionic intermediate.

2.3. Catalyst Recycling Test

A series of recyclability tests were conducted on Amberlyst® 15 to test whether the catalytic activity could be repeated for more than one cycle of the reaction. The reaction between benzaldehyde (**1a**), *p*-toluenesulfonamide (**4a**) and ethyl acrylate (**2a**) was repeated for up to five cycles. After each cycle, the Amberlyst® 15 catalyst was separated from the reaction mixture and retained. It was then dried for 24 h at 100 °C and reused for the next cycle. The catalyst showed a consistent performance over the first four cycles with only a 10% drop in yield, as displayed in the bar chart in Figure 1. A major drop in the catalytic activity was observed in the fifth cycle. This can possibly be attributed to both the physical fracturing of the Amberlyst® 15 beads and the steady loss of sulfonic acid moieties.

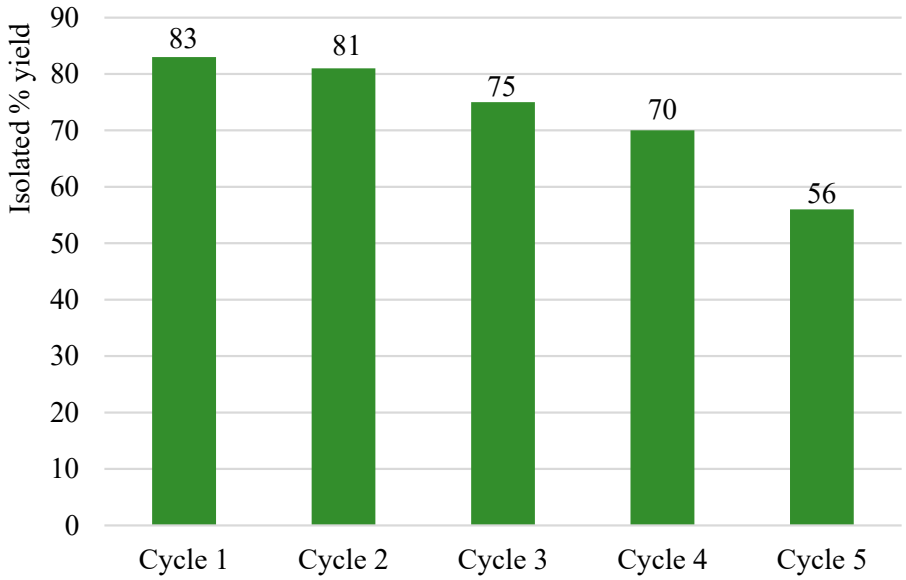


Figure 1. Bar chart showing product % yield following each recycle of Amberlyst® 15.

2.4. Green Metrics

Green metrics are the mathematical tools used to systematically quantify and compare potential environmental impact of a synthesis or process [23–25]. The two most widely adopted green metrics are atom economy (AE) and the E-factor [23]. Atom economy, proposed by Barry M. Trost in 1991, is a mass-based metric defined as the calculation of the number of atoms in the reactants which end up in the final molecule or product [1]. It proposes that for a reaction to be green, it should be designed to maximise the incorporation of all atoms used in the reaction into the final products, hence minimising or eliminating waste. The atom economy for the model reaction was calculated (Equation (1)), with successful incorporation of 95% of all the reactants atoms, and only a H_2O molecule is released.

$$AE = \frac{RMM_{product}}{\Sigma RMM_{reagents}} \times 100 = \frac{345}{171 + 106 + 86} \times 100 = 95\% \quad (1)$$

The Environmental Factor (E-factor) was proposed by Sheldon in 1992. It calculates the amount of unit waste produced per unit of the desired product [26,27]. For ideal synthesis,

the E-factor is equal to zero. Higher E-factor values indicate that more waste is generated with a higher negative environmental and economic impact. In contrast to atom economy, this metric is based on the amount of waste produced in the process, hence accounting for all raw materials consumed but not incorporated into the product. It is the ratio of the total mass of waste produced over the mass of final product, as shown in Equation (2).

$$\mathrm{E-factor} = \frac{\text{Total mass of waste}}{\text{Mass of final product}} = \frac{0.462\ \mathrm{g}}{0.648\ \mathrm{g}} = 0.71 \quad (2)$$

The quantities used in the calculation of the E-factor for the model reaction product (**1a**) are displayed in Table 5. Calculation of the E-factor resulted in a relatively low value of 0.71, indicating that little waste is generated. The generation of such a low E-factor is mainly attributed to the minimal use of excess reagents, solvent and homogeneous DABCO, and also to the recyclability of Amberlyst-15.

Table 5. Actual quantities of reagents used in the calculation of the E-factor for the aza-MBH model reaction product (**6a**).

Reagent	Quantities	Waste
p-Toluenesulfonamide	2.5 mmol	-
Benzaldehyde	2.5 mmol	-
Methyl acrylate	2.75 mmol	0.25 mmol = 0.022 g
Amberlyst® 15	5 mol%	Recyclable
DABCO	10 mol%	0.028 g
Molecular sieves	0.3 g	Recyclable
Propan-2-ol	250 µL	0.196 g
Waste generated:		0.246 g
Extra waste (side products and non-converted reagents):		0.216 g
Total actual waste generated:		0.246 + 0.216 = 0.462 g

3. Materials and Methods

3.1. General

All commercially available chemicals were purchased from Aldrich (St. Louis, MO, USA) and used without further purification. IR spectra were recorded on an IR Affinity-1 FTIR spectrometer (Shimadzu, Kyoto, Japan) calibrated against a 1602 cm^{-1} polystyrene absorbance spectrum. Samples were analysed as thin films in between sodium chloride discs. The ^{1}H and ^{13}C-NMR spectra were recorded on an Avance III HD® NMR spectrometer (Bruker, Coventry, UK), equipped with an Ascend 500 11.75 Tesla Superconducting Magnet, operating at 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C, and a Multinuclear 5 mm PABBO Probe (Bruker, Coventry, UK). Samples were dissolved in the deuterated solvent specified in the section on the analytical information. The melting points of products were measured using a Stuart® SMP11 melting point determination apparatus fitted with a mercury thermometer (Tequipment, Long Branch, NJ, USA). Three separate readings were taken, and the mean average was then calculated to achieve better accuracy. Reactions were monitored using TLC plates composed of silica on PET with a fluorescent indicator and GC on a Shimadzu GC-2010 plus gas chromatograph equipped with a flame ionisation detector and HiCap 5 GC column with dimensions of 0.32 mm (internal diameter) × 30 m (length) × 0.25 mm (film thickness), using nitrogen as the carrier gas. Plates were observed under a UV lamp at a wavelength of 254 nm before staining in an iodine-saturated chamber. Mass spectra were performed using a Waters Acquity® TQD system (Waters, Milford, MA, USA), equipped with a tandem quadrupole mass spectrometer, and analysed directly with a probe. The spectra were obtained in relative abundance compared to m/z and were generated by the software MassLynx®, ver. 4.2.

3.2. General Method for the Three-Component aza-MBH Reaction

The general procedure for the three-component aza-MBH reaction was based on the optimised conditions in Table 3, entry 4. However, for the substrate scope trials, the molarity was increased from 1.5 to 2.5 mmol to have enough product for characterisation. The reaction was set up as follows: 5 mol% Amberlyst® 15 (dried) [28], 10 mol% DABCO, 0.3 g of dried 4 Å molecular sieves and the amide (2.5 mmol) were weighed and transferred into a 10 mL single-necked round-bottomed flask. To the solid mixture, the aldehyde (2.5 mmol) and the activated alkene (2.75 mmol) were added, followed by 250 µL propan-2-ol, which were streamed down the sides of the round-bottomed flask to help homogenise the reaction mixture. The reaction was stirred at room temperature and monitored by TLC and GC at several time intervals. Upon completion of the reaction, 5 mL of acetone were added and left to further stir for 5 more minutes to allow the viscous reaction mixture to dissolve. The catalyst and the molecular sieves were then separated by filtration, using a further 5 mL acetone and 5 mL hot ethanol to wash out any remaining adsorbed reaction components. The crude reaction was then concentrated using rotatory evaporation and purified by column chromatography (hexane/acetone). The isolated yields were measured and calculated, and the products were characterised by melting point determination, IR, ^{1}H, and ^{13}C-NMR spectroscopy and MS spectrometry.

3.3. Analytical Information

Methyl 2-[{[(4-methylphenyl)sulfonyl]amino}(phenyl)methyl]acrylate (**6a**) [6]. MF: $C_{18}H_{19}NO_4S$; MW: 345.4 g/mol. White solid recrystallized from hexane. Yield = 75%; R_f = 0.27 (hexane/acetone, 7.5:2.5 *v*/*v*); Mp. = 76–78 °C; ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.68 (d, 2H, *J* = 8.3 Hz), 7.25–7.20 (m, 5H), 7.18–7.12 (m, 2H), 6.22 (s, 1H), 5.83 (s, 1H), 5.58 (d, 1H, *J* = 8.8 Hz), 5.30 (d, 1H, *J* = 8.6 Hz), 3.61 (s, 3H), 2.41 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 165.8, 143.4, 138.60, 137.7, 129.5, 128.6, 127.9, 127.8, 127.2, 126.5, 59.0, 52.0, 21.5. IR (KBr, cm^{-1}) 3383 (s), 3308 (w), 3258 (w), 3059 (w), 2960 (w), 2923 (w), 2853 (w), 1709 (s), 1627 (m), 1599 (m), 1494 (m), 1439 (s), 1408 (m), 1334 (s), 1164 (s), 1093 (s), 1069 (m), 969 (m), 929 (m), 813 (s), 754 (s), 705 (s), 670 (s). MS(ES+): *m*/*z* (%) = 344.16, 312.10, 270.16, 190.09, 175.05, 154.97.

Methyl 2-[(4-methoxyphenyl){[(4-methylphenyl)sulfonyl]amino}methyl]acrylate (**6b**) [6]. MF: $C_{19}H_{21}NO_5S$ MW: 375.4 g/mol. Colourless solid. Yield = 75%; R_f = 0.20 (hexa ne/acetone, 7.5:2.5 *v*/*v*); Mp. = 112–113 °C; ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.67 (d, 2H, *J* = 8.3 Hz), 7.24 (d, 2H, *J* = 8.0 Hz), 7.04 (d, 2H, *J* = 8.4 Hz), 6.75 (d, 2H, *J* = 8.8 Hz), 6.21 (s, 1H), 5.83 (s, 1H), 5.51 (d, 1H, *J* = 8.6 Hz), 5.25 (d, 1H, *J* = 8.6 Hz), 3.75 (s, 3H), 3.61 (s, 3H), 2.41 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 165.0, 159.2, 143.5, 138.9, 137.7, 130.8, 129.5, 127.9, 127.5, 127.4, 114.1, 58.6, 55.3, 52.1, 21.6. IR (KBr, cm^{-1}) 3264 (s), 3018 (w), 2953 (w), 2839 (w), 1717 (s), 1633(m), 1609 (m), 1501 (s), 1437 (m), 1403 (m), 1326 (s), 1246 (s), 1162 (s), 1073 (m), 1022 (m), 966 (m), 818 (s), 694 (s)

Methyl 2-[(4-methylphenyl){[(4-methylphenyl)sulfonyl]amino}methyl]acrylate (**6c**) [29] MF: $C_{19}H_{21}NO_4S$ MW: 359.4 g/mol. Colourless solid. Yield = 81%; R_f = 0.29 (hexane/acetone, 7.5:2.5 *v*/*v*); Mp. = 130–132 °C; ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.68 (d, 2H, *J* = 8.3 Hz), 7.24 (d, 2H, *J* = 8.0 Hz), 7.02 (m, 4H), 6.21 (s, 1H), 5.83 (1H, s), 5.51 (d, 1H, *J* = 8.6 Hz), 5.26 (d, 1H, *J* = 8.6 Hz), 3.60 (3H, s), 2.41(3H, s), 2.28 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 165.9, 143.5, 138.8, 137.8, 137.6, 135.8, 129.6, 129.4, 127.7, 127.4, 126.5, 58.9, 52.1, 21.6, 21.1. IR (KBr, 1 cm^{-1}) 3239 (s), 3047 (w), 2958 (w), 2918 (w), 1721 (s), 1684 (m), 1653 (m), 1507 (m), 1437 (m), 1327 (s), 1282 (s), 1167 (s), 1096 (w), 1051 (m), 933(m), 816 (m), 727 (w), 667 (w).

Methyl 2-[(4-biphenyl){[(4-methylphenyl)sulfonyl]amino}methyl]acrylate (**6d**) MF: $C_{24}H_{23}NO_4S$ MW: 421.5 g/mol. Colourless solid. Yield = 81%; R_f = 0.3 (hexane/acetone, 7:3, *v*/*v*); Mp. = 165–166 °C; ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.69 (d, 2H, *J* = 8.3 Hz), 7.54–7.50 (m, 2H), 7.45 (d, 2H, *J* = 8.3 Hz), 7.42 (t, 2H, *J* = 7.6 Hz), 7.33 (t, 1H, *J* = 7.3, Hz), 7.24 (d, 2H, *J* = 8.1 Hz), 7.27–7.20 (d, 2H, *J* = 8.2 Hz), 6.25 (s, 1H), 5.86 (s, 1H), 5.65 (d, 1H, *J* = 8.9 Hz),

5.35 (d, 1H, *J* = 8.7 Hz), 3.63 (3H, s), 2.40 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 165.9, 143.5, 140.8, 140.6, 138.7, 137.8, 137.7, 129.6, 128.9, 128.0, 127.6, 127.40, 127.37, 127.2, 127.1, 59.0, 52.2, 21.6. IR (KBr, cm^{-1}) 3270 (m), 3030 (w), 2956 (w), 1718 (s), 1627 (w), 1486 (m), 1446 (m), 1399 (w), 1325 (s), 1159 (s), 1074 (m), 948 (w), 819 (m), 766 (m), 703 (m), 689 (m), 668 (s). MS(ES+): *m*/*z* (%) = 267.29, 266.14, 251.16, 154.97.

Methyl 2-[(4-furanyl){[(4-methylphenyl)sulfonyl]amino}methyl]acrylate (**6e**) [6] MF: $C_{16}H_{17}NO_5S$ MW: 335.4 g/mol. Orange oil. Yield = 74%; R_f = 0.23 (hexane/acetone, 7.5:2.5 *v*/*v*); ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.69 (d, 2H, *J* = 8.3 Hz), 7.24 (d, 2H, *J* = 8.0 Hz), 7.22–7.20 (m, 1H), 6.24 (s, 1H), 6.21 (dd, 1H, *J* = 3.3, 1.8 Hz), 6.06 (dt, 1H, *J* = 3.3, 0.8 Hz), 5.84 (s, 1H), 5.63 (d, 1H, *J* = 9.1 Hz), 5.39 (d, 1H, *J* = 9.1 Hz), 3.68 (s, 3H), 2.41 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 165.7, 151.3, 143.5, 142.4, 137.6, 137.0, 129.6, 128.5, 127.3, 110.6, 107.6, 53.6, 52.2, 21.6. IR (NaCl, cm^{-1}) 3279 (s), 2990 (w), 2953 (m), 2926 (w), 1721 (s), 1635 (m), 1597 (m), 1496 (m), 1439 (s), 1333 (s), 1268 (s), 1159 (s), 1067 (m), 1013 (m), 962 (m), 918 (m), 816 (s), 743 (s), 679 (s).

Methyl 2-[(1-naphthyl){[(4-methylphenyl)sulfonyl]amino}methyl]acrylate (**6f**) MF: $C_{22}H_{21}NO_4S$ MW: 359.5 g/mol. White solid. Yield = 62%; R_f = 0.24 (hexane/acetone, 7.5:2.5 *v*/*v*); Mp. = 152–159 °C; ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.81 (dd, 2H, *J* = 8.3, 2.9 Hz), 7.74 (d, 1H, *J* = 7.7 Hz), 7.65 (d, 2H, *J* = 8.3 Hz), 7.48–7.43 (m, 1H), 7.40–7.35 (m, 1H), 7.34–7.28 (m, 2H), 7.20 (d, 2H, *J* = 7.6 Hz), 6.39 (s, 1H), 6.21 (d, 1H, *J* = 7.3 Hz), 5.94 (s, 1H), 5.08 (d, 1H, *J* = 7.3 Hz), 3.58 (s, 3H). 2.41 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 166.2, 143.5, 139.5, 137.4, 134.4, 134.1, 130.6, 129.6, 129.1, 128.8, 127.7, 127.5, 126.7, 126.0, 125.2, 125.1, 123.0, 54.1, 52.1, 21.6. IR (KBr, cm^{-1}), 3276 (s), 3030 (w), 2952 (w), 2853 (w), 1721 (s), 1597 (w), 1508 (w), 1435 (m), 1321 (s), 1294 (m), 1264 (m), 1155 (s), 1060 (s), 955 (w), 811 (m), 778 (m). MS(ES+): *m*/*z* (%) = 240.13, 225.09, 155.04.

Methyl 2-[(2-chlorophenyl){[(4-methylphenyl)sulfonyl]amino}methyl]acrylate (**6g**) [29] MF: $C_{18}H_{18}ClNO_4S$ MW: 379.9 g/mol. White solid. Yield = 60%; R_f = 0.32 (hexane/acetone, 7.5:2.5 *v*/*v*); Mp. = 119–120 °C; ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.65 (d, 2H, *J* = 8.3 Hz), 7.32 (dd, 1H, *J* = 7.1, 2.3 Hz), 7.26–7.23 (m, 1H), 7.18 (d, 2H, *J* = 8.0 Hz), 7.16–7.09 (m, 2H), 6.29 (s, 1H), 5.89 (s, 1H), 5.74 (d, 1H, *J* = 8.6 Hz), 5.68 (d, 1H, *J* = 8.5 Hz), 3.63 (s, 3H), 2.37 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 165.9, 143.5, 137.8, 137.4, 135.9, 133.1, 129.9, 129.5, 129.1, 129.0, 128.8, 127.3, 127.0, 55.8, 52.2, 21.6. IR (KBr) 3251 (s), 3069 (w), 2953 (w), 2882 (w), 1722 (s), 1629 (w), 1444 (m), 1339 (m), 1321 (s), 1242 (s), 1153 (s), 1133 (m), 1070 (m), 926 (m), 818 (m), 751 (m), 694 (m).

Methyl 2-[(4-chlorophenyl){[(4-methylphenyl)sulfonyl]amino}methyl]acrylate (**6h**) [29] MF: $C_{18}H_{18}ClNO_4S$ MW: 379.9 g/mol. White solid. Yield = 60%; R_f = 0.24 (hexane/acetone, 7.5:2.5 *v*/*v*); Mp. = 119–120 °C; ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.65 (d, 2H, *J* = 8.3 Hz), 7.32 (s, 1H), 7.23 (d, 1H, *J* = 8.0 Hz), 7.20 (d, 2H, *J* = 8.6 Hz), 7.10 (d, 2H, *J* = 8.4 Hz), 6.20 (s, 1H), 5.79 (s, 1H), 5.72 (d, 1H, *J* = 9.1 Hz), 5.26 (d, 1H, *J* = 9.1 Hz), 3.61 (s, 3H), 2.41 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 165.6, 143.7, 138.3, 137.7, 137.3, 133.8, 129.7, 128.8, 128.3, 128.0, 127.3, 58.7, 52.2, 21.6. IR (KBr, cm^{-1}) 3258 (s), 3055 (w) 2959 (w), 2923 (w), 1705 (s), 1626 (w), 1555 (w), 1495 (m), 1455 (m), 1430 (m), 1332 (s), 1163(s), 1094 (m), 1065 (m), 1014 (m), 945 (m), 812 (m), 678 (s).

Methyl 2-[(2,4-dichlorophenyl){[(4-methylphenyl)sulfonyl]amino}methyl]acrylate (**6i**) [30] MF: $C_{18}H_{17}Cl_2NO_4S$ MW: 414.3 g/mol. White solid. Yield = 52%; R_f = 0.31 (hexane/acetone, 7.5:2.5 *v*/*v*); Mp. = 156–157 °C; ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.63 (d, 2H, *J* = 8.3 Hz), 7.28–7.26 (m, 2H), 7.19 (d, 2H, *J* = 8.1 Hz), 7.08 (dd, 1H, *J* = 8.5, 2.1 Hz), 6.28 (s, 1H), 5.88 (s, 1H), 5.73 (d, 1H, *J* = 8.7 Hz), 5.66 (d, 1H, *J* = 8.4 Hz), 3.64 (s, 3H), 2.39 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 165.8, 143.7, 137.33, 137.29, 134.6, 134.4, 133.7, 130.1, 129.6, 129.2, 127.3, 55.6, 52.3, 21.6. IR (KBr, cm^{-1}) 3252 (s), 2954 (w), 1722(s), 1649 (s), 1439(m), 1336 (m), 1320 (m), 1244 (m), 1157 (s), 1135 (w), 1077 (w), 1045 (w), 928 (w), 810 (w), 777 (w).

Methyl 2-[(4-bromophenyl){[(4-methylphenyl)sulfonyl]amino}methyl]acrylate (**6j**) MF: $C_{18}H_{18}BrNO_4S$ MW: 424.3 g/mol. Colourless solid. Yield = 57%; R_f = 0.26 (hexane/acetone, 7:3, *v*/*v*); Mp. = 115–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.65 (d, 2H, *J* = 8.3 Hz), 7.34 (d, 2H, *J* = 8.6), 7.23 (d, 2H, *J* = 8.2), 7.04 (d, 2H, *J* = 8.2), 6.20 (s, 1H), 5.79 (s, 1H), 5.78 (d, 1H, *J* = 9.2 Hz), 5.23 (d, 1H, *J* = 9.2 Hz), 3.61 (3H, s), 2.41 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 165.8, 143.7, 138.3, 137.9, 137.6, 131.8, 129.7, 128.4, 128.3, 121.9, 58.8, 52.2, 21.7. IR (KBr, cm^{-1}) 3279 (s), 2996 (w), 2953 (w), 2926 (w), 1718 (s), 1630 (w), 1596 (w), 1484 (m), 1441 (m),1417 (m), 1396 (m), 1328 (s), 1160 (s), 1073 (s), 1007 (m), 971 (m), 926 (m), 814 (m), 676 (s). MS(ES+): *m*/*z* (%) = 392.10, 255.05, 240.13, 155.04.

Methyl 2-[(3-nitrophenyl){[(4-methylphenyl)sulfonyl]amino}methyl]acrylate (**6k**) [6] MF: $C_{18}H_{18}N_2O_6S$ MW: 390.4 g/mol. Colourless oil. Yield = 42%; R_f = 0.23 (hexane/acetone, 7:3, *v*/*v*); ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ_H 8.07 (dd, 1H, *J* = 8.1, 1.7 Hz), 7.97 (s, 1H), 7.67 (d, 2H, *J* = 8.3 Hz), 7.64–7.61 (m, 1H), 7.45 (t, 1H, *J* = 8.0 Hz), 7.24 (d, 2H, *J* = 8.0 Hz), 6.27 (s, 1H), 5.90 (d, 1H, *J* = 9.3 Hz), 5.86 (s, 1H), 5.37 (d, 1H, *J* = 9.3 Hz), 3.64 (s, 3H), 2.40 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 165.5, 148.4, 145.0, 141.1, 137.7, 137.5, 132.8, 129.8, 129.7, 129.3, 127.3, 126.6, 122.8, 121.7, 58.8, 52.4, 21.6. IR (NaCl disc, cm^{-1}) 3020 (s), 2954 (w), 1717 (s), 1630 (w), 1523 (s), 1441 (m), 1350 (s), 1217 (s) 1160 (s), 1092 (m), 1049 (m), 965 (w), 813 (w), 756 (s), 668 (s).

Methyl 2-[(4-nitrophenyl){[(4-methylphenyl)sulfonyl]amino}methyl]acrylate (**6l**) [6] MF: $C_{18}H_{18}N_2O_6S$ MW: 390.4 g/mol. Yellow oil. Yield = 53%; R_f = 0.21 (hexane/acetone, 7.5:2.5 *v*/*v*); ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ_H 8.10 (d, 2H, *J* = 8.8 Hz), 7.67 (d, 2H, *J* = 8.3 Hz), 7.40 (d, 2H, *J* = 8.4 Hz), 7.25 (d, 2H, *J* = 8.0 Hz), 6.24 (s, 1H), 5.94 (d, 1H, *J* = 9.4 Hz), 5.82 (s, 1H), 5.37 (d, 1H, *J* = 9.4 Hz), 3.62 (s, 3H), 2.41 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 165.5, 147.5, 146.1, 144.0, 137.6, 137.5, 129.8, 129.3, 127.5, 127.3, 123.8, 59.0, 52.4, 21.6. IR (NaCl, cm^{-1}) 3079 (w), 3000 (w), 2953 (m), 1713 (s), 1630 (m), 1606 (m), 1516 (s), 1440 (s), 1436 (w), 1350 (s), 1194 (s), 1151 (s), 1109 (m), 1050 (s), 1014(w), 956 (m), 857 (m), 828 (s). 726 (m), 699 (m).

Ethyl 2-[{[(4-methylphenyl)sulfonyl]amino}(phenyl)methyl]acrylate (**6m**) MF: $C_{19}H_{21}NO_4S$ MW: 359.4 g/mol. White solid. Yield = 83%; R_f = 0.31 (hexane/acetone, 7.5:2.5 *v*/*v*); Mp. = 98–100 °C; ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.68 (d, 2H, *J* = 8.3 Hz), 7.25–7.20 (m, 5H), 7.17–7.13 (m, 2H), 6.21 (s, 1H), 5.80 (s, 1H), 5.61 (d, 1H, *J* = 9.0 Hz), 5.30 (d, 1H, *J* = 9.0 Hz), 4.05 (q, 2H, *J* = 7.2 Hz), 2.41 (s, 3H), 1.14 (t, 3H, *J* = 7.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 165.4, 143.4, 139.0, 138.9, 137.9, 129.6, 128.6, 127.8, 127.6, 127.4, 126.6, 61.1, 59.2, 21.6, 14.0. IR (KBr, cm^{-1}): 3296 (s), 3054 (w), 2982 (w), 2925 (w), 1719 (s), 1635 (m), 1583 (m), 1494 (m), 1450 (m), 1420 (m), 1329 (s), 1315 (s), 1292 (m), 1280 (m), 1235 (m), 1200 (s), 1157 (s), 1091 (s), 1066 (m), 1027 (m), 970 (m), 862 (w). 816 (s), 753 (s), 674 (s). MS(ES+): *m*/*z* (%) = 358.25, 204.18, 189.07, 155.01.

N-(2-cyano-1-phenyl-2-propenyl)-4-methyl-benzenesulfonamide (**6n**) [6] MF: $C_{17}H_{16}N_2O_2S$ MW: 312.4 g/mol. White crystalline solid. Yield = 69%; R_f = 0.20 (hexane/acetone, 7:3, *v*/*v*); Mp. = 112–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.70 (d, 2H, *J* = 8.3 Hz), 7.32–7.26 (m, 5H), 7.13–7.09 (m, 2H), 6.06 (d, 1H, *J* = 1.2 Hz), 6.00 (s, 1H), 5.10 (d, 1H, *J* = 7.1 Hz), 5.06 (d, 1H, *J* = 7.1 Hz, 2.43 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 144.2, 136.9, 136.2, 132.0, 129.9, 129.4, 129.2, 127.4, 127.0, 123.5, 116.7, 59.9, 21.7. IR (KBr, cm^{-1}) 3242 (s), 3064 (w), 3032 (w), 2951 (w), 2919 (w), 2225 (m), 1587 (m), 1493 (m), 1459 (s), 1393 (m), 1322(s), 1190 (m), 1163 (s), 1085 (m), 1064 (m), 953 (m), 921 (m), 846 (m), 813 (m), 699 (s), 673 (s).

4. Conclusions

The combination of Brønsted acidic Amberlyst® 15 and Lewis basic DABCO was found to catalyse the one-pot three-component aza-Morita–Baylis–Hillman reaction in an efficient and environmentally friendly manner. The newly developed protocol enables the production of α-methylene-β-amino compounds at ambient conditions and using negligible amounts of non-hazardous solvent, in a single procedure. The reaction tolerated

changes in the aldehydes and electron-deficient alkenes, producing a library of products with good to excellent yields, including four novel products.

Despite using DABCO as a homogeneous catalyst, the amount of waste produced from the reaction protocol remains significantly low. Quantitative analysis indicates a high atom economy of 95% and a low E-factor of 0.7 for the model reaction, with only a minimal amount of waste produced. The low value of the E-factor is attributed to the near stoichiometric amounts of reactants (1:1:1.1), the recyclability of Amberlyst® 15 and the negligible amount of solvent used. The major advantage in this protocol is the use of Amberlyst® 15 as a co-catalyst, which offers a cheap, sustainable and recyclable alternative to the previously required expensive and hazardous metallic catalysts. Overall, this is a reliable and environmentally friendly go-to protocol which can be used across the fields of chemical synthesis to produce α-methylene-β-amino compounds.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal14120873/s1.

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