CHEMISTRY
AN ASIAN JOURNAL
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Accepted Article

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To be cited as: *Chem. Asian J.* 10.1002/asia.201800645

Link to VoR: http://dx.doi.org/10.1002/asia.201800645

A Journal of

ACES Asian Chemical Editorial Society

A sister journal of **Angewandte Chemie** and **Chemistry – A European Journal**

WILEY-VCH

10.1002/asia.201800645

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Silica Gel as a Promoter of Sequential Aza-Michael/Michael Reactions of Amines and Propiolic Esters: Solvent-free and Metal-free Synthesis of Polyfunctionalized Conjugated Dienes

Jovana Aleksić,[b] Milovan Stojanović[b] and Marija Baranac-Stojanović*[a]

Abstract: We present an efficient and simple, metal-free and solvent-free silica gel-promoted synthesis of functionalized conjugated dienes by sequential aza-Michael/Michael reactions starting from commercially available primary amines and propiolic esters. The scope and usefulness of the method is demonstrated on 31 examples, including a range of propiolic esters, aliphatic amines and differently substituted aromatic amines. In the case of aliphatic amines, the products are obtanied within 0.5-4 h in 52-85% yield compared with 3.5-22 h under classical solution-phase synthesis, proceeding in similar or lower yields. Particular usefulness of the method is found in the case of weakly nucleophilic aromatic amines, which provide products in 21-73% yield during 2.5-9.5 h compared with 0-49% during 1-6 days under standard solution-phase conditions and in the case of more hydrophobic esters yielding products in 47-79% during 1-3 h compared with 0-45% during 4-114 h in the solvent.

Introduction

The conjugated diene motif is present in many biologically important natural products[1] and is broadly applied for the construction of a wide variety of organic compounds.[2] Therefore, a significant effort has been made to develop new and efficient methods for its formation. Main strategies for the formation of a conjugated diene involve the Wittig-type alkenylation of α,β-unsaturated carbonyl compounds,[3] transition metal-catalyzed C–C cross-coupling such as Stille coupling (using vinylstannanes),[4] Suzuki-Miyaura coupling (using organoboranes),[5,6] Heck reaction (using vinyl halides/triflates),[5,7] Negishi coupling (using vinylzincs),[1d,5,8] transition metal-catalyzed direct oxidative cross-coupling *via* double C_{vinyl}–H bond activation,[9] and ruthenium-mediated enyne metathesis.[10] Recently, highly functionalized conjugated dienes were obtained by the base-promoted reaction of enaminones with ethyl propiolate.[11] Most of these syntheses require preparation of substrates, some of which are air- and/or moisture-sensitive, or even toxic (organostannanes), and/or the use of expensive metal catalysts.

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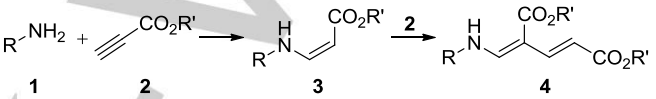
An attractive and simple approach to the highly functionalized conjugated dienes can be envisioned as a sequential aza-Michael/Michael reactions of amines with an activated alkyne, such as propiolic ester (Scheme 1). Even though this approach was used for the formation of conjugated dienes,[2c,2g,2j,2k,12] it is mainly unexplored. Thus, the reported syntheses often require long reaction times (1-3 days),[2c,2j,2k,12] while product yields are moderate or low when an allylic, benzylic or weakly nucleophilic aromatic amine is employed as a substrate (50-60% for the former two and 17-45% for the latter).[2c,2j,2k,12c,d,13]



1 2 3 4

Scheme 1. Formation of a conjugated diene motif by the reaction of an amine with an excess of propiolic ester.

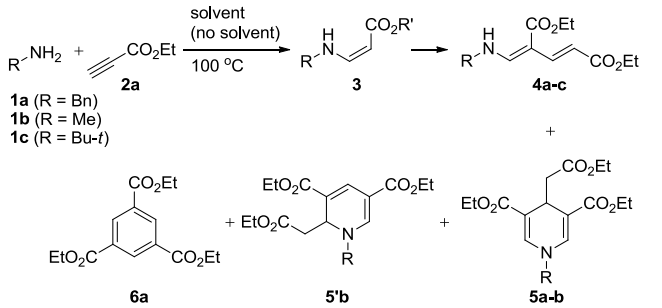
Herein, we re-investigate the environmentally benign construction of a highly functionalized conjugated diene motif by the one-pot, two-sequence reaction of a variety of aliphatic and aromatic amines with excess of propiolic esters. We report a simple and efficient solvent-free silica gel-promoted approach to dienes **4**, particularly useful in the case of weakly nucleophilic aromatic amines which, under classical solution-phase syntheses, require very long reaction times (several days) providing products **4** in low yields (< 50%). The usefulness of the method is also demonstrated for more hydrophobic esters, which, when react with an aromatic amine do not provide dienes under standard solution-phase conditions and when react with an aliphatic amine furnish dienes in low yields (18-45%) with no selectivity with respect to by-products, from which a diene is hardly separable.

Results and Discussion

We commenced our study by exploring the formation of **4a** (R = Bn, R′ = Et) from benzylamine (**1a**) and ethyl propiolate (**2a**) in EtOH, in a closed tube at 100 °C (Table 1, entry 1). After 10 h conversion was completed and **4a** was isolated in 75% yield, along with two by-products, 1,4-dihydropyridine **5a** and 1,3,5-trisubstituted benzene **6a**, isolated in low yields of 5% and 4%, respectively. The formation of trisubstituted benzene **6** as a by-product in the reaction of an amine with propiolic ester was also observed before.[2g] We tested if other solvents such as MeCN, PhMe and water could improve the yield of **4a**, but all they were inferior to EtOH (entries 2-4). Although the solvent-free conditions reduced reaction time to only 1 h, the yield of **4a** was slightly lower than in EtOH (70%) and that of by-products was increased to 11% and 14% for **5a** and **6a**, respectively (entry 5). We next examined the solvent-free synthesis of other two dienes,

4b and **4c**, starting from methylamine (**1b**) and *tert*-butylamine (**1c**). Both reactions resulted in much lower yields of dienes (34% **4b** and 63% **4c**) compared with reactions performed in EtOH (73% **4b** and 82% **4c**), with an increased yield of by-product **6a** and detection of unreacted intermediates **3b** and **3c** in an NMR spectrum of reaction mixture, with estimated 10% and 27% yields, respectively (entries 6-9). Therefore, the eco-friendly EtOH was selected as the solvent to explore diene **4** formation from a series of amines, as is shown in Figure 1 (method A).

Table 1. Optimization of liquid-phase reaction conditions.[a]



entry	amine	solvent	time (h)	yield[b] (%)			
				4	**5**+**5'**	**6a**	**3**
1	**1a**	EtOH	10	75	5	4	0
2	**1a**	MeCN	8	70	5	4	0
3	**1a**	PhMe	12	59	0	15	0
4	**1a**	H_2O	8	41	14	0	0
5	**1a**	no solvent	1	70	11	14	0
6	**1b**	EtOH	9	73	17[c]	0	0
7	**1b**	no solvent	2	34	0	13[d]	10[d]
8	**1c**	EtOH	4	82	0	5	0
9	**1c**	no solvent	2	63	0	13[d]	27[d]

[a] **2a:** 3-4 equiv. in a solvent; 2.2-3.0 equiv. without solvent. [b] Yields of isolated products. [c] Isolated as a mixture of 1,4- and 1,2-isomer 1.7:1. [d] Estimated on the basis of ^{1}H NMR spectrum of reaction mixture.

Aliphatic amines **1a-j** furnished dienes **4a-j** in moderate to good yields (51-86%) within a period of 3.5-20 h. The by-products' yields, where isolated, were low (≤ 17% and ≤ 10% for **5** and **5'**, and for **6a**, respectively). The dihydropyridine by-product was isolated either as the single 1,4-isomer (**5a** and **5h**), or as the mixture of 1,4- and 1,2-isomers (**5** and **5'**, respectively). To the best of our knowledge, there are only two reports on the synthesis of 1,4-dihydropyridine from an amine (aniline) and ethyl propiolate under scandium(III) triflate catalysis[14a] and organocatalysis,[14b] while formation of 1,2-isomer starting from an amine and a propiolic ester has never been reported. This reaction and its regioslectivity will be examined further in our laboratory. The postulated intermediate **8**, leading to 1,2-dihydropyridines **5'** and trisubstituted benzene **6a**, was not detected, whereas the intermediacy of structure **7**, previously suggested in the synthesis of 1,4-dihydropyridines by the Lewis acid-catalyzed dimerization of enamino esters,[15] has been proven in our work by its isolation in several cases (see below).

In contrast to aliphatic amines, the aromatic ones **1k**-**u** were highly unreactive. The reaction times were very long, 30-144 h (1-6 days), and yields of products **4k**-**u** were low 0-49%. A significant percent of intermediate enaminoester **3** was isolated in each case (14-78%), often as the major product or as the sole product in the case of 4-nitroaniline (**1p**) (the unreacted **1p** constituted the major part of the reaction mixture). The isolated dienes **4q** and **4u**, derived from 3-chloro-4-methylaniline (**1q**) and 2-chloro-4-methylaniline (**1u**) contained the intermediate **7q** and **7u** in 12 and 15 weight percent, respectively.

The reactions showed sensitivity to electronic properties of substituents. For example, *t*-butylamine (**1c**) and *i*-propylamine (**1e**) afforded corresponding dienes **4c** and **4e** in 82% and 81%, respectively, after 4 h and 3.5 h, while *n*-propylamine (**1d**) reacted during 20 h to give 72% of product **4d**. Among aromatic amines, the most reactive 4-methoxyaniline (**1l**) gave **4l** in the highest yield of 49% after 30 h, while 3,4-dichloroaniline (**1r**) furnished **4r** in only 8% yield after 6 days. The least reactive 4-nitroaniline (**1p**) gave no trace of diene **4p**, only the enamino ester **3p** in low yield of 14%. Steric hindrance from an *ortho*-substituent is also in play, increasing reaction time and decreasing product yield. Thus, while 4-methylaniline (**1m**) reacted during 96 h to give 38% of **4m**, 2,4-dimethylaniline (**1s**) provided 26% of **4s** after 120 h. Both steric and electronic effects reduced the yield further to 18% in the case of 2-chloro-4-methylaniline (**1u**).

Obviously, the second step of the reaction (**3** → **4**, in Scheme 1) is highly unfavoured for aromatic amines, and even the first step (formation of enamino ester **3** from **1** and **2a**) in the case of highly unreactive 4-nitroaniline (**1p**). Given our fortuitous discovery that diene **4c** (R = Bu-*t*) was formed as the sole product upon standing of **1c** and **2a** at the same spot on TLC plate overnight, we turned our attention to solvent-free silica gel-promoted reactions. Silica gel, as an inexpensive, non-toxic and readily available chemical, has gained popularity as a promoter of chemical reactions, particularly those which involve poorly reactive substrates.[16] Aromatic amines, as intrinsically weak nucleophiles, certainly belong to this kind of partners in an important chemical reaction, such as Michael addition.[17] While silica gel has been used as a promoter of Michael addition reactions onto activated alkenes, with or without a solvent,[18] its potential to mediate sequential additions onto an activated alkyne has yet to be disclosed.[19] Thus, we have first performed all reactions at room temperature by placing the reactants onto the silica gel to form a homogeneous solid mixture (around 0.5 g of silica gel is needed for 0.25 mL of reactants), which was stirred with a magnetic stirrer in a closed tube. The results are shown in Figure 1, as method B.

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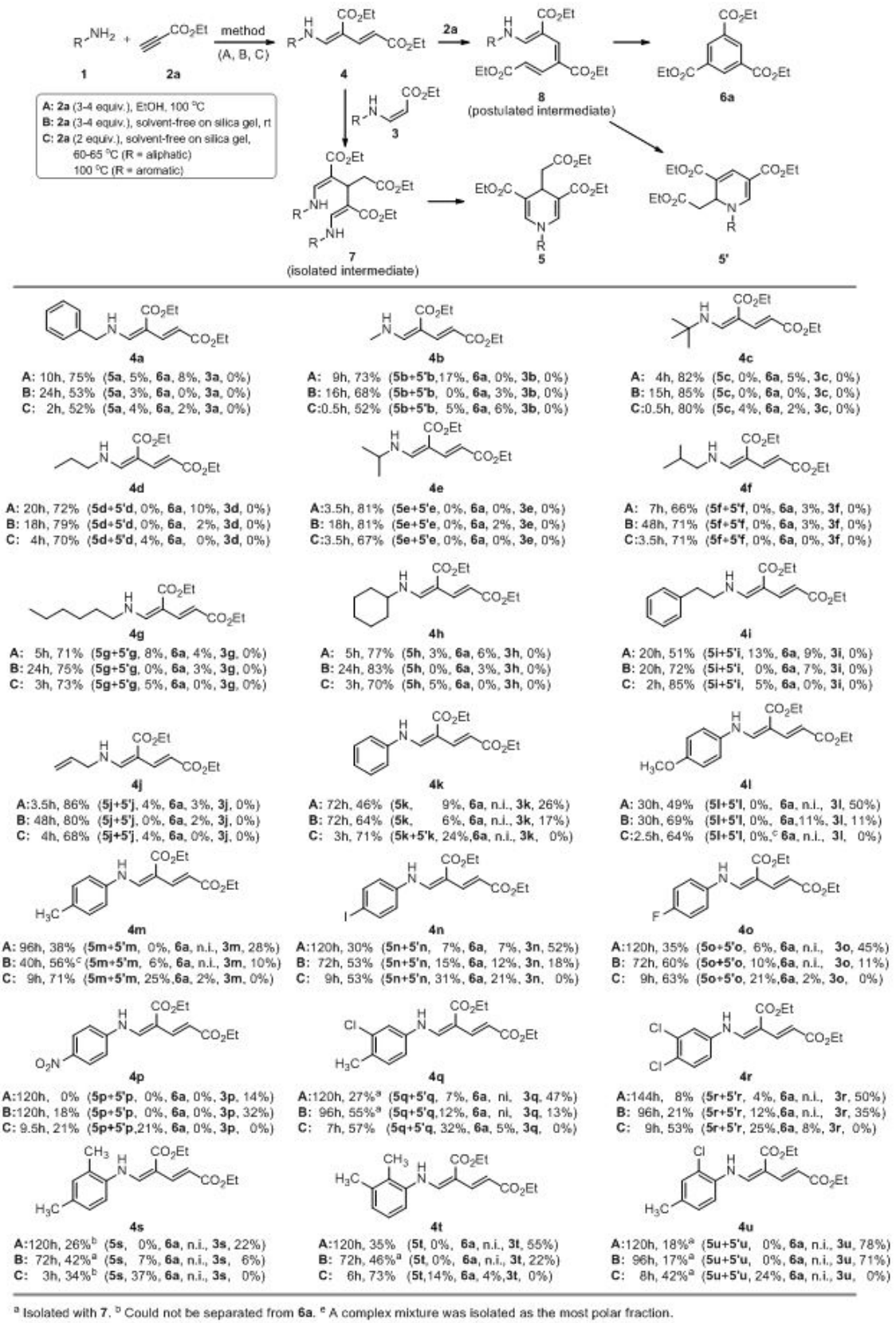


Figure 1. Synthesis of conjugated dienes **4** from various amines and ethyl propiolate (**2a**). The yields refer to isolated products (for mixtures are based on ^{1}H NMR). In the case of methods B and C, ~0.5 g of silica gel was used for 0.25 mL of reactants. Abbreviation n.i. means "formed, but not isolated."

Next, we tried to improve the yields of dienes **4k**-**u**, obtained from aromatic amines, and to reduce reaction times further by performing reactions at an elevated temperature of 100 °C (Figure 1, method C). Under these conditions, the product **4** yields were either similar or higher than at rt (with exception of **4s**) and no enamino esters **3** were isolated. Importantly, the reaction times were reduced to only several hours (2.5-9.5 h). The intermediate **7** was not detected as a contaminant of dienes derived from methyl-substituted aromatic amines, except in one case (diene **4u)**. The elevated temperature, however, also accelerated the side reaction between diene **4** and **3** or **2a** (Figure 1) so that dihydropyridines **5** and **5'** were isolated in higher yields (14-37%) compared to method B (0-15%). Due to this side reaction, the synthesis of dienes **4a**-**j**, starting from aliphatic amines, was performed at somewhat lower temperature of 60-65 °C (Figure 1, method C). These conditions significantly reduced reaction times from 15-48 h at rt to only 0.5-4 h, without affecting yields much, except those of **4b**, **4e**, **4h** and **4j**, which were by ≤16% lower, and that of **4i**, which increased from 72% at rt to 85%. In fact, method C works well for the synthesis of all but four dienes, **4a**, **4b**, **4e** and **4j** for which method A provides better yields in a similar or longer reaction time.

Substituent effects on reaction rates and product yields can be seen in method C, but appear to be less pronounced than in a solvent. Thus, for example, *t*-butylamine (**1c**) provided product **4c** after 0.5 h in 80% yield, while *n*-propylamine (**1d**) needed 4 h to give 70% of product **4d**. In the case of aromatic amines, the shortest reaction time was observed for the most reactive 4-methoxyaniline (**1l**) which yielded **4l** in 64% after 2.5 h. The reaction involving 4-methylaniline (**1m**) required longer time, 9 h, giving **4m** in 71% yield, while the least reactive 4-nitroaniline (**1p**) provided **4p** in 21% yield during 9.5 h. Steric hindrance from an *ortho*-substituent can affect product yields. For instance, a shift of chlorine from *meta*-position in 3-chloro-4-methylaniline (**1q**) into *ortho*-position in 2-chloro-4-methylaniline (**1u**) decreases the yield of **4u** by 15% with respect to the yield of **4q**. However, it is important to realize that in the case of aromatic amines the reaction times and product **4** yields are also affected by the rates of side-reactions that lead to dihydropyridine by-products **5** and **5′**.

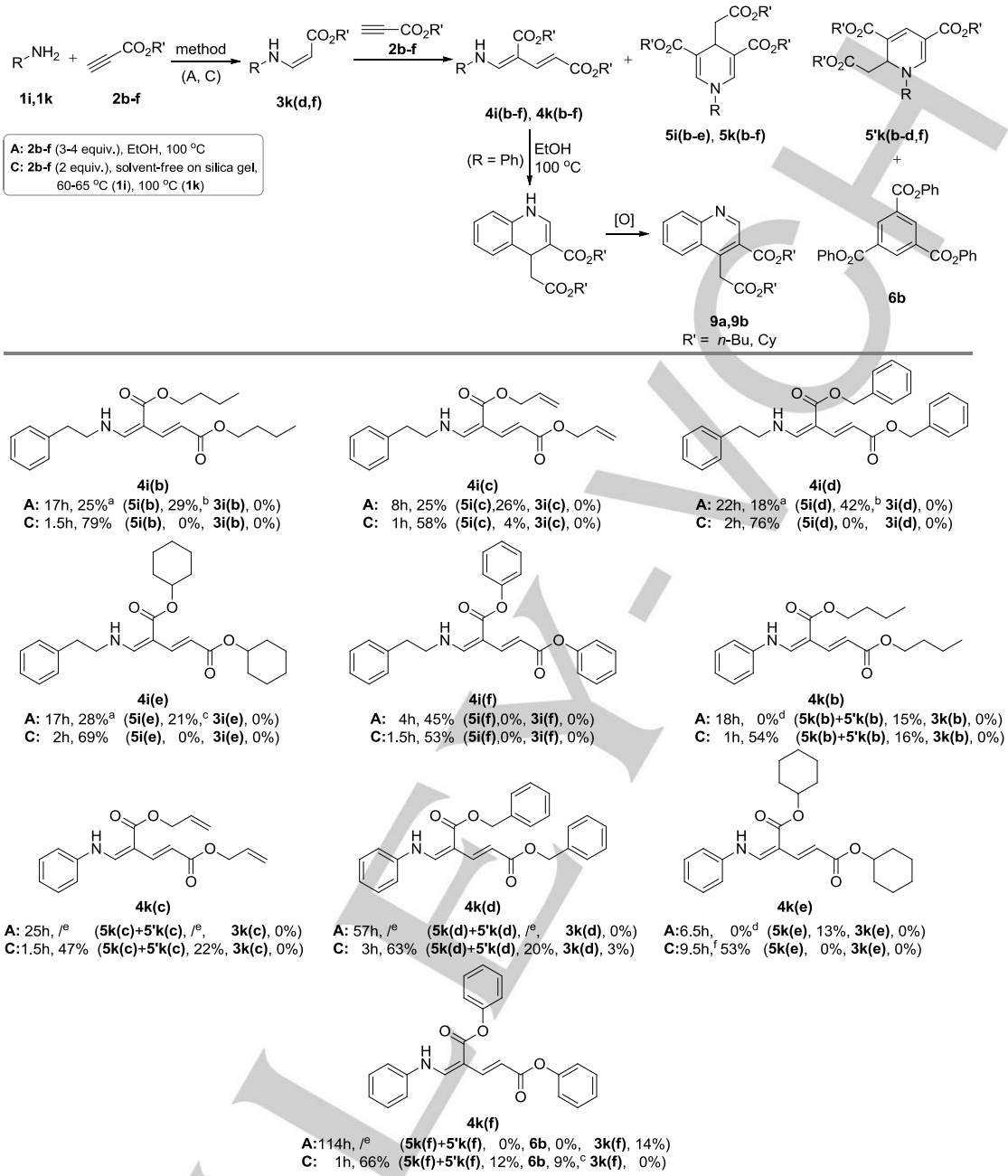
In both methods B and C the work-up procedure was simple, as the silica gel adsorbed reaction mixture was directly transferred to a flash chromatography column. Alternatively, silica gel may easily be recycled after washing with EtOAc, then with MeOH and air-drying, and reused with just a slight loss of catalytic activity, as was shown for substrate **1k**: 71%, 68%, 64% and 61% of **4k** were isolated by using fresh, the first, the second and the third recycled silica gel, respectively.

In reactions which lead to several products from the same starting materials, achievement of good chemoselectivity is an important task. In the case of our method C, chemoselectivity is excellent when aliphatic amines are used as substrates, since all by-products are formed in yields which are ≤ 6%. It is worse, but still satisfactory, in the case of aromatic amines: apart from two cases (amines **1p** and **1s**), diene is the main product in all reactions and its yield exceeds that of **5** and **5′** from 18% to pure diene. This is of particular importance because, by now, the method C presents the only way to obtain the functionalized conjugated dienes **4**, from an aromatic amine and propiolic ester, in satisfactory yields and in a reasonable time, as is shown by the results in Figure 1 and the literature data given in the Introduction.[20]

No propiolic amide was detected as by-product in any of the performed reaction, suggesting that 1,4-addition of an amine onto the propiolic ester is much more favoured patway, under the conditions of methods A, B and C. In fact, synthesis of a propiolic amide, if carried out from an ester, requires very low temperatures (−30 °C to −78 °C) to favour 1,2- over 1,4-addition,[21] or formation of an activated intermediate, such as propiolyl chloride,[22] anhydride,[23] activated ester (*N*-hydroxysuccinimide ester),[23] or the use of enzymes.[24]

The scope of the method C was further tested by varying the ester component that involved *n*-butyl, allyl, benzyl, cyclohexyl and phenyl propiolate **2b**-**f**, four of which are commercially available.[25] Aniline (**1k**) was chosen as a representative of aromatic amines and 2-phenylethanamine (**1i**) was employed as a representative of aliphatic amines. In the case of both amines, method C represented a significant improvement for the synthesis of dienes **4i** and **4k** with respect to both the product yields and reduction of reaction times (Figure 1). Figure 2 shows the results of the extension of method C to esters **2b**-**f**, which are compared with the classical solution-phase method A. As can be seen, under the conditions of method A, 2-phenylethanamine (**1i**) provided dienes **4i(b-f)** in low yields of 18-45% during 4-22 h. Four, out of the five reactions, were also accompanied by the formation of dihydropyridine by-products **5** and **5′**, obtained in similar or higher yields relative to the yield of the corresponding diene. Dienes **4i(b-e)** and dihydropyridines **5i(b-e)** are hardly separable and are often isolated in a mixture. By contrast, all reactions were very clean in the solid state providing dienes as the sole products in improved yields of 53-79% and shorter reaction times 1-2 h (method C). Only in the case of ester **2c**, by-product **5i(c)** was isolated in very low yield of 4%.

In the case of aniline (**1k**), method A failed to provide dienes **4**. This is because the initially formed dienes **4k(b)** and **4k(e)** cyclized into the quinoline derivatives **9a** and **9b**, presumably via the sequence shown in Figure 2. They were isolated in 21% and 23% yields, respectively. These two reactions also yielded dihydropyridines **5** and **5′** in 13-15% yields. For **2c** and **2d** a complex mixtures containing **4**, **5** and **5′** were obtained, as deduced on the basis of NMR spectra. Any attempt to isolate pure compounds failed and their individual yields could not exceed 30% for **2c** and 15% for **2d**. The reaction of aniline (**1k**) with phenyl propiolate (**2f**) also resulted in a complex mixture from which only intermediate enamino ester **3k(f)** could be isolated in pure form, while diene **4k(f)** was detected by NMR spectroscopy and its yield does not exceed 15%. By contrast, method C provided pure dienes **4** in 47-66% yields after 1-3 h. In the case of cyclohexyl propiolate (**2e**), the reaction was conducted at rt to avoid the formation of **5**,[26] form which the diene is hardly separable. The yields of dihydropyridine by-products **5** and **5′** were low (≤ 22%).



[a] Isolated in a mixture with **5**. [b] Isolated pure and in a mixture with **4**.[c] Isolated in a mixture with **4**. [d] Diene cyclized into quinoline derivative **9** (**9a**: 21%, **9b**: 23%). [e] Inseparable from a complex mixture. [f] Reaction was carried out at rt.

Figure 2. Synthesis of conjugated dienes **4i(b-f)** and **4k(b-f)** from 2-phenylethanamine (**1i**) and aniline (**1k**), and propiolic esters **2b-f** employing methods A and C. The yields refer to isolated products (for mixtures are based on ^{1}H NMR). In the case of methods B and C, ~0.5 g of silica gel was used for 0.25 mL of reactants.

In these cases, too, chemoselectivity of method C was excellent for aliphatic amine **1i** which yielded diene as the sole product, except in one case where a trace amount of by-product **5i(c)** was isolated. By contrast, the classical solution-phase synthesis proceeded with almost no selectivity giving **4** and **5** in approximate yields (**4i(b)/5i(b)** 25%/29%, **4i(c)/5i(c)** 25%/26% and **4i(e)/5i(e)** 28%/21%), or even **5** as the main product (**4i(d)/5i(d)** 18%/42%). The selectivity of classical approach was fine only for ester **2f**, but method C provided higher yield of diene **4i(f)** in a shorter reaction time (Figure 2). The success of method C to yield dienes with good chemoselectivity is of particular importance for aromatic amine **1k**, since the classical approach to their formation completely failed. In addition, method C allows the use of stoichiometric amounts of reactants.[27]

While secondary amines easily form enamino esters in the reaction with a propiolic ester **2**,[12c,28] further reaction with **2** to give a diene was reported in just one case in which enamino ester derived from ethyl cinnamate and pyrrolidine reacted with methylpropiolate to yield 50% of the corresponding diene.[12b] We have tested applicability of methods A, B and C for the synthesis of dienes from ethyl propiolate (**2a**) and four secondary amines: pyrrolidine, piperidine, morpholine and diethylamine. Unfortunately, the results were not encouraging. Only one diene **4v**, derived from pyrrolidine, was isolated in 70% yield under the conditions of method A. In the case of other three amines, method A resulted in inseparable mixtures of enamino esters and dienes, in which the former significantly prevailed. The performance of methods B and C was even worse, for all four amines, because, in these cases, silica gel enhanced the formation of benzene by-product **6a**, while the amount of the mixture of enamino ester and diene was smaller than that obtained by method A. In the mixture, enamino ester was the major component. Thus, a further search for efficient methods for the synthesis of this type of compounds is needed. Recently, it has been reported that the metal-catalyzed oxidative amination of alkenes with secondary amine can give the diene.[29]

Stereochemistry Determination

The products **4** were isolated as a single *2E,4Z* stereizomer, or as a mixture of *2E,4Z* and *2E,4E* isomers in the case of **4l** (R = 4-methoxyphenyl, 91:9), **4n** (R = 4-iodophenyl, 91:9), **4o** (R = 4-fluorophenyl, 91:9), **4p** (R = 4-nitrophenyl, 50:50), **4q** (R = 3-chloro-4-methylphenyl, 83:17) and **4r** (R = 3,4-dichlorophenyl, 71:29). The *2E* stereochemistry for all products was established on the basis of the large $J_{H,H}$ = 15.5-16 Hz between the two olefinic hydrogen atoms, while the *4Z* stereochemistry was deduced on the basis of the low field position of NH signal (δ 8.7-9.2 ppm when R = aliphatic and δ 10.6-11.0 ppm when R = aromatic) and NOE cross-peaks between the C4′**H** and C3**H**/C2**H** (Figure 3a and Figure S1 in the Supporting Information). The two NOE cross-peaks, where the former is more intensive, indicate the presence of *s-trans/s-cis* equilibrium which is shifted toward the *s-trans* form. The *4E* stereochemistry was determined on the basis of high field position of NH signal, δ 7.6-7.9 ppm, and NOE cross-peaks between the N**H** and C3**H**/C2**H** (Figure 3b and Figure S1 in the Supporting Information). The two NOE cross-peaks, where the former is more intensive, again point to the existence of *s-trans/s-cis* equilibrium which is shifted toward the *s-trans* form.

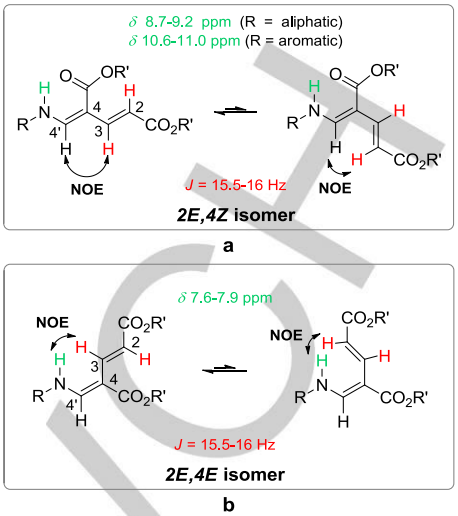
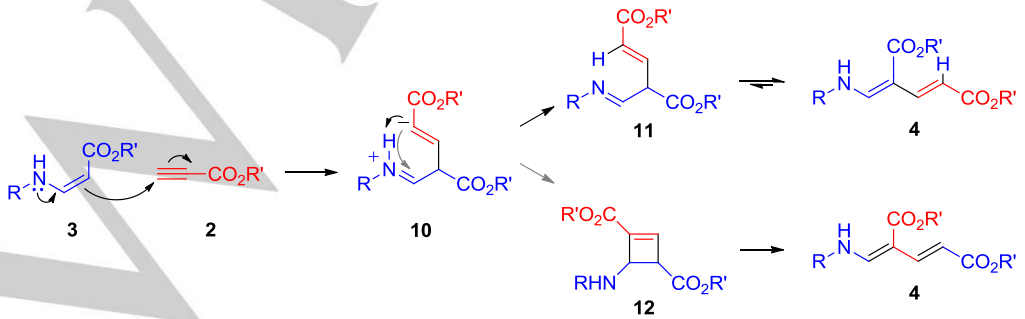


Figure 3. Stereochemistry determination of dienes **4**.

Mechanistic Investigations

The formation of dienes **4** can proceed via two mechanisms, as suggested previously.[12b] Both of them involve the common zwitterionic intermediate **10**, formed by the Michael addition of **3** onto **2** (Scheme 2). This intermediate can be stabilized in two ways: 1) by proton transfer to give **11** which tautomerizes to product **4**, or 2) by formation of cyclobutene **12** which undergoes a conrotatory ring opening to diene **4**. In the first mechanism the two triple-bonded carbons of **2** ends in the terminal double bond, having one vinylic hydrogen taken from the N-H group, while in the second mechanism the two carbons of **2** are inserted between the α and β carbon atoms of enamino ester **3**. In the two mechanisms, the ester groups originating from enamino ester and propiolic ester exchange their position in the product (Scheme 2), thus allowing one to distinguish between them. Previous mechanistic studies based on deuterium labeling (ND instead of NH) and cross reactions of **2a**/**2g** (R′ = Et/Me) with **3** (R′ = Me/Et) derived from crotonic and cinnamic esters (Me and Ph, respectively, instead of β-H in **3**) went in favour of only the first mechanism (via the intermediate **11**). The second one, involving cyclobutene **12**, was shown to operate with secondary amines.[12b] However, the cross reactions of enamines **3** having acrylic ester moiety, as in our case, failed, due to complete decomposition of **3** into amine **1** and propiolate ester **2** upon heating in benzene.[12b]



Scheme 2. Proposed mechanisms for the reaction of enamino ester **3** with propiolate ester **2** to give diene **4**.

We have re-investigated cross experiments under the conditions of our methods A, B and C. First of all, we have unequivocally identified the signal position of the two carbonyl carbon atoms in ^{13}C NMR spectra, by using the HMBC experiment. Thus, the C2**H** can give HMBC cross-peak only with carbonyl carbon of the terminal ester group, via the two bonds, while the C4′**H** can give HMBC cross-peak only with carbonyl carbon of internal ester group, over the three bonds (Figure 4). The remaining vinylic hydrogen attached at C3 can interact with both carbonyl carbons, over the three bonds. We have chosen methylamine derivative **4b** for mechanistic investigations, because of its most simple and well resolved ^{1}H NMR and ^{13}C NMR spectra (see Supporting Information for the two spectra, p. S15). The HMBC experiments were performed on two derivatives, **4b** (R = Me, R′ = Et) and **4′b** (R = Me, R′ = Me), the latter obtained by the reaction of methylamine (**1b**) with methyl propiolate (**2g**). In both cases, the C2**H**, the ^{1}H NMR signal of which is positioned at 6.0 ppm, showed the HMBC cross-peak with the higher field carbonyl carbon signal, while the C4′**H** at 7.2 ppm showed cross-peak with the lower field, hydrogen-bonded carbonyl carbon signal (see Figures S2 and S3 in the Supporting Information). Next, we have determined that OC**H**$_2$ and OC**H**$_3$ protons of internal ester group resonate at lower field with respect to the corresponding protons of terminal ester group by the presence of 169.4/4.24 ppm and 168.9/4.18 ppm HMBC cross-peaks for **4b**, and 170.9/3.76 ppm and 170.6/3.70 ppm for **4′b** (Figures S2 and S3 in the Supporting Information).

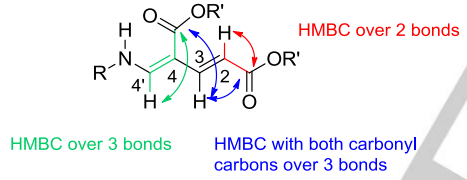
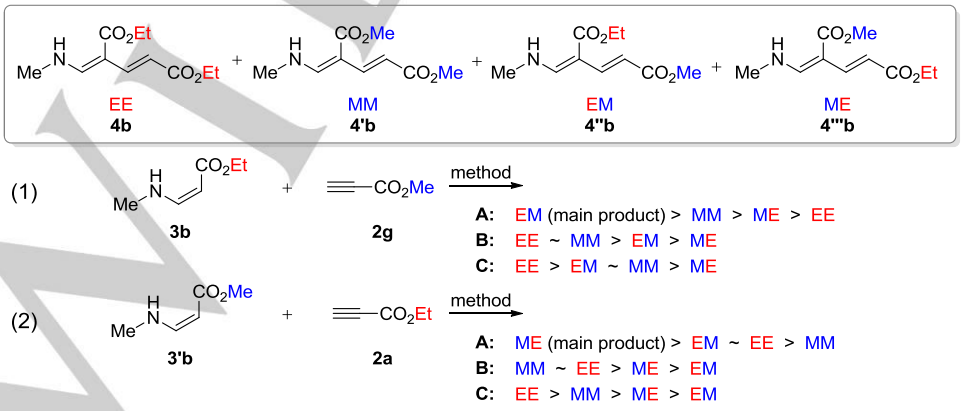


Figure 4. Possible HMBC interactions between carbonyl carbon atoms and vinylic hydrogen atoms in dienes **4**.

Next, we performed two cross reactions under the conditions of methods A, B and C. The first one involved ethyl (3-methylamino)acrylate (**3b**) and methyl propiolate (**2g**) as reactants (reaction (1) in Scheme 3) and the second started from methyl (3-methylamino)acrylate (**3′b**) and ethyl propiolate (**2a**) (reaction (2) in Scheme 3). In all six reactions a mixture of four products was obtained (**4b**, **4′b**, **4″b** and **4‴b** abbreviated as **EE**, **MM**, **EM** and **ME**, Scheme 3), clearly evidenced by the presence of four signals for **C**2 and **C**3 carbon atoms in ^{13}C NMR spectra of reaction mixtures. A precise determination of product ratio was not possible due to overlapping of the two O**R′** ^{1}H NMR signals (R′ = Me or Et) when included in terminal or internal ester group. The formation of four products indicated decomposition of enamino ester **3** into amine **1** and propiolate **2**, as was also observed previously.[12b] However, while esters of type **3** completely decomposed when heated in benzene,[12b] decomposition was only partial under the conditions of our method A, where dominant product was **EM** and **ME** in reaction (1) and (2), respectively, determined on the basis of OC**H**$_2$ and OC**H**$_3$ signal positions and intensity in NMR spectra (Scheme 3 and Figures S4 and S6 in the Supporting Information). In case of complete decomposition, product percent weight would be **MM** (56.25%), **ME** = **EM** (18.75%) and **EE** (6.25%) in reaction (1), and **EE** (56.25%), **ME** = **EM** (18.75%) and **MM** (6.25%) in reaction (2), that is, **MM** and **EE** would have been the major compounds in reaction mixtures. The formation of **EM** and **ME** as the main products in reactions (1) and (2) goes in favour of mechanism involving intermediate **11** (Scheme 2), as the dominant one. We are currently not able to decide if another mixed product **ME** in reaction (1) and **EM** in reaction (2) results from the second mechanism going via cyclobutene **12** (Scheme 2), or if it comes from recombination of amine **1** and propiolate **2** and further reaction with propiolate **2**. The position of methyl and ethyl ester groups in **ME**, where carbonyl carbon signals are separated by 0.7 ppm, could be determined on the basis of HMBC cross-peaks (Figure S7 in the Supporting Information), while for **EM** the situation is less clear due to small chemical shift difference of the two carbonyl carbons (0.1 ppm) and cross-peaks' widening originating from the presence of four compounds in the mixture (Figure S5 in the Supporting Information).

In the case of methods B and C, the cross reaction results, shown in Scheme 3, indicate a higher extent of enamino ester **3** decomposition into **1** and **2** followed by amine **1**/enamino ester **3** reaction with momentarily locally distributed **2a** and **2g**.



Scheme 3. Cross reactions between ethyl (3-methylamino)acrylate (**3b**) and methyl propiolate (**2g**), and between methyl (3-methylamino)acrylate (**3′b**) and ethyl propiolate (**2a**).

The mechanism by which silica gel promotes these sequential aza-Michael/Michael additions onto an activated triple bond is not clearly understood. Since silica gel contains many hydroxyl groups on its surface, a reasonable explanation of its catalytic activity may be the activation of both amine and ester component by formation of N–H···O–Si and C=O···H–OSi hydrogen bonding interactions. These would increase nucleophilicity of amino group and electrophilicity of β-carbon of the unsaturated ester component. Since our mechanistic investigations indicated a high degree of intermediate enamino ester **3** decomposition into starting compounds **1** and **2** on the surface of silica gel, we assume that the next step involves the attack of the hydrogen bonded zwitterionic intermediate **3** onto the activated **2**. The quantitative structure-reactivity relationship (QSRR) analysis of Michael addition reactions onto enones highlights the importance of coulombic interactions in the case of silica gel catalysis.[30] In addition, adsorption of molecules on the surface of silica gel brings them in close proximity which could also be responsible for the reaction rate acceleration.

Conclusions

In conclusion, we have developed an efficient, metal-free and solvent-free, silica gel-promoted method for the construction of functionalized conjugated diene motif by the two-sequence reaction between commercially available reagents, which can be used in their stoichiometric amounts. The method is operationally simple, cheap and environmentally benign. Silica gel showed its important role in these sequential reactions, which is reflected in reduction of reaction times and increase in product yields. This is of particular importance if weakly nucleophilic aromatic amines or/and more hydrophobic esters are used as reactants, since they poorly react under standard solution-state conditions.

Experimental Section

General

All reactions were carried out in closed Pyrex® glass tubes (26 mm × 100 mm) heated in an oil bath. The quoted reaction temperatures refer to the temperature of the oil bath. All reactions were monitored by TLC and were conducted until the disappearance of enamino ester intermediate **3**, or until the reaction mixture started to be more complex while **3** was still present (the latter applies only to methods A and B, and aromatic amines). Silica gel 60 (0.063-0.200 mm, Merck), was used for solvent-free reactions and for column chromatography. Thin layer chromatography was performed on precoated silica gel 60 F_{254} (Merck) and on silica gel 60 Å, 12-26 ICN Biomedicals. Visualization of TLC spots was achieved by UV light and iodine vapour for the former and by iodine vapour and 50% H_2SO_4 for the latter. Melting points were determined on Stuart SMP10 apparatus. NMR spectra were recorded in $CDCl_3$ on Bruker Avance III spectrometer, operating at 500.3 MHz for ^{1}H and 125.8 MHz for ^{13}C, and on Varian Gemini 2000 spectrometer, operating at 200 MHz for ^{1}H and 50.3 MHz for ^{13}C. Chemical shifts are given as δ values in ppm and are referenced to TMS, or to the residual proton resonance of $CHCl_3$ at 7.26 ppm and solvent carbon resonance of $CDCl_3$ at 77.0 ppm. Coupling constants *J* are given in Hz. IR spectra were recorded on Thermo Scientific Nicolet 6700 FT-IR spectrometer using ATR technique. HRMS spectra were recorded only for new compounds on 6210 Time-of-Flight LC/MS (G1969A, Agilent Technologies) coupled with 1200 Series HPLC system (Agilent Technologies) and on LTQ Orbitrap XL mass spectrometer (ThermoFisher Scientific). When a mixture could not be separated, quantities and yields are based on ^{1}H NMR.

Synthesis of propiolic esters 2b-f

***n*-Butyl propiolate (2b)**

To a solution of propiolic acid (210.0 mg, 3.0 mmol) and *n*-butanol (267.0 mg, 3.60 mmol) in toluene (5 mL) conc. H_2SO_4 was added (200 μL) and the mixture was heated at 100 °C for 40 min. The solution was cooled to rt and CH_2Cl_2 (20 mL) was added. It was then washed with 5% $NaHCO_3$ (aq), water and dried over anh. Na_2SO_4. The solvent was evaporated and the residue was subjected to column chromatography on silica gel, using petrol ether (bp 40-60 °C)/EtOAc (100:0 to 95:5), to give 229.0 mg (61%) of **2b**, as a colourless liquid. IR: ν 3266, 2120, 1716, 1241 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 0.93 (t, 3H, J = 7.5 Hz), 1.40 (sext, 2H, J = 7.5 Hz), 1.65 (quint, 2H, J = 7.5 Hz), 2.87 (s, 1H), 4.18 (t, 2H, J = 6.7 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 13.5, 18.9, 30.3, 66.1, 74.4, 74.7, 152.8.

Allyl propiolate (2c)

Allyl propiolate (**2c**) was prepared according to the procedure given in ref. 31. To a solution of propiolic acid (249.0 mg, 3.55 mmol) in DMF (2.0 mL) $NaHCO_3$ (600.0 mg, 7.14 mmol) was added and the mixture was stirred at rt for 1 h. Then, allyl bromide (640.0 mg, 5.3 mmol) was added and the mixture was stirred at rt overnight. The mixture was diluted with ether (30.0 mL), washed with water (5×) and dried over anh. Na_2SO_4. The solvent was evaporated under reduced pressure. The ester **2c** was isolated in 82% yield (319.0 mg), as a reddish liquid. IR: ν 3271, 2120, 1717, 1615, 1225 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 2.90 (s, 1H), 4.68 (dt, 2H, J = 1.5 Hz, J = 6.0 Hz), 5.28-5.39 (m, 2H), 5.88-5.95 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 66.7, 74.5, 74.9, 119.5, 130.8, 152.3.

Benzyl propiolate (2d)

Benzyl propiolate (**2d**) was prepared according to the procedure given in ref. 32. A mixture of propiolic acid (208.0 mg, 2.97 mmol), benzyl bromide (460.0 mg, 2.69 mmol) and K_2CO_3 (410.0 mg, 2.97 mmol) in DMF (3.0 mL) was stirred at rt for 14h. Water (10 mL) was added and the mixture was extracted with EtOAc/*n*-hexane (1:1). Organic layer was dried over anh. Na_2SO_4, solvent was evaporated and the residue was chromatographed on silica gel, using petrol ether (bp 40-60 °C)/EtOAc (100:0 to 95:5), to give 370.0 mg (86%) of **2d**, as a colourless liquid. IR: ν 3277, 2121, 1716, 1223 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 2.90 (s, 1H), 5.23 (s, 2H), 7.39-7.40 (m, 5H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 67.9, 74.6, 75.1, 128.6, 128.7, 128.7, 134.6, 152.5.

Cyclohexyl propiolate (2e)

To a solution of propiolic acid (176.4 mg, 2.52 mmol) and cyclohexanol (323 mg, 3.22 mmol) in toluene (5 mL) conc. H_2SO_4 was added (150 μL) and the mixture was heated at 100 °C for 30 min. The dark-coloured solution was cooled to rt and CH_2Cl_2 (20 mL) was added. It was then washed with 5% $NaHCO_3$ (aq), water and dried over anh. Na_2SO_4. The solvent was evaporated and the residue was subjected to column chromatography on silica gel, using petrol ether (bp 40-60 °C)/EtOAc (100:0 to 95:5), to give 287.0 mg (75%) of **2e**, as a colourless liquid. IR: ν 3263, 2118, 1711, 1235 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$):[33] 1.22-1.56 (m, 6H), 1.73-1.78 (m, 2H), 1.87-1.91 (m, 2H), 2.85 (s, 1H), 4.84-4.89 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$):[2] 23.6, 25.1, 31.3, 73.9, 75.2, 75.3, 152.2.

Phenyl propiolate (2f)

Phenyl propiolate (**2f**) was obtained according to the procedure given for the synthesis of aryl alkynoate esters.[34] A solution of DCC (520.0 mg, 2.5 mmol) in CH_2Cl_2 (2 mL) was added to a solution of propiolic acid (197.0 mg, 2.8 mmol) in CH_2Cl_2 (2 mL), at 0 °C. After 5 min stirring, PhOH (225 mg, 2.4 mmol) was added followed by a solution of DMAP (29.3 mg, 0.24 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at 0 °C for additional 3h, the precipitate was filtered off and washed with CH_2Cl_2. The filtrate was washed with water and dried over anh. Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography using petrol ether (bp 40-60 °C)/EtOAc (100:0 to 95:5) to give 146.0 mg (42%) of **2f**, as a colourless liquid. IR: ν 3275, 2125, 1732, 1199 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 3.08 (s, 1H), 7.16 (d, 2H, J = 8.0 Hz), 7.28 (t, 1H, J = 7.5 Hz), 7.41 (t, 2H, J = 8.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 74.2, 76.8, 121.2, 126.6, 129.6, 149.8, 150.9.

General procedure for preparation of conjugated dienes 4

Method A

Amine **1** (1 mmol) and propiolic ester **2** (3-4 mmol) were heated in abs. EtOH at 100 °C, for 3.5-144 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel, using petrol ether (bp 40-60 °C)/EtOAc (100:0 to 80:20 for dienes derived from aliphatic amines and 100:0 to 90:10 for dienes derived from aromatic amines).

Method B

Silica gel was added to a mixture of amine **1** (1 mmol) and propiolic ester **2** (3-4 mmol) to form a homogeneous solid (~0.5 g for 0.25 mL of reactants), which was kept at r.t. for 15-120 h. The solid mixture was stirred with a magnetic stirrer. After completion of the reaction the solid mixture was directly transferred to a flash chromatography column, which was eluted with petrol ether (bp 40-60 °C)/EtOAc (100:0 to 80:20 for dienes derived from aliphatic amines and 100:0 to 90:10 for dienes derived from aromatic amines).

Method C

Silica gel was added to a mixture of amine **1** (1 mmol) and propiolic ester **2** (2 mmol) to form a homogeneous solid (~0.5 g for 0.25 mL of reactants), which was heated at 60-65 °C for 0.5-4 h in the case of aliphatic amines, and at 100 °C for 1-9.5 h in the case of aromatic amines. The solid mixture was stirred with a magnetic stirrer. After completion of the reaction the solid mixture was directly transferred to a flash chromatography column, which was eluted with petrol ether (bp 40-60 °C)/EtOAc (100:0 to 80:20 for dienes derived from aliphatic amines and 100:0 to 90:10 for dienes derived from aromatic amines).

Silica gel may also be re-used, after washing with EtOAc, then with MeOH and air-drying, with no appreciable loss of activity, as was shown for substrate **1k**: **4k** (71%) and **5/5′k** (24%) after the first reaction (Figure 1), **4k** (68%) and **5/5′k** (24%) after the second reaction, **4k** (64%) and **5/5′k** (18%) after the third reaction, **4k** (61%) and **5/5′k** (15%) after the fourth reaction.

(*2E,4Z*)-diethyl 4-((benzylamino)methylene)pent-2-enedioate (4a)

Method A: 103.8 mg (75%) from **1a** (49.0 mg, 0.46 mmol) and **2a** (145.5 mg, 1.48 mmol) in EtOH (2.0 mL) during 10 h, along with **5a** (10.0 mg, 5%) and **6a** (11.0 mg, 8%).

Method B: 295.0 mg (53%) from **1a**, (196.0 mg, 1.83 mmol) and **2a** (540.0 mg, 5.50 mmol) during 24 h, along with **5a** (22.4 mg, 3%).

Method C: 50.4 mg (52%) from **1a** (34.0 mg, 0.32 mmol) and **2a** (62.3 mg, 0.64 mmol) during 2 h, along with **5a** (5.5 mg, 4%) and **6a** (1.3 mg, 2%).

4a: pale yellow solid, mp 107-108 °C (lit.[12b] 109 °C); IR: ν 3311, 1697, 1653, 1597 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.28 (t, 3H, J = 7.2 Hz), 1.35 (t, 3H, J = 7.0 Hz), 4.18 (d, 2H, J = 7.0 Hz), 4.25 (d, 2H, J = 7.2 Hz), 4.46 (d, 2H, J = 6.0 Hz), 6.05 (d, 1H, J = 15.5 Hz), 7.24 (d, 2H, J = 6.5 Hz), 2.27 (d, 1H, J = 13.5 Hz), 7.30-7.33 (m, 1H), 7.35-7.38 (m, 2H), 7.38 (d, 1H, J = 15.5 Hz), 9.19 (broad t, 1H, J = 6.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.4, 14.4, 52.9, 59.6, 59.9, 95.4, 108.4, 127.3, 128.1, 129.0, 136.8, 143.1, 156.9, 168.8, 169.1.

5a: yellow oil[14b,15] IR: ν 1730, 1700, 1622, 1583 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.16 (t, 3H, J = 7.1 Hz), 1.27 (t, 6H, J = 7.1 Hz), 2.51 (d, 2H, J = 5.0 Hz), 3.99 (q, 2H, J = 7.1 Hz), 4.19 (q, 4H, J = 7.1 Hz), 4.24 (t, 1H, J = 5.0 Hz), 4.51 (s, 2H), 7.20 (s, 2H), 7.22-7.44 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$): 14.2, 29.6, 40.8, 58.1, 59.9, 60.1, 106.5, 127.1, 128.2, 129.0, 136.0, 139.5, 166.8, 171.7.

6a: white crystals, mp 134-135 °C (lit.[35] 135-136 °C); IR: ν 1721, 1238 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.41 (t, 9H, J = 7.1 Hz), 4.42 (q, 6H, J = 7.1 Hz), 8.82 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): 14.3, 61.6, 131.4, 134.4, 165.0.

(*2E,4Z*)-diethyl 4-((methylamino)methylene)pent-2-enedioate (4b)

Method A: 49.8 mg (73%), obtained as following. To a solution of methylamine in THF (1.2 M, 0.25 mL, 0.3 mmol of **1b**) **2a** was added (35.3 mg, 0.36 mmol) and the mixture was stirred at rt overnight. The solvent and excess of **2a** were removed under reduced pressure, EtOH (1.5 mL) and **2a** (58.9 mg, 0.6 mmol) were added. The mixture was heated at 100 °C during 9 h and chromatographed. One side product was isolated, **5/5'b** (16.9 mg, 17%).

Method B: 46.4 mg (68%), obtained as following. To a solution of methylamine in THF (1.2 M, 0.25 mL, 0.3 mmol of **1b**) **2a** was added (97.0 mg, 0.99 mmol) followed by addition of silica gel. The solvent was evaporated under reduced pressure and the solid mixture was left at rt for 16 h. The only side product was **6a** (2.7 mg, 3%).

Method C: 71.2 mg (52%), obtained as following. To a solution of methylamine in THF (1.2 M, 0.5 mL, 0.6 mmol of **1b**) **2a** was added (145.0 mg, 1.48 mmol) and the mixture was stirred at rt for 18 h. The solvent and excess of **2a** were removed under reduced pressure and another quantity of **2a** was added (63.0 mg, 0.6 mmol) followed by addition of silica gel. The solid mixture was kept at 60-65 °C for 30 min and chromatographed. Two side products were isolated, **5b**/**5'b** (9.8 mg, 5%) and **6a** (3.5 mg, 6%).

4b: pale yellow solid, mp 77-78 °C; IR: ν 3287, 1690, 1652, 1585 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.29 (t, 3H, J = 7.2 Hz), 1.35 (t, 3H, J = 7.0 Hz), 3.10 (d, 3H, J = 5.0 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.25 (q, 2H, J = 7.0 Hz), 6.01 (d, 1H, J = 15.5 Hz), 7.20 (d, 1H, J = 14.0 Hz), 7.39 (d, 1H, J = 15.5 Hz), 8.79 (broad s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.4, 35.6, 59.5, 59.7, 94.6, 107.6, 143.2, 158.3, 168.8, 169.1; HRMS calcd. for $C_{11}H_{18}NO_4$ $[M+H]^+$: 228.1236, found: 228.1226.

5b and **5'b:** pale yellow amorphous substance; IR: ν 1724, 1701, 1.630, 1583 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, mixture of 1,4- and 1,2-isomers 1.7:1): 1.18-1.39 (m, 18H, 1,2- and 1,4-isomers), 2.31-2.40 (dd, 1H, J = 4.1 Hz, J = 15.0 Hz, 1,2-isomer), 2.47 (d, 2H, J = 5.0 Hz, 1,4-isomer), 2.59-2.70 (dd, 1H, J = 7.4 Hz, J = 15.0 Hz, 1,2-isomer), 3.17 (s, 3H, 1,4-isomer), 3.25 (s, 3H, 1,2-isomer), 4.04 (q, 4H, J = 7.2 Hz, 1,2- and 1,4-isomer), 4.14-4.25 (m, 9H, 1,2- and 1,4-isomer), 5.00 (dd, 1H, J = 4.1 Hz, J = 7.4 Hz, 1,2-isomer), 7.11 (s, 2H, 1,4-isomer), 7.48 (s, 1H, 1,2-isomer), 7.64 (s, 1H, 1,2-isomer); ^{13}C NMR (50.3 MHz, $CDCl_3$, mixture of 1,4- and 1,2-isomers 1.7:1): 14.0, 14.2, 14.5, 29.2 (1,4-isomer), 38.0 (1,2-isomer), 40.8 (1,4-isomer), 55.5 (1,2-isomer), 60.0, 61.0, 99.2 (1,2-isomer), 107.0 (1,4-isomer), 108.9 (1,2-isomer), 133.1 (1,2-isomer), 140.1 (1,4-isomer), 149.7 (1,2-isomer), 165.5, 166.8, 170.9, 171.8; HRMS calcd. for $C_{16}H_{24}NO_6$ $[M+H]^+$: 326.1604, found: 326.1594.

(*2E,4Z*)-diethyl 4-((*tert*-butylamino)methylene)pent-2-enedioate (4c)

Method A: 105.5 mg (82%) from **1c** (34.8 mg, 0.48 mmol) and **2a** (188.4 mg, 1.92 mmol) in EtOH (2.0 mL) during 4 h, along with **6a** (9.2 mg, 5%).

Method B: 109.0 mg (85%) from **1c** (35.0 mg, 0.48 mmol) and **2a** (176.0 mg, 1.79 mmol) during 15 h.

Method C: 62.2 mg (80%) from **1c** (21.0 mg, 0.29 mmol) and **2a** (57.0 mg, 0.58 mmol) during 30 min, along with **5c** (4.0 mg, 4%) and **6a** (1.1 mg, 2%).

4c: pale yellow solid, mp 77-78 °C (previuosly isolated as an oil[36]); IR: ν 3265, 1699, 1658, 1621, 1593 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.27 (t, 3H, J = 7.2 Hz), 1.31 (s, 9H), 1.33 (t, 3H, J = 7.2 Hz), 4.16 (q, 2H, J = 7.2 Hz), 4.22 (q, 2H, J = 7.2 Hz), 5.99 (d, 1H, J = 15.5 Hz), 7.34 (d, 1H, J = 14.0 Hz), 7.38 (d, 1H, J = 15.5 Hz), 9.19 (d, 1H, J = 14.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.4, 29.9, 52.9, 59.5, 59.6, 94.2, 107.2, 143.8, 153.1, 167.0, 169.2.

5c: yellow oil; IR: ν 1733, 1702, 1663, 1578 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.21 (t, 3H, J = 7.2 Hz), 1.30 (t, 3H, J = 7.2 Hz), 1.39 (s, 9H), 2.42 (d, 2H, J = 5.0 Hz), 4.02 (q, 2H, J = 7.2 Hz), 4.21 (q, 4H, J = 7.2 Hz), (t, 1H is covered by the previous signal), 7.48 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 13.8, 14.0, 28.8, 29.2, 40.6, 57.1, 59.5, 59.6, 106.7, 135.7, 166.8, 171.4; HRMS calcd. for $C_{19}H_{30}NO_6$ $[M+H]^+$: 368.2073, found: 368.2086.

(*2E,4Z*)-diethyl 4-((propylamino)methylene)pent-2-enedioate (4d)

Method A: 225.0 mg (72%) from **1d** (72.0 mg, 1.22 mmol) and **2a** (478.7 mg, 4.88 mmol) in EtOH (2.5 mL) during 20 h, along with **6a** (48.0 mg, 10%).

Method B: 171.0 mg (79%) from **1d** (50.0 mg, 0.85 mmol) and **2a** (333.5 mg, 3.40 mmol) during 18 h, along with **6a** (8.0 mg, 2%).

Method C: 60.0 mg (70%) from **1d** (20.0 mg, 0.34 mmol) and **2a** (66.4 mg, 0.68 mmol) during 4 h, along with **5/5'd** (5.0 mg, 4%).

4d: pale yellow oil; IR: ν 3288, 1696, 1663, 1622, 1598 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 0.96 (t, 3H, J = 7.5 Hz), 1.29 (t, 3H, J = 7.2 Hz), 1.36 (t, 3H, J = 7.0 Hz), 1.62 (sext, 2H, J = 7.5 Hz), 3.26 (q, 2H, J = 7.0 Hz), 4.18 (q, 2H, J = 7.0 Hz), 4.25 (q, 2H, J = 7.2 Hz), 6.01 (d, 1H, J = 15.5 Hz), 7.22 (d, 1H, J = 14.0 Hz), 7.39 (d, 1H, J = 15.5 Hz), 8.94 (broad s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 10.6, 14.1, 14.1, 23.7, 50.8, 59.2, 59.4, 94.0, 107.2, 143.0, 157.0, 168.6, 168.9; HRMS calcd. for $C_{13}H_{22}NO_4$ $[M+H]^+$: 256.1549, found: 256.1543.

5d and **5'd:** yellow oil; IR: ν 1732, 1701, 1580 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, mixture of 1,4- and 1,2-isomers 10:1): 0.88 (t, 3H, J = 7.2 Hz, 1,2-isomer), 0.94 (t, 3H, J = 7.2 Hz, 1,4-isomer), 1.20 (t, 3H, J = 7.0 Hz, 1,4-isomer), 1.24 (t, 3H, J = 7.2 Hz, 1,2-isomer), 1.28 (t, 6H, J = 7.0 Hz, 1,4-isomer), 1.65 (sext, 4H, J = 7.2 Hz, 1,2- and 1,4-isomers), 2.27-2.31 (dd, 1H, J = 4.5 Hz, J = 15.0 Hz, 1,2-isomer), 2.45 (d, 2H, J = 5.0 Hz, 1,4-isomer), 2.59-2.63 (dd, 1H, J = 8.0 Hz, J = 15.0 Hz, 1,2-isomer), 3.26 (t, 4H, J = 7.2 Hz, 1,2- and 1,4-isomers), 4.02 (q, 2H, J = 7.0 Hz, 1,4-isomer), 4.10 (q, 2H, J = 7.2 Hz, 1,2-isomer), 4.17-4.22 (m, 9H, 1,2- and 1,4-isomers), 5.04-5.06 (m, 1H, 1,2-isomer), 7.12 (s, 2H, 1,4-isomer), 7.49 (s, 1H, 1,2-isomer), 7.65 (s, 1H, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$, 1,4-isomer): 10.8, 14.2, 14.4, 23.5, 29.5, 40.9, 56.5, 59.9, 60.0, 106.8, 139.3, 166.9, 171.7; HRMS calcd. for $C_{18}H_{28}NO_6$ $[M+H]^+$: 354.1917, found: 354.1924.

(*2E,4Z*)-diethyl 4-((isopropylamino)methylene)pent-2-enedioate (4e)

Method A: 120.0 mg (81%) from **1e** (34.5 mg, 0.58 mmol) and **2a** (227.6 mg, 2.32 mmol) in EtOH (1.5 mL) during 3.5 h.

Method B: 174.0 mg (81%) from **1e** (50.0 mg, 0.85 mmol) and **2a** (333.5 mg, 3.40 mmol) during 18 h, along with **6a** (7.0 mg, 2%).

Method C: 72.0 mg (67%) from **1e** (25.0 mg, 0.42 mmol) and **2a** (83.0 mg, 0.84 mmol) during 3.5 h.

4e: pale yellow oil;[36] IR: ν 3278, 1698, 1661, 1620, 1595 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.25 (d, 6H, J = 6.5 Hz), 1.25 (t, 3H, J = 7.0 Hz), 1.32 (t, 3H, J = 7.5 Hz), 3.51 (m, 1H, J = 6.5 Hz), 4.15 (q, 2H, J = 7.0 Hz), 4.21 (q, 2H, J = 7.5 Hz), 5.98 (d, 1H, J = 15.5 Hz), 7.25 (d, 1H, J = 14.0 Hz), 7.36 (d, 1H, J = 15.5 Hz), 8.88 (broad signal, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.1, 23.2, 50.3, 59.1, 59.3, 93.9, 107.1, 143.1, 154.8, 168.5, 168.8.

(*2E,4Z*)-diethyl 4-((isobutylamino)methylene)pent-2-enedioate (4f)

Method A: 90.0 mg (66%) from **1f** (36.8 mg, 0.50 mmol) and **2a** (196.2 mg, 2.0 mmol) in EtOH (1.5 mL) during 7 h, along with **6a** (6.0 mg, 3%).

Method B: 105.0 mg (71%) from **1f** (40.0 mg, 0.55 mmol) and **2a** (214.6 mg, 2.20 mmol) during 48 h, along with **6a** (5.5 mg, 3%).

Method C: 55.0 mg (71%) from **1f** (21.0 mg, 0.29 mmol) and **2a** (56.3 mg, 0.57 mmol) during 3.5 h.

4f: pale yellow oil; IR: ν 3286, 1697, 1663, 1599 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 0.91 (d, 6H, J = 7.0 Hz), 1.25 (t, 3H, J = 7.0 Hz), 1.32 (t, 3H, J = 7.0 Hz), 1.79 (sep, 1H, J = 6.5 Hz), 3.08 (t, 2H, J = 6.5 Hz), 4.15 (q, 2H, J = 7.0 Hz), 4.22 (q, 2H, J = 7.0 Hz), 5.99 (d, 1H, J = 15.7 Hz), 7.16 (d, 1H, J = 14.0 Hz), 7.36 (d, 1H, J = 15.7 Hz), 8.97 (broad signal, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.4, 19.6, 29.6, 57.2, 59.5, 59.7, 94.3, 107.6, 143.4, 157.6, 168.8, 169.2; HRMS calcd. for $C_{14}H_{24}NO_4$ $[M+H]^+$: 270.1705, found: 270.1693.

(*2E,4Z*)-diethyl 4-((hexylamino)methylene)pent-2-enedioate (4g)

Method A: 105.0 mg (71%) from **1g** (50.0 mg, 0.49 mmol) and **2a** (192.3 mg, 1.96 mmol) in EtOH (1.5 mL) during 5 h, along with **5g** (15.0 mg, 8%) and **6a** (7.0 mg, 4%).

Method B: 110.0 mg (75%) from **1g** (50.0 mg, 0.49 mmol) and **2a** (192.3 mg, 1.96 mmol) during 24 h, along with **6a** (5.7 mg, 3%).

Method C: 60.0 mg (73%) from **1g** (28.0 mg, 0.28 mmol) and **2a** (54.3 mg, 0.56 mmol) during 3 h, along with **5g** (5.5 mg, 5%).

4g: pale yellow oil; IR: ν 3288, 1696, 1663, 1598 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 0.84 (t, 3H, J = 7.0 Hz), 1.21-1.28 (m, 6H), 1.24 (t, 3H, J = 7.0 Hz), 1.31 (t, 3H, J = 7.2 Hz), 1.54 (quint, 2H, J = 7.0 Hz), 3.24 (q, 2H, J = 7.0 Hz), 4.14 (q, 2H, J = 7.0 Hz), 4.20 (q, 2H, J = 7.2 Hz), 5.97 (d, 2H, J = 15.5 Hz), 7.17 (d, 2H, J = 14.0 Hz), 7.34 (d, 2H, J = 15.5 Hz), 8.89 (broad signal, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 13.8, 14.4, 14.4, 22.3, 26.0, 30.7, 31.2, 49.4, 59.4, 59.6, 94.2, 107.4, 143.3, 157.2, 168.8, 169.1; HRMS: calcd. for $C_{16}H_{28}NO_4$ $[M+H]^+$: 298.2018, found: 298.2011.

5g and **5'g:** yellow oil; IR: ν 1733, 1702, 1581 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, 1,4- and 1,2-isomers 5:1): 0.84-0.90 (m, 6H, 1,2- and 1,4-isomer), 1.19 (t, 3H, J = 7.0 Hz, 1,4-isomer), 1.23 (t, 3H, J = 7.0 Hz, 1,2-isomer), 1.28 (t, 3H, J = 7.0 Hz, 1,4-isomer), 1.25-1.31 (m, 24H, 1,2- and 1,4-isomer), 1.60 (quint, 4H, J = 7.0 Hz, 1,2- and 1,4-isomer), 2.27-2.31 (dd, 1H, J = 4.0 Hz, J = 14.5 Hz, 1,2-isomer), 2.44 (d, 2H, J = 5.5 Hz, 1,4-isomer), 2.58-2.62 (dd, 1H, J = 7.7 Hz, J = 14.5 Hz, 1,2-isomer), 3.28 (t, 2H, J = 7.0 Hz, 1,4-isomer), 4.02 (q, 2H, J = 7.0 Hz, 1,4-isomer), 4.09 (q, 2H, J = 7.0 Hz, 1,2-isomer), 4.16-4.23 (m, 9H, 1,2- and 1,4-isomer), 5.04-5.06 (m, 1H, 1,2-isomer), 7.11 (s, 2H, 1,4-isomer), 7.49 (s, 1H, 1,2-isomer), 7.64 (s, 1H, 1,2-isomer); ^{11}C NMR (125.8 MHz, $CDCl_3$, 1,4-isomer): 13.9, 14.1, 14.4, 22.4, 25.8, 29.5, 30.2, 31.3, 40.9, 54.9, 59.9, 60.0, 106.8, 139.3, 166.9, 171.7; HRMS: calcd. for $C_{21}H_{34}NO_6$ $[M+H]^+$: 396.2386, found: 396.2368.

(*2E,4Z*)-diethyl 4-((cyclohexylamino)methylene)pent-2-enedioate (4h)

Method A: 138.0 mg (77%) from **1h** (60.0 mg, 0.60 mmol) and **2a** (235.4 mg, 2.40 mmol) in EtOH (1.5 mL) during 5 h, along with **5h** (8.0 mg, 3%) and **6a** (13.0 mg, 6%).

Method B: 123.5 mg (83%) from **1h** (50.0 mg, 0.5 mmol) and **2a** (197.8 mg, 2.02 mmol) during 24 h, along with **6a** (5.6 mg, 3%).

Method C: 65.0 mg (70%) from **1h** (31.0 mg, 0.31 mmol) and **2a** (61.3 mg, 0.62 mmol) during 3 h, along with **6a** (6.0 mg, 5%).

4h: pale yellow oil; IR: ν 3278, 1698, 1661, 1596 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.16-1.21 (broad m, 1H), 1.24 (t, 3H, J = 7.0 Hz), 1.31 (t, 3H, J = 7.0 Hz), 1.30-1.35 (m, 4H), 1.56-1.58 (broad m, 1H), 1.71-1.74 (broad m, 2H), 1.88-1.90 (broad m, 2H), 3.13 (broad signal, 1H), 4.13 (q, 2H, J = 7.0 Hz), 4.20 (q, 2H, J = 7.0 Hz), 5.96 (d, 1H, J = 15.7 Hz), 7.25 (d, 1H, J = 13.5 Hz), 7.35 (d, 1H, J = 15.7 Hz), 8.95 (broad signal, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.4, 24.3, 25.0, 33.8, 57.5, 59.4, 59.6,

94.1, 107.2, 143.4, 155.2, 168.8, 169.1; HRMS: calcd. for $C_{16}H_{26}NO_4$ $[M+H]^+$: 296.1862, found: 296.1852.

5h: yellow oil; IR: ν 1734, 1701, 1578 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.13-1.19 (m, 1H), 1.20 (t, 3H, *J* = 7.0 Hz), 1.29 (t, 3H, *J* = 7.0 Hz), 1.27-1.30 (m, 1H), 1.42-1.50 (m, 2H), 1.62-1.70 (m, 2H), 1.86-1.90 (m, 4H), 2.44 (d, 2H, *J* = 5.0 Hz), 3.11-3.15 (m, 1H), 4.01 (q, 2H, *J* = 7.0 Hz), 4.19 (q, 4H, *J* = 7.0 Hz), 4.21 (t, 1H, *J* = 5.0 Hz), 7.21 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.2, 14.4, 25.0, 25.6, 30.0, 32.5, 40.8, 59.9, 60.0, 63.6, 106.7, 137.7, 167.0, 171.7; HRMS: calcd. for $C_{21}H_{32}NO_6$ $[M+H]^+$: 394.2230, found: 394.2213.

(*2E,4Z*)-diethyl 4-((phenethylamino)methylene)pent-2-enedioate (4i)

Method A: 90.0 mg (51%) from **1i** (68.0 mg, 0.56 mmol) and **2a** (219.5 mg, 2.24 mmol) in EtOH (1.5 mL) during 20 h, along with **5/5'i** (30.0 mg, 13%) and **6a** (20.0 mg, 9%).

Method B: 106.8 mg (72%) from **1i** (57.0 mg, 0.47 mmol) and **2a** (184.5 mg, 1.88 mmol) during 20 h, along with **6a** (13.2, 7%).

Method C: 60.0 mg (85%) from **1i** (27.0 mg, 0.22 mmol) and **2a** (43.7 mg, 0.44 mmol) during 2 h, along with **5/5'i** (5.0, 5%).

4i: pale yellow amorphous substance; IR ν 3325, 1728, 1696, 1665, 1620, 1600 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.28 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 2.88 (t, 2H, *J* = 7.0 Hz), 3.52 (q, 2H, *J* = 7.0 Hz), 4.17 (q, 2H, *J* = 7.0 Hz), 4.23 (q, 2H, *J* = 7.0 Hz), 5.97 (d, 1H, *J* = 15.5 Hz), 7.06, (d, 1H, *J* = 13.5 Hz), 7.16 (d, 2H, *J* = 7.5 Hz), 7.25 (t, 1H, *J* = 7.5 Hz), 7.32 (t, 2H, *J* = 7.5 Hz), 7.32 (d, 1H, *J* = 15.5 Hz), 8.91 (broad signal, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.1, 14.1, 37.2, 50.6, 59.2, 59.4, 94.4, 107.6, 126.6, 128.4, 128.5, 137.1, 142.9, 156.6, 168.5, 168.7; HRMS calcd. for $C_{18}H_{24}NO_4$ $[M+H]^+$: 318.1705, found: 318.1705.

5i and **5'i:** yellow oil, only 1,4-isomer was already reported;[37] IR ν 1731, 1700, 1580 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, 1,4- and 1,2-isomers 5:1): 1.19 (t, 3H, *J* = 7.0 Hz, 1,4-isomer), 1.21 (t, 3H, *J* = 7.0 Hz, 1,2-isomer), 1.26 (t, 3H, *J* = 7.0 Hz, 1,4-isomer), 1.28 (t, 3H, *J* = 7.0 Hz, 1,2-isomer), 2.21-2.25 (dd, 1H, *J* = 3.7 Hz, *J* = 15.2 Hz, 1,2-isomer), 2.41 (d, 2H, *J* = 4.5 Hz, 1,4-isomer), 2.57-2.62 (dd, 1H, *J* = 8.2 Hz, *J* = 15.2 Hz, 1,2-isomer), 2.89 (t, 2H, *J* = 7.5 Hz, 1,4-isomer), 3.52 (t, 2H, *J* = 7.5 Hz, 1,4-isomer), 4.01 (q, 2H, *J* = 7.0 Hz, 1,4-isomer), 4.08 (q, 2H, *J* = 7.0 Hz, 1,2-isomer), 4.14-4.18 (m, 9H, 1,2- and 1,4-isomer), 4.93 (dd, 1H, *J* = 3.7 Hz, *J* = 8.2 Hz, 1,2-isomer), 7.04 (s, 2H, 1,4-isomer), 7.08 (d, 2H, *J* = 7.0 Hz, 1,2-isomer), 7.16 (d, 2H, *J* = 7.0 Hz, 1,4-isomer), 7.22 (t, 1H, *J* = 7.5 Hz, 1,4-isomer), 7.29 (t, 2H, *J* = 7.0 Hz, 1,4-isomer), 7.33 (s, 1H, 1,2-isomer), 7.60 (s, 1H, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$, 1,4- and 1,2-isomers 5:1): 14.0, 14.1, 14.3, 14.4, 29.3 (1,4-isomer), 36.3, 36.7, 38.2 (1,2-isomer), 40.9 (1,4-isomer), 53.6 (1,2-isomer), 56.2, 57.3, 59.6, 59.9, 60.0, 60.2, 60.7, 100.1, 107.0, 109.1, 126.8, 126.9, 128.6, 128.7, 128.8, 133.2, 137.0, 139.0, 148.3, 165.2, 165.6, 166.7, 170.8, 171.5; HRMS calcd. for $C_{23}H_{30}NO_6$ $[M-H]^+$: 414.1911, found: 414.1901.

(*2E,4Z*)-diethyl 4-((allylamino)methylene)pent-2-enedioate (4j)

Method A: 190.0 mg (86%) from **1j** (50.0 mg, 0.88 mmol) and **2a** (345.3 mg, 3.52 mmol) in EtOH (2 mL) during 3.5 h, along with **5/5'j** (13.0 mg, 4%) and **6a** (10.0 mg, 3%).

Method B: 176.7 mg (80%) from **1j** (50.0 mg, 0.88 mmol) and **2a** (345.3 mg, 3.52 mmol) during 48 h, along with **6a** (8.3 mg, 2%).

Method C: 63.0 mg (68%) from **1j** (21.0 mg, 0.37 mmol) and **2a** (72.2 mg, 0.74 mmol) during 4 h, along with **5/5'j** (5.5 mg, 4%).

4j: pale yellow oil;[2c] IR ν 3290, 1697, 1664, 1597 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.26 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 3.86-3.89 (m, 2H), 4.16 (q, 2H, *J* = 7.0 Hz), 4.23 (q, 2H, *J* = 7.0 Hz), 5.20-5.24 (m, 2H), 5.80-5.88 (m, 1H), 6.01 (d, 1H, *J* = 15.5 Hz), 7.18 (d, 1H, *J* = 13.5 Hz), 7.35 (d, 1H, *J* = 15.5 Hz), 8.92 (broad signal, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.4, 51.1, 59.5, 59.8, 95.2, 108.2, 117.8, 133.4, 143.1, 156.9, 168.8, 169.1.

5j and **5'j:** yellow oil; IR ν 1732, 1701, 1583 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, 1,4- and 1,2-isomers 2:1): 1.20 (t, 3H, *J* = 7.0 Hz, 1,4-isomer), 1.25 (t, 3H, *J* = 7.0 Hz, 1,2-isomer), 1.28 (t, 6H, *J* = 7.0 Hz, 1,4-isomer), 1.27-1.31 (m, 6H, 1,2-isomer), 2.29-2.33 (dd, 1H, *J* = 4.0 Hz, *J* = 15.0 Hz, 1,2-isomer), 2.48 (d, 2H, *J* = 5.0 Hz, 1,4-isomer), 2.62-2.66 (dd, 1H, *J* = 8.0 Hz, *J* = 15.0 Hz, 1,2-isomer), 3.91-3.92 (m, 2H, 1,4-isomer), 4.04 (q, 2H, *J* = 7.0 Hz, 1,4-isomer), 4.09-4.15 (m, 4H, 1,2-isomer), 4.17-4.23 (m, 9H, 1,2- and 1,4-isomer), 5.03-5.06 (m, 1H, 1,2-isomer), 5.27-5.30 (m, 4H, 1,2- and 1,4-isomer), 5.79-5.86 (m, 2H, 1,2- and 1,4-isomer), 7.12 (s, 2H, 1,4-isomer), 7.50 (s, 1H, 1,2-isomer), 7.66 (s, 1H, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$, 1,4- and 1,2-isomers 2:1): 14.1, 14.2, 14.4, 14.5, 29.6 (1,4-isomer), 38.3 (1,2-isomer), 40.7 (1,4-isomer), 53.6 (1,2-isomer), 56.8, 58.1, 59.8, 60.0, 60.1, 60.3, 60.9, 100.2, 106.3, 109.5, 119.0, 119.4, 132.0, 132.5, 133.3, 139.2, 148.6, 165.4, 165.7, 166.8, 170.9, 171.8; HRMS: calcd. for $C_{18}H_{26}NO_6$ $[M+H]^+$: 352.1760, found: 352.1746.

(*2E,4Z*)-diethyl 4-((phenylamino)methylene)pent-2-enedioate (4k)

Method A: 145.0 mg (46%) from **1k** (102.2 mg, 1.10 mmol) and **2a** (431.6 mg, 4.40 mmol) in EtOH (2.5 mL) during 72 h, along with **3k** (55.0 mg, 26%) and **5k** (40.0 mg, 9%).

Method B: 101.0 mg (64%) **1k** (51.0 mg, 0.55 mmol) and **2a** (214.9 mg, 2.20 mmol) during 72 h, along with **3k** (18.0 mg, 17%) and **5k** (12.0 mg, 6%).

Method C: 66.0 mg (71%) from **1k** (30.0 mg, 0.32 mmol) and **2a** (62.8 mg, 0.64 mmol) during 3 h, along with **5/5'k** (30.0 mg, 24%).

4k: pale yellow solid, mp 35-36 °C (previously isolated as a yellow oil[15]); IR ν 3280, 1670, 1663, 1629, 1596 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.29 (t, 3H, *J* = 7.5 Hz), 1.38 (t, 3H, *J* = 7.0 Hz), 4.20 (q, 2H, *J* = 7.5 Hz), 4.30 (q, 2H, *J* = 7.0 Hz), 6.16 (d, 1H, *J* = 15.8 Hz), 7.05 (d, 2H, *J* = 8.0 Hz), 7.10 (t, 1H, *J* = 7.5 Hz), 7.34 (t, 2H, *J* = 8.0 Hz), 7.46 (d, 1H, *J* = 15.8 Hz), 7.74 (d, 1H, *J* = 13.0 Hz), 10.75 (d, 1H, *J* = 13.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 15.9, 16.0, 61.5, 62.0, 100.1, 112.6, 118.2, 125.9, 131.4, 140.9, 143.9, 149.3, 170.0, 170.5.

3k: *Z* isomer, white solid, mp 95-96 °C (previously isolated as a colourless oil);[15] IR ν 3316, 1669, 1631, 1602 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.29 (t, 3H, *J* = 7.2 Hz), 4.17 (q, 2H, *J* = 7.2 Hz), 4.83 (d, 1H, *J* = 8.4 Hz), 6.92-7.02 (m, 3H), 7.18-7.32 (m, 3H), 9.90 (d, 1H, *J* = 11.6 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 14.3, 59.2, 87.3, 115.2, 122.4, 129.6, 140.6, 142,9, 170.3.

5k: yellow oil;[14b,15] IR (1,4-isomer): ν 1734, 1705, 1594 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, 1,4-isomer): 1.18 (t, 3H, *J* = 7.0 Hz), 1.31 (t, 6H, *J* = 7.0 Hz), 2.60 (d, 2H, *J* = 5.0 Hz), 4.04 (q, 2H, *J* = 7.0 Hz), 4.23 (q, 2H, *J* = 7.0 Hz), 4.24 (q, 2H, *J* = 7.0 Hz), 4.27 (t, 1H, *J* = 5.0 Hz), 7.22-7.24 (m, 2H), 7.25-7.29 (m, 1H), 7.41-7.44 (m, 2H), 7.58 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$, 1,4-isomer): 14.2, 14.4, 29.6, 40.6, 60.0, 60.3, 108.3, 120.8, 126.4, 129.8, 137.6, 143.1, 166.7, 171.6.

5k and **5'k:** yellow oil; IR (1,4- and 1,2-isomer 1.5:1) ν 1733, 1704, 1627, 1598 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, 1,4- and 1,2-isomer 1.5:1): 1.14 (t, 3H, *J* = 7.0 Hz, 1,2-isomer), 1.17 (t, 3H, *J* = 7.0 Hz, 1,4-isomer), 1.29-1.34 (m, 12H, 1,2- and 1,4-isomers), 2.51-2.55 (dd, 1H, *J* = 6.5 Hz, *J* = 13.5 Hz, 1,2-isomer), 2.59 (d, 2H, *J* = 5.0 Hz), 2.63-2.67 (dd, 1H, *J* = 6.0 Hz, *J* = 13.5 Hz, 1,2-isomer), 3.89-3.95 (m, 2H, 1,2-isomer), 4.04 (q, 2H, *J* = 7.0 Hz, 1,4-isomer), 4.21-4.27 (m, 9H, 1,2- and 1,4-isomers), 5.68 (dt, 1H, *J* = 1.5 Hz, *J* = 6.0 Hz, 1,2-isomer), 7.21-7.23 (m, 2H, 1,4-isomer), 7.25-7.28 (m, 1H, 1,4-isomer), 7.32-7.34 (m, 2H, 1,2-isomer), 7.40-7.43 (m, 4H, 1,2- and 1,4-isomers), 7.57 (s, 2H, 1,4-isomer), 7.73 (d, 1H, *J* = 0.5 Hz, 1,2-isomer), 7.86 (t, 1H, *J* = 1.5 Hz, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$): 13.8, 14.1, 14.3, 14.5, 29.6 (1,4-isomer), 38.4 (1,2-isomer), 40.5 (1,4-isomer), 55.0 (1,2-isomer), 60.0, 60.1, 60.3, 60.5, 60.8, 104.3, 108.3, 113.1, 120.8, 121.0, 126.1, 126.3, 129.7, 129.8, 132.1, 137.6, 143.1, 143.7, 144.4, 165.2, 165.5, 166.7, 169.9, 171.6; HRMS calcd. for $C_{21}H_{26}NO_6$ $[M+H]^+$: 388.1760, found: 388.1783.

(*2E,4Z*)- and (*2E,4E*)-diethyl 4-(((4-methoxyphenyl)amino)methylene)pent-2-enedioate (4l)

Method A: 63.0 mg (49%) from **1l** (50.0 mg, 0.41 mmol) and **2a** (157.0 mg, 1.60 mmol) in EtOH (1.5 mL) during 30 h, along with **3l** (45.0 mg, 50%).

Method B: 90.0 mg (69%) from **1l** (50.0 mg, 0.41 mmol) and **2a** (159.3 mg, 1.62 mmol) during 30 h, along with **3l** (10.0 mg, 11%) and **6a** (17.0 mg, 11%).

Method C: 50.0 mg (64%) from **1l** (30.0 mg, 0.24 mmol) and **2a** (47.1 mg, 0.48 mmol) during 2.5 h.

4l: pale yellow solid, mp 93-95 °C; IR (*2E,4Z* and *2E,4E* 10:1) ν 3221, 3182, 1689, 1655, 1628, 1602 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, *2E,4Z* and *2E,4E* 10:1): 1.31 (t, 3H, *J* = 7.0 Hz, *2E,4Z*), 1.33 (t, 3H, *J* = 7.0 Hz, *2E,4E*), 1.39 (t, 3H, *J* = 7.0 Hz, *2E,4Z*), 3.80 (s, 3H, *2E,4Z* and *2E,4E*), 4.21 (q, 2H, *J* = 7.0 Hz, *2E,4Z*), 4.26 (q, 2H, *J* = 7.2 Hz, *2E,4E*), 4.31 (q, 2H, *J* = 7.2 Hz, *2E,4Z*), 6.15 (d, 1H, *J* = 15.5 Hz, *2E,4Z*), 6.46 (d, 1H, *J* = 16.0 Hz, *2E,4E*), 6.89 (d, 2H, *J* = 9.0 Hz, *2E,4Z*), 7.01 (d, 2H, *J* = 9.0 Hz, *2E,4Z*), 7.47 (d, 1H, *J* = 15.5 Hz, *2E,4Z*), 7.64 (d, 1H, *J* = 16.0 Hz, *2E,4E*), 7.66 (d, 1H, *J* = 13.5 Hz, *2E,4Z*), 8.09 (d, 1H, *J* = 14.5 Hz, *2E,4E*), 10.73 (d, 1H, *J* = 13.5 Hz, *2E,4Z*); ^{13}C NMR (125.8 MHz, $CDCl_3$, *2E,4Z* isomer): 14.4, 14.4, 55.5, 59.8, 60.2, 97.5, 110.1, 115.0, 118.2, 132.9, 142.5, 148.7, 156.8, 168.5, 169.1; HRMS calcd. for $C_{17}H_{22}NO_5$ $[M+H]^+$: 320.1498, found: 320.1498.

3l: *Z* isomer, yellow solid, mp 81-83 °C (previously isolated as a yellow oil);[15] IR ν 3304, 3274, 1695, 1612, 1587, 1509 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.30 (t, 3H, *J* = 7.0 Hz), 3.78 (s, 3H), 4.17 (q, 2H, *J* = 7.0 Hz), 4.77 (d, 1H, *J* = 8.0 Hz), 6.84-6.86 (m, 2H), 6.90-6.92 (m, 2H), 7.15 (dd, 1H, *J* = 8.0 Hz, *J* = 12.2 Hz), 9.81 (d, 1H, *J* = 12.2 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.5, 55.6, 59.1, 86.1, 114.9, 116.9, 134.5, 144.1, 155.5, 170.5.

(*2E,4Z*)-diethyl 4-((p-tolylamino)methylene)pent-2-enedioate (4m)

Method A: 48.0 mg (38%) from **1m** (45.0 mg, 0.42 mmol) and **2a** (164.8 mg, 1.68 mmol) in EtOH (1.5 mL) during 96 h, along with **3m** (24.0 mg, 28%).

Method B: 71.4 mg (56%), obtained in a mixture with **7m** (83.0 mg of the mixture containing 86% of **4m** and 14% of **7m**), from **1m** (45.0 mg, 0.42 mmol) and **2a** (164.8 mg, 1.68 mmol) during 40 h, along with **3m** (9.0 mg, 10%) and **5/5'm** (10.0 mg, 6%).

Method C: 60.0 mg (71%) from **1m** (30.0 mg, 0.28 mmol) and **2a** (54.9 mg, 0.56 mmol) during 9 h, along with **5/5'm** (28.0 mg, 25%) and **6a** (1.1 mg; 2%).

4m: pale yellow solid, mp 61-63 °C; IR ν 3273, 1694, 1655, 1599 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.29 (t, 3H, *J* = 7.0 Hz), 1.37 (t, 3H, *J* = 7.0 Hz), 2.20 (s, 3H), 4.20 (q, 2H, *J* = 7.0 Hz), 4.30 (q, 2H, *J* = 7.0 Hz), 6.15 (d, 1H, *J* = 15.5 Hz), 6.94 (d, 2H, *J* = 8.2 Hz), 7.13 (d, 2H, *J* = 8.2 Hz), 7.46 (d, 1H, *J* = 15.5 Hz), 7.70 (d, 1H, *J* = 13.5 Hz), 10.72 (d, 1H, *J* = 13.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.3, 14.4, 20.6, 59.7, 60.2, 97.9, 110.4, 116.5, 130.3, 134.1, 136.9, 142.4, 148.0, 168.4, 168.9; HRMS calcd. for $C_{17}H_{22}NO_4$ $[M+H]^+$: 304.1549, found: 304.1535.

3m: pale yellow oil (also reported previoulsy);[19] IR (64% *Z* and 36% *E*) ν 3300, 3274, 1683, 1613, 1582, 1521 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 64% *Z* and 36% *E*): *Z* isomer 1.30 (t, 3H, *J* = 7.2 Hz), 2.29 (s, 3H), 4.17 (q, 2H, *J* = 7.2 Hz), 4.79 (d, 1H, *J* = 8.2 Hz), 6.85 (d, 2H, *J* = 8.4 Hz), 7.09 (d, 2H, *J* = 8.4 Hz), 7.21 (dd, 1H, *J* = 8.2 Hz, *J* = 12.8 Hz), 9.84 (broad d, 1H), *E* isomer 1.28 (t, 3H, *J* = 7.2 Hz), 2.29 (s, 3H), 4.17 (q, 2H, *J* = 7.2 Hz), 5.17 (d, 1H, *J* = 13.0 Hz), 6.85 (d, 2H, *J* = 8.4 Hz), 7.09 (d, 2H, *J* = 8.4 Hz), 7.89 (t, 1H, *J* = 13.0 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): *Z* isomer 14.5, 20.6, 59.2, 86.7, 115.4, 130.1, 132.1, 138.3, 143.4, 170.4.

5m and **5'm:** yellow solid, only 1,4-isomer was already reported;[14b] IR ν 1734, 1703, 1626 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, 1,4- and 1,2-isomer 1:1.8): 1.16 (t, 3H, *J* = 7.0 Hz, 1,2-isomer), 1.19 (t, 3H, *J* = 7.2 Hz, 1,4-isomer), 1.30-1.35 (m, 12H, 1,2- and 1,4-isomers), 2.36 (s, 3H, 1,2-isomer), 2.37 (s, 3H, 1,4-isomer), 2.51-2.55 (dd, 1H, *J* = 6.0 Hz, *J* = 13.5 Hz, 1,2-isomer), 2.59 (d, 2H, *J* = 4.5 Hz, 1,4-isomer), 2.62-2.66 (dd, 1H, *J* = 6.0 Hz, *J* = 13.5 Hz, 1,2-isomer), 3.90-4.00 (m, 2H, 1,2-isomer), 4.04 (q, 2H, *J* = 7.2 Hz, 1,4-isomer), 4.22-4.29 (m, 9H, 1,2- and 1,4-isomers), 5.64 (dt, 1H, *J* = 1.5 Hz, *J* = 6.0 Hz, 1,2-isomer), 7.12 (d, 2H, *J* = 8.5 Hz, 1,4-isomer), 2.22 (d, 2H, *J* = 8.5 Hz, 1,4-isomer), 7.22 (s, 4H, 1,2-isomer), 7.54 (s, 2H, 1,4-isomer), 7.73 (s, 1H, 1,2-isomer), 7.84 (s, 1H, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$, 1,4- and 1,2-isomer 1:1.8): 13.5, 13.8, 14.0, 14.2, 20.5 (1,2- and 1,4-isomer), 29.3 (1,4-isomer), 38.0 (1,2-isomer), 40.3 (1,4-isomer), 55.0 (1,2-isomer), 59.7, 59.9, 60.2, 60.5, 103.3, 107.5, 111.8, 120.5, 120.8, 129.9, 129.9, 132.0, 135.9, 136.0, 137.5, 140.4, 141.0, 144.4, 164.9, 165.3, 166.4, 169.6, 171.3; HRMS calcd. for $C_{22}H_{28}NO_6$ $[M+H]^+$: 402.1917, found: 402.1925.

7m: ^1H NMR (500.3 MHz, $CDCl_3$) ^1H NMR (500.3 MHz, $CDCl_3$): 1.19 (t, 3H, *J* = 7.0 Hz), 1.24 (t, 6H, *J* = 7.0 Hz), 2.27 (s, 6H), 2.89 (d, 2H, *J* = 8.0 Hz), 4.07-4.12 (m, 3H), 6.85 (d, 4H, *J* = 8.5 Hz), 7.07 (d, 4H, *J* = 8.5 Hz), 7.38 (d, 2H, *J* = 13.0 Hz), 9.96 (d, 2H, *J* = 13.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.2, 14.2, 20.5, 37.3, 38.4, 59.4, 99.2, 115.1, 130.0, 131.5, 138.6, 142.7, 169.7, 172.3; HRMS calcd. for $C_{29}H_{36}N_2NaO_6$ $[M+Na]^+$: 531.2471, found: 531.2448.

(*2E,4Z*)- and (*2E,4E*)-diethyl 4-(((4-iodophenyl)amino)methylene)-pent-2-enedioate (4n)

Method A: 23.0 mg (30%) from **1n** (40.0 mg, 0.18 mmol) and **2a** (70.6 mg, 0.72 mmol) in EtOH (1 mL) during 120 h, along with **3n** (30.0 mg, 52%), **5/5'n** (7.0 mg, 7%) and **6a** (5.0 mg; 7%).

Method B: 35.3 mg (53%) from **1n** (35.0 mg, 0.16 mmol) and **2a** (62.7 mg, 0.64 mmol) during 72 h, along with **3n** (9.0 mg, 18%), **5/5'n** (12.0 mg, 15%) and **6a** (7.7 mg; 12%).

Method C: 30.2 mg (53%) from **1n** (30.0 mg, 0.14 mmol) and **2a** (27.5 mg, 0.28 mmol) during 9 h, along with **5/5'n** (22.0 mg, 31%) and **6a** (5.8 mg; 21%).

4n: pale yellow solid, mp 120-122 °C; IR (*2E,4Z* and *2E,4E* 10:1) ν 3166, 1694, 1633 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, *2E,4Z* and *2E,4E* 10:1): 1.31 (t, 3H, *J* = 7.0 Hz, *2E,4Z*), 1.34 (t, 3H, *J* = 7.0 Hz, *2E,4E*), 1.39 (t, 3H, *J* = 7.0 Hz, *2E,4Z*), 4.22 (q, 2H, *J* = 7.0 Hz, *2E,4Z*), 4.27 (t, 2H, *J* = 7.0 Hz, *2E,4E*), 4.32 (q, 2H, *J* = 7.0 Hz, *2E,4Z*), 6.19 (d, 1H, *J* = 16.0 Hz, *2E,4Z*), 6.50 (d, 1H, *J* = 16.0 Hz, *2E,4E*), 6.83 (d, 2H, *J* = 8.5 Hz, *2E,4Z*), 7.44 (d, 1H, *J* = 16.0 Hz, *2E,4Z*), 7.64 (d, 2H, *J* = 8.5 Hz, *2E,4Z*), 7.67 (d, 1H, *J* = 13.0 Hz, *2E,4Z*), 8.09 (d, 1H, *J* = 14.0 Hz, *2E,4E*), 10.74 (d, 1H, *J* = 13.0 Hz, *2E,4Z*); ^{13}C NMR (125.8 MHz, $CDCl_3$, *2E,4Z* isomer): 14.3, 14.4, 59.9, 60.5, 87.0, 99.4, 111.8, 118.2, 138.7, 139.1, 141.8, 146.7, 168.2, 168.8; HRMS calcd. for $C_{16}H_{19}INO_4$ $[M+H]^+$: 416.0359, found: 416.0340.

3n: *Z* isomer, pale yellow solid, mp 91-93 °C (lit.[15] 90-95 °C); IR ν 3363, 1725, 1665, 1620, 1586 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$) 1.31 (t, 3H, *J* = 7.0 Hz), 4.18 (q, 2H, *J* = 7.0 Hz), 4.88 (d, 1H, *J* = 8.5 Hz), 6.73 (d, 2H, *J* = 8.5 Hz), 7.18 (dd, 1H, *J* = 8.5 Hz, *J* = 12.5 Hz), 7.58 (d, 2H, *J* = 8.5 Hz), 9.90 (broad d, 1H, *J* = 12.5 Hz), there is also another set of signals of lower intensity, the origin of which has not been determined: 1.32 (t, 3H, *J* = 7.0 Hz), 4.24 (q, 2H, *J* = 7.0 Hz), 4.99 (d, 1H, *J* = 8.5 Hz), 7.14 (dd, 1H, *J* = 8.5 Hz, *J* = 12.0 Hz), 8.08 (d, 1H, *J* = 2.0 Hz), 10.16 (broad d, 1H, *J* = 12.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.4, 59.4, 84.6, 88.5, 117.2, 138.4, 140.5, 142.2, 170.3.

5n and **5'n:** yellow solid, only 1,4-isomer was already reported;[15] IR ν 1734, 1702, 1627 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, 1,4- and 1,2-isomer 1:4): 1.16 (t, 3H, *J* = 7.0 Hz, 1,2-isomer), 1.17 (t, 3H, *J* = 7.0 Hz, 1,4-isomer), 1.29-1.35 (m, 12H, 1,2- and 1,4-isomer), 2.49-2.53 (dd, 1H, *J* = 6.2 Hz, *J* = 13.5 Hz, 1,2-isomer), 2.59 (d, 2H, *J* = 5.0 Hz, 1,4-isomer), 2.0-2.64 (dd, 1H, *J* = 6.0 Hz, *J* = 13.5 Hz, 1,2-isomer), 3.91-4.04 (m, 4H, 1,2- and 1,4-isomer), 4.21-4.29 (m, 9H, 1,2- and 1,4-isomer), 5.61 (m, 1H, 1,2-isomer), 6.98 (d, 2H, *J* = 9.0 Hz, 1,4-isomer), 7.09 (d, 2H, *J* = 9.0 Hz, 1,2-isomer), 7.52 (s, 2H, 1,4-isomer), 7.7 (s, 1H, 1,2-isomer), 7.72 (d, 2H, *J* = 9.0 Hz, 1,2-isomer), 7.72 (d, 2H, *J* = 9.0 Hz, 1,4-isomer), 7.80 (s, 1H, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$): 13.9, 14.2, 14.3, 14.5, 29.7

(1,4-isomer), 38.3 (1,2-isomer), 40.3 (1,4-isomer), 54.7 (1,2-isomer), 60.1, 60.3, 60.4, 60.7, 61.0, 89.9, 106.4, 109.0, 113.5, 122.5, 131.8, 137.0, 138.8, 138.9, 143.2, 143.4, 165.0, 165.4, 169.9; HRMS calcd. for $C_{21}H_{25}INO_6$ $[M+H]^+$: 514.0727, found: 514.0731.

(*2E,4Z*)- and (*2E,4E*)-diethyl 4-(((4-fluorophenyl)amino)methylene)-pent-2-enedioate (4o)

Method A: 46.0 mg (35%) from **1o** (48.0 mg, 0.43 mmol) and **2a** (168.7 mg, 1.72 mmol) in EtOH (1.5 mL) during 120 h, along with **3o** (41.0 mg, 45%) and **5/5'o** (10.0 mg, 6%).

Method B: 80.0 mg (60%) from **1o**, 48.0 mg, 0.43 mmol) and **2a** (168.7 mg, 1.72 mmol) during 72 h, along with **3o** (10.0 mg, 11%) and **5/5'o** (17.0 mg, 10%).

Method C: 52.0 mg (63%) from **1o** (30.0 mg, 0.27 mmol) and **2a** (53.0 mg, 0.54 mmol) during 9 h, along with **5/5'o** (23.0 mg, 21%) and **6a** (1.1 mg; 2%).

4o: pale yellow solid, mp 70-72 °C (lit.[12c] 74-78 °C), IR (*2E,4Z* and *2E,4E* 10:1) ν 3422, 1676, 1655, 1593 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, *2E,4Z* and *2E,4E* 10:1): 1.31 (t, 3H, *J* = 7.0 Hz, *2E,4Z*), 1.34 (t, 3H, *J* = 7.0 Hz, *2E,4E*), 1.39 (t, 3H, *J* = 7.0 Hz, *2E,4Z*), 4.21 (q, 2H, *J* = 7.0 Hz, *2E,4Z*), 4.26 (q, 2H, *J* = 7.0 Hz, *2E,4E*), 4.31 (q, 2H, *J* = Hz, *2E,4Z*), 6.18 (d, 1H, *J* = 16.0 Hz, *2E,4Z*), 6.57 (d, 1H, *J* = 15.7 Hz, *2E,4E*), 7.03-7.07 (m, 4H, *2E,4Z* and *2E,4E*), 7.32 (d, 1H, *J* = 12.5 Hz, *2E,4E*), 7.46 (d, 1H, *J* = 16.0 Hz, *2E,4Z*), 7.65 (d, 1H, *J* = 13.0 Hz, *2E,4Z*), 7.67 (d, 1H, *J* = 15.7 Hz, *2E,4E*), 10.75 (d, 1H, *J* = 13.0 Hz, *2E,4Z*); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.3, 14.3, 59.8, 60.4, 98.5, 111.0, 116.5 (d, $J_{C\text{-}F}$ = 23.1 Hz), 118.1 (d, $J_{C\text{-}F}$ = 6.8 Hz), 135.7 (d, $J_{C\text{-}F}$ = 2.4 Hz), 159.5 (d, $J_{C\text{-}F}$ = 244.2 Hz), 168.3, 168.9.

3o: *Z* isomer, pale yellow solid, mp 36-38 °C (lit.[15] 35-38 °C); IR ν 3366, 1665, 1594, 1512 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.30 (t, 3H, *J* = 7.0 Hz), 4.18 (q, 2H, *J* = 7.0 Hz), 4.83 (d, 1H, *J* = 8.5 Hz), 6.90-6.92 (m, 2H), 7.00 (t, 2H, *J* = 8.5 Hz), 7.14 (dd, 1H, *J* = 8.5 Hz, *J* = 12.5 Hz), 9.87 (broad d, 1H, *J* = 12.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.4, 59.3, 87.4, 116.3 (d, $J_{C\text{-}F}$ = 22.6 Hz), 116.7 (d, $J_{C\text{-}F}$ = 7.5 Hz), 137.1, 143.5, 158.6 (d, $J_{C\text{-}F}$ = 241.5 Hz), 170.4.

5o and **5'o:** yellow solid, only 1,4-isomer was already reported;[15] IR ν 1733, 1692, 1628, 1511 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, 1,4- and 1,2-isomer 1:2): 1.15 (t, 3H, *J* = 7.0 Hz, 1,2-isomer), 1.18 (t, 3H, *J* = 7.0 Hz, 1,4-isomer), 1.29-1.35 (m, 12H, 1,2- and 1,4-isomers), 2.48-2.52 (dd, 1H, *J* = 6.0 Hz, *J* = 13.7 Hz, 1,2-isomer), 2.60 (d, 2H, *J* = 5.0 Hz, 1,4-isomer), 2.63-2.67 (dd, 1H, 6.0 Hz, *J* = 13.7 Hz, 1,2-isomer), 3.91-4.07 (m, 4H, 1,2- and 1,4-isomers), 4.22-4.28 (m, 8H, 1,2- and 1,4-isomers), 5.60 (dt, 1H, *J* = 1.5 Hz, *J* = 6.0 Hz, 1,2-isomer), 7.10-7.13 (m, 4H, 1,2- and 1,4-isomers), 7.20-7.22 (m, 2H, 1,4-isomer), 7.30-7.33 (m, 2H, 1,2-isomer), 7.48 (s, 2H, 1,4-isomer), 7.72 (d, 1H, *J* = 1.0 Hz, 1,2-isomer), 7.77 (t, 1H, *J* = 1.5 Hz, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$, 1,4- and 1,2-isomer 1:2): 15.5, 15.8, 15.9, 16.1, 31.1 (1,4-isomer), 39.9 (1,2-isomer), 42.0 (1,4-isomer), 57.2 (1,2-isomer), 61.6, 61.8, 61.9, 62.2, 62.5, 106.8, 109.8, 114.1, 118.2 (d, $J_{C\text{-}F}$ = 23.9 Hz, 1,2-isomer), 118.2 (d, $J_{C\text{-}F}$ = 22.6 Hz, 1,4-isomer), 124.7 (d, $J_{C\text{-}F}$ = 8.8 Hz, 1,4-isomer), 125.0 (d, $J_{C\text{-}F}$ = 7.5 Hz, 1,2-isomer), 133.7, 139.4, 141.1, 141.7, 146.3, 166.7, 167.1, 168.2, 171.6, 173.2; HRMS calcd. for $C_{21}H_{25}FNO_6$ $[M+H]^+$: 406.1666, found: 406.1670.

(*2E,4Z*)- and (*2E,4E*)-diethyl 4-(((4-nitrophenyl)amino)methylene)-pent-2-enedioate (4p)

Method A: Only **3p** (11.0 mg, 14%) was obtained from **1p** (45.0 mg, 0.33 mmol) and **2a** (125.6 mg, 1.28 mmol) in EtOH (1.3 mL) during 120 h.

Method B: 20.0 mg (18%) from **1p** (45.0 mg, 0.33 mmol) and **2a** (125.6 mg, 1.28 mmol) during 120 h, along with **3p** (25.0 mg, 32%).

Method C: 15.0 mg (21%) from **1p** (30.0 mg, 0.22 mmol) and **2a** (42.6 mg, 0.44 mmol) during 9.5 h, along with **5/5'p** (20.0 mg, 21%).

4p: pale yellow solid, mp 136-137 °C; IR (*2E,4Z* and *2E,4E* 1:1) ν 3193, 1706, 1658, 1620, 1588, 1517, 1331 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, *2E,4Z* and *2E,4E* 1:1): 1.31 (t, 3H, *J* = 7.0 Hz), 1.32 (t, 3H, *J* = 7.5 Hz), 1.36 (t, 3H, *J* = 7.2 Hz), 1.41 (t, 3H, *J* = 7.2 Hz), 4.22 (q, 2H, *J* = 7.5 Hz), 4.24 (q, 2H, *J* = 7.0 Hz), 4.30 (q, 2H, *J* = 7.2 Hz), 4.35 (q, 2H, *J* = 7.2 Hz), 6.27 (d, 1H, *J* = 16.0 Hz, *2E,5Z*), 6.59 (d, 1H, *J* = 15.5 Hz, *2E,5E*), 7.14 (d, 2H, *J* = 9.5 Hz, *2E,5Z*), 7.17 (d, 2H, *J* = 9.0 Hz, *2E,5E*), 7.45 (d, 1H, *J* = 16.0 Hz, *2E,5Z*), 7.60 (d, 1H, *J* = 15.5 Hz, *2E,5E*), 7.74 (d, 1H, *J* = 13.0 Hz, *2E,5Z*), 7.92 (d, 1H, *J* = 14.0 Hz, *2E,5E*), 8.14 (d, 1H, *J* = 14.0 Hz, *2E,5E*), 8.25 (d, 2H, *J* = 9.5 Hz, *2E,5Z*), 8.25 (d, 2H, *J* = 9.0 Hz, *2E,5E*), 8.25 (d, 2H, *J* = 9.5 Hz, *2E,5Z*), 11.02 (d, 1H, *J* = 13.0 Hz, *2E,5Z*); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.3, 14.4, 14.4, 60.2, 60.6, 60.8, 61.1, 102.3, 104.4, 114.1 (*2E,5Z*), 115.4, 115.6, 119.4 (*2E,5E*), 126.1 (*2E,5Z*), 126.1 (*2E,5E*), 134.2 (*2E,5E*), 140.5 (*2E,5E*), 140.8 (*2E,5Z*), 143.1, 143.3, 144.6, 144.7, 145.4, 166.2, 167.8, 168.1, 168.6; HRMS calcd. for $C_{16}H_{18}N_2NaO_6$ $[M+Na]^+$: 357.1063, found: 357.1053.

3p: *Z* isomer, orange solid, mp 127-129 °C; IR ν 3294, 3112, 1668, 1639, 1600, 1334 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 1.32 (t, 3H, *J* = 7.2 Hz), 4.21 (q, 2H, *J* = 7.2 Hz), 5.06 (d, 1H, *J* = 8.6 Hz), 7.00 (d, 2H, *J* = 9.2 Hz), 7.27 (dd, 1H, *J* = 8.6 Hz, *J* = 12.2 Hz), 8.20 (d, 2H, *J* = 9.2 Hz), 10.29 (d, 1H, *J* = 12.2 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 14.1, 59.9, 92.3, 114.1, 126.1, 140.5, 142.0, 146.0, 169.8; HRMS calcd. for $C_{11}H_{13}N_2O_4$ $[M+H]^+$: 237.0875, found: 237.0865.

5p and **5'p:** yellow-brown solid; IR ν 1710, 1692, 1635, 1596, 1553, 1518, 1344 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, mixture of 1,4- and 1,2-isomers 1:4): 1.16 (t, 3H, *J* = 7.0 Hz, 1,4-isomer), 1.19 (t, 3H, *J* = 7.0 Hz, 1,2-isomer), 1.33 (t, 9H, *J* = 7.0 Hz, 1,2- and 1,4-isomer), 1.36 (t, 3H, *J* = 7.0 Hz, 1,2-isomer), 2.56-2.60 (dd, 1H, *J* = 6.5 Hz, *J* = 14.0 Hz, 1,2-isomer), 2.64 (d, 2H, *J* = 4.5 Hz, 1,4-isomer), 2.65-2.69 (dd, 1H, *J* = 6.5 Hz, *J* = 14.0 Hz, 1,2-isomer), 3.99-4.07 (m, 4H, 1,2- and 1,4-isomer), 4.21-4.33 (m, 9H, 1,2- and 1,4-isomer), 5.71 (dt, 1H, *J* = 1.5 Hz, *J* = 6.5 Hz, 1,2-isomer), 7.36 (d, 2H, *J* = 9.0 Hz, 1,4-isomer), 7.44 (d, 2H, *J* = 9.0 Hz, 1,2-isomer), 7.68 (s, 2H, 1,4-isomer), 7.69 (s, 1H, 1,2-isomer), 7.89 (s, 1H, 1,2-isomer), 8.29 (d, 2H, *J* = 9.0 Hz, 1,2-isomer), 8.30 (d, 2H, *J* = 9.0 Hz, 1,4-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$, 1,4- and 1,2-isomer 1:4): 14.7, 14.9, 15.0, 15.1, 15.2, 30.4 (1,4-isomer), 38.8 (1,2-isomer), 40.5 (1,4-isomer), 54.4 (1,2-isomer), 60.8, 61.5, 61.7, 61.9, 109.5, 111.8, 117.0, 119.6, 120.1, 126.3, 126.5, 131.7, 136.4, 141.3, 145.0, 149.0, 165.4, 165.6, 166.8, 170.4, 172.1; HRMS calcd. for $C_{21}H_{25}N_2O_8$ $[M-H]^+$: 431.1449, found: 431.1441.

(*2E,4Z*)- and (*2E,4E*)-diethyl 4-(((3-chloro-4-methylphenyl)amino)methylene)pent-2-enedioate (4q)

Method A: 25.5 mg (27%), obtained in a mixture with **7q** (29.0 mg of the mixture containing 88% of **4q** and 12% of **7q**), from **1q** (40.0 mg, 0.28 mmol) and **2a** (109.9 mg, 1.12 mmol) in EtOH (1.2 mL) during 120 h, along with **3q** (32.0 mg, 47%) and **5/5'q** (9.0 mg, 7%).

Method B: 52.4 mg (55%), obtained in a mixture with **7q** (57.0 mg of the mixture containing 92% of **4q** and 8% of **7q**), from **1q** (40.0 mg, 0.28 mmol) and **2a** (109.9 mg, 1.12 mmol) during 96 h, along with **3q** (9.0 mg, 13%) and **5/5'q** (15.0 mg, 12%).

Method C: 41.0 mg (57%) from **1q** (30.0 mg, 0.21 mmol) and **2a** (41.6 mg, 0.42 mmol) during 7 h, along with **5/5'q** (30.0 mg, 32%) and **6a** (2.1 mg; 5%).

4q: yellow oil; IR (*2E,4Z* and *2E,4E* 5:1) ν 3287, 1701, 1664, 1601 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, *2E,4Z* and *2E,4E* 5:1): 1.31 (t, 3H, *J* = 7.0 Hz, *2E,4Z*), 1.34 (t, 3H, *J* = 7.5 Hz, *2E,4E*), 1.39 (t, 3H, *J* = 7.0 Hz, *2E,4Z*), 2.30 (s, 3H, *2E,4E*), 2.33 (s, 3H, *2E,4Z*), 4.22 (q, 2H, *J* = 7.0 Hz, *2E,4Z*), 4.32 (q, 2H, *J* = 7.0 Hz, *2E,4Z*), 6.18 (d, 1H, *J* = 15.7 Hz, *2E,4Z*), 6.49 (d, 1H, *J* = 16.0 Hz, *2E,4E*), 6.86 (dd, 1H, *J* = 2.5 Hz, *J* = 8.0 Hz, *2E,4Z*), 7.08 (d, 1H, *J* = 2.5 Hz, *2E,4Z*), 7.11 (d, 1H, *J* = 2.0 Hz, *2E,4E*), 7.19 (d, 1H, *J* = 8.0 Hz, *2E,4Z*), 7.46 (d, 1H, *J* = 15.7 Hz, *2E,4Z*), 7.60 (d, 1H, *J* = 16.0 Hz, *2E,4E*), 7.66 (d, 1H, *J* = 13.0 Hz, *2E,4Z*), 8.08 (d, 1H, *J* = 14.0 Hz, *2E,4E*), 10.70 (d, 1H, *J* = 13.0 Hz, *2E,4Z*); ^{13}C NMR (125.8 MHz, $CDCl_3$, only signals for *2E,4Z* isomer are clearly visible): 14.3, 14.4, 19.3, 59.9, 60.5, 98.9, 111.4, 114.9, 117.0, 131.9, 135.5, 138.3, 141.9, 147.2,

168.3, 168.9; HRMS calcd. for $C_{17}H_{21}ClNO_4$ [M+H]$^+$: 338.1159, found: 338.1152.

3q: *Z* isomer, pale yellow solid, mp 103-105 °C; IR ν 3296, 3269, 1692, 1666, 1608, 1573 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 1.31 (t, 3H, *J* = 7.2 Hz), 2.31 (s, 3H), 4.18 (q, 2H, *J* = 7.2 Hz), 4.84 (d, 1H, *J* = 8.4 Hz), 6.75 (dd, 1H, *J* = 2.4 Hz, *J* = 8.2 Hz), 6.98 (d, 1H, *J* = 2.4 Hz), 7.13 (d, 1H, *J* = 8.2 Hz), 7.16 (dd, 1H, *J* = 8.4 Hz, *J* = 12.8 Hz), 9.85 (d, 1H, *J* = 12.8 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 14.2, 19.2, 59.3, 88.0, 113.9, 115.6, 115.7, 129.8, 131.6, 135.2, 139.7, 142.7, 170.3; HRMS calcd. for $C_{12}H_{14}ClNNaO_2$ [M+Na]$^+$: 262.0611, found: 262.0602.

5q and **5'q:** yellow solid; IR ν 1734, 1704, 1605 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$, mixture of 1,4- and 1,2-isomers 1:3.3): 1.18 (t, 3H, *J* = 7.2 Hz, 1,2-isomer), 1.18 (t, 3H, *J* = 7.2 Hz, 1,4-isomer), 1.30-1.35 (m, 12H, 1,2- and 1,4-isomers), 2.37 (s, 3H, 1,2-isomer), 2.37 (s, 3H, 1,4-isomer), 2.49-2.53 (dd, 1H, *J* = 6.0 Hz, *J* = 13.7 Hz, 1,2-isomer), 2.59 (d, 2H, *J* = 5.0 Hz, 1,4-isomer), 2.61-2.65 (dd, 1H, *J* = 6.0 Hz, *J* = 13.7 Hz, 1,2-isomer), 3.94-4.06 (m, 4H, 1,2- and 1,4-isomers), 4.22-4.29 (m, 9H, 1,2- and 1,4-isomers), 5.60 (dt, 1H, *J* = 1.5 Hz, *J* = 6.0 Hz, 1,2-isomer), 7.03 (dd, 1H, *J* = 2.5 Hz, *J* = 8.2 Hz, 1,4-isomer), 7.14 (dd, 1H, *J* = 2.5 Hz, *J* = 8.5 Hz, 1,2-isomer), 7.23 (d, 1H, *J* = 2.5 Hz, 1,4-isomer), 7.26 (d, 1H, *J* = 8.5 Hz, 1,2-isomer), 7.32, (d, 1H, *J* = 2.5 Hz, 1,2-isomer), 7.51 (s, 2H, 1,4-isomer), 7.70 (s, 1H, 1,2-isomer), 7.79 (s, 1H, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$, mixture of 1,4- and 1,2-isomers 1:3.3): 13.9, 14.2, 14.3, 14.5, 18.9 (1,4-isomer), 19.5 (1,2-isomer), 29.6 (1,4-isomer), 38.3 (1,2-isomer), 40.4 (1,4-isomer), 55.1 (1,2-isomer), 60.1, 60.2, 60.4, 60.6, 61.0, 104.8, 108.6, 113.1, 113.7, 119.0, 119.1, 121.4, 121.6, 131.3, 131.8, 132.0, 134.0, 135.3, 137.2, 141.8, 142.6, 143.7, 165.1, 165.4, 166.6, 169.9, 171.6; HRMS calcd. for $C_{22}H_{27}ClNO_6$ [M+H]$^+$: 436.1527, found: 436.1518.

7q: ^{1}H NMR (500.3 MHz, $CDCl_3$): 2.29 (s, 6H), 2.89 (d, 2H, *J* = 8.0 Hz), 4.00 (t, 1H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 12.5 Hz), 9.97 (d, 2H, *J* = 12.5 Hz), assignation of other signals is not safe; due to the low concentration, signals of **7q** are not visible in the ^{13}C NMR spectrum; HRMS calcd. for $C_{29}H_{34}Cl_2N_2NaO_6$ [M+Na]$^+$: 599.1692, found: 599.1688.

(*2E,4Z*)-and (*2E,4E*)-diethyl 4-(((3,4-dichlorophenyl)amino)methylene)pent-2-enedioate (4r)

Method A: 9.0 mg (8%) from **1r** (50.0 mg, 0.31 mmol) and **2a** (121.1 mg, 1.23 mmol) in EtOH (1.5 mL) during 144 h, along with **3r** (40.0 mg, 50%) and **5/5'r** (6.0 mg, 4%).

Method B: 25.0 mg (21%) from **1r** (55.0 mg, 0.34 mmol) and **2a** (133.2 mg, 1.36 mmol) during 96 h, along with **3r** (31.0 mg, 35%) and **5/5'r** (18.0 mg, 12%).

Method C: 35.0 mg (53%) from **1r** (30.0 mg, 0.19 mmol) and **2a** (36.3 mg, 0.37 mmol) during 9 h, along with **5/5'r** (21.0 mg, 25%) and **6a** (3.0 mg; 8%).

4r: yellow oil; IR (*2E,4Z* and *2E,4E* 2.5:1) ν 3416, 1677, 1661, 1630, 1589 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$, *2E,4Z* and *2E,4E* 2.5:1): 1.31 (t, 3H, *J* = 7.2 Hz, *2E,4E*), 1.31 (t, 3H, *J* = 7.2 Hz, *2E,4Z*), 1.35 (t, 3H, *J* = 7.2 Hz, *2E,4E*), 1.39 (t, 3H, *J* = 7.2 Hz, *2E,4Z*), 4.22 (q, 2H, 7.2 Hz, *2E,4Z* and *2E,4E*), 4.28 (q, 2H, *J* = 7.2 Hz, *2E,4E*), 4.32 (q, 2H, *J* = 7.2 Hz, *2E,4Z*), 6.20 (d, 1H, *J* = 15.5 Hz, *2E,4Z*), 6.53 (d, 1H, *J* = 16.0 Hz, *2E,4E*), 6.90 (dd, 1H, *J* = 2.5 Hz, *J* = 8.7 Hz, *2E,4Z*), 6.94 (dd, 1H, *J* = 2.5 Hz, *J* = 8.7 Hz, *2E,4E*), 7.18 (d, 1H, *J* = 2.5 Hz, *2E,4Z*), 7.21 (d, 1H, *J* = 2.5 Hz, *2E,4E*), 7.39 (d, 1H, *J* = 8.7 Hz, *2E,4E*), 7.40 (d, 1H, *J* = 8.7 Hz, *2E,4Z*), 7.44 (d, 1H, *J* = 15.5 Hz, *2E,4Z*), 7.58 (d, 1H, *J* = 16.0 Hz, *2E,4E*), 7.62 (d, 1H, *J* = 12.5 Hz, *2E,4Z*), 7.67 (d, 1H, *J* = 13.7 Hz, *2E,4E*), 8.02 (d, 1H, *J* = 13.7 Hz, *2E,4E*), 10.75 (d, 1H, *J* = 12.5 Hz, *2E,4Z*); ^{13}C NMR (125.8 MHz, $CDCl_3$, only signals for *2E,4Z* isomer are clearly visible): 14.3, 14.4, 60.0, 60.7, 100.1, 112.5, 115.8, 118.0, 127.4, 131.4, 133.9, 139.0, 141.4, 146.3, 168.1, 168.8; HRMS calcd. for $C_{16}H_{18}Cl_2NO_4$ [M+H]$^+$: 358.0613, found: 358.0605.

3r: *Z* isomer, yellow amorphous substance; IR ν 3313, 1664, 1634, 1598, 1568 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 1.30 (t, 3H, *J* = 7.2 Hz), 4.18 (q, 2H, *J* = 7.2 Hz), 4.90 (d, 1H, *J* = 8.4 Hz), 6.77 (dd, 1H, *J* = 2.6 Hz, *J* = 8.6 Hz), 7.05 (d, 1H, *J* = 2.6 Hz), 7.12 (dd, 1H, *J* = 8.4 Hz, *J* = 12.4 Hz), 7.32 (d, 1H, *J* = 8.6 Hz), 9.92 (d, 1H, *J* = 12.4 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 14.2, 15.6, 89.5, 114.8, 116.7, 125.3, 131.2, 133.5, 140.3, 141.9, 170.2; HRMS calcd. for $C_{11}H_{12}Cl_2NO_2$ [M+H]$^+$: 260.0245, found: 260.0237.

5r and **5'r:** yellow solid; IR ν 1731, 1694, 1629, 1592 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$, mixture of 1,4- and 1,2-isomers 1:5.6): 1.17 (t, 3H, *J* = 7.2 Hz, 1,2- and 1,4-isomers), 1.29 (t, 3H, *J* = 7.0 Hz, 1,4-isomer), 1.30 (t, 3H, *J* = 7.2 Hz, 1,2-isomer), 1.32 (t, 3H, *J* = 7.0 Hz, 1,2-isomer), 2.47-2.51 (dd, 1H, *J* = 6.0 Hz, *J* = 14.0 Hz, 1,2-isomer), 2.58 (d, 2H, *J* = 5.0 Hz, 1,4-isomer), 2.59-2.63 (dd, 1H, *J* = 6.0 Hz, *J* = 14.0 Hz, 1,2-isomer), 3.95-4.00 (m, 4H, 1,2- and 1,4-isomers), 4.21-4.28 (m, 9H, 1,2- and 1,4-isomers), 5.56 (dt, 1H, *J* = 1.5 Hz, *J* = 6.0 Hz, 1,2-isomer), 7.07 (dd, 1H, *J* = 3.0 Hz, *J* = 9.0 Hz, 1,4-isomer), 7.18 (dd, 1H, *J* = 3.0 Hz, *J* = 9.0 Hz, 1,2-isomer), 7.32 (d, 1H, *J* = 3.0 Hz, 1,4-isomer), 7.41 (d, 1H, *J* = 3.0 Hz, 1,2-isomer), 7.44 (d, 1H, *J* = 9.0 Hz, 1,2-isomer), 7.45 (d, 1H, *J* = 9.0 Hz, 1,4-isomer), 7.48 (s, 2H, 1,4-isomer), 7.66 (d, 1H, *J* = 1.0 Hz, 1,2-isomer), 7.74 (t, 1H, *J* = 1.0 Hz, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$, mixture of 1,4- and 1,2-isomers 1:5.6): 14.6, 14.9, 15.0, 15.2, 30.2 (1,4-isomer), 38.9 (1,2-isomer), 40.8 (1,4-isomer), 55.4 (1,2-isomer), 60.8, 61.1, 61.2, 61.5, 61.8, 107.0, 110.2, 114.9, 120.4, 120.5, 123.1, 123.2, 130.3, 132.0, 132.1, 132.2, 134.4, 137.3, 142.9, 143.2, 143.7, 165.6, 165.9, 167.1, 170.5, 172.2; HRMS calcd. for $C_{21}H_{24}Cl_2NO_6$ [M+H]$^+$: 456.0981, found: 456.0967.

(*2E,4Z*)-diethyl 4-(((2,4-dimethylphenyl)amino)methylene)pent-2-enedioate (4s)

Method A: 23.4 mg (26%), obtained in a mixture with **6a** (26.0 mg of the mixture containing 90% of **4s** and 10% of **6a**), from **1s** (35.0 mg, 0.29 mmol) and **2a** (113.3 mg, 1.16 mmol) in EtOH (1.2 mL) during 120 h, along with **3s** (14.0 mg, 22%).

Method B: 38.2 mg (42%), obtained in a mixture with **7s** (46.0 mg of the mixture containing 83% of **4s** and 17% of **7s**), from **1s** (35.0 mg, 0.29 mmol) and **2a** (113.3 mg, 1.16 mmol) during 72 h, along with **3s** (4.0 mg, 6%) and **5s** (8.0 mg, 7%).

Method C: 26.7 mg (34%), obtained in a mixture with **6a** (31.0 mg of the mixture containing 86% of **4s** and 14% of **6**), from **1s** (30.0 mg, 0.25 mmol) and **2a** (48.6 mg, 0.50 mmol) during 3 h, along with **5s** (38.0 mg, 37%); **6a** (2.0 mg; 4%).

4s: yellow solid; IR ν 3427, 3279, 1673, 1656, 1593 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 1.31 (t, 3H, *J* = 7.0 Hz), 1.40 (t, 3H, *J* = 7.0 Hz), 2.30 (s, 3H), 2.32 (s, 3H), 4.22 (q, 2H, *J* = 7.0 Hz), 4.33 (q, 2H, *J* = 7.0 Hz), 6.17 (d, 1H, *J* = 15.5 Hz), 7.02-7.06 (m, 3H), 7.50 (d, 1H, *J* = 15.5 Hz), 7.76 (d, 1H, *J* = 13.0 Hz), 10.83 (d, 1H, *J* = 13.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.5, 17.4, 20.7, 59.8, 60.4, 98.1, 110.3, 114.8, 126.8, 127.9, 131.9, 134.4, 135.6, 142.6, 148.5, 168.6, 169.2; HRMS calcd. for $C_{18}H_{24}NO_4$ [M+H]$^+$: 318.1705, found: 318.1693.

3s: *Z* isomer, reddish oil; IR ν 3431, 3277, 1676, 1654, 1622, 1594 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 1.31 (t, 3H, *J* = 7.0 Hz), 2.28 (s, 3H), 2.30 (s, 3H), 4.20 (q, 2H, *J* = 7.0 Hz), 4.84 (d, 1H, *J* = 8.0 Hz), 6.93 (d, 1H, *J* = 9.0 Hz), 6.98-7.00 (m, 3H), 7.27 (dd, 1H, *J* = 8.0 Hz, *J* = 12.5 Hz), 9.92 (d, 1H, *J* = 12.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.5, 17.4, 20.6, 59.2, 86.8, 113.2, 125.4, 127.6, 131.7, 131.9, 136.8, 143.8, 170.7; HRMS calcd. for $C_{13}H_{18}NO_2$ [M+H]$^+$: 220.1338, found: 220.1325.

5s: yellow solid, mp 62-64 °C (lit.[14b] 76-77 °C); IR ν 1734, 1705, 1588 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 1.23 (t, 3H, *J* = 7.0 Hz), 1.30 (t, 6H, *J* = 7.0 Hz), 2.28 (s, 3H), 2.36 (s, 3H), 2.62 (d, 1H, *J* = 5.0 Hz), 4.09 (q, 2H, *J* = 7.0 Hz), 4.22 (2 × q, 4H, *J* = 7.0 Hz), 4.31 (t, 1H, *J* = 5.0 Hz), 7.07 (2 × s, 2H), 7.11 (s, 1H), 7.24 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.9, 15.1, 18.3, 21.7, 30.2, 41.3, 60.7, 60.8, 107.1, 126.7, 128.6, 132.9, 134.6, 139.0, 140.3, 140.8, 167.6, 172.5.

7s: ^{1}H NMR (500.3 MHz, $CDCl_3$): 1.20 (t, 3H, *J* = 7.0 Hz), 1.26 (t, 3H, *J* = 7.0 Hz), 2.27 (s, 12H), 2.92 (d, 2H, *J* = 8.0 Hz), 4.09 (t, 1H, *J* = 8.0 Hz),

4.11 (q, 2H, *J* = 7.0 Hz), signal of another ester group is covered by the signal of **4s**, 6.95-6.98 (m, 6H), 7.46 (d, 2H, *J* = 12.5 Hz), 10.01 (d, 2H, *J* = 12.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$, not all signals are clearly visible): 14.2, 14.3, 17.5, 20.6, 37.4, 38.5, 59.5, 99.6, 112.7, 127.6, 131.6, 134.4, 137.2, 142.9, 169.9; HRMS calcd. for $C_{31}H_{40}N_2NaO_6$ $[M+H]^+$: 559.2784, found: 559.2764.

(*2E,4Z*)-diethyl 4-(((2,3-dimethylphenyl)amino)methylene)pent-2-enedioate (4t)

Method A: 46.0 mg (35%) from **1t** (50.0 mg, 0.41 mmol) and **2a** (160.9 mg, 1.64 mmol) in EtOH (1.5 mL) during 120 h, along with **3t** (50.0 mg, 55%).

Method B: 60 mg (46%), obtained in a mixture with **7t** (80.0 mg of the mixture containing 75% of **4t** and 25% of **7t**), from **1t**, 50.0 mg, 0.41 mmol) and **2a** (160.9 mg, 1.64 mmol) during 72 h, along with **3t** (20.0 mg, 22%).

Method C: 57.0 mg (73%) from **1t** (30.0 mg, 0.25 mmol) and **2a** (48.6 mg, 0.50 mmol) during 6 h, along with **5t** (14.0 mg, 14%) and **6a** (2.0 mg; 4%).

4t: pale yellow solid, mp 70-72 °C; IR ν 3280, 1692, 1657, 1627, 1590 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 1.31 (t, 3H, *J* = 7.0 Hz), 1.40 (t, 3H, *J* = 7.0 Hz), 2.25 (s, 3H), 2.32 (s, 3H), 4.21 (q, 2H, *J* = 7.0 Hz), 4.33 (q, 2H, *J* = 7.0 Hz), 6.17 (d, 1H, *J* = 15.5 Hz), 6.96 (d, 1H, *J* = 7.7 Hz), 6.99 (d, 1H, *J* = 7.7 Hz), 7.13 (t, 1H, *J* = 7.7 Hz), 7.49 (d, 1H, *J* = 15.5 Hz), 7.75 (d, 1H, *J* = 12.5 Hz), 10.90 (d, 1H, *J* = 12.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 13.1, 14.4, 14.4, 20.5, 59.8, 60.3, 98.3, 110.4, 113.2, 125.6, 126.3, 126.6, 138.1, 138.2, 142.5, 149.0, 168.5, 169.2; HRMS calcd. for $C_{18}H_{24}NO_4$ $[M+H]^+$: 318.1705, found: 318.1690.

3t: *Z* isomer, yellow solid, mp 70-72 °C; IR ν 3375, 1691, 1658, 1589 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 1.31 (t, 3H, *J* = 7.2 Hz), 2.23 (s, 3H), 2.31 (s, 3H), 4.20 (q, 2H, *J* = 7.2 Hz), 4.85 (d, 1H, *J* = 8.2 Hz), 6.86 (d, 1H, *J* = 7.8 Hz), 6.90 (d, 1H, *J* = 7.8 Hz), 7.08 (t, 1H, *J* = 7.8 Hz), 7.27 (dd, 1H, *J* = 8.2 Hz. *J* = 12.6 Hz), 10.03 (d, 1H, *J* = 12.6 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 13.0, 14.3, 20.5, 59.2, 87.0, 111.5, 124.1, 124.4, 126.3, 137.9, 139.2, 144.1, 170.7; HRMS calcd. for $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1338, found: 220.1330.

5t: pale yellow solid, mp 103-105 °C; IR ν 1730, 1703, 1665, 1626, 1587 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 1.21 (t, 3H, *J* = 7.0 Hz), 1.27 (t, 6H, *J* = 7.0 Hz), 2.19 (s, 3H), 2.32 (s, 3H), 2.61 (d, 2H, *J* = 5.0 Hz), 4.07 (q, 2H, *J* = 7.0 Hz), 4.20 (2 × q, 6H, *J* = 7.0 Hz), 4.29 (t, 1H, *J* = 5.0 Hz), 7.02-7.03 (broad signal, 1H), 7.13-7.16 (m, 2H), 7.22 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.4, 14.5, 20.6, 29.7, 40.7, 60.1, 60.3, 97.9, 106.6, 126.7, 129.9, 133.2, 139.3, 139.8, 147.9, 167.0, 172.0; HRMS calcd. for $C_{23}H_{30}NO_6$ $[M+H]^+$: 416.2073, found: 416.2072.

7t: ^{1}H NMR (500.3 MHz, $CDCl_3$): 1.20 (t, 3H, *J* = 7.0 Hz), 1.27 (t, 3H, *J* = 7.0 Hz), 2.20 (s, 6H), 2.30 (s, 6H), 2.93 (d, 2H, *J* = 8.0 Hz), 4.10 (t, 1H, *J* = 8.0 Hz), 4.11 (q, 2H, *J* = 7.0 Hz), 4.21 (q, 2H, *J* = 7.0 Hz), 6.82 (d, 2H, *J* = 7.5 Hz), 7.08 (t, 2H, *J* = 7.5 Hz), the third H_{arom} is not visible, 7.48 (d, 2H, *J* = 12.5 Hz), 10.14 (d, 2H, *J* = 12.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 12.9, 14.4, 20.5, 37.4, 38.4, 59.4, 99.8, 110.9, 123.7, 123.8, 126.2, 137.6, 139.5, 143.1, 169.8, 172.3; HRMS calcd. for $C_{31}H_{40}N_2NaO_6$ $[M+H]^+$: 559.2784, found: 559.2763.

(*2E,4Z*)-diethyl 4-(((2-chloro-4-methylphenyl)amino)methylene)pent-2-enedioate (4u)

Method A: 17.0 mg (18%), obtained in a mixture with **7u** (20.0 mg of the mixture containing 85% of **4u** and 15% of **7u**), from **1u** (40.0 mg, 0.28 mmol) and **2a** (109.9 mg, 1.12 mmol) in EtOH (1.2 mL) during 120 h, along with **3u** (53.0 mg, 78%).

Method B: 16.0 mg (17%), obtained in a mixture with **7u** (28.0 mg of the mixture containing 57% of **4u** and 43% of **7u**), from **1u** (40.0 mg, 0.28 mmol) and **2a** (109.9 mg, 1.12 mmol) during 96 h, along with **3u** (48.0 mg, 71%).

Method C: 30.0 mg (42%), obtained in a mixture with **7u** (40.0 mg of the mixture containing 75% of **4u** and 25% of **7u**), from **1u**, 30.0 mg, 0.21 mmol) and **2a** (41.6 mg, 0.42 mmol) during 8 h, along with **5/5'u** (22.0 mg, 24%).

4u: pale yellow solid; IR ν 3424, 1664, 1626, 1597 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$, **4u** and **7u** 5:1): 1.20 (t, 3H, *J* = 7.2 Hz, **7u**), 1.28 (t, 6H, *J* = 7.2 Hz, **7u**), 1.31 (t, 3H, *J* = 7.2 Hz, **4u**), 1.40 (t, 3H, *J* = 7.2 Hz, **4u**), 2.28 (s, 6H, **7u**), 2.31 (s, 3H, **4u**), 2.94 (d, 2H, *J* = 8.0 Hz, **7u**), 4.09 (t, 1H, *J* = 8.0 Hz, **7u**), 4.11 (q, 2H, *J* = 7.2 Hz, **7u**), 4.22 (q, *J* = 7.2 Hz, **4u**), 4.21-4.24 (m, 4H, **7u**), 4.36 (q, *J* = 7.2 Hz, **4u**), 6.23 (d, 1H, *J* = 15.5 Hz, **4u**), 7.03 (broad s, 4H, **7u**), 7.10 (broad s, 2H, **4u**), 7.17 (broad signal, 2H, **7u**), 7.22 (broad s, 1H, **4u**), 7.42 (d, 2H, *J* = 12.0 Hz, **7u**), 7.47 (d, 1H, *J* = 15.5 Hz, **4u**), 7.71 (d, 1H, *J* = 13.0 Hz, **4u**), 10.25 (broad d, 2H, *J* = 12.0 Hz, **7u**), 11.02 (broad d, 1H, *J* = 13.0 Hz, **4u**); ^{13}C NMR (125.8 MHz, $CDCl_3$, **4u** and **7u** 5:1): 14.4, 20.3 (**7u**), 20.5 (**4u**), 37.8 (**7u**), 38.3 (**7u**), 59.8 (**7u**), 59.9 (**4u**), 60.4 (**7u**), 60.6 (**4u**), 99.8 (**4u**), 101.2 (**7u**), 111.8 (**4u**), 113.1 (**7u**), 114.6 (**4u**), 121.4 (**7u**), 122.8 (**4u**), 128.5 (**7u**), 128.7 (**4u**), 130.3 (**7u**), 130.5 (**4u**), 131.9, 134.0, 134.6, 135.5, 140.9, 142.1 (**4u**), 146.2 (**4u**), 168.3 (**4u**), 168.5 (**4u**), 169.2 (**7u**), 172.3 (**7u**); HRMS calcd. for **4u** $C_{17}H_{21}ClNO_4$ $[M+H]^+$: 338.1159, found: 338.1149; HRMS calcd. for **7u** $C_{29}H_{34}Cl_2N_2NaO_6$ $[M+H]^+$: 599.1692, found: 599.1678.

3u: pale yellow solid, mp 48-50 °C; IR ν 3275, 3225, 1668, 1623 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 1.31 (t, 3H, *J* = 7.2 Hz), 2.27 (s, 3H), 4.22 (q, 2H, *J* = 7.2 Hz), 4.91 (d, 1H, *J* = 8.4 Hz), 6.94-7.04 (m, 2H), 7.17 (s, 1H), 7.21 (dd, 1H, *J* = 8.4 Hz, *J* = 12.4 Hz), 10.25 (d, 1H, *J* = 12.4 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 14.3, 20.4, 59.4, 89.1, 113.3, 121.5, 128.4, 130.2, 132.4, 135.1, 141.6, 170.0; HRMS calcd. for $C_{12}H_{15}ClNO_2$ $[M+H]^+$: 240.0791, found: 240.0786.

5u and **5'u:** yellow solid; IR ν 1731, 1702, 1629, 1597 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$, mixture of 1,4- and 1,2-isomers 2.5:1): 1.07 (t, 3H, *J* = 7.0 Hz, 1,2-isomer), 1.20 (t, 3H, *J* = 7.2 Hz, 1,4-isomer), 1.27 (t, 3H, *J* = 7.0 Hz, 1,4-isomer), 1.28 (t, 3H, *J* = 7.2 Hz, 1,2-isomer), 1.31 (t, 3H, *J* = 7.2 Hz, 1,2-isomer), 2.34 (s, 3H, 1,2-isomer), 2.35 (s, 3H, 1,4-isomer), 2.35-2.39 (dd, 1H, *J* = 4.5 Hz, *J* = 14.5 Hz, 1,2-isomer), 2.58 (d, 2H, *J* = 5.0 Hz, 1,4-isomer), 2.68-2.72 (dd, 1H, *J* = 7.0 Hz, *J* = 14.5 Hz, 1,2-isomer), 4.06 (q, 2H, *J* = 7.2 Hz, 1,4-isomer), 4.19 (q, 4H, *J* = 7.0 Hz, 1,4-isomer), 4.26 (t, 1H, *J* = 5.0 Hz, 1,4-isomer), 5.47 (ddd, 1H, *J* = 1.0 Hz, *J* = 4.5 Hz, *J* = 7.0 Hz, 1,2-isomer), 7.11 (d, 1H, *J* = 8.0 Hz, 1,4-isomer), 7.12 (d, 1H, *J* = 8.0 Hz, 1,2-isomer), 7.18 (d, 1H, *J* = 8.0 Hz, 1,4-isomer), 7.24 (s, 2H, 1,4-isomer), 7.28 (s, 1H, 1,2- and 1,4-isomers), 7.31 (d, 1H, *J* = 8.0 Hz, 1,2-isomer), 7.56 (t, 1H, *J* = 1.0 Hz, 1,2-isomer), 7.71 (d, 1H, *J* = 1.0 Hz, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$, mixture of 1,4- and 1,2-isomers 2.5:1): 14.5, 14.9, 15.0, 15.2, 21.6, 30.1 (1,4-isomer), 39.1 (1,2-isomer), 41.4 (1,4-isomer), 57.0 (1,2-isomer), 60.7, 60.8, 61.0, 61.2, 61.4, 102.4, 107.9, 112.9, 128.0, 129.5, 129.7, 130.5, 130.9, 131.9, 133.4, 138.7, 139.8, 140.0, 140.4, 140.6, 149.4, 165.9, 166.2, 167.4, 170.8, 172.3; HRMS calcd. for $C_{22}H_{27}ClNO_6$ $[M+H]^+$: 436.1527, found: 436.1517.

(*2E,4Z*)-diethyl 4-(pyrrolidin-1-ylmethylene)pent-2-enedioate (4v)

Method A: 139.0 mg (70%) from **1v** (53.0 mg, 0.75 mmol) and **2a** (220.7 mg, 2.25 mmol) in EtOH (2.0 mL) during 30 h, along with **3v** (18.0 mg, 14%) and **6a** (27.0 mg, 12%).

Due to overlapping of C(3)*H* and C(5)*H* signals, a precise determination of stereochemistry around the C(4)C(5) double bond was not possible.

4v: pale yellow solid, mp 52-53 °C; IR ν 2984, 1692, 1580, 1416, 1283 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 1.26 (t, 3H, *J* = 7.2 Hz), 1.30 (t, 3H, *J* = 7.2 Hz), 1.95 (broad m, 4H), 3.62-3.64 (broad m, 4H), 4.16 (q, 2H, *J* = 7.2 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 6.26 (d, 1H, *J* = 15.3 Hz), 7.82 (s, 1H), 7.83 (d, 1H, *J* = 15.3 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.4, 14.5, 25.2 53.2, 59.6, 59.7, 96.4, 112.1, 138.1, 151.2, 168.4, 169.4.

3v: *E* isomer; pale yellow solid, mp 39-40 °C (previously isolated as an oil);[39] IR ν 2975, 2867, 1686, 1613, 1149 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 1.26 (t, 3H, *J* = 7.2 Hz), 1.90-1.97 (m, 4H), 3.27 (broad s, 4H),

4.13 (q, 2H, *J* = 7.2 Hz), 4.47 (d, 1H, *J* = 12.8 Hz), 7.65 (d, 1H, *J* = 12.8 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 14.4, 25.2, 58.7, 84.4, 148.6, 169.6.

(*2E,4Z*)-di-*n*-butyl 4-((phenetylamino)methylene)pent-2-enedioate (4i(b))

Method A: 20.4 mg (25%), obtained in a mixture with **5i(b)**, from **1i** (26.0 mg, 0.21 mmol) and **2b**, 84.8 mg, 0.67 mmol) in EtOH (1.5 mL) during 17 h; **5i(b)** (30.9 mg, 29%).

Method C: 72.6 mg (79%) from **1i** (30.0 mg, 0.25 mmol) and **2b (**63.1 mg, 0.50 mmol) during 1.5 h.

4i(b): pale orange solid, mp 72-73 °C; IR ν 3287, 1699, 1663, 1598 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 0.94 (t, 3H, *J* = 7.0 Hz), 0.95 (t, 3H, *J* = 7.5 Hz), 1.36-1.45 (m, 4H), 1.60-1.71 (m, 4H), 2.87 (t, 2H, *J* = 7.0 Hz), 3.52 (q, 2H, *J* = 7.0 Hz), 4.11 (t, 2H, *J* = 6.7 Hz), 4.17 (t, 2H, *J* = 6.7 Hz), 5.95 (d, 1H, *J* = 15.5 Hz), 7.06 *J* = 13.5 Hz), 7.15-7.17 (m, 2H), 7.23-7.26 (m, 1H), 7.29-7.33 (m, 2H), 7.32 (d, 1H, *J* = 15.5 Hz), 8.91 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 13.7, 13.7, 19.2, 19.3, 30.8, 30.9, 37.5, 50.9, 63.5, 63.7, 94.8, 107.9, 126.9, 128.7, 128.8, 137.5, 143.1, 156.8, 168.9, 169.1; HRMS calcd. for $C_{22}H_{32}NO_4$ [M+H] $^+$: 374.2331, found: 374.2333.

5i(b): yellow oil; IR ν 1732, 1702, 1582 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 0.91 (t, 3H, *J* = 7.5 Hz), 0.95 (t, 6H, *J* = 7.5 Hz), 1.31-1.43 (m, 6H), 1.56 (quint, 2H, *J* = 7.0 Hz), 1.63 (quint, 4H, *J* = 7.0 Hz), 2.44 (d, 2H, *J* = 5.0 Hz), 2.90 (t, 2H, *J* = 7.5 Hz), 3.53 (t, 2H, *J* = 7.5 Hz), 3.96 (t, 2H, *J* = 7.0 Hz), 4.12 (t, 2H, *J* = 7.0 Hz), 4.13 (t, 2H, *J* = 7.0 Hz), 4.17 (t, 1H, *J* = 5.0 Hz), 7.04 (s, 2H), 7.17 (d, 2H, *J* = 7.0 Hz), 7.24 (t, 1H, *J* = 7.5 Hz), 7.31 (t, 2H, *J* = 7.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 13.8, 14.1 19.1, 19.2, 29.5, 29.7, 30.8, 36.8, 40.8, 56.3, 63.0, 106.1, 126.9, 128.8, 137.1, 139.1, 166.9, 171.7; HRMS calcd. for $C_{29}H_{42}NO_6$ [M–H] $^+$: 498.2850, found: 498.2836.

(*2E,4Z*)-di-*n*-butyl 4-((phenylamino)methylene)pent-2-enedioate (4k(b))

Method A: Only **5**/**5′k(b)** (20.6 mg, 15%) and **9a** (21.4 mg, 21%) were obtained from **1k** (28.0 mg, 0.30 mmol) and **2b** (151.2 mg, 1.20 mmol) in EtOH (0.8 mL) during 18 h.

Method C: 60.0 mg (54%) from **1k** (30.0 mg, 0.32 mmol) and **2b** (81.3 mg, 0.64 mmol) during 1 h, along with **5**/**5′k(b)** (24.3 mg, 16%).

4k(b): yellow oil; IR ν 3286, 1704, 1664, 1628, 1596 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 0.96 (t, 3H, *J* = 7.5 Hz), 0.98 (t, 3H, *J* = 7.5 Hz), 1.39-1.51 (m, 4H), 1.67 (quint, 2H, *J* = 7.0 Hz), 1.75 (quint, 2H, *J* = 7.0 Hz), 4.16 (t, 2H, *J* = 6.7 Hz), 4.27 (t, 2H, *J* = 6.7 Hz), 6.17 (d, 1H, *J* = 15.5 Hz), 7.07 (d, 2H, *J* = 7.5 Hz), 7.12 (t, 1H, *J* = 7.5 Hz), 7.36 (t, 2H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 15.5 Hz), 7.76 (d, 1H, *J* = 13.0 Hz), 10.76 (d, 1H, *J* = 13.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 13.7, 13.8, 19.2, 19.3, 30.7, 30.9, 63.8, 64.3, 98.6, 111.0, 116.6, 124.4, 129.9, 139.4, 142.2, 147.6, 168.5, 169.0; HRMS calcd. for $C_{20}H_{28}NO_4$ [M+H] $^+$: 346.2018, found: 346.2022.

5k(b) and **5'k(b):** yellow oil; IR (1,4- and 1,2-isomer 1:0.25) ν 1730, 1707, 1626, 1598 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$, 1,4- and 1,2-isomer 1:0.25): 0.85 (t, 3H, *J* = 7.5 Hz, 1,4-isomer), 0.95 (t, 6H, *J* = 7.5 Hz, 1,4-isomer), 1.30 (sext, 2H, *J* = 7.5 Hz, 1,4-isomer), 1.41 (sext, 4H, *J* = 7.5 Hz, 1,4-isomer), 1.52 (quint, 2H, *J* = 7.5 Hz, 1,4-isomer), 1.66 (quint, 4H, *J* = 7.5 Hz, 1,4-isomer), 2.50-2.54 (dd, 1H, *J* = 6.5 Hz, *J* = 13.5 Hz, 1,2-isomer), 2.60 (d, 2H, *J* = 4.5 Hz, 1,4-isomer), 2.64-2.68 (dd, 1H, *J* = 6.2 Hz, *J* = 13.5 Hz, 1,2-isomer), 3.96 (t, 2H, *J* = 6.7 Hz, 1,4-isomer), 4.16-4.21 (m, 4H, 1,4-isomer), 4.25 (t, 1H, *J* = 4.5 Hz, 1,4-isomer), 5.67 (dt, *J* = 1.0 Hz, *J* = 6.5 Hz, 1,2-isomer), 7.21 (d, 2H, *J* = 7.5 Hz, 1,4-isomer), 7.27 (t, 1H, *J* = 7.5 Hz, 1,4-isomer), 7.42 (t, 2H, *J* = 7.5 Hz, 1,4-isomer), 7.57 (s, 2H, 1,4-isomer), 7.71 (s, 1H, 1,2-isomer), 7.85 (s, 1H, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$, only signals of 1,4-isomer are visible): 13.6, 13.8, 19.1, 19.2, 29.8, 30.6, 30.8, 40.4, 64.0, 64.2, 108.3, 120.7, 126.3, 129.8, 137.6, 143.1, 166.8, 171.7; HRMS calcd. for $C_{27}H_{38}NO_6$ [M+H] $^+$: 470.2537, found: 470.2550.

9a: yellow oil; IR ν 3062, 2960, 2929, 2872, 1732, 1462 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 0.90 (t, 3H, *J* = 7.5 Hz), 1.00 (t, 3H, *J* = 7.5 Hz), 1.34 (sext, 2H, *J* = 7.5 Hz), 1.50 (sext, 2H, *J* = 7.5 Hz), 1.60 (quint, 2H, *J* = 7.5 Hz), 1.79 (quint, 2H, *J* = 7.5 Hz), 4.12 (t, 2H, *J* = 6.5 Hz), 4.36 (t, 2H, *J* = 6.5 Hz), 4.46 (s, 2H), 7.60 (t, 1H, *J* = 7.5 Hz), 7.81 (t, 1H, *J* = 7.5 Hz), 7.92 (d, 1H, *J* = 8.5 Hz), 8.10 (d, 1H, *J* = 8.5 Hz), 8.85 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 13.6, 13.7, 19.0, 19.3, 30.6, 30.7, 44.6, 64.8, 65.5, 121.1, 123.7, 126.3, 127.2, 128.6, 128.9, 131.9, 140.4, 154.6, 166.0, 170.9; HRMS calcd. for $C_{20}H_{26}NO_4$ [M+H]$^+$: 344.1862, found: 344.1846.

(*2E,4Z*)-diallyl 4-((phenetylamino)methylene)pent-2-enedioate (4i(c))

Method A: 20.1 mg (25%) from **1i** (29.0 mg, 0.24 mmol) and **2c** (104.7 mg, 0.95 mmol) in EtOH (1.5 mL) during 8 h, along with **5i(c)** (27.9 mg, 26%).

Method C: 38.2 mg (58%) from **1i** (23.4 mg, 0.19 mmol) and **2c** (43.0 mg, 0.39 mmol) during 1 h, along with **5i(c)** (3.7 mg, 4%).

4i(c): pale yellow oil; IR ν 3288, 1700, 1665, 1596 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 2.81 (t, 2H, *J* = 7.0 Hz), 3.46 (q, 2H, *J* = 7.0 Hz), 4.56 (dt, 2H, *J* = 1.5 Hz, *J* = 5.5 Hz), 4.62 (dt, 2H, *J* = 1.5 Hz, *J* = 5.5 Hz), 5.12-5.18 (m, 2H), 5.22-5.28 (m, 2H), 5.85-5.94 (m, 2H), 5.92 (d, 1H, *J* = 15.5 Hz), 7.00 (d, 1H, *J* = 13.5 Hz), 7.09 (d, 2H, *J* = 8.0 Hz), 7.18 (t, 1H, *J* = 7.5 Hz), 7.25 (t, 2H, *J* = 8.0 Hz), 7.29 (d, 1H, *J* = 15.5 Hz), 8.85 (t, 1H, *J* = 6.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 37.7, 51.2, 64.7, 64.8, 94.8, 107.8, 117.7, 118.1, 127.2, 129.0, 129.1, 132.9, 133.3, 137.6, 143.8, 157.4, 168.6, 168.9; HRMS calcd. for $C_{20}H_{24}NO_4$ [M+H] $^+$: 342.1705, found: 342.1704.

5i(c): pale yellow oil; IR ν 1732, 1702, 1580 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 2.49 (d, 2H, *J* = 5.0 Hz), 2.91 (t, 2H, *J* = 7.2 Hz), 3.54 (t, 2H, *J* = 7.5 Hz), 4.23 (t, 2H, *J* = 5.0 Hz), 4.48 (dt, 2H, *J* = 1.5 Hz, *J* = 5.5 Hz), 4.63 (d, 4H, *J* = 5.5 Hz), 5.17-5.33 (m, 6H), 5.84-5.98 (m, 3H), 7.08 (s, 2H), 7.17 (d, 2H, *J* = 8.0 Hz), 7.24 (t, 1H, *J* = 7.5 Hz), 7.31 (t, 2H, *J* = 7.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 29.4, 36.8, 40.7, 56.4, 64.8, 105.7, 117.6, 117.7, 127.0, 128.8, 128.9, 132.5, 132.6, 137.0, 139.5, 166.3, 171.2; HRMS calcd. for $C_{26}H_{30}NO_6$ [M–H] $^+$: 450.1911, found: 450.1896.

(*2E,4Z*)-diallyl 4-((phenylamino)methylene)pent-2-enedioate (4k(c))

Method A: The reaction of **1k**, 32.0 mg, 0.34 mmol) and **2c** (132.4 mg, 1.20 mmol) in EtOH (0.8 mL) during 25 h gave a complex mixture from which **4k(c)** and **5/5′k(c)**, detected by NMR, could not be isolated in pure form. Their yields do not exceed 30%.

Method C: 50.5 mg (47%) from **1k** (32.0 mg, 0.34 mmol) and **2c** (74.9 mg, 0.68 mmol) during 1.5 h, along with **5/5′k(c)** (32.0 mg, 22%).

4k(c): pale yellow oil; IR ν 3279, 1704, 1666, 1595 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 4.67 (dt, 2H, *J* = 1.5 Hz, *J* = 5.5 Hz), 4.78 (dt, 2H, *J* = 1.5 Hz, *J* = 5.5 Hz), 5.23-5.40 (m, 4H), 5.95-6.07 (m, 2H), 6.22 (d, 1H, *J* = 15.7 Hz), 7.08 (d, 2H, *J* = 8.0 Hz), 7.13 (t, 1H, *J* = 7.0 Hz), 7.36 (t, 2H, *J* = 8.0 Hz), 7.53 (d, 1H, *J* = 15.7 Hz), 7.78 (d, 1H, *J* = 13.0 Hz), 10.74 (d, 1H, *J* = 13.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 64.7, 65.0, 98.3, 110.6, 116.7, 117.8, 118.3, 124.6, 129.9, 132.2, 132.8, 139.2, 142.6, 148.1, 168.0, 168.5; HRMS calcd. for $C_{18}H_{20}NO_4$ [M+H] $^+$: 314.1392, found: 314.1376.

5k(c) and **5'k(c):** yellow oil; IR (1,4- and 1,2-isomer 0.5:1) ν 1734, 1701, 1628, 1597 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$, 1,4- and 1,2-isomer 0.5:1): 2.56-2.60 (dd, 1H, *J* = 6.5 Hz, *J* = 13.5 Hz, 1,2-isomer), 2.66 (d, 2H, *J* = 5.0 Hz, 1,4-isomer), 2.67-2.71 (dd, 1H, *J* = 6.0 Hz, *J* = 13.5 Hz, 1,2-isomer), 4.30 (t, 1H, *J* = 5.0 Hz, 1,4-isomer), 4.31-4.35 (m, 1H, 1,2-isomer), 4.39-4.43 (m, 1H, 1,2-isomer), 4.48 (dt, 2H, *J* = 1.5 Hz, *J* = 5.5 Hz, 1,4-isomer), 4.63-4.69 (m, 4H, 1,2-isomer), 4.71 (dt, 2H, *J* = 1.5 Hz, *J* = 5.5 Hz, 1,4-isomer), 5.11-5.37 (m, 12H, 1,2- and 1,4-isomer), 5.70 (dt, 1H, *J* = 1.0 Hz, *J* = 6.5 Hz, 1,2-isomer), 5.75-5.85 (m, 3H, 1,4-isomer), 5.93-6.00 (m, 3H, 1,2-isomer), 7.22 (d, 2H, *J* = 7.5 Hz, 1,4-isomer), 7.24-7.29 (m, 3H, 1,4-isomer), 7.33 (d, 2H, *J* = 8.0 Hz, 1,2-isomer), 7.42 (t, 3H, *J* = 7.7 Hz, 1,2-isomer), 7.60 (s, 2H, 1,4-isomer), 7.78 (s, 1H, 1,2-isomer), 7.89 (s, 1H, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$): 29.6 (1.4-isomer), 38.3 (1,2-isomer), 40.3 (1.4-isomer), 55.2 (1.2-isomer), 64.9, 65.0, 65.2, 65.7, 103.9, 107.9, 112.1, 115.4, 117.9, 118.0, 118.0, 118.0 118.6, 120.9,

121.2, 126.4, 126.5, 129.6, 129.8, 131.8, 132.3, 132.4, 132.5, 132.6, 132.7, 138.1, 143.0, 143.6, 144.9, 164.7, 165.1, 166.2, 169.5, 171.2; HRMS calcd. for $C_{24}H_{26}NO_6$ [M−H]$^+$: 422.1598, found: 422.1594.

(*2E,4Z*)-dibenzyl 4-((phenetylamino)methylene)pent-2-enedioate (4i(d))

Method A: 15.5 mg (18%), obtained in a mixture with **5i(d)**, from **1i** (24.0 mg, 0.20 mmol) and **2d** (113.6 mg, 0.71 mmol) in EtOH (1.2 mL) during 22 h; **5i(d)** (50.1 mg, 42%).

Method A′: 10.3 mg (12%), isolated in a mixture with **5i(d)**, from **1i** (24.0 mg, 0.20 mmol) and **2d (**64.1 mg, 0.40 mmol) in EtOH (1.2 mL) during 17 h, along with **3i(d)** (14.4 mg, 26%) and **5i(d)** (26.5 mg, 22%), the latter isolated in a mixture with **4i(d)**.

Method C: 85.0 mg (76%) from **1i** (30.9 mg, 0.25 mmol) and **2d** (81.7 mg, 0.50 mmol) during 2 h.

4i(d): pale yellow solid, mp 53-55 °C; IR ν 3288, 1700, 1664, 1596 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 2.88 (t, 2H, J = 7.0 Hz), 3.53 (q, 2H, J = 7.0 Hz), 5.20 (s, 2H), 5.27 (s, 2H), 6.07 (d, 1H, J = 15.5 Hz), 7.10 (d, 1H, J = 13.5 Hz), 7.17 (d, 2H, J = 7.5 Hz), 7.27 (t, 1H, J = 7.2 Hz), 7.32-7.41 (m, 12H), 7.45 (d, 1H, J = 15.5 Hz), 8.95 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 37.4, 50.9, 65.4, 94.5, 107.5, 126.9, 127.7, 127.8, 127.9, 128.4, 128.5, 128.7, 128.8, 136.4, 136.8, 137.4, 143.5, 157.1, 168.5, 168.6; HRMS calcd. for $C_{28}H_{28}NO_4$ [M+H]$^+$: 442.2018, found: 442.2000.

3i(d): *Z* and *E* isomers, 1:0.4, pale yellow oil; IR ν 3336, 1666, 1614 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 2.83 (t, 2H, J = 7.0 Hz, *Z* isomer), 2.87 (t, 2H, J = 7.0 Hz, *E* isomer), 3.32 (q, 2H, J = 7.0 Hz, *E* isomer), 3.40 (q, 2H, J = 7.0 Hz), 4.52 (d, 1H, J = 8.0 Hz, *Z* isomer), 4.86 (d, 1H, J = 13.5 Hz, *E* isomer), 5.12 (s, 2H, *Z* isomer), 5.15 (s, 2H, *E* isomer), 6.55 (dd, 1H, J = 8.0 Hz, J = 13.5 Hz, *Z* isomer), 7.18-7.40 (m, 20H, *Z* and *E* isomers), 7.51 (dd, 1H, J = 8.0 Hz, J = 13.5 Hz, *E* isomer), 7.90 (broad signal, 1H, *Z* isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$): 38.0, 50.2, 64.5 (*Z* isomer), 64.9 (*E* isomer), 75.0 (*E* isomer), 81.7 (*Z* isomer), 85.8 (*E* isomer), 126.6 (*Z* isomer), 126.7 (*E* isomer), 127.0, 127.7, 127.8, 128.4, 128.5, 128.6, 128.6, 128.7, 128.7, 128.8, 137.2, 137.3, 138.1, 138.3, 152.4, 169.3, 170.4; HRMS calcd. for $C_{18}H_{20}NO_2$ [M+H]$^+$: 282.1494, found: 282.1482.

5i(d): yellow amorphous substance; IR ν 1730, 1701, 1582 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 2.56 (d, 2H, J = 5.0 Hz), 2.80 (t, 2H, J = 7.5 Hz), 3.39 (t, 2H, J = 7.5 Hz), 4.29 (t, 1H, J = 5.0 Hz), 4.98 (s, 2H), 5.14 (d, 2H, J = 12.5 Hz), 5.19 (d, 2H, J = 12.5 Hz), 7.01 (s, 2H), 7.11 (d, 2H, J = 7.0 Hz), 7.20 (t, 1H, J = 7.5 Hz), 7.26-7.37 (m, 17H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 29.5, 36.6, 40.7, 56.1, 65.4, 65.0, 106.5, 126.8, 127.8, 127.9, 128.0, 128.1, 128.3, 128.5, 128.8, 136.2, 136.4, 137.0, 139.6, 166.5, 171.4; HRMS calcd. for $C_{38}H_{35}NO_6$ [M−H]$^+$: 600.2381, found: 600.2369.

(*2E,4Z*)-dibenzyl 4-((phenylamino)methylene)pent-2-enedioate (4k(d))

Method A: The reaction of **1k** (30.0 mg, 0.32 mmol) and **2d (**205.0 mg, 1.28 mmol) in EtOH (0.8 mL) during 57 h gave a complex mixture from which **4k(d)** and **5/5′k(d)**, detected by NMR, could not be isolated in pure form. Their yields do not exceed 15%.

Method A′: The reaction of **1k** (25.0 mg, 0.27 mmol) and **2d** (86.0 mg, 0.54 mmol) in EtOH (0.7 mL) during 48 h gave a complex mixtrure from which only **3k(d)** (15.0 mg, 22%) could be isolated in pure form. The yields of **4k(d)** and **5k(d)**, which were detected by NMR spectroscopy, do not exceed 30% and 10%, respectively.

Method C: 90.0 mg (63%) from **1k** (32.0 mg, 0.34 mmol) and **2d** (110.0 mg, 0.68 mmol) during 3 h, along with **3k(d)** (3.0 mg, 3%) and **5/5'k(d)** (40.0 mg, 20%).

4k(d): yellow solid, mp 77-79 °C; IR ν 3283, 1705, 1665, 1628, 1595 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 5.11 (s, 2H), 5.23 (s, 2H), 6.18 (d, 1H, J = 15.7 Hz), 6.95 (d, 2H, J = 7.5 Hz), 7.02 (t, 1H, J = 7.5 Hz), 7.22-7.34 (m, 12H), 7.48 (d, 1H, J = 15.7 Hz), 7.68 (d, 1H, J = 13.5 Hz), 10.62 (d, 1H, J = 13.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 65.7, 66.0, 98.2, 110.6, 116.7, 124.5, 127.8, 127.9, 128.0, 128.1, 128.4, 128.6, 129.8, 136.0, 136.6, 139.2, 142.6, 147.9, 168.1, 168.4; HRMS calcd. for $C_{26}H_{24}NO_4$ [M+H]$^+$: 414.1705, found: 414.1702.

3k(d): *Z* isomer, white solid, mp 157-159 °C; IR ν 3281, 1668, 1621, 1582 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 4.91 (d, 1H, J = 8.0 Hz), 5.19 (s, 2H), 6.97 (d, 2H, J = 8.0 Hz), 7.01 (t, 1H, J = 7.2 Hz), 7.28-7.41 (m, 8H), 9.88 (d, 1H, J = 12 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 65.2, 87.0, 115.4, 122.7, 127.9, 128.0, 128.5, 129.6, 136.7, 140.6, 143.4, 170.0; HRMS calcd. for $C_{16}H_{16}NO_2$ [M+H]$^+$: 254.1181, found: 254.1169.

5k(d) and **5'k(d):** yellow oil; IR (1,4- and 1,2-isomer 0.5:1) ν 1731, 1700, 1626, 1595 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$, 1,4- and 1,2-isomer 0.5:1): 2.60-2.64 (dd, 1H, J = 6.5 Hz, J = 13.5 Hz, 1,2-isomer), 2.71 (d, 2H, J = 4.5 Hz, 1,4-isomer), 2.70-2.74 (dd, 1H, J = 6.0 Hz, J = 13.5 Hz, 1,2-isomer), 4.35 (t, 1H, J = 4.5 Hz, 1,4-isomer), 4.80 (d, 1H, J = 12.0 Hz, 1,2-isomer), 4.92 (d, 1H, J = 12.0 Hz, 1,2-isomer), 4.99 (s, 2H, 1,4-isomer), 5.15 (d, 1H, J = 12.5 Hz, 1,2-isomer), 5.19 (d, 1H, J = 12.5 Hz, 1,2-isomer), 5.24 (d, 1H, J = 12.5 Hz, 1,2-isomer), 5.26 (d, 1H, J = 12.5 Hz, 1,2-isomer), 5.26 (s, 2H, 1,4-isomer), 5.74 (dt, 1H, J = 1.0 Hz, J = 6.0 Hz, 1,2-isomer), 7.06-7.40 (m, 40H, 1,2- and 1,4-isomers), 7.50 (s, 2H, 1,4-isomer), 7.82 (s, 1H, 1,2-isomer), 7.88 (s, 1H, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$): 29.8 (1,4-isomer), 38.4 (1,2-isomer), 40.2 (1,4-isomer), 55.3 (1,2-isomer), 65.9, 66.1, 66.3, 66.8, 103.8, 107.6, 112.2, 120.1, 121.2, 126.4, 126.5, 127.9, 128.1, 128.2, 128.2, 128.3, 128.3, 128.5, 128.5, 128.5, 129.7, 129.8, 132.8, 135.4, 136.1, 136.2, 136.3, 136.5, 138.2, 142.9, 143.5, 145.1, 164.9, 165.2, 166.4, 169.7, 171.4; HRMS calcd. for $C_{36}H_{32}NO_6$ [M−H]$^+$: 572.2068, found: 572.2076.

(*2E,4Z*)-dicyclohexyl 4-((phenethylamino)methylene)pent-2-enedioate (4i(e))

Method A: 27 mg (28%), obtained in a mixture with **5i(e)**, from **1i** (27.0 mg, 0.22 mmol) and **2e** (101.7 mg, 0.67 mmol) in EtOH (1.4 mL) during 17 h; **5i(e)** (27.0 mg, 21%).

Method C: 60.5 mg (69%) from **1i** (25.0 mg, 0.21 mmol) and **2e** (64.6 mg, 0.42 mmol) during 2 h.

4i(e): pale yellow oil; IR ν 3287, 1692, 1659, 1597 cm^{-1}; ^{1}H NMR (500.3 MHz, $CDCl_3$): 1.25-1.57 (m, 12H), 1.74-1.78 (m, 4H), 1.86-1.91 (m, 4H), 2.88 (t, 2H, J = 7.0 Hz), 3.53 (q, 2H, J = 7.0 Hz), 4.79-4.90 (m, 2H), 5.96 (d, 1H, J = 15.7 Hz), 7.08 (d, 1H, J = 13.5 Hz), 7.17 (d, 2H, J = 7.0 Hz), 7.25 (t, 1H, J = 7.5 Hz), 7.33 (t, 2H, J = 7.5 Hz), 7.35 (d, 1H, J = 15.7 Hz), 8.87-8.92 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 23.8, 23.8, 25.4, 25.5, 31.7, 31.8, 37.5, 50.8, 71.5, 72.2, 95.1, 108.4, 126.9, 128.7, 128.8, 137.5, 143.0, 156.5, 168.3, 168.5; HRMS calcd. for $C_{26}H_{36}NO_4$ [M+H]$^+$: 426.2644, found: 426.2637.

5i(e): ^{1}H NMR (500.3 MHz, $CDCl_3$, from the mixture with **4i(e)**; only the most diagnostic signals for the structure of **5i(e)** are listed): 2.47 (d, 2H, J = 4.5 Hz), 4.17 (t, 1H, J = 4.5 Hz), 7.02 (s, 2H); HRMS calcd. for $C_{35}H_{48}NO_6$ [M−H]$^+$: 576.3320, found: 576.3337.

(*2E,4Z*)-dicyclohexyl 4-((phenylamino)methylene)pent-2-enedioate (4k(e))

Method A: Only **5k(e)** (20.0 mg; 13%) and **9b** (26.8 mg; 23%) were isolated from the reaction of **1k** (27.0 mg, 0.29 mmol) and **2e** (176.5 mg, 1.16 mmol) in EtOH (0.8 mL) during 6.5 h.

Method C: 13.6 mg (16%), obtained in a mixture with **5k(e)**, from **1k** (20.0 mg, 0.21 mmol) and **2e** (64.0 mg, 0.42 mmol) during 3 h, along with pure **5k(e)** (46.4 mg, 39%; given quantity and yield are based on pure compound and the mixture with **4k(e)**).

Method C′: 36.7 mg (34%), obtained in a mixture with **5k(e)**, from **1k** (25.0 mg, 0.27 mmol) and **2e** (81.7 mg, 0.54 mmol) during 2.5 h at 65 °C, along with pure **5k(e)** (27.8 mg, 19%; given quantity and yield are estimated on the basis of pure compound and the mixture).

Method C″: 45.0 mg (53%) from **1k** (20.0 mg, 0.21 mmol) and **2e** (64.0 mg, 0.42 mmol) during 9.5 h at rt.

4k(e): yellow oil; IR ν 3281, 1695, 1660, 1596 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.38-1.47 (m, 8H), 1.57-1.62 (m, 4H), 1.74-1.81 (m, 4H), 1.89-1.97 (m, 4H), 4.82-4.88 (m, 1H), 4.93-4.98 (m, 1H), 6.17 (d, 1H, *J* = 16.0 Hz), 7.07 (d, 2H, *J* = 7.5 Hz), 7.11 (t, 1H, *J* = 7.5 Hz), 7.35 (t, 2H, *J* = 7.5 Hz), 7.49 (d, 1H, *J* = 16.0 Hz), 7.76 (d, 1H, *J* = 13.0 Hz), 10.77 (d, 1H, *J* = 13.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 23.8, 23.9, 25.4, 25.5, 31.7, 31.8, 71.9, 73.0, 98.9, 111.5, 116.5, 124.2, 129.8, 139.5, 142.0, 147.2, 167.9, 168.4; HRMS calcd. for $C_{24}H_{32}NO_4$ $[M+H]^+$: 398.2331, found: 398.2346.

5k(e): yellow oil; IR ν 1726, 1704, 1625, 1598 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.28-1.88 (m, 30H), 2.62 (d, 2H, *J* = 4.5 Hz), 4.25 (t, 1H, *J* = 4.5 Hz), 4.63-4.67 (m, 1H), 4.87-4.92 (m, 2H), 7.20 (d, 2H, *J* = 7.5 Hz), 7.25 (t, 1H, *J* = 7.5 Hz), 7.41 (t, 2H, *J* = 8.0 Hz), 7.55 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 23.6, 23.7, 25.3, 25.4, 30.0, 31.5, 31.6, 40.3, 72.1, 72.3, 108.6, 120.6, 126.1, 129.8, 137.4, 143.1, 166.2, 171.2; HRMS calcd. for $C_{33}H_{44}NO_6$ $[M-H]^+$: 548.3007, found: 548.2997.

9b: yellow oil; IR ν 3060, 2936, 2858, 1725, 1451 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 1.28-1.50 (m, 8H), 1.58-1.66 (m, 6H), 1.81-1.83 (m, 4H), 1.99-2.02 (m, 2H), 4.46 (s, 2H), 4.79-4.84 (m, 1H), 5.02-5.07 (m, 1H), 7.60 (t, 1H, *J* = 7.5 Hz), 7.81 (t, 1H, *J* = 7.5 Hz), 7.92 (d, 1H, *J* = 8.0 Hz), 8.10 (broad d, 1H), 8.84 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 23.6, 23.9, 25.4, 25.4, 31.5, 31.6, 44.8, 73.2, 74.1, 124.4, 126.4, 127.2, 128.6, 131.8, 140.4, 154.7, 165.3, 170.1; HRMS calcd. for $C_{24}H_{30}NO_4$ $[M+H]^+$: 396.2175, found: 396.2160.

(*2E,4Z*)-diphenyl 4-((phenethylamino)methylene)pent-2-enedioate (4i(f))

Method A: 42.5 mg (45%) from **1i** (28.0 mg, 0.23 mmol) and **2f (**107.6 mg, 0.74 mmol) in EtOH (1.5 mL) during 4 h.

Method C: 50.4 mg (53%) from **1i** (28.0 mg, 0.23 mmol) and **2f** (67.9 mg, 0.46 mmol) during 1.5 h.

4i(f): pale yellow oil; IR ν 3292, 1716, 1674, 1593 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 2.88 (t, 2H, *J* = 7.0 Hz), 3.58 (q, 2H, *J* = 7.0 Hz), 6.24 (d, 2H, *J* = 15.7 Hz), 7.11-7.17 (m, 7H), 7.19 (t, 1H, *J* = 7.5 Hz), 7.23-7.26 (m, 2H), 7.32 (t, 2H, *J* = 7.5 Hz), 7.36 (t, 2H, *J* = 7.5 Hz), 7.41 (t, 2H, *J* = 7.5 Hz), 7.62 (d, 1H, *J* = 15.7 Hz), 9.04 (broad m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 37.3, 51.2, 94.0, 107.4, 121.8, 122.0, 125.2, 125.7, 127.1, 128.7, 128.9, 129.2, 129.4, 137.1, 144.6, 150.4, 151.2, 158.4, 167.1, 167.6; HRMS calcd. for $C_{26}H_{24}NO_4$ $[M+H]^+$: 414.1705, found: 414.1692.

(*2E,4Z*)-diphenyl 4-((phenylamino)methylene)pent-2-enedioate (4k(f))

Method A: The reaction of **1k** (29.0 mg, 0.31 mmol) and **2f** (158.3 mg, 1.08 mmol) in EtOH (0.9 mL) during 114 h gave a complex mixture from which only **3k(f)** (10.7 mg, 14%) was isolated, while **4k(d)**, detected by NMR spectroscopy, could not be isolated in pure form.

Method C: 73.2 mg (66%) from **1k** (27.0 mg, 0.29 mmol) and **2f** (84.7 mg, 0.58 mmol) during 1 h, along with **5/5′k(f)** (18.0 mg, 12%) and **6b** (7.8 mg, 9%; isolated in a mixture with small amount of **4k(f)**).

4k(f): yellow oil; IR ν 3284, 1721, 1676, 1629, 1583 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 6.51 (d, 1H, *J* = 15.5 Hz), 7.11 (d, 2H, *J* = 7.5 Hz), 7.16-7.24 (m, 6H), 7.31 (t, 1H, *J* = 7.5 Hz), 7.37-7.41 (m, 4H), 7.46 (t, 2H, *J* = 7.5 Hz), 7.81 (d, 1H, *J* = 15.5 Hz), 7.99 (d, 1H, *J* = 13.5 Hz), 10.86 (d, 1H, *J* = 13.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 97.5, 110.3, 116.9, 121.8, 121.9, 125.1, 125.4, 126.1, 129.3, 129.5, 130.0, 138.8, 143.6, 149.6, 150.2, 151.1, 166.7, 167.7; HRMS calcd. for $C_{24}H_{19}NO_4$ $[M+H]^+$: 386.1392, found: 386.1405.

3k(f): *Z* isomer, white solid, mp 138-140 °C; IR ν 3300, 1692, 1620, 1583 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 5.09 (d, 1H, *J* = 8.5 Hz), 6.98 (d, 2H, *J* = 8.5 Hz), 7.04 (t, 1H, *J* = 7.5 Hz), 7.15 (m, 2H), 7.24 (t, 1H, *J* = 7.5 Hz), 7.31 (m, 2H), 7.39-7.45 (m, 3H), 9.96 (d, 1H, *J* = 12.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 86.1, 115.6, 121.9, 123.1, 125.5, 129.3, 129.7, 140.3, 144.9, 150.8, 168.9; HRMS calcd. for $C_{15}H_{14}NO_2$ $[M+H]^+$: 240.1025, found: 240.1014.

5k(f) and **5'k(f):** yellow amorphous substance; IR ν 1751, 1719, 1626, 1593 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$, 1,2- and 1,4-isomer 0.6:1): 2.94-2.98 (dd, 1H, *J* = 6.5 Hz, *J* = 13.5 Hz, 1,2-isomer), 3.00-3.04 (dd, 1H, *J* = 5.5 Hz, *J* = 13.5 Hz, 1,2-isomer), 3.05 (d, 2H, *J* = 4.5 Hz, 1,4-isomer), 4.64 (t, 1H, *J* = 4.5 Hz, 1,4-isomer), 5.98 (t, 1H, *J* = 6.5 Hz, 1,2-isomer), 6.81-6.98 (m, 4H, 1,2- and 1,4-isomer), 7.06-7.49 (m, 36H, 1,2- and 1,4-isomer), 7.87 (s, 2H, 1,4-isomer), 8.16 (s, 1H, 1,2-isomer), 8.18 (s, 1H, 1,2-isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$, only signals of 1,4-isomer are clearly visible): 30.0, 40.3, 107.4, 121.4, 121.6, 121.8, 125.6, 125.7, 129.3, 129.4, 130.0, 139.5, 142.8, 150.8, 165.1, 170.0; HRMS calcd. for $C_{33}H_{26}NO_6$ $[M-H]^+$: 530.1598, found: 530.1592.

6b: ^1H NMR (500.3 MHz, $CDCl_3$, from the mixture with **4k(f)**):[38] 9.26 (s, 3H), other signals are covered by those of **4k(f)**).

Cross experiments

Synthesis of (*2E,4Z*)-dimethyl 4-((methylamino)methylene)pent-2-enedioate (4′b)

The product **4′b** (55.0 mg, 69%) was obtained as following. To a solution of methylamine in THF (1.2 M, 0.33 mL, 0.4 mmol of **1b**) methyl propiolate (**2g**, 104.0 mg, 1.20 mmol) and EtOH (1 mL) were added and the mixture heated at 100 °C for 9 h. The solvents were removed under reduced pressure and the residue purified by column chromatography. Pale yellow crystals, mp 138-140 °C (lit.[12a] 143 °C); IR ν 3318, 1699, 1662, 1593 cm^{-1}; ^1H NMR (500.3 MHz, $CDCl_3$): 3.10 (d, 3H, *J* = 5.0 Hz), 3.71 (s, 3H), 3.76 (s, 3H), 6.00 (d, 1H, *J* = 15.7 Hz), 7.18 (d, 1H, *J* = 14.0 Hz), 7.37 (d, 1H, *J* = 15.7 Hz), 8.76 (broad s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 35.7, 50.8, 51.0, 94.6, 107.3, 143.3, 158.4, 169.2, 169.6.

Synthesis of (*Z*)- and (*E*)-ethyl 3-(methylamino)acrylate (3b)

To a solution of methylamine in THF (1.2 M, 0.5 mL, 0.6 mmol of **1b**) ethyl propiolate (**2a**) was added (87.3 mg, 0.89 mmol) and the mixture was stirred at rt overnight. The solvent and excess of **2a** were removed under reduced pressure to give **3b** as a pale yellow oil (47.0 mg, 61%). ^1H NMR ^1H NMR (500.3 MHz, $CDCl_3$, *Z* and *E* 1:0.9): *Z* isomer 1.20 (t, 3H, *J* = 7.0 Hz), 2.90 (d, 3H, *J* = 5.0 Hz), 4.04 (q, 2H, *J* = 7.0 Hz), 4.40 (d, 1H, *J* = 8.0 Hz), 6.53 (dd, 1H, *J* = 8.0 Hz, *J* = 13.5 Hz), 7.58 (broad s, 1H), *E* isomer 1.21 (t, 3H, *J* = 7.0 Hz), 2.70 (d, 3H, *J* = 5.0 Hz), 4.07 (q, 2H, *J* = 7.0 Hz), 4.63 (d, 1H, *J* = 13.0 Hz), 4.90 (broad s, 1H), 7.51 (dd, 1H, *J* = 7.5 Hz, *J* = 13.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.4, 14.4, 34.7, 58.4, 58.7, 81.6 (*Z* isomer), 85.0 (*E* isomer), 153.3, 169.6, 170.8.

Synthesis of (*Z*)- and (*E*)-methyl 3-(methylamino)acrylate (3′b)

To a solution of methylamine in THF (1.2 M, 0.5 mL, 0.6 mmol of **1b**) methyl propiolate (**2g**) was added (76.3 mg, 0.90 mmol) and the mixture was stirred at rt overnight. The solvent and excess of **2g** were removed under reduced pressure to give **3′b** as a pale yellow oil (49.2 mg, 71%). ^1H NMR (500.3 MHz, $CDCl_3$, *Z* and *E* 1.5:1): *Z* isomer 2.95 (d, 3H, *J* = 5.0 Hz), 3.63 (s, 3H), 4.46 (d, 1H, *J* = 8.0 Hz), 6.58 (dd, 1H, *J* = 8.0 Hz, *J* = 13.0 Hz), 7.62 (broad s, 1H), *E* isomer 2.75 (d, 3H, *J* = 5.0 Hz), 3.65 (s, 3H), 4.55 (broad s, 1H), 4.70 (d, 1H, *J* = 13.0 Hz), 7.55 (dd, 1H, *J* = 7.5 Hz, *J* = 13.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): 34.8, 50.1 (*Z* isomer), 50.5 (*E* isomer), 81.3 (*Z* isomer), 85.2 (*E* isomer), 153.4, 169.9 (*E* isomer), 171.2 (*Z* isomer).

Cross reaction (1)

Method A

A mixture of **3b** (47.0 mg, 0.36 mmol) and methyl propiolate (**2g**, 90.8 mg, 1.08 mmol) in EtOH (1.5 mL) was heated at 100 °C for 12 h. Solvent was removed under reduced pressure and the residue chromatographed to give 35.0 mg of mixture of four dienes. The NMR spectrum of both the crude reaction mixture and of chromatographed product indicated **4″b** as the main compound.

(*2E,4Z*)-5-ethyl 1-methyl 4-((methylamino)methylene)pent-2-enedioate (4″b)

^{1}H NMR (500.3 MHz, $CDCl_3$): 1.31 (t, 3H, J = 7.0 Hz), 3.07 (d, 3H, J = 5.0 Hz), 3.68 (s, 3H), 4.21 (q, 2H, J = 7.0 Hz), 5.99 (d, 1H, J = 16.0 Hz), 7.16 (d, 1H, J = 13.5 Hz), 7.35 (d, 1H, J = 16.0 Hz), 8.76 (broad s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.4, 35.6, 50.9, 59.7, 94.6, 107.1, 143.5, 158.4, 169.1, 169.2.

Cross reaction (2)
Method A

A mixture of **3′b** (49.2 mg, 0.43 mmol) and ethyl propiolate (**2a**, 126.5 mg, 1.29 mmol) in EtOH (1.5 mL) was heated at 100 °C for 12 h. Solvent was removed under reduced pressure and the residue chromatographed to give 40.0 mg of mixture of four dienes. The NMR spectrum of both the crude reaction mixture and of chromatographed product indicated **4‴b** as the main compound.

(*2E,4Z*)-5-methyl 1-ethyl 4-((methylamino)methylene)pent-2-ene-dioate (4‴b)
^{1}H NMR (500.3 MHz, $CDCl_3$): 1.23 (t, 3H, J = 7.0 Hz), 3.06 (d, 3H, J = 5.0 Hz), 3.72 (s, 3H), 4.13 (q, 2H, J = 7.0 Hz), 5.95 (d, 1H, J = 15.2 Hz), 7.15 (d, 1H, J = 13.5 Hz), 7.32 (d, 1H, J = 15.2 Hz), 8.73 (broad s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): 14.3, 50.7, 59.4, 94.4, 107.6, 143.0, 158.3, 168.7, 169.4.

Acknowledgements

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, project No. 172020. The authors acknowledge the support of the FP7 RegPot project FCUB ERA GA No. 256716, the equipment of which was used for recording HRMS (LTQ Orbitrap XL). The EC does not share responsibility for the content of the article.

Keywords: amines • conjugated dienes • green chemistry • propiolic esters • Michael addition

[1] a) R. Li, S. L. Morris-Natschke, K.-H. Lee, *Nat. Prod. Rep.* **2016**, *33*, 1166-1226; b) S. Carosso, M. J. Miller, *Org. Biomol. Chem.* **2014**, *12*, 7445-7468; (c) W. Erb, J. Zhu, *Nat. Prod. Rep.* 2013, **30**, 161-174; d) E.-i. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738-6764; e) E.-i. Negishi, Z. Huang, G. Wang, S. Mohan, C. Wang, H. Hattori, *Acc. Chem. Res.* **2008**, *41*, 1474-1485.

[2] a) J. M. J. Nolsøe, M. Aursnes, J. E. Tungen, T. V. Hansen, *J. Org. Chem.* **2015**, *80*, 5377-5385; b) C. Challa, J. Vellekkatt, J. Ravindran, R. S. Lankalapalli, *Org. Biomol. Chem.* **2014**, *12*, 8588-8592; c) C. Challa, M. John, R. S. Lankalapalli, *Tetrahedron Lett.* **2013**, *54*, 3810-3812; d) J.-L. Li, T.-Y. Liu, Y.-C. Chen, *Acc. Chem. Res.* **2012**, *45*, 1491-1500; e) K. Kaur, I. N. N. Namboothiri, *Chimia* **2012**, *66*, 913-920; f) J. M. Sorbetti, K. N. Clary, D. A.; Rankic, J. E. Wulff, M. Parvez, T. G. Back, *J. Org. Chem.* **2007**, *72*, 3326-3331; g) J. Adams, A. Hardin, F. Vounatsos, *J. Org. Chem.* **2006**, *71*, 9895-9898; h) K.-i. Takao, R. Munakata, K.-i. Tadano, *Chem. Rev.* **2005**, *105*, 4779-4807; i) C. Agami, L. Dechoux, L. Hamon, S. Hebbe, *Synthesis* 2003, 859-862; j) C. Agami, L. Dechoux, S. Hebbe, J. Moulinas, *Synthesis* **2002**, 79-82; k) C. Agami, L. Dechoux, S. Hebbe, *Synlett* **2001**, 1440-1442; (l) X. Xie, X. Lu, *Tetrahedron Lett.* **1999**, *40*, 8415-8418.

[3] a) Y. A. Jasem, R. El-Esawi, T. Thiemann, *J. Chem. Res.* **2014**, *38*, 453-463; b) P. A. Burne, D. G. Gilheany, *Chem. Soc. Rev.* **2013**, *42*, 6670-6696; c) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863-927.

[4] a) C. Cordovilla, C. Bartolomé, J. M. Martínez-Ilarduya, P. Espinet, *ACS Catal.* **2015**, *5*, 3040-3053; b) J. K. Stille, *Angew. Chem. Int. Ed.* **1986**, *25*, 508-524.

[5] X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 9047-9050.

[6] a) R. Rossi, F. Bellinja, M. Lessi, *Tetrahedron* **2011**, *67*, 6969-7025; b) M. Tobisu, N. Chatani, *Angew. Chem. Int. Ed.* **2009**, *48*, 3565-3568; c) N. Miyaura, A. Suzuki, *Chem. Rev.*, **1995**, *95*, 2457-2483.

[7] a) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009-3066; b) G. T. Crisp, *Chem. Soc. Rev.* **1998**, *27*, 427-436; c) W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2-7.

[8] a) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540-1552; b) M. M. Heravi, E. Hashemi, N. Nazari, *Mol. Divers.* **2014**, *18*, 441-472.

[9] a) X. Shang, Z.-Q. Liu, *Chem Soc. Rev.* **2013**, *42*, 3253-3260; b) Z.-K. Wen, Y.-H. Xu, T.-P. Loh, *Chem. Sci.* **2013**, *4*, 4520-4524; c) N. Gigant, J.-E. Bäckwall, *Chem. Eur. J.* **2013**, *19*, 10799-10803.

[10] a) J. Li, D. Lee, *Eur. J. Org. Chem.* **2011**, 4269-4287; b) C. Fischmeister, C. Bruneau, *Beilstein J. Org. Chem.* **2011**, *7*, 156-166; c) M. Mori, *Materials* **2010**, *3*, 2087-2140; d) S. Kotha, M. Meshram, A. Tiwari, *Chem. Soc. Rev.* **2009**, *38*, 2065-2092; e) S. T. Diver, *Coord. Chem. Rev.* **2007**, *251*, 671-701; f) M. Mori, *Adv. Synth. Catal.* **2007**, *349*, 121-135; g) E. C. Hansen, D. Lee, *Acc. Chem. Res.* **2006**, *39*, 509-519; h) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317-1382.

[11] Y. Zhao, F. Zhang, W. Yao, C. Wang, Y. Liu, Y. Li, *Eur. J. Org. Chem.* **2015**, 7984-7991.

[12] a) W. Bottomley, *Tetrahedron Lett.* **1967**, *8*, 1997-1999; b) N. Anghelide, C. Draghici, D. Raileanu, *Tetrahedron* **1974**, *30*, 623-632; c) M. A. Khan, H. Adams, *Tetrahedron Lett.* **1999**, *40*, 5389-5390; d) J.-C. Zhuo, *Molecules* **1999**, *4*, M118.

[13] No yields were given in ref. 2g and 12a. The use of the pre-formed and isolated enamino ester **3** in the reaction with propiolate **2** can increase the yields of dienes **4** to > 60% (see, ref. 12b and 12d).

[14] a) S. Kikuchi, M. Iwai, H. Murayama, S.-I. Fukuzawa, *Tetrahedron Lett.* **2008**, *49*, 114-166; b) D. Hu, Y. Liu, J.-P. Wan, *Tetrahedron* **2015**, *71*, 6094-6098.

[15] T. Sirijindalert, K. Hansuthirakul, P. Rashatasakhon, M. Sukwattanasinitt, A. Ajavakom, *Tetrahedron* **2010**, *66*, 5161-5167.

[16] a) G. Szalóki, L. Sanguinet, *J. Org. Chem.* **2015**, *80*, 3949-3956; b) D. Susanti, L. L. R. Ng, P. W. H. Chan, *Adv. Synth. Catal.* **2014**, *356*, 353-358; c) A. K. Chaturvedi, A. S. Negi, P. Khare, *RSC Adv.* **2013**, *3*, 4500-4504; d) A. Serra-Muns, A. Guérinot, S. Reymond, J. Cossy, *Chem. Commun.* **2010**, *46*, 4178-4180; e) Q. Ding, B. Cao, Z. Zong, Y. Peng, *J. Comb. Chem.* **2010**, *12*, 370-373.

[17] a) V. Modrocká, E. Veverková, R. Baran, R. Šebesta, *ChemistrySelect* **2018**, *3*, 1466-1471; b) C. Hui, F. Pu, J. Xu, *Chem. Eur. J.* **2017**, *23*, 4023-4036; c) C. Despotopoulou, S. C. McKeon, R. Connon, V. Coeffard, H. Müller-Bunz, P. J. Guiry, *Eur. J. Org. Chem.* **2017**, 6734-6738; d) J. Zhang, G. Yin, Y. Du, Z. Yang, Y. Li, L. Chen, *J. Org. Chem.* **2017**, *82*, 13594-13601; e) S. Kim, S. Kang, G. Kim, Y. Li, *J. Org. Chem.* **2016**, *81*, 4048-4057.

[18] a) Y. Zhou, C.-X. Zhuo, Q, Gu, S.-L. You, *Adv. Synth. Catal.* **2015**, *357*, 912-016; b) X. Pan, J. Zhu, J. Zou, Z. Zhang, Z. Cheng, N. Zhou, W. Zhang, X. Zhu, *Org. Lett.* **2012**, *14*, 6170-6173; c) D. K. Barange, B. R. Raju, V. Kavala, C.-W. Kuo, Y.-C. Tu, C.-F. Yao, *Tetrahedron* **2010**, *66*, 3754-3760; d) A. M. A. Shumaila, R. S. Kusurkar, *Synth. Commun.* **2010**, *40*, 2935-2940; e) L. You, S. Feng, R. An, X. Wang, D. Bai, *Tetrahedron Lett.* **2008**, *49*, 5147-5149; f) H. Firouzabadi, N. Iranpoor, M. Jafarpour, A. Ghaderi, *J. Mol. Catal. A: Chem.* **2006**, *249*, 98-102; g) B. Basu, P. Das, I. Hossain, *Synlett*, **2004**, 2630-2632.

[19] Solvent-free, silica gel-catalyzed Michael addition of amines onto dialkyl acetylenedicarboxylates and alkyl propiolates to form enamino (di)esters has been examined before: R. Thorwirth, A. Stolle, *Synlett* **2011**, 2200-2202.

[20] Synthesis of conjugated dienes from (methyl-substituted)aniline and an internal alkyne was reported and it requires metal catalyst. See, Zhang, X.; Yang, B.; Li, G.; Shu, X.; Mungra, D. C.; Zhu, J. *Synlett* **2012**, *23*, 622-626.

[21] a) W. D. Crow, N. J. Leonard, *Tetrahedron Lett.* **1964**, *5*, 1477-1480; b) L. A. Hay, T. M. Koenig, F. O. Ginah, J. D. Copp, D. Mittchel, *J. Org. Chem.* **1998**, *63*, 5050-5058.

[22] a) B. J. Balfour, C. C. Greig, S. Visaisouk, *J. Org. Chem.* **1974**, *39*, 725-726; b) A. S. Medvedeva, M. V.Andreev, L. P. Safronova, *Russ. J. Org. Chem.* **2010**, *46*, 1466-1470.

[23] G. M. Coppola, R. E. Damon, *Synth. Comm.* **1993**, *23*, 2003-2010.

[24] S. Bonte, I. O. Ghinea, I. Baussanne, J.-P. Xuereb, R. Dinica, M. Demeunynck, *Tetrahedron* **2013**, *69*, 5495-5500.

[25] Even though four of the tested esters are commercially available (*n*-Bu, Allyl, Bn and Ph), they were synthesized for the purpose of this work, as is described in the Experimental Section.

[26] Method C (100 °C): **4k(e)** 16%, **5k(e)** 39%. Method C′ (65 °C): **4k(e)** 34%, **5k(e)** 19%. Method C′′ (rt): **4k(e)** 53%, **5k(e)** 0%. In methods C and C′ compounds **4** and **5** were isolated in a mixture. Also see Experimental Section.

[27] Under the solution-phase conditions, no improvement of chemoselectivity could be achieved if the number of equivalents of ester **2** was reduced to stoichiometric. For example, the reaction of **1i** with 2 moles of **2d** gave 12% of diene **4i(d)**, 26% of enamino ester intermediate **3i(d)** and 22% of **5i(d)**, while the the reaction of **1k** with 2 moles of **2d** again resulted in a complex mixture from which only **3k(d)** was isolated in 22% yield, while the yields of diene **4k(d)** and dihydropyridine **5k(d)** must be less than 30% and 10%, respectively. See, Experimental Section, method A′.

[28] a) N. A. Randive, V. Kumar, V. A. Nair, *Monatsh. Chem.* **2010**, *141*, 1329-1332; b) G. Choudhary, R. K. Peddinty, *Green Chem.* **2011**, *13*, 3290-3299.

[29] Y. Obora, Y. Shimizu, Y. Ishii, *Org. Lett.* **2009**, *11*, 5058-5061.

[30] B. Hemmateenejad, M. Sanchooli, A. Mehdipour, *J. Phys. Org. Chem.* **2009**, *22*, 613-618.

[31] L. Feray, M. P. Bertrand, *Eur. J. Org. Chem.* **2008**, 3164-3170.

[32] A. E. G. Baker, E. Marchal, K.-I. A. R. Lund, A. Thompson, *Can. J. Chem.* **2014**, *92*, 1175-1185.

[33] M. Shiotsuki, H. Kai, T. Endo, *J. Polym. Sci. A Polym. Chem.* **2014**, *52*, 2528-2536.

[34] M. D. Aparece, P. A. Vadola, *Org. Lett.* **2014**, *16*, 6008-6011.

[35] L. S. Meriwether, E. C. Colthup, G. W. Kennerly, R. N. Reusch, *J. Org. Chem.* **1961**, *26*, 5155-5163.

[36] C.-H. Lee, Y. S. Chung, B. Y. Chung, *Bull. Korean Chem. Soc.* **1993**, *14*, 592-594.

[37] J. Porter, G. Radomski, J. Seagren, B. Batura, S. David, *Lett. Org. Chem.* **2011**, *8*, 610-613.

[38] H.-F. Yiang, Y.-X. Shen, Z.-Y. Wang, *Tetrahedron Lett.* **2007**, *48*, 7542-7545.

[39] C. B. Kanner, U. K. Pandit, *Tetrahedron* **1982**, *38*, 3597-3604.

10.1002/asia.201800645

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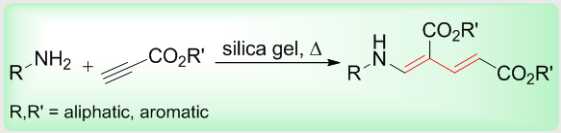

• simple • metal-free • solvent-free • 31 examples

A green and simple method for the construction of functionalized conjugated diene motif has been developed. The reaction takes place on the surface of silica gel, in the solid state. The method is particularly useful for weakly nucleophilic aromatic amines and for hydrophobic esters, which poorly react under standard solution-state conditions.

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Silica Gel as a Promoter of Sequential Aza-Michael/Michael Reactions of Amines and Propiolic Esters: Solvent-free and Metal-free Synthesis of Polyfunctionalized Conjugated Dienes